in an argon atmosphere was added dropwise by syringe 0.66 mL (1 mmol) of a 1.5 M ethereal MeLi–LiBr solution, and stirring was continued at −78 °C for 20 min. $BF_3{\cdot}Et_2O$ (0.122 mL, 1 mmol) was added to the above mixture at −78 °C, and the mixture was stirred for 5 min. A solution of **40** (139 mg, 0.33 mmol) in dry THF (3 mL) was added to the above reagent at −78 °C with stirring and stirring was continued for 30 min. The usual workup of the reaction mixture led to an oily residue, which was flash chromatographed on a silica gel column. Elution with *n*-hexane–EtOAc (3:1) gave 106 mg (95% yield) of **41** as a colorless oil: $[\alpha]^{20}_D$ −48.1° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3050,3010, 2970, 1729, 1672, 1472, 1463, 1439, 1365, 1179, 1150, 1085, 996, 966, 892, 869, 826 cm^{-1}; ^1H NMR (200 MHz) δ 1.33 (s, 6 H), 1.39 (s, 3 H), 1.52 (s, 3 H), 3.06 (s, 3 H), 3.68 (s, 3 H), 4.10 (dd, *J* = 10.75, 6.84 Hz, 1 H), 4.17 (dd, *J* = 10.75, 4.64 Hz, 1 H), 4.40 (td, *J* = 6.84, 4.39 Hz, 1 H), 4.72 (m, 1 H), 5.50 (dd, *J* = 15.63, 7.33 Hz, 1 H), 6.06 (dd, *J* = 15.63, 0.97 Hz, 1 H); nominal mass spectrum, *m/z* 336 (M^+), 321, 277, 261, 235, 219, 198, 183, 165, 137, 123, 97 (base peak); exact mass spectrum, *m/z* calcd for $C_{14}H_{24}O_7S$ 336.1242, found 336.1246.

Methyl (5*R*,2*S*,6*S*,2*E*)-2-Butyl-5,6-(isopropylidenedioxy)-7-[(methylsulfonyl)oxy]-2-methyl-3-heptenoate (42). By a procedure identical with that described for the preparation of **14**, **40** (139 mg, 0.33 mmol) was converted to **42** (120 mg, 95% yield) by treatment with BuCu(CN)Li·BF at −78 °C for 30 min. **42**: a colorless oil; $[\alpha]^{20}_D$ −31.1° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3050, 3010, 2960, 2880, 1727, 1670, 1463, 1458, 1439, 1362, 1345, 1180, 1086, 988, 966, 894, 870, 827 cm^{-1}; ^1H NM (200 MHz) δ 0.89 (t, *J* = 6.84 Hz, 3 H), 1.29 (s, 3 H), 1.39 (s, 3 H), 1.52 (s, 3 H), 3.06 (s, 3 H), 3.68 (s, 3 H), 4.05–4.20 (m, 2 H), 4.40 (td, *J* = 6.83, 4.63 Hz, 1 H), 4.72 (m, 1 H), 5.47 (dd, *J* = 15.62, 7.32 Hz, 1 H), 6.04 (dd, *J* = 15.62, 0.98 Hz, 1 H); nominal mass spectrum, *m/z* 378 (M^+), 363, 319, 303, 277, 261,240, 235, 207, 137, 97 (base peak); exact mass spectrum, *m/z* calcd for $C_{17}H_{30}O_7S$ 378.1711, found 378.1705.

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Supplementary Material Available: Synthetic methods and spectral data [$[\alpha]_D$, IR, ^1H NMR, and MS] for **7b**, **8b**, **9b**, **10b**, **13**, **16**, **24**, **25**, **26a**, **22b**, **23**, **26b**, **29**, **30**, **31**, and **32** (6 pages). Ordering information is given on any current masthead page.

