Syntheses and Binding Properties of Bibracchial Lariat Ethers (BiBLEs): Survey of Synthetic Methods and Cation Selectivities

Vincent J. Gatto, Kristin A. Arnold, Anthony M. Viscariello, Steven R. Miller, Charles R. Morgan,† and George W. Gokel*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received August 7, 1986

A new, two-step method for the synthesis of 4,10-diaza-15-crown-5 and 4,13-diaza-18-crown-6 and their N,N′-disubstituted derivatives from bis(secondary amines) and 1,2-bis(2-iodoethoxy)ethane is described. Essentially, the method utilizes the incipient sidearms as nitrogen-protecting groups prior to cyclization. The yields for cyclization are high, ranging from 32% to 77%. The N,N′-disubstituted derivatives of 4,10-diaza-15-crown-5 produced by alkylation or acylation (A), acylation followed by reduction (AR), cyclization (C), hydrogenolysis (H), or single-step cyclization (O) have the following sidearms: H (H, 91%), $MeOCH_2CH_2$ (C, 38%), $EtOCOCH_2$ (A, 62%), $PhCH_2$ (C, 72%), 2-MeOPh (C, 52%), 2-furanylmethyl (C, 67%), and 2-nitrobenzyl (A, 50%). *N,N′*-Dibenzyl-4,10-diaza-18-crown-6 was obtained by cyclization in 63% yield. The N,N′-disubstituted derivatives of 4,13-diaza-18-crown-6 produced with the new method have the following sidearms: H (H, 92%), CO–Et (A, 100%), *n*-propyl (AR, 78%), *n*-butyl (C, 77%), *n*-hexyl (C, 32%; A, 50%; O, 7%), *n*-octyl (AR, 45%), CO–*n*-heptyl (A, 71%), *n*-nonyl (O, 11%; A, 45%; AR, 48%), CO–*n*-octyl (A, 80%), CO–*n*-nonyl (A, 100%), *n*-decyl (AR, 96%), *n*-dodecyl (O, 11%; AR, 39%), CO–*n*-undecyl (A, 87%), *n*-tetradecyl (AR, 26%), CO–*n*-tridecyl (A, 78%), *n*-hexadecyl (A, 25%), *n*-octadecyl (AR, 60%), CO–*n*-heptadecyl (A, 100%), allyl (O, 26%), propargyl (O, 22%), $HOCH_2CH_2$ (O, 28%), $MeOCH_2CH_2$ (C, 43%; AR, 76%), $HOCOCH_2$ (hydrolysis, 81%), $EtOCOCH_2$ (A, 92%), $PhCH_2$ (O, 29%; C, 66%), 2-furanylmethyl (O, 27%; C, 62%), 2-hydroxybenzyl (A, 85%), 2-methoxybenzyl (O, 30%), 2-cyanobenzyl (A, 95%), 2-nitrobenzyl (A, 90%), 3-nitrobenzyl (A, 95%), and 4-nitrobenzyl (A, 70%). The new cyclization method is compared with other, previously published cyclization reactions with respect to overall yield and ease of purification. When this new cyclization cannot be used, diaza crown ethers can be prepared by alkylation of 4,10-diaza-15-crown-5 or 4,13-diaza-18-crown-6. The homogeneous equilibrium cation binding constants (log K_S) have been determined in anhydrous methanol solution for many of the compounds described herein with Na^+, K^+, and Ca^{2+}. The cation selectivities are rationalized in terms of polar, structural, and lipophilicity effects.

Introduction

Our interest in the function and selectivity of neutral cation carriers like valinomycin has resulted in studies of both carbon-pivot[1] and nitrogen-pivot[2] lariat ethers. These compounds were designed to rapidly bind cations like Na^+, K^+, and Ca^{2+} using a macroring and a donor group bearing sidearm appended thereto. Our expectation was that the combination of sidearm and macroring would afford greater binding dynamics than cryptands[3] or spherands,[4] but several questions were obvious. First, would both sidearm and macroring cooperate in binding cations, and if so, how? It seemed possible to us that sandwich structures or intermolecular [bis(ligand)metal]$^+$ complexes would compete with two-armed lariat monomers. Second, when additional donor groups are present in a sidearm or when additional sidearms were present, what would be the cooperativity of the various components? Third, by varying the sidearm donor groups, could we alter the selectivity of these compounds for various cations? We were particularly interested in neutral, Ca^{2+}-selective systems since they should exhibit considerable biological activity.[5]

The results of several studies with single-armed lariat ether molecules[1,2] suggested that "ring size", although not completely irrelevant, was less important than had previously been assumed.[6] This led to a study of binding interactions in the simple 12-crown-4 to 24-crown-8 series with Na^+, K^+, Ca^{2+}, and NH_4^+ and the finding that the so-called "hole-size relationship" is not the general rule it was thought to be.[7] It appears instead that the cation can organize the available donor groups about itself to provide the most favorable coordination geometry, at least so long as the molecule is flexible.[8]

In order to extend the concepts noted and answer the questions posed above, we undertook a program to synthesize two-armed macrocycles. We call such molecules bibracchial lariat ethers from the Latin bracchium, meaning arm, and we use the acronym BiBLEs.[9] Three-armed systems are TriBLEs, etc.

We have recently reported a novel, one-step synthesis of BiBLEs and a survey of their complexation properties with Na^+, K^+, and Ca^{2+}.[9] All the macrocycles reported in that study were *N,N′*-disubstituted-4,13-diaza-18-crown-6 derivatives,[10] so any change in cation binding selectivity

*Address correspondence to this author.
†Washington Research Center, W. R. Grace & Co., 7379 Route 32, Columbia, MD 21044.

(1) Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586.

(2) Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6659.

(3) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49; *Science* **1985**, *227*, 849.

(4) (a) Cram, D. J. *Science* **1983**, *219*, 1177. (b) Cram, D. J.; Trueblood, K. N. "Concept, Structure, and Binding in Complexation"; In *Host Guest Complex Chemistry: Macrocycles*; Voegtle, F., Weber, E., Eds.; Springer Verlag: New York, 1985; pp 125–188.

(5) Kolbeck, R. C.; Bransome, E. D.; Spier, W. A.; Hendry, L. B. *Experentia* **1984**, *40*, 727.

(6) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1982**, *104*, 625.

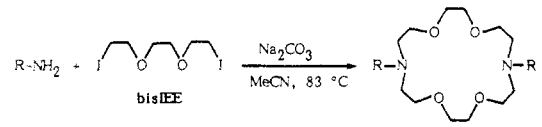
(7) Gokel, G. W.; Goli, D. M.; Minganti, C.; Echegoyen, L. *J. Am. Chem. Soc.* **1983**, *105*, 6786.

(8) (a) Fronczek, F. R.; Gatto, V. J.; Schultz, R. A.; Jungk, S. J.; Colucci, W. J.; Gandour, R. D.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 6717. (b) Fronczek, F. R.; Gatto, V. J.; Minganti, C.; Schultz, R. A.; Gandour, R. D.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 7244. (c) White, B. D.; Arnold, K. A.; Fronczek, F. R.; Gandour, R. D.; Gokel, G. W. *Tetrahedron Lett.* **1985**, *26*, 4035. (d) Gandour, R. D.; Fronczek, F. R.; Gatto, V. J.; Minganti, C.; Schultz, R. A.; White, B. D.; Arnold, K. A.; Mazzocchi, D.; Miller, S. R.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 4078.

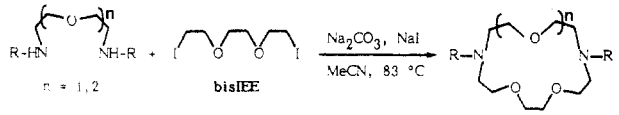
(9) Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 8240.

0022-3263/86/1951-5373$01.50/0

Scheme I



Scheme II



resulted from changes in the sidearms. We found that more polar sidearm donor groups (ester, hydroxyl) favored Ca^{2+} over Na^+ or K^+ complexation, whereas the opposite selectivity was observed for the less polar donor groups.

Although the hole-size relationship is tenuous,[7] spatial relationships are of fundamental importance in cation complexation. Studies of space-filling, CPK molecular models suggest that different cation-macroring-sidearm interactions are possible depending on sidearm donor groups and whether the BiBLEs are based on a 15- or 18-membered macroring. An example of the difference in sidearm donors is found in the crystal structures of the 2-hydroxyethyl (**30**) and 2-methoxyethyl (**31**) derivatives of 4,13-diaza-18-crown-6. Compound **30** complexes Na^+ and K^+ by using sidearm oxygens from the same side (a basket-like arrangement), and **31** uses donors from opposite sides.[8]

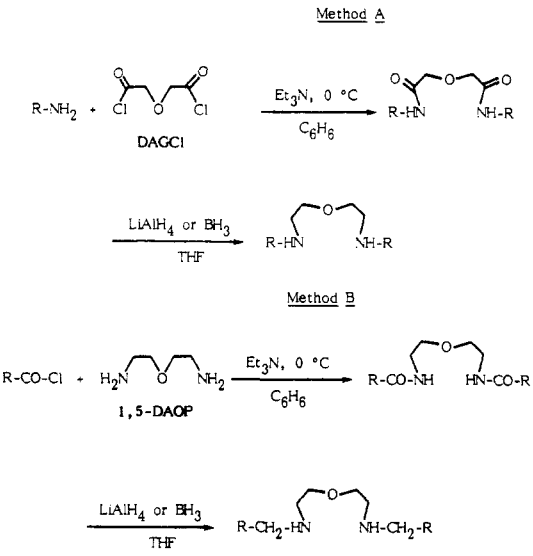
We have now extended our studies of BiBLEs to the 4,10-diaza-15-crown-5 system and to a variety of previously unstudied sidearms. We report here new, general, and efficient synthetic access to both 15- and 18-membered bibracchial lariat ethers and our conclusions about their cation binding strengths, cation selectivities, and utility.

Results and Discussion

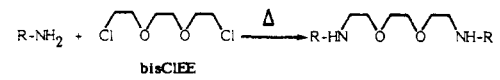
Diaza-18-crown-6 Derivatives by a Single-Step Cyclization. The reaction of primary alkylamines with 1,2-bis(2-iodoethoxy)ethane (bisIEE) in the presence of Na_2CO_3 and MeCN (Scheme I) is a versatile and useful preparation for certain 18-membered ring BiBLEs.[9] The parent compound in this series, 4,13-diaza-18-crown-6 (**9**), is accessible in two steps by (i) stirring together benzylamine with bisIEE and then (ii) hydrogenolyzing the product (Pd/C, EtOH).

This one-step cyclization method involves the formation of four new C–N bonds and an 18-membered ring so the yields (typically 20–30%) are quite acceptable. In addition, the sodium complexes occasionally crystallize directly from solution, making the work-up simple. Despite these obvious advantages, the method is, by its very nature, inappropriate for the synthesis of 15-membered ring BiBLEs.

Scheme III



Scheme IV



Syntheses Using the Two-Step Approach. Several methods for the synthesis of 4,10-diaza-15-crown-5 (**1**) have been reported.[11] These are generally complicated and require either high dilution conditions[11a] or a nitrogen protection/deprotection sequence.[11b,c,d] Furthermore, alkylation or acylation of 4,10-diaza-15-crown-5 would be required in order to prepare the BiBLEs of interest to us. While more rapid syntheses of **1** have recently been published,[12] it is still necessary to carry out alkylations or acylations on the macrocycle in order to obtain the desired two-armed systems. Indeed, we have also used such an approach to prepare some of the examples presented in this paper.

Our synthesis of 15-membered ring diaza-BiBLEs is outlined in Scheme II. This method involves cyclization of bis(secondary amines) [$(RNHCH_2CH_2)_2O$], with bisIEE in the presence of Na_2CO_3, NaI, and MeCN. The reaction may readily be extended to 18-membered ring BiBLEs by using the appropriate bis(secondary amines) in an otherwise identical sequence. An important advantage of the present method is that the sidearms are incorporated prior to cyclization, eliminating the need for a protection/deprotection scheme.

Syntheses of Two-Armed Precursors. The syntheses of a variety of bis(secondary amines) derived from 1,5-diamino-3-oxapentane are illustrated in Scheme III. Method A involves reaction of primary amines with diglycolic acid dichloride (DGACl) to give bis(amides). Reduction of the bis(amides) with either lithium aluminum hydride (LAH) or diborane–tetrahydrofuran complex (BH_3·THF) leads to the formation of the desired bis(secondary amines).

Method B is an alternate procedure which involves reaction of 1,5-diamino-3-oxapentane with an acid chloride

(10) (a) Takagi, M.; Tazaki, M.; Ueno, K. *Chem. Lett.* **1978**, 179. (b) Wester, N.; Voegtle, F. *J. Chem. Res.* **1978**, 400. (c) Kulstad, S.; Malmsten, L. A. *Acta Chem. Scand., Ser. B* **1979**, *B33*, 469. (d) Cho, I.; Chang, S. K. *Bull. Korean Chem. Soc.* **1980**, *1*, 145. (e) Gramain, P.; Kleiber, M.; Frere, Y. *Polymer* **1980**, *21*, 915. (f) Kulstad, S.; Malmsten, L. A. *J. Inorg. Nucl. Chem.* **1981**, *43*, 1299. (g) Cho, I.; Chang, S.-K. *Chem. Lett.* **1981**, 515. (h) Tazaki, M.; Nita, K.; Takagi, M.; Ueno, K. *Chem. Lett.* **1982**, 571. (i) Frere, Y.; Gramain, P. *Makromol. Chem.* **1982**, *183*, 2163. (j) Bogatsky, A. V.; Lukyanenko, N. G.; Pastushok, V. N.; Kostyanovsky, R. G. *Synthesis* **1983**, 992. (k) DeJong, F.; Van Zon, A.; Reinhoudt, D. N.; Torny, G. J.; Tomassen, H. P. M. *Recl. J. R. Neth. Chem. Soc.* **1983**, *102*, 164. (l) Kobayashi, H.; Okahara, M. *J. Chem. Soc., Chem. Commun.* **1983**, 800. (m) Shinkai, S.; Kinda, H.; Araragi, Y.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 559. (n) Keana, J. F. W.; Cuomo, J.; Lex, L.; Seyedrezai, S. E. *J. Org. Chem.* **1983**, *48*, 2647. (o) Tsukube, H. *J. Chem. Soc., Chem. Commun.* **1983**, 970. (p) Tsukube, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2685. (q) Tsukube, H. *J. Chem. Soc., Chem. Commun.* **1984**, 315. (r) Ricard, A.; Capillon, J.; Quivoeron, C. *Polymer* **1985**, *25*, 1136.