A New Building Block Method To Synthesize Symmetrical and Asymmetrical Per-*N*-alkyl-Substituted Polyaza-Crown Compounds

Krzysztof E. Krakowiak,† Jerald S. Bradshaw,* Reed M. Izatt, and Daria J. Zamecka-Krakowiak

Department of Chemistry, Brigham Young University, Provo, Utah 84602

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A new approach for the synthesis of a variety of per-N-alkylated polyaza-crown compounds is described. *N*-[2-(2-Chloroethoxy)ethyl]acetamide (**25**) and its benzamide analogue **26** are the key building blocks for the synthesis of the new polyaza-crowns. These chloroamides were reacted with primary amines or secondary diamines, followed by reduction of the resulting diamides, to produce polyamine intermediates containing two terminal *N*-ethyl or *N*-benzyl secondary amine functional groups. These secondary diamines were further reacted with dihalides in the presence of metal carbonates to form the polyaza-crowns. The overall yields for crown formation were generally very good. All of the new polyaza-crowns were prepared without the need for special nitrogen protecting reagents. Thus, the crowns were formed in a minimum number of steps. Twenty-three new polyaza-crowns containing from three to six nitrogen atoms in the macroring and from 16 to 36 ring members are reported.

Introduction

There is continuing interest in the synthesis of aza-crown compounds. The aza-crowns have complexation properties that are intermediate between the all-oxygen crowns, which strongly complex alkali and alkaline earth metal ions, and the all-nitrogen cyclams, which strongly complex heavy metal cations.[1] The aza-crowns also complex organic cations and anions and have important uses as synthetic receptors in molecular recognition processes.[2] In some cases, anion complexation by aza-crowns is similar to complexation processes in certain biological systems.[3-5] The aza-crowns have an enhanced affinity for ammonium salts compared to the all-oxygen crown compounds.[1,6] The aza-crowns are also important intermediates for the synthesis of the cryptands[7,8] and the nitrogen-pivot lariat crown ethers,[9] as catalysts in nucleophilic substitution and oxidation reactions,[10,11] and in the design of chromogenic reagents, which are sensitive to the alkali and alkaline earth metal ions.[12-14]

Silica gel bound aza-crown compounds have the same affinity for metal ions in aqueous solution as do the unbound crowns for the same metal ion.[15] These silica gel materials have been used to separate specific metal ions from mixtures of metal ions.[16-18] Thus, using a silica gel

† Permanent address: Department of Chemical Technology, School of Medicine, 90145 Lodz, Poland.

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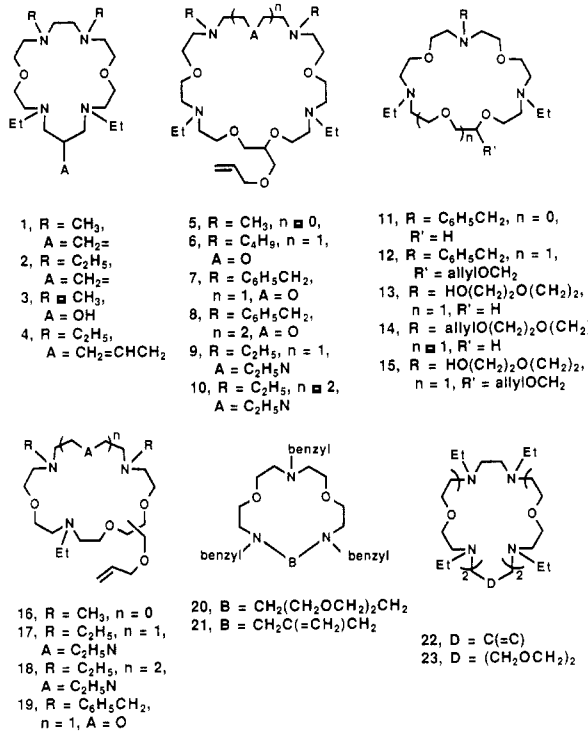
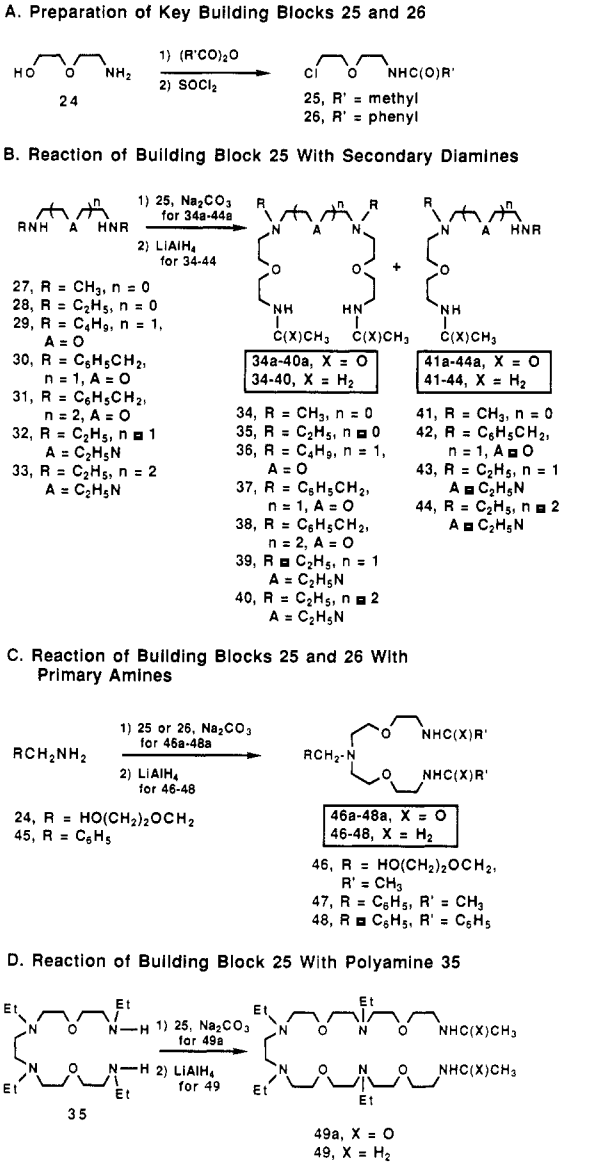


Figure 1. New polyaza-crown compounds.

bound diaza-crown, Hg^{2+} was separated from mixtures of Hg^{2+}, Cd^{2+}, and Zn^{2+} ions,[16] Ag^+ ions were separated from solutions containing 100 times excess quantities of Mg^{2+}, Ca^{2+}, K^+, and/or Na^+ ions,[17] and Cu^{2+} ions were separated from aqueous solutions also containing Ca^{2+} and Mg^{2+} at higher concentrations.[18] Although triaza- and tetraaza-crowns capable of further reactions to attach them to silica gel have been prepared,[19] cation separation studies by those compounds have not been completed.

The synthesis of diaza-crowns has been studied extensively.[16,20-22] Aza-crowns with more than two nitrogen atoms in the macroring have only been synthesized sporadically. Most aza-crown syntheses require the use of nitrogen protecting groups, which adds at least two steps to the overall synthesis and, as a consequence, reduces the overall yield. A symmetrical *N,N',N''*-trialkyl-substituted $[^{18}O]N_3O_3$, first reported by Graf and Lehn,[23] later required 12 steps including protecting and deprotecting processes for its synthesis.[24] Sutherland and his co-workers have prepared symmetrical triaza-crown ethers with propylene or mixed propylene and ethylene bridges.[25] Asymmetrical per-*N*-alkyl-substituted aza-crown ethers have been prepared by many workers using the Richman–Atkins cyclization procedure.[3,6,22,26-29] All of these methods require

Scheme I. Preparation of Aza Starting Materials



the use of nitrogen protecting groups, such as the toluenesulfonyl group, and those groups must then be removed and the alkyl groups added. Tabushi and Pellisard and their co-workers used other methods to make polyaza-crowns without protecting groups, but their methods gave only moderate yields or required specialized starting materials.[30-32]

We have designed a general strategy for the preparation of per-*N*-alkyl-substituted polyaza-crown compounds using only a few steps.[19] Our new method uses *N*-[2-(2-chloroethoxy)ethyl]acetamide (**25**) and its benzamide analogue (**26**) as building blocks to form new bis-secondary amines capable of undergoing ring closure with various dihalide compounds. Since the above mentioned key building blocks are used in different ways to form new polyamine intermediates, we have called this a building block method

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to prepare the polyaza-crowns. All of the aza-crowns prepared by this method have alkyl groups attached to all of the macroring nitrogen atoms. It is instructive to note that the per-*N*-alkyl-substituted polyaza-crown compounds have about the same affinity for metal cations as do the non-*N*-alkyl-substituted polyaza-crowns.[1] This paper describes the building block method to prepare the per-*N*-alkylpolyaza-crowns and lists 23 new polyaza-crown compounds prepared by this method.