(11) (a) Lehn, J. M. U.S. Patent 3 888 877, 1975. (b) Atkins, T. J.; Richman, J. E.; Oettle, W. F. *Org. Synth.* **1978**, *58*, 86. (c) Desreux, J. F.; Renard, A.; Duyckuerts, G. *J. Inorg. Nucl. Chem.* **1977**, *39*, 1587. (d) Bogatsky, A. V.; Lukyanenko, N. G.; Basok, S. S.; Ostrovskaya, L. K. *Synthesis* **1984**, 138.

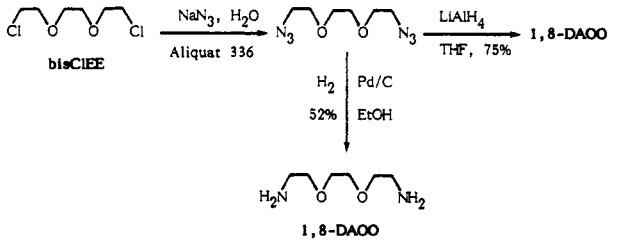
(12) (a) Kulstad, S.; Malmsten, L. A. *Tetrahedron* **1980**, *36*, 521. (b) Maeda, H.; Furuyoshi, S.; Nakatsuji, Y.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 212.

Table I. Syntheses of Bis(secondary amine) BiBLE Precursors

compd[a]	BiBLE	sidearm[b]	from amine	method[c]	yields, %[d] acyln	redn	overall
A15	2	$CH_2CH_2OCH_3$	$CH_3OCH_2CH_2NH_2$	A/LAH	60	90	54
B15	4	CH_2Ph	$PhCH_2NH_2$	A/BH_3	93	88	82
B15	4	CH_2Ph	$PhCH_2NH_2$	A/LAH	93	73	68
B15	4	CH_2Ph	$O(CH_2CH_2NH_2)_2$	B/BH_3	93	94	87
B15	4	CH_2Ph	$O(CH_2CH_2NH_2)_2$	B/LAH	93	61	57
C15	5	$CH_2C_6H_4$-2-OCH_3	CH_3O-2-$C_6H_4CH_2NH_2$	A/BH_3	90	94	85
D15	6	CH_2-2-furanyl	2-furanylamine	A/LAH	90	83	75
D15	6	CH_2-2-furanyl	$O(CH_2CH_2NH_2)_2$	B/LAH	89	56	50
A18	13	$CH_2CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2NH_2$	alkyln			85
B18	14	$(CH_2)_5CH_3$	1-aminohexane	alkyln			87
C18	28	$CH_2CH_2OCH_3$	$CH_3OCH_2CH_2NH_2$	alkyln			88
D18	31	CH_2Ph	$PhCH_2NH_2$	alkyln			86
E18	32	CH_2-2-furanyl	2-furanylamine	alkyln			94

[a] Identified as precursor to specific ring system. [b] Sidearm present on resulting BiBLE indicated in column 2. [c] See Scheme III and text for a discussion of the methods used. [d] Yields are for isolated, purified products of reactions conducted on gram or multigram scale.

Scheme V



to give bis(amides) which are structurally different from, but isomeric with, the bis(amides) resulting from method A. LAH or BH_3·THF reduction of these bis(amides) also affords the desired bis(secondary amines).

The precursor syntheses are summarized in Table I which contains yields for a variety of bis(secondary amine) preparations. In general, we have found that reduction using BH_3·THF gives better yields and purer products than reduction with LAH. The acylation yields were all high (89–93%) with the exception of $(CH_3OCH_2CH_2NHCOCH_2)_2$, for which the yield was only 60%. The low isolated yield in the latter case is due to water solubility of this bis(amide) which resulted in some loss during workup procedures.

The syntheses of a variety of bis(secondary amines) derived from 1,8-diamino-3,6-dioxaoctane are shown in Scheme IV. As seen in Table I, the alkylation yields are all high, ranging from 85% to 94%. This procedure, originally developed by Krespan,[13] is more straightforward than the syntheses we have just described (Scheme III). Unfortunately, this approach cannot be used for the synthesis of bis(secondary amines) derived from 1,5-diamino-3,6-dioxaoctane.

The synthesis of 1,8-diamino-3,6-dioxaoctane, which was required for a comparison between our cyclization reactions and those reported by Kulstad and Malmsten,[10c] is illustrated in Scheme V. We have prepared 1,8-diazido-3,6-dioxaoctane from the corresponding dichloride using a phase-transfer reaction developed by Reeves.[14] Reduction (LAH/THF) of the diazide gave the diamine in 75% overall yield.

Two-Step Cyclization. The cyclization reactions (Scheme II) are carried out in 0.05 M MeCN solutions of the bis(secondary amines) using a 25% excess of diiodide, a fivefold excess of Na_2CO_3, and 0.5 equiv of NaI. The compounds prepared using this method and their isolated

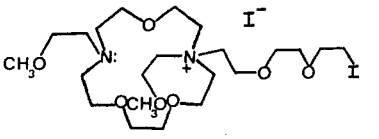
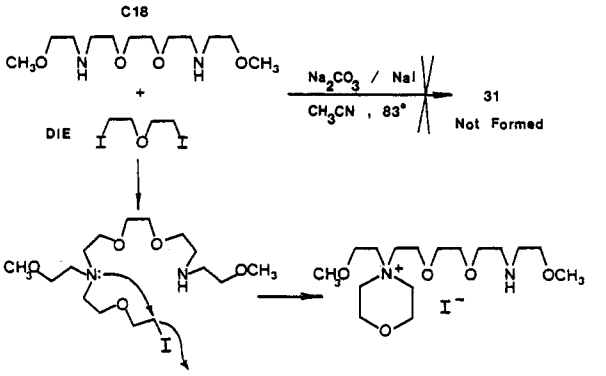


Figure 1. Postulated ammonium salt formed during cyclization.

Scheme VI



Scheme VII

yields are shown in Table II. When cyclization was attempted using $(MeOENHEOCH_2)_2$ with bis(2-iodoethyl) ether (DIE), no cyclization to the 15-membered bibracchial lariat ether was observed (Scheme VI). This failure was apparently due to competitive morpholinium salt formation. On the other hand, when $(MeOCH_2CH_2NHCH_2CH_2)_2O$ was reacted with bisIEE, **2** was formed in 38% yield. In the latter case, complexation of sodium (template effect) favors cyclization to the 15-membered bibracchial lariat ether (Scheme VII) over cyclization to the nine-membered-ring ammonium salt.

We have found that added NaI (ca. 0.5 equiv) generally gave fewer byproducts making the reaction mixtures easier to purify. The solubility of Na_2CO_3 in CH_3CN is quite low while NaI is quite soluble. In the initial stages of the reaction, the presence of a small amount of NaI acts as a template and aids in the cyclization reaction. As the reaction progresses, more NaI is formed which serves the same purpose as that which was originally added.

The use of excess diiodide (ca. 25%) generally gave higher yields than when an equivalent amount of diiodide

(13) King, A. P.; Krespan, C. G. *J. Org. Chem.* **1977**, *39*, 1315.
(14) Reeves, W. P.; Bahr, M. L. *Synthesis* **1976**, 823.

Table II. Survey of Syntheses and Cation Binding Properties for 15- and 18-Membered Bibracchial Lariat Ethers (BiBLEs)

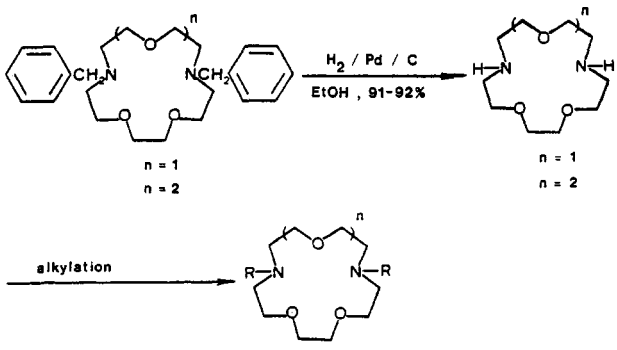
compd	ring size	sidearm on each nitrogen	method[e]	yield	mp, °C (bp, °C/torr)	log K_S in MeOH[a]			cation selectivities[b]		
						Na^+	K^+	Ca^{2+}	Na/K	Ca/K	Ca/Na
			A. Derivatives of 4,10-Diaza-15-crown-5								
1	15	H	H	91	86–89	<1.5	<1.5	ND	1.0		
2	15	2-methoxyethyl	C	38	(120–2/0.04)	5.09	4.86	4.97	1.70	1.29	0.76
3	15	carbethoxymethyl	A	62	(170–3/0.43)	5.34	4.65	6.04	4.90	24.5	5.0
4	15	benzyl	C	72	oil	2.59	2.12	2.34	2.95	1.66	0.56
5	15	2-methoxybenzyl	C	52	oil	3.59	3.13	3.04	2.88	0.81	0.28
6	15	2-furanylmethyl	C	67	(153–5/0.05)	3.99	3.87	3.45	1.32	0.38	0.29
7	15	2-nitrobenzyl	A	50	oil	ND	ND	ND			
			B. Derivatives of 4,10-Diaza-18-crown-6								
8	18	benzyl	C	63	(170–80/0.03)	2.88	ND	ND			
			C. Derivatives of 4,13-Diaza-18-crown-6								
9	18	H	H	92	115–6	1.5	1.8	ND	0.5		
10	18	methyl	[c]			3.7	5.3	na	0.03		
11	18	CO–Et	A	100	(209–11/0.03)	ND	ND	ND			
12	18	*n*-propyl	AR	78	(130–1/0.06)	2.86	3.77	ND			
13	18	*n*-butyl	C	77	(146–9/0.25)	2.84	3.82	2.86	0.10	0.11	1.0
14	18	*n*-hexyl	C	32	oil	2.89	3.78	ND	0.13		
			A	50							
			O	7							
15	18	*n*-octyl	AR	45	(181–90/0.04)	ND	ND	ND			
16	18	CO–*n*-heptyl	A	71	54.5–55	ND	ND	ND			
17	18	*n*-nonyl	O	11	oil	2.95	3.70	ND			
			A	45							
			AR	48							
18	18	CO–*n*-octyl	A	80	61–62.5	<1.5	<1.5	ND			
19	18	CO–*n*-nonyl	A	100	65.5–67	ND	ND	ND			
20	18	*n*-decyl	AR	96	(205–215/0.07)	ND	ND	ND			
21	18	*n*-dodecyl	O	11	46–48	2.99	3.80	ND	0.15		
			AR	39							
22	18	CO–*n*-undecyl	A	87	74–75	ND	ND	ND			
23	18	*n*-tetradecyl	AR	26	54–55	ND	ND	ND			
24	18	CO–*n*-tridecyl	A	78	78–80	ND	ND	ND			
25	18	*n*-hexadecyl	A	25	63–64	ND	ND	ND			
26	18	*n*-octadecyl	AR	60	66–67.5	ND	ND	ND			
27	18	CO–*n*-heptadecyl	A	100	86–89	ND	ND	ND			
28	18	allyl	O	26	44–45	3.00	4.03	2.84	0.09	0.06	0.69
29	18	propargyl	O	22	41–42	3.67[d]	5.00	3.52	0.05	0.03	0.71
30	18	2-hydroxyethyl	O	28	(194–200/0.1)	4.87	5.08	6.02	0.62	8.71	14.1
31	18	2-methoxyethyl	C	43	(136–8/0.05)	4.75	5.46	4.48	0.20	0.10	0.54
			AR	76							
32	18	carboxymethyl	Hy	81	173–175	ND	1.8	ND			
33	18	carbethoxymethyl	A	92	(195–7/0.02)	5.51	5.78	6.78	0.54	10.0	18.6
34	18	benzyl	O	29	80–81	2.72	3.38	2.79	0.22	0.26	1.17
			C	66							
35	18	2-furanylmethyl	O	27	34–36	3.77	4.98	ND	0.06		
			C	62							
36	18	2-hydroxybenzyl	A	85	120–122	2.40	2.59	2.95	0.64	2.29	3.55
37	18	2-methoxybenzyl	O	30	86–87	3.65	4.94	3.27	0.05	0.02	0.42
38	18	2-cyanobenzyl	A	95	96–98	ND	ND	ND			
39	18	2-nitrobenzyl	A	90	77–78.5	ND	ND	ND			
40	18	3-nitrobenzyl	A	95	106–107	ND	ND	ND			
41	18	4-nitrobenzyl	A	70	116–118	ND	ND	ND			

[a] Measured at 25 °C; see text. [b] Selectivities are expressed as ratios of equilibrium constants. [c] This compound was not prepared as part of this study. [d] Compound **29** analyzes as the trihydrate and the X-ray crystal structure shows four waters per molecule. Binding constants and ratios for these two forms of **29** are as follows: trihydrate 3.80, 5.14, 3.52, 0.05, 0.02, 0.52; tetrahydrate 3.84, 5.19, 3.53, 0.04, 0.02, 0.49. [e] A means alkylation or acylation. AR means A followed by reduction. C means cyclization using nonidentical fragments. H means hydrogenolysis. Hy means hydrolysis. O means single step cyclization using a primary amine and triethylene glycol diiodide. ND means not determined.

was used. In addition, reaction times longer than 18 h generally gave lower yields of the BiBLEs. The latter result is probably due to an increase in ammonium salt formation (see Figure 1) as the reaction proceeded. The lower yields obtained when an equivalent amount of diiodide is used are probably due to similar factors. If a molecule of macrocycle reacts with a molecule of diiodide when equivalent amounts of reagents are used, two potential product molecules are destroyed. When excess diiodide is used, only one molecule of product is destroyed.

Comparison of Single- and Two-Step Approaches. All of the cyclization yields reported in Table II are for 18–25-h reaction times. Comparative yields obtained by using the alkylation–cyclization approach indicate that this method is more efficient than the one-step method despite the greater number of steps involved in the former. *N,N'*-Dibenzyl-4,13-diaza-18-crown-6 (**34**) is a key compound since it can be hydrogenolyzed to the parent, **9**. It is obtained readily by the one-step approach in 29% yield but in more than double that (66%) when the new approach is used. The choice of method would therefore be made based on the quantity of product desired. An additional advantage is that generally, purification of BiBLEs prepared using this new cyclization reaction is easier than purification of the same compounds obtained from the one-step method.