Results and Discussion

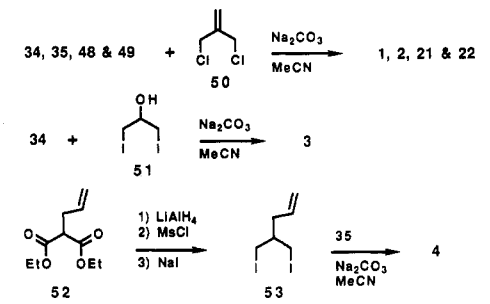
The key building blocks for the synthesis of all of the compounds shown in Figure 1 are *N*-[2-(2-chloroethyoxy)ethyl]acetamide (**25**) and *N*-[2-(2-chloroethoxy)ethyl]benzamide (**26**). These compounds were prepared in good yields by first reacting 2-(2-aminoethoxy)ethanol (**24**) with acetic anhydride or benzoic anhydride followed by thionyl chloride (see Scheme IA). Each of the starting materials for the two step processes is readily available. Both benzamide **26** and its *p*-toluenesulfonamide analogue cyclize to form morpholine derivatives under strong basic conditions.[33] Thus, a weak base must be used for the further reactions of **26** and presumably of **25**. The iodo analogue of **25** was prepared by treating **25** with sodium iodide in 2-butanone. Even though the iodo form of **25** was more reactive with amines and gave somewhat higher product yields, **25** was used in all reactions because the small increase in overall yields did not warrant the extra iodination step. But, in two cases, **25** and **26** were converted to the iodide form during the reaction with amines using sodium iodide in the reaction mixture (to prepare **48a** and **49a**).

Key building blocks **25** and **26** were then reacted with primary amines or secondary diamines to form oligoaza intermediates containing one or two terminal acetamido or benzamido groups (**34a–44a** and **46a–49a**) (see Scheme I, parts B and C). These amides were purified by column chromatography and reduced by lithium aluminum hydride to form the oligoethylene polyamines where all nitrogen atoms contain one alkyl group (**34–44** and **46–49**). All of the polyamines (except **49**) were purified by distillation. The terminal amine groups of these polyaza intermediates are all secondary, allowing for subsequent ring closure reactions with a dihalide. The reaction of **25** with diamines **27–33** (Scheme IB) gave two products. Where 2.2 equiv of **25** was used, mostly the 2:1 adducts (**34a–40a**) were formed. In each case, a small amount of the 1:1 adduct was observed on column chromatography using silica gel. To maximize the 1:1 adduct, a 1:1 mixture of reactants was used. Mostly 1:1 addition products **41a–44a** from **27**, **30**, **32**, and **33** were isolated and purified.

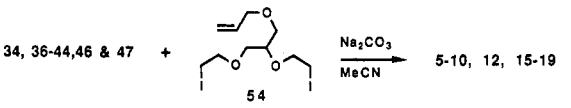
The reaction of building blocks **25** and **26** with benzylamine or 2-(2-aminoethoxy)ethanol (**24**) gave azadiamides **46a–48a** (Scheme IC). These products are 2:1 adducts of **25** or **26** to the primary amine. No significant amounts of the 1:1 adducts were observed in these reactions. The diamides were reduced by lithium aluminum hydride to give the per-*N*-alkyl-substituted tetraethylenetriamine compounds **46–48**.

Building blocks **25** and **26** can also be reacted with **34–44** and **46–48** to further lengthen the polyamine chain. For example, building block **25** was reacted with tetraamine **35** to give tetraazadiamide **49a** (Scheme ID). The diamide was purified by silica gel chromatography. Some 1:1 addition product was observed. The purified diamide was reduced in the usual manner to give **49**. Because of its size, polyamine **49** was not distilled but was used to prepare macrocycles **22** and **23** without further purification.

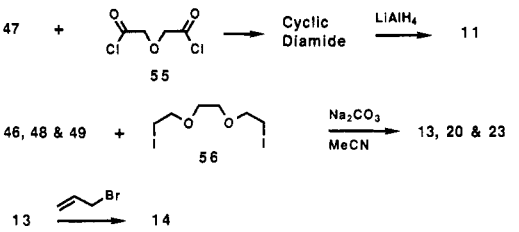
Scheme II. Preparation of Macrocycles 1–4, 21, and 22



Scheme III. Preparation of Macrocycles 5–10, 12, and 15–19



Scheme IV. Preparation of Macrocycles 11, 13, 14, 20, and 23



The reactions given in Scheme I show the versatility of building blocks **25** and **26** to build a variety of per-*N*-alkyl-substituted polyamine intermediates. Building blocks **25** and **26** could be reacted with any of the new bis-secondary amines to form other polyamines similar to **49** These building blocks can also be reacted with a variety of other diamines, such as those containing aromatic groups, to form other interesting synthons for new macrocyclic ligands.

The new oligoaza bis-secondary amines were reacted with various dihalide compounds to form the macrocyclic polyaza-crowns shown in Figure 1. The reactions were carried out in acetonitrile usually using sodium carbonate as the base (see Schemes II–IV). For the preparation of crowns with 24 or more ring members, mixed sodium, potassium, and cesium carbonates were used so that any template effects[34,35] of the cations would be maximized. Diiodides along with a trace of sodium iodide were used for most reactions because they are more reactive and give higher yields of cyclization products than do the dichlorides in acetonitrile.[20] Dichloride **50** and diacid chloride **55** were exceptions to the use of diiodides for ring closure reactions.

Yields of 20–74% were obtained for all ring closure reactions except for the preparation of **3**, **22**, and **23**. Macrocycles **22** and **23** are extra large. Large multimembered macrocycles are formed in moderate or low yields. Starting diamine **49** was not purified, which could also cause a lower yield of products **22** and **23**. The low yield for the preparation of **3** is not understood. It is possible that, under basic conditions, **51** undergoes an elimination reaction and therefore is not as available for cyclization with **34**. Since

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Table I. Yields, NMR Data, and Chromatographic Solvents for the Preparation of 34a–40a (Scheme IB)

compd	R	A	n	chrom solv[a]	yld, %	NMR, δ
34a	CH_3	–	0	E, M/E	60	1.95 (s, 6 H), 2.30 (s, 6 H), 2.60 (m, 8 H), 3.5 (m, 12 H), 6.8 (b, 2 H)
35a	C_2H_5	–	0	E, M/E	58	1.15 (m, 6 H), 2.3 (s, 6 H), 2.7 (m, 12 H), 3.6 (m, 12 H), 4.8 (b, 2 H)
36a	C_4H_9	O	1	I, I/E, E	59	0.9 (t, 6 H), 1.3 (m, 8 H), 2.0 (s, 6 H), 2.5 (t, 4 H), 2.7 (m, 8 H), 3.5 (m, 16 H), 6.5 (b, 2 H)
37a	$C_6H_5CH_2$	O	1	I, I/E, E	59	2.0 (s, 6 H), 2.75 (m, 8 H), 3.6 (m, 20 H), 6.2 (b, 2 H), 7.3 (s, 10 H)
38a	$C_6H_5CH_2$	O	2	I, I/E, E	61	1.95 (s, 6 H), 2.75 (m, 8 H), 3.45 (m, 20 H), 3.7 (s, 4 H), 6.2 (b, 2 H), 7.3 (m, 10 H)
39a	C_2H_5[b]	C_2H_5N	1	M, M/A	32	1.0 (t, 9 H), 2.0 (s, 6 H), 2.6 (m, 18 H), 3.5 (m, 12 H), 6.5 (b, 2 H)
40a	C_2H_5[b]	C_2H_5N	2	M, M/A	37	1.0 (m, 12 H), 2.0 (s, 6 H), 2.6 (m, 24 H), 3.5 (m, 12 H), 6.5 (b, 2 H)

[a] E = ethanol; I = isopropyl alcohol; M = methanol; M/A = 2–10% ammonium hydroxide in methanol. [b] Xylene was used for the reaction instead of toluene.

weak carbonate bases which do not deprotonate the alcohol function were used for the cyclization reactions, the secondary amines are the most reactive nucleophiles present. Therefore, reaction of the secondary amines with the dihalide to form the macrocycle is the preferred reaction.

It is instructive to note that symmetrical triaza-18-crown-6 (**11**) was prepared in only six steps with an overall yield of 25% [via **25** (85%), **47a** (71%), **47** (73%), and **11** (69% + 74%)]. This is in contrast to the many step synthesis of a similar tri-*N*-alkyl-substituted symmetrical triaza-18-crown-6.[23,24] This shows the importance of these new building block reactions to prepare per-*N*-alkyl-substituted polyaza-crowns in relatively high yields and in only a few steps.