Scheme VIII



When primary amines or acid chlorides were not commercially available or when the use of excess primary amines was not practical, it became necessary to prepare the desired BiBLEs by alkylation of the unsubstituted diazacrown ether (Scheme VIII). The preparation of 4,13-diaza-18-crown-6 (**9**) from the dibenzyl derivative (**34**) has been described previously.[9] Thus, hydrogenolysis (H_2/Pd–C) of **34** in EtOH gave a 92% yield of **9**. Using this same procedure, we have now prepared 4,10-diaza-15-crown-5 (**1**) from the dibenzyl derivative (**4**).

Cation Binding Strengths. The cation affinities, log K_S in anhydrous methanol solution at 25 ± 0.1 °C, were determined as previously described,[2,7] for many of the compounds reported here with Na^+, K^+, and Ca^{2+} and are recorded in Table II. As in all previous studies, superior binding is observed when appropriately placed sidearm donors are present. A tenfold increase in Na^+ binding strength was observed when *o*-methoxy groups (compound **5**) are added to the benzyl sidearms of **4**. For 4,10-diaza-15-crown-5 derivatives, the Na^+ affinity decreases in the following sidearm order: $CH_2COOEt > CH_2CH_2OCH_3 >$ 2-furanylmethyl > 2-methoxybenzyl > benzyl > H. The order for Ca^{2+} affinity is similar, but there is a reversal of CH_2COOEt and $CH_2CH_2OCH_3$ for the K^+ case. It is especially interesting that the ester donor groups of **3** bind Ca^{2+} much more strongly than do the ether links in **2**. Moreover, the ratios of binding strengths (K_S **3**/K_S **2**) for Na^+ and Ca^{2+} are 1.8 and 11.7, respectively. This is in accord with our view that more polar donors favor more charge-dense cations, other variables being the same. We have previously noted a Ca^{2+}-selectivity trend for the 18-membered ring systems, carbethoxymethyl (**33**), hydroxyethyl (**30**), and methoxyethyl (**31**).

Confirmation of the cooperativity between ring and sidearm donor groups is found in the X-ray crystal structure of bis(hydroxyethyl)BiBLE, **30**. Its Na^+ complex exists in a "basket" or pseudocryptate arrangement in which both sidearms bind Na^+ from the same side of the macroring (Figure 2). In this case, Na^+ is eight-coordinate.[8a,d]

The carbonyl groups of BiBLEs bearing –COR substituents do not show enhanced Ca^{2+} selectivity. Since the amide (>NCO–) linkage prefers planarity, the oxygen donor groups are not appropriately disposed to fold back and further solvate a ring-bound cation. Indeed, the cation binding strengths observed for these compounds are less than observed for the simple alkyl derivatives (cf. **17** and **18** in Table II).

Lipophilicity Effects. The precise effect of lipophilicity on cation binding strengths and selectivities is difficult to predict because of the well-known[15] enthalpy–entropy compensation principle. An increase in binding strength which accompanies an increase in lipophilicity, all other factors being equal, indicates that a favorable entropy effect dominates the cation binding. In other words, the cation complex would be more isolated from the solvent, causing greater solvent disorder. Should the binding decrease as the lipophilicity increases, an unfavorable enthalpic effect would be blamed. In such a case, the solvent would be unable to aid the macroring in solvating the cation.

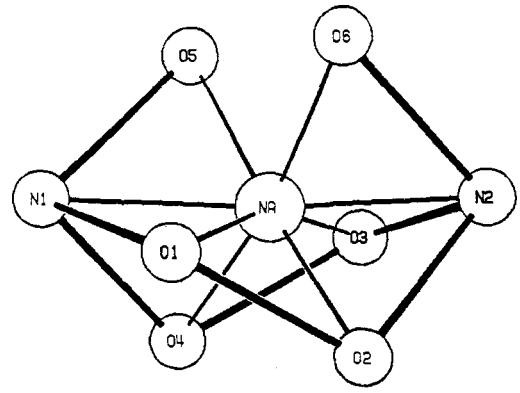


Figure 2. Computer-drawn framework diagram of *N*,*N*′-bis(2-hydroxyethyl)-4,13-diaza-18-crown-6 (**30**) derived from X-ray crystal structure data. Only the cation, donor groups, and connectivities are illustrated. For additional information and experimental details, see ref 8a.

Sodium cation binding strengths (log K_S) are, for BiBLEs having the following sidearms, *n*-butyl (**13**), 2.84; *n*-hexyl (**14**), 2.89; *n*-nonyl (**17**), 2.95; and *n*-dodecyl (**21**), 2.99. The corresponding K^+ binding strengths are: *n*-butyl, 3.82; *n*-hexyl, 3.78; *n*-nonyl, 3.70; and *n*-dodecyl, 3.80. It is clear that neither enthalpic nor entropic effects dominates and the trends are not far enough outside of experimental error to draw significant conclusions. Work to separate the binding constants into enthalpic and entropic components is underway and will be reported shortly.

A final comment on this problem is the paucity of data recorded in Table II for the most lipophilic compounds. The compounds having the longest hydrocarbon sidearms are the least soluble in anhydrous methanol and their binding constants cannot be determined by our method.

Double- and Triple-Bond-Containing Sidearms. The series of 18-BiBLEs having propyl (**12**), allyl (**28**), and propargyl (**29**) sidearms is an interesting one. Our original interest in these unsaturated materials was the hope that proximity would force a previously undocumented interaction between the ring-bound alkali metal cation and the sidearm π bond. The trend in binding strengths for these three compounds (log K_S, Na^+) is as follows: *n*-propyl (**12**), 2.86; allyl (**28**), 3.00; and propargyl (**29**), 3.67. The K^+-binding strengths showed a similar trend (log K_S, K^+), which is as follows: **12**, 3.77; **28**, 4.03; and **29**, 5.00. The K^+ binding results were expected to show evidence for K^+-triple-bond interaction if it could be observed anywhere, since steric interactions should be most favorable in this case.

An X-ray crystal structure (see Figure 3) determination conducted on the complex **29**·KSCN showed that the propargyl sidearms did not interact with the ring-bound K^+, but were turned away from the macroring.[16] Since no direct evidence could be obtained for a sidearm inter-

(15) Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev.* **1985**, *85*, 271.

(16) Fronczek, F. R.; Gandour, R. D.; Viscariello, A. M.; Gokel, G. W., unpublished results, 1986.

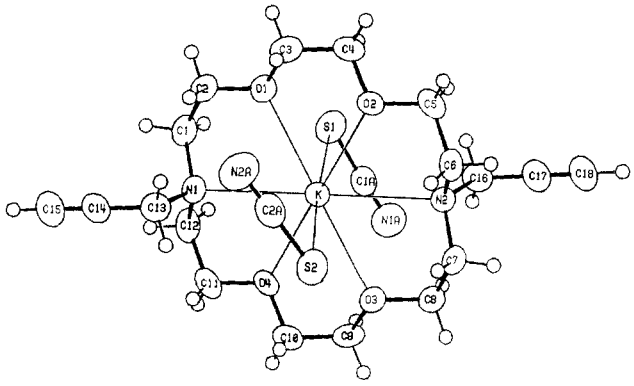


Figure 3. Computer-drawn structure of *N,N'*-dipropargyl-4,13-diaza-18-crown-6 (**29**) complexed by KSCN. Full experimental details to be published separately.

action in either case, we have concluded that the high binding observed for **29** is due to a steric effect. The triple bond is an especially small substituent, having an A value little larger than H.[17] The smaller substituent enables solvent to interact as a donor group along with the macroring donors. This hypothesis is confirmed by the unusually high cation binding strengths observed for the methyl compound, **10** compared to *n*-propyl BiBLE, **12**.

BiBLEs with Ionizable Sidearms. The 18-BiBLEs prepared as part of this study which have ionizable sidearms show relatively poor cation binding properties at "neutral pH" in anhydrous methanol. Both the glycine **32** and phenol (2-hydroxybenzyl, **36**) sidearm compounds show very weak binding. This is almost certainly due to zwitterion formation. We anticipate that at high pH, neither nitrogen nor $-COO^-$ would be protonated. The work of Van Zon[10k,18] has shown that **36** is a powerful and selective cation binder for divalent cations and the compound has proved commercially useful for demineralizing (ton scale) oilwell casings.

Summary

We have shown that N,N'-disubstituted derivatives of 4,10-diaza-15-crown-5, 4,10-diaza-18-crown-6, and 4,13-diaza-18-crown-6 can be prepared by reaction of the appropriate bis(secondary amines) with the appropriate ethylene glycol diiodide. The advantages of this method are the following: (i) versatility in starting materials—both primary amines and acid chlorides can be used to introduce the eventual sidearm; (ii) high yield of cyclization—typically 38–77%; (iii) ease of purification; (iv) ease of preparation—4,10-diaza-15-crown-5, 4,10-diaza-18-crown-6, and 4,13-diaza-18-crown-6 can be prepared by hydrogenolysis of the appropriate dibenzyl derivative. This allows greater synthetic versatility since alkylation of the unsubstituted crowns will give additional bibracchial lariat ethers. All of the evidence obtained to date suggests that cation binding is accomplished by cooperative ring and sidearm interactions when the latter contain donor groups. Binding is relatively weak when no sidearm donors are present in the BiBLEs.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. Infrared (IR) spectra were recorded (Perkin-Elmer 281) as neat films on NaCl plates unless otherwise specified. Infrared spectral bands [reciprocal centimeters (cm^{-1})] are calibrated against the 1601 cm^{-1} band of polystyrene. Strong (s) peaks are specified. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded as ca. 15 vol % solutions on a Varian EM-360 or Perkin-Elmer R600 spectrometer in $CDCl_3$ solvent containing 1% Me_4Si unless otherwise specified. Data are reported in the following order: chemical shift, spin multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and assignment. Proton-decoupled ^{13}C NMR spectra were recorded at 25.2 MHz on a Varian Associates XL-100 instrument in $CDCl_3$ and are reported in ppm (δ) downfield from internal Me_4Si. Osmometric molecular weights were determined on a Wescor vapor phase osmometer (Model 5100C) calibrated using 10–70 mmol of dibenzo-18-crown-6 per kg of dichloroethane using ca. 10-mg samples. Bulb-to-bulb distillations were conducted in a Kugelrohr apparatus and the temperatures quoted refer to the oven temperature.

Combustion analyses were performed by Atlantic Microlabs, Atlanta, GA. All commercial grade solvents ($CHCl_3$, CH_2Cl_2, hexanes, EtOAc, and 2-propanol) were distilled prior to use. Reagent grade solvents (MeCN, MeOH, EtOAc, DMF, Me_2SO) were stored over dry molecular sieves (4 Å) prior to use. Tetrahydrofuran (THF) and benzene (C_6H_6) were purified and dried using previously reported procedures.[1,2] All primary amines, except *o*-methoxybenzylamine, were dried over CaO and distilled prior to use. All reactions were performed under a dry nitrogen atmosphere. The acylations and reductions were performed using oven-dried (115 °C) glassware. 1,5-Diamino-3-oxapentane (1,5-DAOP) was a gift from W. R. Grace & Co.

Synthesis of 1,8-Diamino-3,6-dioxaoctane (1,8-DAOO). 1,2-Bis(2-azidoethoxy)ethane. Reeves' method[14] was used to prepare this compound. A vigorously stirred solution containing bisClEE (73.2 g, 0.39 mol), NaN_3 (104 g, 1.6 mol) and Aliquat 336 (9.4 g, 18.8 mol) in water (300 mL) was heated at 98 °C for 15 h. The reaction was cooled, the phases were separated, and the organic layer was washed (water, 2 × 50 mL) and dried ($MgSO_4$), giving crude diazide as a yellow oil.

1,8-Diamino-3,6-dioxaoctane (1,8-DAOO) by Reduction with LAH. Fleischer's method[19] served as a model for the preparation of this compound. A solution of the above diazide (89.5 g, 0.45 mol) in dry THF (350 mL) was slowly added to a stirred solution of LAH (45.3 g, 1.19 mol) in dry THF (350 mL) at 0 °C. After the addition the reaction was heated at reflux for 16 h and cooled, water (200 mL) was added, and the inorganic salts removed by filtration. The gelatinous salts were extracted for 24 h in a Soxhlet thimble with THF from the refluxing mother liquor. The THF was evaporated and the resulting oil was dried by stirring with refluxing C_6H_6 and collecting the water in a Dean–Stark Trap. The C_6H_6 solution was concentrated in vacuo. Vacuum distillation (bp 57–70 °C, 0.32 torr) gave 1,8-DAOO (49.7 g, 75%) as a transparent oil with physical properties identical with those reported.[10c]

Diglycolic acid dichloride (DGACl) was prepared from diglycolic acid and phosphorus pentachloride by the method of Lehn[11a] in 88% yield. The red liquid (bp 56–57 °C, 0.5 torr) possessed physical properties identical with those reported.

General Procedure for Acyl Chloride Formation. The acyl chlorides required for these studies were prepared by dissolving 0.095 mol of the acid in 15 mL of $SOCl_2$ and allowing the reaction to stir for 10 h. After evaporation and subsequent azeotropic distillation (C_6H_6) to remove $SOCl_2$, the product, usually a pale oil, was used without further purification.

Bis(2-iodoethyl) ether (DIE) was prepared from bis(2-chloroethyl) ether (DClE) and NaI by the method of Kulstad and Malmsten[10c] in 92% yield. The orange liquid possessed physical properties identical with those reported.

1,2-Bis(2-iodoethoxy)ethane (bisIEE) was prepared from 1,2-bis(2-chloroethoxy)ethane (bisClEE) and NaI by the method of Kulstad and Malmsten[10c] in 85% yield. The orange liquid (bp 100–105 °C, 0.2 torr) possessed physical properties identical with those reported.