Most of the new polyaza-crown compounds reported here contain vinyl functional groups. We have used the hydrosilylation reaction of trimethoxysilane and allyloxymethyl-substituted crowns to prepare the trimethoxysilane-substituted crowns.[15,16] The trimethoxysilane-containing crown was then coated and heated on silica gel to form a silica gel bound crown material. These new silica gel crown materials are important for the separation of heavy metal cations from mixtures of cations.[15–18] The new polyaza-crowns **4–10**, **12**, and **14–19** could be attached to silica gel by the above process. The large polyaza-crowns can complex with two cations, in some cases,[35] and in the protonated form, have been used to bind anions. New macrocycles **1**, **2**, **21**, and **22** have pendant methylene groups. These macrocycles, likewise, could possibly be attached to silica gel by the above mentioned process. It is likely that the silica gel material containing these latter materials would not be as effective in complexing metal ions because the macrocycle would be too close to the silica gel. Others have found that interacting functional groups must be many atoms removed from the solid support surface so that the functional group can interact with large molecules.[36–38] Hydroxy-substituted macrocycles **3**, **13**, and **15** could be attached to many different solid supports. They also could be reacted with allyl bromide (as was **13**) to form allyloxymethyl-substituted polyaza-crowns for attachment by the above process.

Experimental Section

Infrared (IR) spectra were obtained on a Beckman Acculab 2 spectrometer. The proton magnetic resonance (NMR) spectra were obtained on JEOL FX-90 Q and Varian Gemni 200 spectrometers in deuteriochloroform. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Molecular weights were obtained by mass spectrometry on a Finnigan 8430 high-resolution mass spectrometer. Diamines and other starting materials were purchased from Aldrich, Alfa, or Phaltz and Bauer and were used without purification.

***N*-[2-(2-Chloroethoxy)ethyl]acetamide (25)** (Scheme IA). *N*-[2-(2-Hydroxyethoxy)ethyl]acetamide was first prepared by slowly adding 105 g (1.03 mol) of acetic anhydride to 105 g (1 mol) of 2-(2-aminoethoxy)ethanol (**24**) in 150 mL of ethanol. This mixture was refluxed for 30 min, and the solvent was then evaporated. The residue was distilled to give 144 g (98%) of the intermediate hydroxy acetamide: bp 128–131 °C (0.07 mm); NMR δ 2.00 (s, 3 H), 3.30 (b, 1 H), 3.45 (m, 2 H), 3.55 (m, 4 H), 3.60 (m, 2 H), 6.60 (b, 1 H); IR 3500, 1680, 1100 cm^{-1}. Thionyl chloride (200 g) in 200 mL of chloroform was slowly added to 147 g (1 mol) of the above hydroxy acetamide in 300 mL of chloroform at 10–15 °C. The mixture was refluxed for 20 min, and the excess thionyl chloride and solvent were evaporated under reduced pressure. Benzene (200 mL) was added three times during the evaporation step to completely remove all the thionyl chloride. The excess thionyl chloride can also be removed by adding 30 mL of ethanol and evaporating all the solvents. The residue was distilled through a short distillation column to give 140 g (85%) of **25**: bp 115–117 °C (0.1 mm); NMR δ 2.00 (s, 3 H), 3.55 (m, 8 H), 6.10 (b, 1 H); IR 3250, 1660, 1100 cm^{-1}. Compound **25** was used without further purification for the preparation of many intermediates as shown in Scheme I, parts B, C, and D.

***N*-[2-(2-Chloroethoxy)ethyl]benzamide (26)** (Scheme IA). Benzoic anhydride (22.6 g, 0.1 mol) was slowly added to 10.5 g (0.1 mol) of **24** in 50 mL of ethanol at room temperature. This mixture was refluxed for 36 h. The mixture was evaporated under reduced pressure, and the residue was dissolved in 300 mL of 5% aqueous sodium carbonate. The aqueous solution was extracted four times with 300-mL portions of chloroform. The combined chloroform solutions were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give 18 g (86%) of *N*-[2-(2-hydroxyethoxy)ethyl]benzamide: NMR δ 2.80 (b, 1 H), 3.60 (m, 8 H), 6.90 (b, 1 H), 7.35 (m, 3 H), 7.70 (m, 2 H); IR 3350, 1640, 1100 cm^{-1}. Thionyl chloride (30 g) in 100 mL of chloroform was slowly added to 28 g (0.134 mol) of the above hydroxy benzamide in 100 mL of chloroform at 0–10 °C. The resulting mixture was stirred at room temperature for 1 h and then refluxed for 4 h. The excess thionyl chloride and solvent were removed under reduced pressure. Benzene (30 mL) was added three times during the evaporation step to completely remove all the thionyl chloride. The residue was distilled to give 20 g (65%) of **26**: bp 118–122 °C (0.06 mm); NMR δ 3.70 (m, 8 H), 6.70 (b, 1 H), 7.40 (m, 3 H), 7.80 (m, 2 H); IR 3150, 1650, 1120 cm^{-1}; MS *m/z* 227. Compound **26** can be further purified by chromatography on silica gel (chloroform then isopropyl alcohol or toluene/ethanol).