4,10-Diaza-15-crown-5 (1). *N,N'*-Dibenzyl-4,10-diaza-15-crown-5 (4.0 g, 0.010 mol), 10% Pd/C catalyst (0.4 g) and absolute

(17) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.
(18) Van Zon, A. Presented at the Ninth Annual Symposium on Macrocycle Chemistry, Provo, UT, August 1985.
(19) Fleischer, E. B.; Gebala, A. E.; Levey, A.; Tasker, V. A. *J. Org. Chem.* **1971**, *36*, 3042.

EtOH (5 mL) were shaken in a Parr Series 3900 hydrogenation apparatus at 70 psi H_2 pressure and 25 °C for 24 h. The reaction was filtered and concentrated in vacuo. Bulb-to-bulb distillation (120–122 °C, 0.1 torr) gave **1** (2.0 g, 91%) as a white solid (mp 86–89 °C) with physical properties identical with those reported.[11a]

1,7-Bis(2-methoxyethyl)-2,6-dioxo-4-oxa-1,7-diazaheptane (42). A solution of 2-methoxyethylamine (13.5 g, 0.18 mol) and triethylamine (18.2 g, 0.18 mol) in C_6H_6 (75 mL) was slowly added to a stirred solution of DGACl (13.7 g, 0.08 mol) in C_6H_6 (75 mL). The temperature of the reaction was maintained at 0–8 °C during the addition. The mixture was brought to ambient temperature for 1 h and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (200 mL) and consecutively washed with 3 N HCl (20 mL), 1 N NaOH (20 mL), and water (20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Recrystallization (C_6H_6) gave 11.9 g (60%) of the title compound as a white solid (mp 88–89 °C): ^{1}H NMR 3.36–3.49 (m, 14 H, CH_3 and NCH_2CH_2O), 4.05 (s, 4 H, OCH_2CO), 7.10 (bs, 2 H, NH); ^{13}C NMR 39.08, 59.07, 71.58, 169.91; IR (KBr) 3300 (s), 2900, 1680 (s), 1640 (s), 1550 (s), 1460, 1430, 1340, 1290, 1190, 1110 (s), 1090, 1050, 1010, 750, 690. Anal. Calcd for $C_{10}H_{20}N_2O_5$: C, 48.37; H, 8.13; N, 11.28. Found: C, 48.24; H, 8.40; N, 11.37.

1,7-Bis(2-methoxyethyl)-4-oxa-1,7-diazaheptane (A15). A solution of the bis(amide) described above (7.5 g, 0.030 mol) in dry THF (100 mL) was slowly added to a stirred solution of LAH (6.9 g, 0.18 mol) in dry THF (300 mL) at 0 °C. After addition, the reaction was stirred at reflux for 18 h. The reaction was cooled to 0 °C, and excess LAH was destroyed by consecutive addition of water (7 mL), 15% NaOH (7 mL), and water (21 mL). The granular precipitate was removed by filtration, and the filtrate was concentrated in vacuo. Bulb-to-bulb distillation (70–73 °C, 0.05 torr) gave 6.0 g (90%) of the title compound as a transparent liquid: ^{1}H NMR 1.82 (s, 2 H, NH), 2.79 (t, 8 H, CH_2N), 3.36–3.57 (m, 14 H, CH_2O and CH_3O); ^{13}C NMR 49.70, 59.06, 71.07, 72.76; IR 2860 (s), 1450, 1330, 1240, 1190, 1110 (s). Anal. Calcd for $C_{10}H_{24}N_2O_3$: C, 54.50; H, 11.00; N, 12.72. Found: C, 54.20; H, 11.30; N, 12.73.

***N,N'*-Bis(2-methoxyethyl)-4,10-diaza-15-crown-5 (2).** A solution of A15 (3.3 g, 0.015 mol), bisIEE (7.2 g, 0.020 mol), Na_2CO_3 (7.9 g, 0.075 mol) and NaI (1.1 g, 0.0075 mol) in MeCN (300 mL) was heated at reflux for 18 h. The workup procedure was analogous to that for **31** (see below). Column chromatography (alumina, 50% EtOAc/hexanes) followed by bulb-to-bulb distillation (120–122 °C, 0.04 torr) gave 1.9 g (38%) of **2** as a transparent oil: ^{1}H NMR 2.72, 2.82 (t and t, 12 H, CH_2N), 3.32 (s, 6 H, OCH_3), 3.43–3.70 (m, 16 H, OCH_2); ^{13}C NMR 54.84, 55.10, 55.66, 58.61, 69.64, 70.55, 70.64, 71.30; IR 2860 (s), 1450, 1350, 1120 (s), 1070. Anal. Calcd for $C_{16}H_{34}N_2O_5$: C, 57.44; H, 10.27; N, 8.38. Found: C, 57.18; H, 10.40; N, 8.32.

***N,N'*-Bis(carbethoxymethyl)-4,10-diaza-15-crown-5 (3).** A solution of **1** (1.1 g, 0.005 mol), ethyl bromoacetate (1.8 g, 0.011 mol), and Na_2CO_3 (1.2 g, 0.011 mol) in MeCN (22 mL) was heated at reflux for 18 h. The reaction was cooled, filtered, and concentrated in vacuo. Recrystallization of the resulting solid (THF) gave **3** as its NaBr complex (1.7 g, mp 127–129 °C): ^{1}H NMR 1.26 (t, 6 H, CH_3), 2.72 (t, 8 H, NCH_2), 3.36, 3.47, and 3.66 (s, t, and s, 16 H, NCH_2CO and OCH_2), 4.10 (q, 4 H, CH_2OCO); ^{13}C NMR 14.11, 54.08, 55.83, 57.06, 61.52, 66.85, 67.11, 68.92, 173.39; IR (KBr) 3000, 2960, 2900, 2840, 1730 (s), 1470, 1440, 1380, 1370, 1350, 1300, 1250, 1210 (s), 1120, 1080, 1060, 1030, 940, 930 cm^{-1}. Anal. Calcd for $C_{18}H_{34}N_2O_7NaBr$: C, 43.81; H, 6.96; N, 5.68. Found: C, 43.72; H, 7.13; N, 5.63. Bulb-to-bulb distillation of the complex (170–173 °C, 0.43 torr) gave 1.2 g (62%) of **3** as a transparent oil: ^{1}H NMR 1.26 (t, 6 H, CH_3), 2.93 (t, 8 H, NCH_2), 3.50 and 3.63 (s,s and t, 16 H, NCH_2CO and OCH_2), 4.14 (q, 4 H, CH_2OCO); ^{13}C NMR 14.31, 54.30, 54.64, 56.75, 60.06, 69.53, 70.35, 70.61, 171.39; IR 3000, 2940, 2860, 1740 (s), 1180, 1130, 1080, 1030. Anal. Calcd for $C_{18}H_{34}N_2O_4$: C, 55.35; H, 8.79; N, 7.17. Found: C, 55.14; H, 9.04; N, 7.10.

Synthesis of *N,N'*-Dibenzyl-4,10-diaza-15-crown-5 (4). 1,7-Dibenzyl-2,6-dioxo-4-oxa-1,7-diazaheptane (43). A solution of benzylamine (19.3 g, 0.18 mol) and triethylamine (18.2 g, 0.18 mol) in C_6H_6 (100 mL) was slowly added to a stirred solution of DAGCl (13.0 g, 0.076 mol) in C_6H_6 (100 mL). The temperature of the reaction was kept at 0–8 °C during the addition. The mixture was brought to ambient temperature for 1 h and concentrated in vacuo. The remainder of the workup procedure was analogous to that for **42**. Recrystallization (C_6H_6) gave the title compound (22.2 g, 93%) as a white solid (mp 124–125 °C): ^{1}H NMR 3.77 (s, 4 H, OCH_2CO), 4.27 (d, 4 H, benzyl), 7.24–7.51 (s and bt, 12 H, aromatic and NH); ^{13}C NMR 43.09, 71.43, 128.38, 129.32, 138.99, 169.88; IR (KBr) 3360, 3260, 1650 (s), 1560, 1530, 1450, 1130, 740, 690. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.47; N, 8.97. Found: C, 69.08; H, 6.36; N, 9.00.

1,7-Bis(phenylcarbonyl)-4-oxa-1,7-diazaheptane (44). A solution of 1,5-DAOP (10.4 g, 0.10 mol) and triethylamine (22.2 g, 0.22 mol) in C_6H_6 (100 mL) was slowly added to a stirred solution of benzoyl chloride (30.9 g, 0.22 mol) in C_6H_6 (100 mL). The temperature of the reaction was maintained at 0 °C during the addition. The mixture was brought to ambient temperature for 3 h and concentrated in vacuo. The remainder of the workup procedure was analogous to that described above. Recrystallization (C_6H_6), gave 28.9 g (93%) of the title compound as a white solid (mp 103–105 °C): ^{1}H NMR 3.53–3.60 (m, 8 H, OCH_2CH_2N), 7.05–7.82 (m, 12 H, aromatic H and NH); IR (KBr) 3280 (s), 3070, 2930, 2870, 1635 (s), 1605, 1580, 1440 (s), 1490, 1310 (s), 1120 (s), 695. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.47; N, 8.97. Found: C, 69.12; H, 6.36; N, 8.97.

LAH Reduction of 1,7-Bis(phenylcarbonyl)-4-oxa-1,7-diazaheptane to 1,7-Dibenzyl-4-oxa-1,7-diazaheptane (B15). A solution of **44** (15.6 g, 0.050 mol) in dry THF (100 mL) was slowly added to a stirred solution of LAH (5.7 g, 0.150 mol) in dry THF (150 mL) at 0 °C. After addition the reaction was stirred at reflux for 14 h. The reaction was cooled to 0 °C, and excess LAH was destroyed by consecutive addition of water (6 mL), 15% NaOH (6 mL), and water (18 mL). The granular precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (150 mL) and washed with brine (30 mL) and water (30 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation (150–155 °C, 0.2 torr) gave B15 (8.7 g, 61%) as a slightly yellow oil: ^{1}H NMR 1.69 (s, 2 H, NH), 2.77 (t, 4 H, NCH_2), 3.55 (t, 4 H, OCH_2), 3.77 (2, 4 H, benzyl), 7.31 (s, 10 H, aromatic); ^{13}C NMR 49.07, 54.21, 70.92, 127.66, 128.92, 129.13, 141.41; IR 3340, 2860 (s), 1500, 1450, 1350, 1120 (s), 1030, 730, 700. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.00; H, 8.42; N, 9.85. Found: C, 75.93; H, 8.68; N, 9.66.

Alternate Reduction Using BH_3·THF Complex. To a stirred solution of BH_3·THF complex (192 mL, 1.0 M) was added **44** (7.4 g, 24 mol) as a solid at 0 °C. The reaction was brought to ambient temperature and stirred for 3 days. Water was added dropwise until the liberation of H_2 stopped. The mixture was concentrated in vacuo and 6 N HCl (50 mL) was added. The aqueous solution was heated at reflux for 4 h, cooled, and adjusted to pH 9 with NaOH. The aqueous phase was diluted until all salts dissolved and then extracted with $CHCl_3$ (3 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation (129–131 °C, 0.05 torr) gave 1,7-dibenzyl-4-oxa-1,7-diazaheptane (6.4 g, 94%) as a transparent oil with physical properties identical with those noted above.

LAH Reduction of 1,7-Dibenzyl-2,6-dioxo-4-oxa-1,7-diazaheptane (43) to 1,7-Dibenzyl-4-oxa-1,7-diazaheptane (B15). A solution of **43** (15.6 g, 0.04 mol) in dry THF (100 mL) was added slowly to a stirred solution of LAH (11.4 g, 0.30 mol) in dry THF (300 mL) at 0 °C. The workup procedure was analogous to that for the reduction described above. Bulb-to-bulb distillation (135–139 °C, 0.05 torr) gave the title diamine (10.3 g, 73%) as a slightly yellow oil with physical properties identical with those noted above.

Alternate Reduction Using BH_3·THF Complex. To a stirred solution of BH_3·THF complex (96 mL, 1.0 M) was added **43** (3.7 g, 0.012 mol), as a solid, at 0 °C. The reaction was brought to ambient temperature and stirred for 2 days. Hydrolysis and workup were analogous to that described for reduction of **44** with BH_3·THF. Bulb-to-bulb distillation using a Kugelrohr apparatus (150–155 °C, 0.2 torr) gave 1,7-dibenzyl-4-oxa-1,7-diazaheptane (3.0 g, 88%) as a transparent oil with physical properties identical with those described previously.

***N,N'*-Dibenzyl-4,10-diaza-15-crown-5 (4).** A solution of 1,7-dibenzyl-4-oxa-1,7-diazaheptane (4.3 g, 0.015 mol), bisIEE (7.4 g, 0.020 mol), Na_2CO_3 (10.6 g, 0.10 mol), and NaI (1.5 g, 0.010 mol) in MeCN (400 mL) was heated at reflux for 19 h. The workup

procedure was analogous to that for **31**. Column chromatography (alumina, 10% EtOAc/hexanes) gave 4.3 g (72%) of **4** as a transparent oil: ^{1}H NMR 2.65–2.90 (m, 8 H, NCH_2), 3.47–3.63 (m, 16 H, OCH_2 and benzyl), 7.28 (s, 10 H, aromatic); ^{13}C NMR 54.29, 54.38, 60.62, 69.51, 70.47, 70.61, 126.56, 127.88, 128.55, 139.62; IR 2860 (s), 1500, 1450, 1350, 1120 (s), 1070, 1050, 1020, 730 (s), 700 (s). Anal. Calcd for $C_{24}H_{34}N_2O_3$: C, 72.31; H, 8.62; N, 7.03. Found: C, 72.64; H, 8.70; N, 7.07.

Synthesis of *N,N'*-Bis(2-methoxybenzyl)-4,10-diaza-15-crown-5 (5). 1,7-Bis(2-methoxybenzyl)-2,6-dioxo-4-oxa-1,7-diazaheptane. A solution of *o*-methoxybenzylamine (15.1 g, 0.11 mol) and triethylamine (11.1 g, 0.11 mol) in C_6H_6 (75 mL) was slowly added to a stirred solution of DAGCl (8.5 g, 0.05 mol) in C_6H_6 (75 mL). The temperature of the reaction was kept at 0–8 °C during the addition. The mixture was brought to ambient temperature for 1 h and concentrated in vacuo. The remainder of the workup procedure was analogous to that for **42**. Recrystallization (C_6H_6) gave the title compound (16.7 g, 90%) as a white solid (mp 103–105 °C): ^{1}H NMR 3.66 (s, 6 H, OCH_3), 3.81 (s, 4 H, OCH_2CO), 4.40 (d, 4 H, benzyl), 6.72–7.40 (m, 10 H, aromatic and NH); ^{13}C NMR 38.88, 55.64, 71.44, 111.27, 121.50, 126.87, 129.74, 130.16, 158.56, 169.36; IR (KBr) 3320, 1650 (s), 1550, 1240 (s), 1130, 1030, 750. Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.49; H, 6.51; N, 7.52. Found: C, 64.63; H, 6.56; N, 7.49.

1,7-Bis(2-methoxybenzyl)-4-oxa-1,7-diazaheptane (C15). To a stirred solution of BH_3·THF complex (160 mL, 1.0 M) was added the diamide described above (7.4 g, 0.020 mol), as a solid, at 0 °C. The reaction was brought to room temperature and stirred for 42 h. Hydrolysis and workup were analogous to that described above for reduction of **44** with BH_3·THF. Bulb-to-bulb distillation (160–163 °C, 0.7 torr) gave the title compound (6.5 g, 94%) as a transparent oil: ^{1}H NMR 2.08 (s, 2 H, NH), 2.72 (t, 4 H, CH_2), 3.52 (t, 4 H, OCH_2), 3.72 and 3.77 (s and s, 10 H, OCH_3 and benzyl), 6.70–7.30 (m, 8 H, aromatic); IR 3340, 3000, 2840 (s), 1600, 1590, 1490 (s), 1460 (s), 1440, 1350, 1290, 1240 (s), 1180, 1120, 1050, 1020, 930, 830, 750 (s), 720. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.72; H, 8.21; N, 8.13. Found: C, 68.35; H, 8.50; N, 7.98. This material was used without further purification.

***N,N'*-Bis(2-methoxybenzyl)-4,10-diaza-15-crown-5 (5)** was prepared from C15 (5.2 g, 0.015 mol) and bisIEE (7.0 g, 0.019 mol) as described for **4**. Column chromatography (alumina, 20% EtOAc/hexanes) gave **5** (3.6 g, 52%) as a thick, transparent oil: ^{1}H NMR 2.72–2.92 (m, 8 H, NCH_2), 3.50–3.75 (m, 22 H, OCH_2 and benzyl), 6.72–7.50 (m, 8 H, aromatic); ^{13}C NMR 54.23, 55.04, 55.69, 70.22, 71.08, 71.26, 111.14, 121.22, 128.51, 128.93, 131.19, 158.83; IR 2940 (s), 2860 (s), 1600, 1590, 1490 (s), 1460 (s), 1440, 1350, 1290, 1240 (s), 1120 (s), 1050, 1030, 750 (s). Anal. Calcd for $C_{26}H_{38}N_2O_5$: C, 68.08; H, 8.37; N, 6.11. Found: C, 68.21; H, 8.50; N, 5.95.

Synthesis of *N,N'*-Difurfuryl-4,10-diaza-15-crown-5 (6). 1,7-Difurfuryl-2,6-dioxo-4-oxa-1,7-diazaheptane. A solution of furfurylamine (17.5 g, 0.18 mol) and triethylamine (18.2 g, 0.18 mol) in C_6H_6 (100 mL) was slowly added to a stirred solution of DGACl (13.7 g, 0.08 mol) in C_6H_6 (100 mL). The temperature of the reaction was maintained at 0–8 °C during the addition. The mixture was brought to ambient temperature for 1 h and then concentrated in vacuo. The workup procedure was analogous to that for **42**. Recrystallization (C_6H_6) gave 21.1 g (90%) of the title compound as a white solid (mp 62–64 °C): ^{1}H NMR 3.97 (s, 4 H, OCH_2), 4.35 (d, 4 H, furfuryl), 6.14–6.32 (m, 4 H, furan H), 7.35 (bs, 2 H, 5-furan H), 7.70 (broad t, 2 H, NH); ^{13}C NMR 36.11, 71.45, 108.22, 111.26, 143.16, 152,21, 169.97; IR (KBr) 3320 (s), 1680 (s), 1650 (s), 1540 (s), 1330, 1280, 1270, 1210, 1200, 1150, 1120 (s), 1070, 1050, 1010, 990, 920, 740 (s), 720, 620. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.53; N, 9.59. Found: C, 57.39; H, 5.53; N, 9.55.

1,7-Bis(2-furylcarbonyl)-4-oxa-1,7-diazaheptane. A solution of 1,5-DAOP (4.2 g, 0.04 mol) and triethylamine (10.1 g, 0.10 mol) in C_6H_6 (50 mL) was slowly added to a stirred solution of 2-furoyl chloride (13.1 g, 0.1 mol) in C_6H_6 (50 mL). The temperature of the reaction was maintained at 0–8 °C during the addition. The mixture was brought to ambient temperature for 2 h and concentrated in vacuo. The workup procedure was analogous to that for **42**. Recrystallization (C_6H_6) gave the title compound (10.4 g, 89%) as a white solid (mp 95–97.5 °C): ^{1}H NMR 3.59–3.65 (m, 8 H, NCH_2CH_2O), 6.39–6.47 (m, 2 H, 4-furan H), 7.39 (bs, 2 H, 5-furan H); ^{13}C NMR 39.26, 70.08, 112.71, 114.74, 144.99, 149.21, 159.74; IR (KBr) 3260 (s), 2860, 1640 (s), 1600 (s), 1570 (s), 1530 (s), 1470, 1310 (s), 1150, 1120, 1010, 750. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.52; H, 5.53; N, 9.59. Found: C, 57.24; H, 5.64; N, 9.50.

1,7-Difurfuryl-4-oxa-1,7-diazaheptane (D15). A solution of 1,7-difurfuryl-2,6-dioxo-4-oxa-1,7-diazaheptane (11.7 g, 0.04 mol) in dry THF (100 mL) was slowly added to a stirred solution of LAH (9.1 g, 240 mol) in dry THF (300 mL) at 0 °C. After addition, the reaction was stirred at reflux for 18 h. The workup procedure was analogous to that described for A15. Bulb-to-bulb distillation (105–112 °C, 0.04 torr) gave 8.7 g (83%) of the title compound as a transparent oil: ^{1}H NMR 1.88 (s, 2 H, NH), 2.88 (t, 4 H, CH_2N), 3.53 (t, 4 H, CH_2O), 3.78 (s, 4 H, furfuryl), 6.12–6.31 (m, 4 H, furan H), 7.36 (d, 2 H, 5-furan H); ^{13}C NMR 46.54, 48.86, 70.91, 107.42, 110.82, 142.66, 155.23; IR 3320, 3100, 2860 (s), 1500, 1450 (s), 1340, 1140 (s), 1110 (s), 1000 (s), 910, 880, 800, 730 (s). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.60; H, 7.64; N, 10.60. Found: C, 63.49; H, 7.74; N, 10.70.

1,7-Difurfuryl-4-oxa-1,7-diazaheptane (D15). A solution of 1,7-bis(furfurylcarbonyl)-4-oxa-1,7-diazaheptane (4.0 g, 0.014 mol) in dry THF (100 mL) was slowly added to a stirred solution of LAH (4.7 g, 0.123 mol) in dry THF (100 mL) at 0 °C. After addition, the reaction was stirred at reflux for 3 days. The reaction was cooled to 0 °C, and excess LAH was destroyed by consecutive addition of water (5 mL), 15% NaOH (5 mL), and water (15 mL). The granular precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL) and washed with brine (20 mL) and water (20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation (108–110 °C, 0.5 torr) gave the title compound (2.0 g, 56%) as a slightly yellow oil with physical properties identical with those noted above.

***N,N'*-Difurfuryl-4,10-diaza-15-crown-5 (6).** A solution of 1,7-difurfuryl-4-oxa-1,7-diazaheptane (4.0 g, 0.015 mol), bisIEE (7.0 g, 0.019 mol), Na_2CO_3 (7.9 g, 0.075 mol), and NaI (1.1 g, 0.0075 mol) in MeCN (300 mL) was heated at reflux for 18 h. The workup procedure was analogous to that for **31**. Column chromatography (alumina, 35% EtOAc/hexanes) followed by bulb-to-bulb distillation using a Kugelrohr apparatus (153–155 °C, 0.05 torr) gave BiBLE **6** (3.8 g, 67%) as a transparent oil: ^{1}H NMR 2.80 (m, 8 H, NCH_2), 3.50–3.62 (m, 16 H, OCH_2 and furfuryl), 6.12–6.32 (m, 4 H, furan H), 7.36 (d, 2 H, 4-furan H); ^{13}C NMR 52.19, 53.82, 54.14, 69.36, 70.17, 70.61, 108.00, 109.86, 141.57, 152.82; IR 2860 (s), 1500, 1450, 1350, 1120 (s), 1070, 1010, 920, 810, 730. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.46; H, 8.00; N, 7.40. Found: C, 63.44; H, 8.15; N, 7.43.

***N,N'*-Bis(2-nitrobenzyl)-4,10-diaza-15-crown-5 (7)** was prepared from 4,10-diaza-15-crown-5 (1.0 g, 0.0046 mol) and *o*-nitrobenzyl chloride (1.6 g, 0.0094 mol) in a manner analogous to that of **39**. Column chromatography (alumina, 30% EtOAc/hexanes followed by silica, $CHCl_3$) gave **7** (1.1 g, 50%) as a thick oil: ^{1}H NMR 2.68–2.88 (m, 8 H, NCH_2), 3.40–3.60 (m, 12 H, OCH_2), 3.95 (s, 4 H, benzyl), 7.28–7.90 (m, 8 H, aromatic); ^{13}C NMR 54.93, 57.30, 69.36, 70.18, 70.64, 123.91, 127.38, 131.05, 132.24, 135.37, 149.50; IR 2860 (s), 1530 (s), 1450, 1350 (s), 1300, 1130 (s), 1070, 860, 780, 730. Anal. Calcd for $C_{24}H_{32}N_4O_7$: C, 58.99; H, 6.61; N, 11.47. Found: C, 58.78; H, 6.52; N, 11.08.

***N,N'*-Dibenzyl-4,10-diaza-18-crown-6 (8).** A solution of 1,7-dibenzyl-4-oxa-1,7-diazaheptane (1.00 g, 0.0035 mol), tetraethylene glycol diiodide (1.82 g, 0.0044 mol), Na_2CO_3 (1.86 g, 0.0176 mol), and NaI (0.26 g, 0.0018 mol) in MeCN (70 mL) was heated at reflux for 19 h. The reaction mixture was cooled, filtered, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL) and extracted with 6 N HCl (2 × 100 mL). The combined aqueous phases were adjusted to pH 8–10 using Na_2CO_3, extracted with $CHCl_3$ (2 × 100 mL), and concentrated in vacuo. Column chromatography (alumina, 10% EtOAc:hexanes) followed by bulb-to-bulb distillation (Kugelrohr apparatus, 170–180 °C, 0.03 torr) afforded pure **8** (0.98 g, 63%) as a transparent and colorless oil: ^{1}H NMR 7.28 (s, 10 H, aromatic) 3.47–3.63 (m, 20 H, CH_2O and CH_2Ar), 2.63–2.88 (m, 8 H, CH_2N); IR 3010, 2860 (s), 1600, 1450, 1350, 1120. Anal. Calcd for $C_{26}H_{38}N_2O_4$: C, 70.55; H, 8.65. Found: C, 70.59; H, 8.68.

4,13-Diaza-18-crown-6 (9) from 1,8-DAOO. 4,13-Diaza-18-crown-6 was prepared from 1,8-DAOO (3.7 g, 0.025 mol) and bisIEE (9.3 g, 0.025 mol) by the method of Kulstad and Malmsten.[10c] Recrystalliation (hexanes) gave **9** (2.0 g, 30%) as a white solid (mp 115–116 °C) with physical properties identical with those reported.[11a]

4,13-Diaza-18-crown-6 (9) by Hydrogenolysis of 34. 4,13-Diaza-18-crown-6 was prepared from **34** by the method we have described previously.[9] Recrystallization (hexanes) gave **9** (9.7 g, 92%) as a white solid (mp 114–115 °C) with physical properties identical with those reported.[11a]

***N,N'*-Dimethyl-4,13-diaza-18-crown-6 (10).** Compound **10** was prepared as described by Lehn and co-workers and had properties identical with those reported.[11a]

***N,N'*-Dipropanoyl-4,13-diaza-18-crown-6 (11).** To a vigorously stirred solution of 4,13-diaza-18-crown-6 (0.50 g, 1.90 mmol) and Na_2CO_3 (0.45 g, 4.24 mmol) in benzene (35 mL) was added propanoyl chloride (0.40 g, 4.33 mmol) at ambient temperature. The mixture was stirred for 12 h, filtered, and concentrated in vacuo. Bulb-to-bulb distillation afforded **11** (0.71 g, 100%) as a transparent and colorless oil (bp 209–211 °C/0.03 torr): ^{1}H NMR 3.60 (m, 24 H, NCH_2, OCH_2); 2.20 (m, 4 H, $COCH_2$); 1.10 (t, 6 H, CH_3); IR 2920 (s), 2840, 1630, 1450, 1370, 1120. Anal. Calcd for $C_{18}H_{34}N_2O_6$: C, 57.73; H, 9.15. Found: C, 57.66; H, 9.21.

***N,N'*-Dipropyl-4,13-diaza-18-crown-6 (12).** To a stirred solution of BH_3·THF complex (1.0 M, 19 mL) was added **11** (0.71 g, 1.90 mmol) at once and the mixture heated to reflux for 24 h. The mixture was cooled, H_2O:THF (1:1, 10 mL) was added slowly until H_2 evolution ceased, and the mixture was concentrated in vacuo. HCl (6 N, 30 mL) was added and the mixture heated at reflux for 24 h. The mixture was then cooled, basified (pH 9–10) with solid NaOH, and extracted with $CHCl_3$ (6 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Bulb-to-bulb distillation afforded **12** (0.51 g, 78%) as a transparent oil (bp 130–131/0.06 torr): ^{1}H NMR 3.70 (m, 16 H, CH_2O); 2.70 (m, 12 H, CH_2N); 1.40 (m, 4 H, CH_2); 0.9 (t, 6 H, CH_2); IR 2920 (s), 2850, 1460, 1360, 1120. Anal. Calcd for $C_{18}H_{38}N_2O_4$: C, 62.39; H, 11.05. Found: C, 62.30; H, 11.08.