Preparation of Diamide Intermediates 34a–40a (Scheme IB). A mixture of 10.76 g (65 mmol) of **25**, 30 mmol of the appropriate diamine **27–33**, and 20 g of sodium carbonate was stirred under reflux in 150 mL of toluene for 48–72 h using a Dean–Stark trap to remove water. Xylene can be used instead of toluene. The mixture was filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel to give mostly **34a–40a**. Some 1:1 addition products (such as **41a–44a**) were also isolated from the chromatography column. The yields, NMR data, and chromatography solvents used for the preparation of **34a–40a** are listed in Table I.

Preparation of Monoamide Intermediates 41a–44a (Scheme IB). A mixture of 4.5 g (27 mmol) of **25**, 30 mmol of the ap-

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Table II. Yields, NMR Data, and Chromatography Solvents for the Separation of 41a–44a (Scheme IB) and 49a (Scheme ID)

compd	R	A	n	chrom solv[a]	yld, %	NMR, δ
41a	CH_3	–	0	I, E, M, M/A	38	1.7 (b, 1 H), 2.0 (s, 3 H), 2.3 (s, 3 H), 2.45 (s, 3 H), 2.6 (m, 6 H), 3.5 (m, 6 H)
42a	$C_6H_5CH_2$	O	1	I, E	28	1.9 (s, 3 H), 2.05 (b, 1 H), 2.75 (m, 6 H), 3.4 (m, 10 H), 3.7 (s, 2 H), 3.8 (s, 2 H), 6.3 (b, 1 H), 7.3 (m, 10 H)
43a	C_2H_5	C_2H_5N	1	M, M/A	19	1.0 (m, 9 H), 2.0 (s, 3 H), 2.6 (m, 16 H), 3.5 (m, 6 H), 6.9 (b, 1 H)
44a	C_2H_5	C_2H_5N	2	M, M/A	21	NMR data is not available
49a[b]				E, M, M/A	40	0.95 (m, 12 H), 1.9 (s, 6 H), 2.6 (m, 24 H), 3.4 (m, 20 H), 6.6 (b, 2 H)

[a] I = isopropyl alcohol; E = ethanol; M = methanol; M/A = 2–10% ammonium hydroxide in methanol. [b] The 1:1 adduct was also isolated in a 13% yield.

Table III. Yields and NMR Data for the Preparation of 46a–48a (Scheme IC)

amide	R	R	yld, %	NMR, δ
46a	$HO(CH_2)_2OCH_2$	CH_3	70	2.0 (s, 6 H), 2.75 (m, 6 H), 3.50 (m, 19 H), 7.2 (b, 2 H)
47a	C_6H_5	CH_3	71	1.95 (s, 6 H), 2.75 (t, 4 H), 3.50 (m, 12 H), 3.72 (s, 2 H), 6.15 (b, 2 H), 7.35 (s, 5 H)
48a	C_6H_5	C_6H_5	55	2.70 (m, 4 H), 3.55 (m, 12 H), 3.70 (s, 2 H), 6.7 (b, 2 H), 7.6–7.8 (m, 15 H)

propriate amine (**27**, **30**, **32**, **33**), and 15 g of sodium carbonate was refluxed in 150 mL of toluene as above for 48 h. The product monoamides were isolated as above and are listed in Table II.