1,10-Di-*n*-butyl-4,7-dioxa-1,10-diazadecane (A18) was prepared from *n*-butylamine (117 g, 1.6 mol) and bisClEE (18.7 g, 0.1 mol) as described for compound B18. Bulb-to-bulb distillation (98–100 °C, 0.25 torr) gave the title compound (22.0 g, 85%) as a transparent oil: ^{1}H NMR 0.90 (t, 6 H, CH_3), 1.18–1.52 (m, 10 H, $CH_2CH_2CH_2CH_3$ and NH), 2.50–2.82 (m, 8 H, NCH_2), 3.60 (s and t, 8 H, OCH_2); ^{13}C NMR 14.09, 20.67, 32.68, 49.84, 50,08, 70.90, 71.29; IR 2920 (s), 2860 (s), 1460, 1120 (s). Anal. Calcd for $C_{14}H_{32}N_2O_2$: C, 64.55; H, 12.41; N, 10.76. Found: C, 64.27; H, 12.70; N, 10.63.

***N,N'*-Di-*n*-butyl-4,13-diaza-18-crown-6 (13).** The title BiBLE was prepared from A18 (above, 5.2 g, 0.020 mol) and bisIEE (9.2 g, 0.025 mol) as described for **31**. Column chromatography (alumina, 20% EtOAc/hexanes) followed by bulb-to-bulb distillation (146–149 °C, 0.25 torr) gave **13** (5.8 g, 77%) as a transparent oil: ^{1}H NMR 0.90 (t, 6 H, CH_3), 1.12–1.52 (m, 8 H, $NCH_2CH_2CH_3$), 2.50 (t, 4 H, $NCH_2CH_2CH_2CH_3$, 2.78 (t, 8 H, NCH_2CH_2O), 3.60 (s and t, 16 H, OCH_2); ^{13}C NMR 14.11, 20.76, 29.91, 54.62, 56.19, 70.73; IR 2920 (s), 2850 (s), 1460, 1350, 1300, 1120 (s), 1070. Anal. Calcd for $C_{20}H_{42}N_2O_4$: C, 64.11; H, 11.32; N, 7.48. Found: C, 63.85; H, 11.55; N, 7.19.

***N,N'*-Di-*n*-hexyl-4,13-diaza-18-crown-6 (14). *N,N'*-Di-*n*-hexyl-1,8-diamino-3,6-octane (B18).** A solution of 1-aminohexane (51.48 g, 0.51 mol) and bisCIEE (5.91 g, 0.032 mol) was stirred and heated at reflux for 38 h. The reaction was cooled, NaOH pellets (2.61 g, 0.064 mol) were added, and the mixture was heated at reflux for an additional 1 h. After cooling, the mixture was concentrated in vacuo and the residue dissolved in $CHCl_3$ (100 mL). The precipitated salts were removed and the filtrate concentrated in vacuo. Bulb-to-bulb distillation (bp 107–110 °C, 0.45 torr) afforded the title compound (8.72 g, 87%) as a pale yellow oil: ^{1}H NMR 3.7 (m, 8 H, CH_2O), 2.7 (m, 8 H, CH_2N), 1.4, (pseudo-s, 18 H, CH_2 and NH), 0.9 (t, 6 H, CH_3); IR 3300, 2925 (s), 2850 (s), 1460 (s), 1380, 1350, 1120 (s). This material was used without further purification.

***N,N'*-Di-*n*-hexyl-4,13-diaza-18-crown-6 (14) by a Two-Step Method.** A solution of B18 (5.00 g, 0.016 mol), bisIEE (7.77 g, 0.021 mol), Na_2CO_3 (10.6 g, 0.1 mol), and NaI (1.20 g, 0.008 mol) in MeCN (300 mL) was heated at reflux for 25 h. The mixture was cooled, filtered, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL) and extracted with HCl (6 N, 2 × 100 mL). The combined aqueous phases were adjusted to pH 8–10 with Na_2CO_3 and then extracted with $CHCl_3$ (2 × 100 mL) and concentrated in vacuo. Column chromatography (alumina, 20% EtOAc/hexanes) followed by bulb-to-bulb distillation (170–175 °C, 0.1 torr) afforded **14** (2.21 g, 32%) as a pale yellow oil: ^{1}H NMR 3.7 (m, 16 H, CH_2O), 2.7 (m, 12 H, CH_2N), 1.4 (pseudo-s, 16 H, CH_2), 0.9 (t, 6 H, CH_3); IR 2920 (s), 2850 (s), 1470, 1360, 1130 (s). Anal. Calcd for $C_{24}H_{50}N_2O_4$: C, 66.94; H, 11.70; N, 6.50. Found: C, 66.70; H, 11.90; N, 6.25.

***N,N'*-Di-*n*-hexyl-4,13-diaza-18-crown-6 (14) by a Single-Step Method.** The synthesis was accomplished using the previously reported method.[9] Chromatography (alumina, 10% EtOAc/hexanes) afforded pure **14** (0.12 g, 7%) as a pale yellow oil having physical properties identical with those reported above.

***N,N'*-Di-*n*-hexyl-4,13-diaza-18-crown-6 (14) by Alkylation of 9.** A solution of 4,13-diaza-18-crown-6 (**9**, 2.00 g, 0.0076 mol), 1-bromohexane (2.52 g, 0.015 mol), and Na_2CO_3 (3.24 g, 0.031 mol) in MeCN (50 mL) was stirred at reflux for 27 h. The reaction was cooled, filtered, and concentrated in vacuo. Column chromatography (aluming, 10% EtOAc/hexanes) afforded **14** (1.64 g, 50%) as a pale yellow oil having properties identical with those described above.

***N,N'*-Dioctyl-4,13-diaza-18-crown-6 (15).** *N,N'*-Dioctanoyl-4,13-diaza-18-crown-6 (**16**) (see below, 1.00 g, 0.0022 mol) was added at once to B_2H_6·THF (1.0 M, 60 mL) at 0 °C. The mixture was heated at reflux for 2 days and then excess diborane was destroyed by cautious addition of water. HCl (6 N, 30 mL) was added and the mixture heated at reflux for 24 h. The solution was cooled, neutralized by addition of solid NaOH, and extracted with $CHCl_3$ (2 × 100 mL), and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. Bulb-to-bulb distillation (bp 181–190 °C, 0.04 torr) afforded **15** (0.68 g, 63%) as a colorless oil: ^{1}H NMR 3.7 (m, 16 H, CH_2), 2.7 (m, 12 H, NCH_2), 1.4 (pseudo-s, 20 H, CH_2), 0.9 (t, 6 H, CH_3); IR 2920 (s), 2850, 1470, 1360, 1130 (s). Anal. Calcd for $C_{28}H_{58}N_2O_4$: C, 69.09; H, 12.01; N, 5.75. Found: C, 68.88; H, 12.04; N, 5.68.

***N,N'*-Dioctanoyl-4,13-diaza-18-crown-6 (16) by Acylation of 9.** To a mixture of 4,13-diaza-18-crown-6 (**9**, 1.2 g, 0.0046 mol) and Na_2CO_3 (1.4 g, 0.0013 mol) in benzene (35 mL) was added octanoyl chloride (1.6 g, 0.0092 mol) in benzene (25 mL) over 30 min at ambient temperature. The mixture was stirred 16 h. The mixture was filtered through celite and concentrated in vacuo. After crystallization (hexanes, 0.2 g/mL), **16** (1.4 g, 71%) was obtained as a white solid (mp 54.5–55 °C): ^{1}H NMR 3.62 (pseudo-s, 24 H, ring CH_2); 2.31 (t, 4 H, $COCH_2$); 1.29 (m, 24 H, CH_2); 0.86 (t, 6 H, CH_3); IR (KBr) 2900 (s), 2840, 1640, 1480, 1460, 1440, 1150, 1130, 1110, 725. Anal. Calcd for $C_{28}H_{54}N_2O_6$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.30; H, 10.61; N, 5.42.

***N,N'*-Dinonyl-4,13-diaza-18-crown-6 (17) by Alkylation of 9.** To a vigorously stirred solution of **9** (0.5 g, 0.002 mol), NaI (0.57 g, 0.004 mol), and Na_2CO_3 (0.81 g, 0.008 mol) in boiling MeCN (20 mL) was added a solution of 1-chlorononane (0.62 g, 0.004 mol) in MeCN (5 mL). After 4 days at reflux, the mixture was cooled, filtered, and concentrated in vacuo. Chromatography (alumina, 10% EtOAc/hexanes) afforded **17** (0.44 g, 45%) as a pale yellow oil: ^{1}H NMR 3.7 (m, 16 H, CH_2O), 2.7 (m, 12 H, CH_2N), 1.4 (s, 28 H, CH_2), 0.9 (t, 6 H, CH_3); IR 2920 (s) 2850, 1470, 1360 (s). Anal. Calcd for $C_{30}H_{62}N_2O_4$: C, 69.99; H, 12.14. Found: C, 69.86; H, 12.14.

***N,N'*-Dinonyl-4,13-diaza-18-crown-6 (17) by a Single-Step Cyclization.** To a stirred solution containing bisIEE (37.0 g, 0.10 mol) and Na_2CO_3 (53.0 g, 0.50 mol) in boiling MeCN (900 mL) was added a solution of 1-aminononane (14.33 g, 0.10 mol) in MeCN (100 mL). After 30 h of reflux, the mixture was cooled, filtered, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL), and the organic phase was washed with water (100 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (alumina, 0–10% EtOAc/hexanes) afforded **17** (2.83 g, 11%) as a pale yellow oil having the physical properties noted above.

***N,N'*-Dinonanoyl-4,13-diaza-18-crown-6 (18)** was synthesized by the method described above for **16** using nonanoyl chloride.

The product (**18**) was obtained (2.0 g, 80%) as a white solid (mp 61–62.5 °C): ^{1}H NMR 3.62 (pseudo-s, 24 H, ring CH_2), 2.31 (t, 4 H, $COCH_2$), 1.29 (s with shoulder, 28 H, CH_2), 0.86 (t, 6 H, CH_3); IR (KBr) 2920, 2840, 1630 (s), 1470, 1450, 1430, 1145, 1130, 1110, 730 (w). Anal. Calcd for $C_{30}H_{58}N_2O_6$: C, 66.38; H, 10.77. Found: C, 66.39; H, 10.82.

***N,N'*-Didecanoyl-4,13-diaza-18-crown-6 (19)** was synthesized by the method described above for **16** using decanoyl chloride. The product (**19**) was obtained (2.48 g, 100%) as a white solid (mp 65.5–67 °C): ^{1}H NMR 3.64 (s, 24 H, crown CH_2's), 2.31 (t, 4 H, $-(C{=}O)CH_2$), 1.74 (t, 4 H, $-(C{=}O)CH_2CH_2-$), 1.27 (s, 24 H, CH_2), 0.88 (t, 6 H, CH_3); IR (KBr) 2920, 2860, 1640 (s), 1480, 1440, 1150, 1135, 1115, 1085, 1075, 1045, 820, 730. Anal. Calcd for $C_{32}H_{62}N_2O_6$: C, 67.33; H, 10.95. Found: C, 67.44; H, 10.96.

***N,N'*-Didecyl-4,13-diaza-18-crown-6 (20).** To a stirred solution of borane–tetrahydrofuran complex (16 mL, 1.0 M) was added **19** (1.2 g, 2.1 mmol). The reaction was refluxed for 24 h followed by a dropwise addition of 6.0 M HCl. The reaction was refluxed for an additional 3 h, cooled to ambient temperature, basified to pH 10 with NaOH pellets, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried with $MgSO_4$ and concentrated in vacuo. Bulb-to-bulb distillation (bp 205–215 °C/0.07 mm) afforded 1.1 g (96%) of a colorless crystalline solid, mp 34.5–36.5 °C: ^{1}H NMR 3.65 (t, 16 H, OCH_2), 2.60 (m, 12 H, NCH_2), 1.30 (s, 32 H, CH_2), 0.90 (t, 6 H, CH_3); IR (KBr): 2930, 2850, 1470, 1390, 1370, 1300, 1130, 1080, 1000, 730.

***N,N'*-Didodecyl-4,13-diaza-18-crown-6 (21) and *N*-Dodecylmonoaza-9-crown-3 (21a).** A vigorously stirred solution containing dodecylamine (11.10 g, 0.05 mol), triethylene glycol diiodide (18.5 g, 0.05 mol), and Na_2CO_3 (26.5 g, 0.025 mol) in MeCN (500 mL) was heated at reflux for 27 h. The mixture was cooled, filtered, and concentrated in vacuo. Column chromatography (alumina, 0–10% EtOAc/hexanes) afforded two products. The first product (**21a**) (2.99 g, 20%) was isolated, after bulb-to-bulb distillation, as a colorless oil (bp 111–115 °C, 0.04 torr): ^{1}H NMR 3.6 (m, 8 H, CH_2O), 2.7 (m, 6 H, NCH_2), 1.4 (s, 20 H, CH_2), 0.9 (t, 3 H, CH_3); IR 2920, 2860, 1470, 1370, 1310, 1135. Osmometric molecular weight: calcd 299; found 297 g/mol. Anal. Calcd for $C_{18}H_{37}NO_2$: C, 72.26; H, 12.37; N, 4.68. Found: C, 71.99; H, 12.58; N, 4.82. The second product was isolated by chromatography (as above) followed by distillation (bp 219–228 °C, 0.04 torr). Compound **21** (1.70 g, 11%) was a white solid (mp 46–48 °C): ^{1}H NMR 3.7 (m, 16 H, CH_2O), 2.7 (m, 12 H, NCH_2), 1.4 (s, 44 H, CH_2), 0.9 (t, 6 H, CH_3); IR (mineral oil) 2920 (s), 2850, 1470, 1360, 1130. Anal. Calcd for $C_{36}H_{74}N_2O_4$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.12; N, 12.49; N, 4.67.

***N,N'*-Didodecyl-4,13-diaza-18-crown-6 (21)** was also obtained by a route similar to that described for **23**. Distillation (Kugelrohr apparatus, bp 219–228 °C, 0.04 torr) afforded **21** (0.45 g, 45%) as a white solid (mp 46–47 °C).

***N,N'*-Didodecanoyl-4,13-diaza-18-crown-6 (22)** was prepared essentially as described for **24**, below. Crystallization (hexanes) afforded **22** (3.17 g, 87%) as a white solid (mp 74–75 °C): ^{1}H NMR 3.6 (m, 24 H, NCH_2, OCH_2), 2.2 (m, 4 H, $COCH_2$), 1.3 (s, 36 H, CH_2), 0.9 (t, 6 H, CH_3); IR (mineral oil) 2920 (s), 2840, 1630, 1450, 1370, 1120, 1110. Anal. Calcd for $C_{36}H_{70}N_2O_6$: C, 68.97; H, 11.25; N, 4.47. Found: C, 68.87; H, 11.27; N, 4.44.

***N,N'*-Ditetradecyl-4,13-diaza-18-crown-6 (23).** *N,N'*-Ditetradecanoyl-4,13-diaza-18-crown-6 (**24**) (0.50 g, 0.73 mmol) was added at once to a 0 °C solution of diborane in THF (1.0 M, 15 mL). The mixture was brought to reflux temperature and stirred for 24 h. Excess diborane was destroyed by cautious addition of water until there was no further H_2 evolution. HCl (6 N, 50 mL) was added, and the mixture was heated for 24 h at reflux temperature. The mixture was neutralized by addition of solid NaOH, and extracted with $CHCl_3$ (2 × 200 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Crystallization (hexanes) afforded **23** (0.32 g, 67%) as a white solid (mp 54–55 °C): ^{1}H NMR 3.7 (m, 16 H, CH_2O), 2.7 (m, 12 H, CH_2N), 1.4 (pseudo-s, 48 H, CH_2), 0.9 (t, 6 H, CH_3); IR (mineral oil) 2920 (s), 2850, 1470, 1360, 1130 (s). Anal. Calcd for $C_{40}H_{82}N_2O_4$: C, 73.34; H, 12.62. Found: C, 73.12; H, 12.60.

***N,N'*-Ditetradecanoyl-4,13-diaza-18-crown-6 (24).** A solution of myristic acid (3.69 g, 0.016 mol) in $SOCl_2$ (30 mL) was stirred at 0 °C for 15 h. The excess $SOCl_2$ was removed by azeotropic distillation of toluene (3 × 50 mL). To a vigorously stirred solution of diaza-18-crown-6 (1.92 g, 0.0073 mol) and Na_2CO_3 (1.71 g, 0.016 mol) in C_6H_6 (25 mL) was added a solution of myristoyl chloride (obtained as described above) in C_6H_6 (25 mL). After stirring at ambient temperature for 16 h, the mixture was diluted with $CHCl_3$ (50 mL), filtered, and concentrated in vacuo. Recrystallization (abs EtOH) afforded pure **24** (3.92 g, 78%) as a white solid (mp 78–80 °C): ^{1}H NMR 3.6 (m, 24 H, NCH_2, OCH_2), 2.2 (m, 4 H, $COCH_2$), 1.3 (s, 44 H, CH_2) 0.9 (t, 6 H, CH_3); IR (mineral oil) 2920 (s), 2840, 1630, 1450, 1370, 1120, 1110. Anal. Calcd for $C_{40}H_{78}N_2O_4$: C, 70.33; H, 11.51; N, 4.10. Found: C, 70.06; H, 11.54; N, 4.05.

***N,N'*-Dihexadecyl-4,13-diaza-18-crown-6 (25).** The title compound was prepared by alkylation of **9** as described for the synthesis of **14**, quad vide. Column chromatography (alumina, 20% EtOAc/hexanes) and crystallization from abs EtOH afforded pure **25** (1.23 g, 25%) as a white solid (mp 63–64 °C): ^{1}H NMR 3.7 (m, 16 H, CH_2O); 2.7 (m, 12 H, NCH_2); 1.4 (s, 56 H, CH_2); 0.9 (t, 6 H, CH_3); IR (mineral oil) 2920 (s), 2850, 1470, 1360, 1120. Anal. Calcd for $C_{44}H_{90}N_2O_4$: C, 74.31; H, 12.75; N, 3.94. Found: C, 74.09; H, 12.78; N, 3.88. Note that Cinquini and Tundo[20] report a melting point for this compound of 90–92 °C. In addition to the spectral and analytical data presented above, the osmometric molecular weight was determined to resolve this conflict: calcd 711; found 700 g/mol.

***N,N'*-Dioctadecyl-4,13-diaza-18-crown-6 (26).** To a stirred solution of borane–tetrahydrofuran complex (18 mL, 1.0 M) was added **27** (1.2 g, 1.5 mmol). The reaction was refluxed for 24 h followed by a dropwise addition of 6 M HCl. The reaction was refluxed for an additional 8 h, cooled to ambient temperature, basified to pH 10 with NaOH pellets, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried with $MgSO_4$ and concentrated in vacuo. The residue was recrystallized once from hexanes (0.1 g/mL) and then once from ethanol (0.1 g/mL) to give 0.7 g (60%) of a white powder (mp 66–67.5 °C): ^{1}H NMR 3.62 (t, 16 H, OCH_2); 2.76 (t, 8 H, crown NCH_2's); 2.46 (t, 4 H, NCH_2); 1.25 (s, 64 H, CH_2); 0.88 (t, 6 H, CH_3); IR (KBr) 2900, 2840, 1470, 1380, 1360, 1330, 1290, 1250, 1130, 1095, 1070, 885, 845, 720. Anal. Calcd for $C_{48}H_{98}N_2O_4$: C, 75.14; H, 12.87. Found: C, 75.15; H, 12.91.

***N,N'*-Distearoyl-4,13-diaza-18-crown-6 (27)** was synthesized by the method described above for **16** using stearoyl chloride. The product, **27**, was obtained (3.63 g, 100%) as a white solid (mp 86–89 °C): ^{1}H NMR 3.6 (s, 24 H, crown CH_2's), 2.3 (m, 4 H, $N(C{=}O)CH_2$), 1.6 (m, 4 H, $(C{=}O)CH_2CH_2$), 1.3 (s, 56 H, CH_2), 0.9 (t, 6 H, CH_3); IR (KBr) 2900, 2840, 1630 (s), 1460, 1450, 1430, 1130, 1115, 1080, 1040, 810, 720, 625, 600. Anal. Calcd for $C_{48}H_{94}N_2O_6$: C, 72.49; H, 11.91. Found: C, 72.57; H, 11.96.

***N,N'*-Diallyl-4,13-diaza-18-crown-6 (28) by the Single-Step Method.** The synthesis was accomplished using the previously reported method.[9] Chromatography (alumina, 1% 2-propanol/hexanes) followed by crystallization (hexanes) yielded **28** (0.44 g, 26%) as a white crystalline solid (mp 44–45 °C) having physical properties identical with those previously reported.[9]

***N,N'*-Dipropargyl-4,13-diaza-18-crown-6 (29).** This compound was prepared by the previously reported, single-step method.[9] Chromatography (alumina, 0–5% 2-propanol/hexanes) afforded an impure oil which was dissolved in $CHCl_3$ (20 mL). To this solution was added excess, solid KSCN while stirring. After 30 min, the solution was filtered and concentrated in vacuo. Crystallization of this ($CHCl_3$/hexanes) oil afforded **29**·KSCN as a white crystalline solid (mp 214–215 °C). Anal. Calcd for $C_{18}H_{30}N_2O_4$·KSCN: C, 52.38; H, 6.94. Found: C, 52.11; H, 6.97.

The solid was dissolved in $CHCl_3$ and washed with water (2 × 250 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Crystallization ($CHCl_3$/hexanes) afforded pure **29** (7.00 g, 22%) as a white solid (mp 41–42 °C): ^{1}H NMR 3.6 (m, 20 H, propargyl methylene and CH_2O), 2.8 (t, 8 H, NCH_2), 2.2 (s, 2 H, acetylene H); IR (KBr) 3140 (s), 2100, 1630, 1450, 1350. Anal. Calcd for $C_{18}H_{30}N_4O_2$: C, 63.87; H, 8.93; N, 8.20. Found: C, 63.94; H, 9.10; N, 8.30.

***N,N'*-Bis(2-hydroxyethyl)-4,13-diaza-18-crown-6 (30)** was prepared as previously reported.[9]

Synthesis of *N,N'*-Bis(2-methoxyethyl)-4,13-diaza-18-crown-6 (31). 1,10-Bis(2-methoxyethyl)-4,7-dioxa-1,10-dia-

(20) Cinquini, M.; Tundo, P. *Synthesis* **1976**, 516.

zadecane (C18). A solution of 2-methoxyethylamine (120 g, 1.6 mol) and bisIEE (18.7 g, 0.1 mol) was stirred and heated at reflux for 24 h. The reaction was cooled, NaOH pellets (8.0 g, 0.2 mol) were added, and the mixture was heated at reflux, with stirring, for 1 h. The reaction was cooled and concentrated in vacuo, and the residue was dissolved in $CHCl_3$ (50 mL). The precipitated salts were removed by filtration, and the filtrate was concentrated in vacuo. Bulb-to-bulb distillation (bp 109–111 °C, 0.2 torr) gave 23.1 g (88%) of the title compound as a transparent liquid: ^{1}H NMR 1.80 (s, 2 H, NH), 2.78 (t, 8 H, CH_2N), 3.35–3.60 (m, 18 H, CH_2O and CH_3O); ^{13}C NMR 49.70, 59.04, 70.88, 71.26, 72.75; IR 2860 (s), 1450, 1190, 1110 (s). Anal. Calcd for $C_{12}H_{28}N_2O_4$: C, 54.50; H, 10.70;, N, 10.60. Found: C, 54.22; H, 10.90; N, 10.44.

***N,N'*-Bis(2-methoxyethyl)-4,13-diaza-18-crown-6 (31).** A solution of C18 (5.3 g, 0.02 mol), bisIEE (9.2 g, 0.025 mol), Na_2CO_3 (10.6 g, 0.1 mol), and NaI (1.5 g, 10 mol) in MeCN (400 mL) was heated at reflux for 18 h. The reaction was cooled, filtered, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (100 mL) and extracted with 6 N HCl (2 × 50 mL). The combined aqueous phases were adjusted to pH 8–10 with Na_2CO_3 and then extracted with $CHCl_3$ (2 × 100 mL) and concentrated in vacuo. Column chromatography (alumina, 2% 2-propanol/hexanes) followed by bulb-to-bulb distillation (bp 136–138 °C, 0.05–0.06 torr) gave 3.3 g (43%) of **31** as a transparent oil with physical properties identical with those reported previously.[10c]

***N,N'*-Bis(carboxymethyl)-4,13-diaza-18-crown-6 (32)** was prepared as previously reported.[9]

***N,N'*-Bis(carbethoxymethyl)-4,13-diaza-18-crown-6 (33)** was prepared as previously reported.[9]

Synthesis of *N,N'*-Dibenzyl-4,13-diaza-18-crown-6 (34). 1,10-Dibenzyl-4,7-dioxa-1,10-diazadecane (D18). A solution of benzylamine (172 g, 1.6 mol) and bisIEE (18.7 g, 0.1 mol) was stirred and heated at 120 °C for 28 h, and then cooled. NaOH pellets (8.0 g, 0.2 mol) were added, and the mixture was heated at 120 °C, with stirring, for 1 h. The reaction was cooled, and excess benzylamine was removed by distillation using water aspirator vacuum. The residue was dissolved in $CHCl_3$ (100 mL), filtered, and washed with water (50 mL). The aqueous phase was extracted with $CHCl_3$ (100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation (bp 175–177 °C, 0.2 torr) gave the title compound (28.2 g, 86%) as a slightly yellow oil: ^{1}H NMR 1.82 (s, 2 H, NH), 2.72 (t, 4 H, NCH_2), 3.58 (s and t, 8 H, OCH_2), 3.72 (s, 4 H, benzyl), 7.28 (s, 10 H, aromatic); ^{13}C NMR 49.09, 54.22, 70.80, 71.15, 127.64, 128.96, 129.12, 141.45; IR 3320, 3060, 3015, 2860 (s), 1490, 1450, 1350, 1110 (s), 1025, 730, 690. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.12; H, 8.61; N, 8.53. Found: C, 72.80; H, 8.63; N, 8.52.

***N,N'*-Dibenzyl-4,13-diaza-18-crown-6 (34).** A solution of the above diamine (6.6 g, 0.02 mol), bisIEE (9.2 g, 0.025 mol), Na_2CO_3 (10.6 g, 0.10 mol), and NaI (1.5 g, 0.010 mol) in MeCN (400 mL) was heated at reflux for 21 h. The reaction was cooled, filtered, and concentrated in vacuo. The crude solid was dissolved in a refluxing solution of acetone/dioxane (40 mL of each) and allowed to crystallize in a freezer. The precipitated crystals (mixture of NaI and NaI complex of **34**) were dried and dissolved in a minimum amount of water. The aqueous solution was extracted with $CHCl_3$ (3 × 25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Recrystallization (hexanes) gave 5.8 g (66%) of **34** as a white solid (mp 80–81 °C) having physical properties identical with those previously reported.[10b]

Synthesis of *N,N'*-Bis(2-furanylmethyl)-4,13-diaza-18-crown-6 (35). 1,10-Difurfuryl-4,7-dioxa-1,10-diazadecane (E18). A solution of furfurylamine (31.1 g, 0.32 mol) and bisIEE (3.7 g, 0.02 mol) was stirred and heated at approximately 100 °C for 24 h. The reaction was cooled, NaOH pellets (1.6 g, 0.07 mol) were added, and the mixture was heated at 100 °C for 1 h. Excess furfurylamine was removed by distillation using a water aspirator. The residue was dissolved in $CHCl_3$ (100 mL) and washed with water (30 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Bulb-to-bulb distillation (bp 136–139 °C, 0.04 torr) gave 5.8 g (94%) of the title compound as a slightly yellow oil: ^{1}H NMR 1.88 (s, 2 H, NH), 2.77 (t, 4 H, CH_2N), 3.60 (s and t, 8 H, CH_2O), 3.76 (s, 4 H, furyl CH_2) 6.12–6.32 (m, 4 H, furan H), 7.33 (d, 2 H, 5-furan H); ^{13}C NMR 46.17, 48.47, 70.24, 70.55, 106.51, 109.90, 141.43, 154.00; IR 3320, 3100, 2860 (s), 1500, 1450, 1350, 1330, 1130 (s), 920, 880, 800, 730. Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.30; H, 7.86; N, 9.09. Found: C, 62.22; H, 7.89; N, 9.30.

***N,N'*-Bis(2-furanylmethyl)-4,13-diaza-18-crown-6 (35).** A solution of E18 (3.1 g, 0.01 mol), bisIEE (4.6 g, 0.013 mol), Na_2CO_3 (5.3 g, 0.050 mol) and NaI (0.75 g, 0.005 mol) in MeCN (200 mL) was heated at reflux for 18 h. The workup procedure was analogous to that for **31**. Column chromatography (alumina, 35% EtOAc/hexanes) followed by bulb-to-bulb distillation (bp 167–170 °C, 0.05 torr) gave 2.6 g (62%) of **35** as a slightly yellow oil having physical properties identical with those previously reported.[9]

***N,N'*-Bis(2-hydroxybenzyl)-4,13-diaza-18-crown-6 (36)** was prepared as previously described.[9]

***N,N'*-Bis(2-methoxybenzyl)-4,13-diaza-18-crown-6 (37)** was prepared as previously described.[9]

***N,N'*-Bis(2-cyanobenzyl)-4,13-diaza-18-crown-6 (38)** was prepared from 4,13-diaza-18-crown-6 (1.0 g, 0.0038 mol) and 2-cyanobenzyl bromide (1.6 g, 0.008 mol) as described for **39** (see below). Recrystallization (95% EtOH) gave **38** (1.8 g, 96%) as a white solid (mp 96–98 °C): ^{1}H NMR 2.88 (t, 8 H, NCH_2), 3.60 and 3.64 (s and t, 16 H, OCH_2), 3.94 (s, 4 H, benzyl), 7.2–7.7 (m, 8 H, aromatic); ^{13}C NMR 53.97, 57.73, 69.74, 70.67, 112.20, 117.59, 127.06, 129.71, 132.33, 132.51, 143.98; IR (KBr) 2880 (s), 2840 (s), 2220, 1480, 1440, 1360, 1340, 1310, 1270, 1240, 1210, 1150, 1140, 1120 (s), 1110, 1090, 1060 (s), 1050, 980, 930, 880, 840, 800, 780, 710. Anal. Calcd for $C_{28}H_{36}N_4O_4$: C, 68.26; H, 7.38; N, 11.37. Found: C, 68.20; H, 7.53; N, 11.49.

***N,N'*-Bis(2-nitrobenzyl)-4,13-diaza-18-crown-6 (39).** A solution of 4,13-diaza-18-crown-6 (1.0 g, 0.0038 mol), *o*-nitrobenzyl chloride (1.3 g, 7.8 mol), and Na_2CO_3 (2.0 g, 0.019 mol) in MeCN (20 mL) was stirred at reflux temperature for 16 h. The reaction was cooled, filtered, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (20 mL) and washed with water (20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Recrystallization of the residue (95% EtOH) gave **39** (1.8 g, 90%) as a yellow solid (mp 77–78.5 °C): ^{1}H NMR 2.80 (t, 8 H, NCH_2), 3.60 (s and t, 16 H, OCH_2), 4.00 (s, 4 H, benzyl), 7.33–7.92 (m, aromatic); ^{13}C NMR 54.35, 56.74, 69.79, 70.67, 123.88, 127.35, 130.93, 132.16, 135.39, 149.50; IR (KBr) 2960, 2860, 2800, 1520 (s), 1360, 1350 (s), 1140 (s), 1060, 1000, 860, 800, 730. Anal. Calcd for $C_{26}H_{36}N_4O_8$: C, 58.62; H, 6.83; N, 10.52. Found: C, 58.59; H, 7.02; N, 10.55.

***N,N'*-Bis(3-nitrobenzyl)-4,13-diaza-18-crown-6 (40)** was prepared from 4,13-diaza-18-crown-6 (1.0 g, 0.0038 mol) and *m*-nitrobenzyl chloride (1.4 g, 8.2 mol) as described for **39**. Recrystallization (95% EtOH) gave **40** (1.9 g, 95%) as a yellow solid (mp 106–107 °C): ^{1}H NMR 2.80 (t, 8 H, NCH_2), 3.60 and 3.77 (s,t and s, 20 H, OCH_2 and benzyl), 7.28–8.23 (m, 8 H, aromatic); ^{13}C NMR 54.65, 59.62, 70.57, 71.38, 122.64, 124.17, 129.85, 135.49, 143.89, 149.58; IR (KBr) 2880 (s), 2820 (s), 1520 (s), 1430 (s), 1300, 1250, 1150, 1130, 1120 (s), 1110, 1060 (s), 1040, 970, 890, 880, 820, 800, 730, 690, 670. Anal. Calcd for $C_{26}H_{36}N_4O_8$: C, 58.62; H, 6.83; N, 10.52. Found: C, 58.64; H, 6.93; N, 10.37.

***N,N'*-Bis(4-nitrobenzyl)-4,13-diaza-18-crown-6 (41)** was prepared from 4,13-diaza-18-crown-6 (1.0 g, 0.0038 mol) and *p*-nitrobenzyl bromide (1.7 g, 7.8 mol) as described for **39**. Recrystallization (95% EtOH) gave **41** (1.4 g, 70%) as a yellow solid (mp 116–118 °C): ^{1}H NMR 2.80 (t, 8 H, NCH_2), 3.60 and 3.77 (s,t and s, 20 H, OCH_2 and benzyl), 7.50 (d, 4 H, aromatic), 8.15 (d, 4 H, aromatic); ^{13}C NMR 54.80, 59.84, 70.58, 71.35, 124.18, 130.00, 148.18, 149.43; IR (KBr) 2840 (s), 1600, 1520, 1340 (s), 1330, 1320, 1130, 1100, 1080, 1070, 1050, 1020, 850, 810, 740. Anal. Calcd for $C_{26}H_{36}N_4O_8$: C, 58.62; H, 6.83; N, 10.52. Found: C, 58.71; H, 6.80; N, 10.43.

Acknowledgment. We thank the National Institutes of Health (Grants GM-29150, GM-31846, and GM-36262) and W. R. Grace & Co. for support of this work. We warmly thank Professors Richard D. Gandour and Frank R. Fronczek for communicating the results of crystal structure studies to us and for permitting their presentation here.

Registry No. 1, 31249-95-3; 2, 87057-95-2; 3, 105399-88-0; 3·NaBr, 105374-20-7; 4, 94195-16-1; 5, 105399-92-6; 6, 99313-91-4; 7, 94978-64-0; 8, 105399-96-0; 9, 23978-55-4; 10, 31255-13-7; 11, 105399-97-1; 12, 77112-68-6; 13, 105399-98-2; 14, 105400-00-8; 15,

105400-01-9; **16**, 105400-02-0; **17**, 90633-87-7; **18**, 105400-03-1; **19**, 105400-04-2; **20**, 79495-97-9; **21**, 100330-77-6; **21a**, 105400-05-3; **22**, 105400-06-4; **23**, 105400-07-5; **24**, 105400-08-6; **25**, 60742-69-0; **26**, 100330-78-7; **27**, 105400-09-7; **28**, 93000-67-0; **29**, 105400-10-0; **29**·KSCN, 105400-18-8; **30**, 69930-74-1; **31**, 72911-99-0; **32**, 105400-12-2; **33**, 62871-83-4; **34**, 69703-25-9; **35**, 90633-85-5; **36**, 88104-28-3; **37**, 93000-66-9; **38**, 105400-14-4; **39**, 94978-65-1; **40**, 105400-15-5; **41**, 105400-16-6; **42**, 105399-86-8; **43**, 33051-25-1; **44**, 105399-89-1; bisCIEE, 112-26-5; 1,8-DAOO, 929-59-9; DGACL, 21062-20-4; DCIE, 111-44-4; DIE, 34270-90-1; bisIEE, 36839-55-1; A15, 105399-87-9; 1,5-DAOP, 2752-17-2; B15, 66582-25-0; C15, 105399-91-5; D15, 105399-95-9; A18, 86577-64-2; B18, 105399-99-3; C18, 105400-11-1; D18, 66582-26-1; E18, 105400-13-3; Ca, 7440-70-2; Na, 7440-23-5; K, 7440-09-7; 1,2-bis(2-azidoethoxy)ethane, 59559-06-7; diglycolic acid, 110-99-6; 2-methoxyethylamine, 109-85-3; ethyl bromoacetate, 105-36-2; *o*-methoxybenzylamine, 6850-57-3; 1,7-bis(2-methoxybenzyl)-2,6-dioxo-4-oxa-1,7-diazaheptane, 105399-90-4; furfurylamine, 617-89-0; 1,7-difurfuryl-2,6-dioxo-4-oxa-1,7-diazaheptane, 105399-93-7; 2-furoyl chloride, 527-69-5; 1,7-bis(2-furylcarbonyl)-4-oxa-1,7-diazaheptane, 105399-94-8; tetraethyleneglycol diiodide, 36839-56-2; 1-aminohexane, 111-26-2; 1-bromohexane, 111-25-1; octanoyl chloride, 111-64-8; 1-chlorononane, 2473-01-0; 1-aminononane, 112-20-9; nonanoyl chloride, 764-85-2; decanoyl chloride, 112-13-0; dodecylamine, 124-22-1; myristic acid, 544-63-8; myristoyl chloride, 112-64-1; 1-bromohexadecane, 112-82-3; stearoyl chloride, 112-76-5; 2-cyanobenzyl bromide, 22115-41-9; dodecanoic acid, 143-07-7; 2-hydroxybenzyl bromide, 58402-38-3.

Structure of 1-Chloro-1,1-dihydro-1-phenyl-3,3-dimethyl-3*H*-2,1-benzoxathiole, a Chlorosulfurane. Structural Manifestations of an Electronically Unbalanced Hypervalent Bond

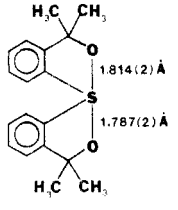
Peter D. Livant

Department of Chemistry, Auburn University, Auburn, Alabama 36849

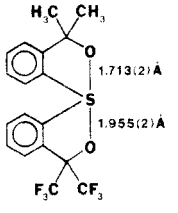
Received June 16, 1986

The X-ray crystal structure of 1-chloro-1,1-dihydro-1-phenyl-3,3-dimethyl-3*H*-2,1-benzoxathiole, chlorosulfurane **5**, is reported (R = 0.030). The axial S–Cl bond of **5** is extremely long (2.747 (1) Å), and the axial S–O bond is the shortest axial S–O bond of any reported sulfurane having the 3,3-dimethyl-3*H*-2,1-benzoxathiole moiety (1.639 (2) Å). The axial three-center four-electron bond of **5** is thus remarkably polarized. There is a good linear correlation between the electronegativity/apicophilicity of an axial ligand and the length of the S–O bond of a 3,3-dimethyl-3*H*-2,1-benzoxathiole moiety trans to it along a three-center four-electron array. The O–S–Cl bond angle of **5** (measured in an arc which includes the sulfur lone pair) of 173.6 (1)° is unusual in being less than 180°, but is similar to the axial angles of previously reported dichlorosulfuranes. The compressed endocyclic C–C–O angle of **5** (103.0 (2)°) is not due to the *gem*-dimethyl group, since 2-[(2-phenylsulfinyl)phenyl]-2-propanol (**6**) exhibits an analogous C–C–O angle of 110.6 (2)°. The X-ray crystal structure of **6** is also reported (R = 0.058).

The axial three-center four-electron bond of sulfuranes[1] is remarkably pliable, responding to subtle electronic changes in the axial ligands with large changes in bond length. For example, the symmetrical O–S–O system of **1**[2] becomes grossly distorted in the related sulfurane **2**.[3]



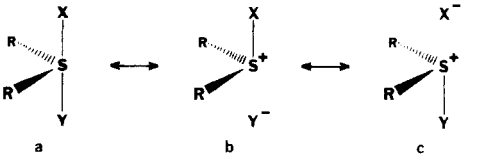
1



2

3

Such electronic elasticity is expected theoretically: Musher's[4] MO view of the X–S–X system of **3** results in a bond order of 1.0 for the three-atom array, or 0.5 per S–X bond. More rigorous theoretical treatments[5] confirm this view, which may be summarized in a familiar way by writing resonance structures a–c. For X ≠ Y, structures



a b c

b and c will contribute unequally, and even if X = Y, structures b and c will contribute heavily relative to structure a.

Recently we reported[6] that chlorosulfurane **4** hydrolyzed roughly 2000 times faster than **5**, even though the electronic effect of the cyclopropyl group would tend to stabilize **4** relative to **5**. A tentative explanation was advanced based on expansion (in the case of **4**) or com-

(1) (a) Hayes, R. A.; Martin, J. C. *Studies in Organic Chemistry*; Elsevier, Amsterdam, 1985; Vol. 19, Chapter 8, p 408. (b) Bond distortions similar to those discussed here for the 10-S-4 sulfuranes have been reviewed for the 10-S-3 trithiapentalenes and related 10-S-3 compounds: Gleiter, R.; Gygax, R. In *Topics in Current Chemistry*; Boschke, F., Managing Ed.; Springer-Verlag: Berlin, Heidelberg, New York, 1976; Vol. 63, pp 49–88.

(2) Lam, W. Y.; Duesler, E. N.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 127.

(3) Adzima, L. J.; Duesler, E. N.; Martin, J. C. *J. Org. Chem.* **1977**, *42*, 4001.

(4) Musher, J. I. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 54.

(5) (a) Csizmadia, V. M. In *Progress in Theoretical Organic Chemistry*; Csizmadia, I. G., Ed.; Elsevier: Amsterdam, 1977, Vol. 2, p 280. (b) Schwenzer, G. M.; Schaefer, H. F. *J. Am. Chem. Soc.* **1975**, *97*, 1393. (c) Yoshioka, Y; Goddard, J. D.; Schaefer, H. F. *J. Chem. Phys.* **1981**, *74*, 1855. (d) Gleiter, R.; Veillard, A. *Chem. Phys. Lett.* **1976**, *37*, 33. (e) Chen, M. M. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1647.

(6) Datta, A. K.; Livant, P. *J. Org. Chem.* **1983**, *48*, 2445.

0022-3263/86/1951-5384$01.50/0