Preparation of Diamide Intermediates 46a–48a (Scheme IC). Compounds **46a** and **47a** were prepared as above from 10 g (60 mmol) of **25**, 30 mmol of **24** or **45**, and 15 g of sodium carbonate. Compounds **46a** and **47a** (see Table III for yields and NMR data) were used in the next step without purification by chromatography. However, when **46a** and **47a** were chromatographed on silica gel (isopropyl alcohol/methanol), reduction products **46** and **47** were easier to purify. Compound **48a** was prepared by refluxing a mixture of 9.08 g (40 mmol) of **26**, 2.14 g (20 mmol) of **45**, 30 g of sodium carbonate, and 8 g of sodium iodide in 100 mL of acetonitrile for 48 h. The mixture was filtered and evaporated under reduced pressure. Chloroform (100 mL) was added to the residue, and this mixtue was filtered and evaporated under reduced pressure. The residue was allowed to stand in 20 mL of dioxane for 48 h. The dioxane mixture was filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (toluene/ethanol) to give **48a** (see Table III).

General Procedure To Prepare Starting Polyamines 34–44 and 46–48 (Scheme I, Parts B and C). The amide (20 mmol) (**34a–44a** and **46a–48a**) in 50 mL of THF was slowly dropped into a stirred mixture of 50 mL of THF and 2.0 g of lithium aluminum hydride at 0–10 °C. The resulting mixture was refluxed for 24 h and cooled. Aqueous 5% sodium hydroxide (10 mL) was added to the mixture at 0–10 °C. After sitting for 2 h, the mixture was filtered, and the residue was washed several times with 30-mL portions of hot THF. The filtrate was evaporated under reduced pressure, and the residue was distilled. The yields, boiling points, and NMR data for the polyamine products are listed in Table IV. Combustion analyses were not obtained for the starting polyamines, but a satisfactory analysis was obtained for each macrocycle prepared from these polyamines.

9,15,18,24-Tetraethyl-3,9,15,18,24,30-hexaaza-6,12,21,27-tetraoxadotriacontane (49) (Scheme ID). A mixture of 1.73 g (5 mmol) of **35**, 1.8 g (12 mmol) of **25**, 10 g of sodium carbonate, and 2 g of sodium iodide in 50 mL of acetonitrile was refluxed for 3 days. The mixture was filtered and evaporated, and 100 mL of chloroform was added to the residue. The resulting mixture was filtered, and the filtrate was evaporated. The residue was purified as above (see Table II) and then reduced as above with lithium aluminum hydride to give **49** (see Table IV).

13,17-Diethyl-4,7-dimethyl-15-methylene-4,7,13,17-tetraaza-1,10-dioxacyclononadecane (1) (Scheme II). A mixture of 1.6 g (5 mmol) of **34**, 0.63 g (5 mmol) of 3-chloro-2-chloromethyl-1-propene (**50**), and 5 g of sodium carbonate in 300 mL of toluene was stirred under reflux for 48 h. A Dean–Stark trap was used to remove water. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was chromatographed on neutral alumina (toluene/ethanol, 50/1) to give 0.66 g (36%) of **1** as an oil: NMR δ 0.95 (t, 6 H), 2.25 (s, 6 H), 2.50 (m, 16 H), 3.00 (s, 4 H), 3.50 (q, 8 H), 5.00 (s, 2 H); MS *m/z* 370. Anal. Calcd for $C_{20}H_{42}N_4O_2$: C, 64.82; H, 11.42. Found: C, 64.62; H, 11.28. Compound **1** was obtained in a 65% yield when acetonitrile was used as the solvent rather than toluene.

4,7,13,17-Tetraethyl-15-methylene-4,7,13,17-tetraaza-1,10-dioxacyclononadecane (2) (Scheme II). Macrocycle **2** was prepared from 1.73 g (5 mmol) of **35**, 0.65 g (5 mmol) of **50**, and 5 g of potassium carbonate in 200 mL of acetonitrile under reflux for 24 h. The residue after the solvent was evaporated was added to 50 mL of chloroform. The chloroform mixture was stirred for 5 min, filtered, and evaporated under reduced pressure. The residue was chromatographed on neutral alumina (toluene/ethanol, 100/1) to give 1.1 g (55%) of **2** as an oil: NMR δ 1.00 (dt, 12 H), 2.65 (m, 20 H), 3.10 (s, 4 H), 3.55 (m, 8 H), 5.05 (s, 2 H);

Table IV. Yields, Boiling Points, and NMR Data for Polyamines 34–44 and 46–49 (Scheme I, Parts B–D)

amine	bp, °C/mmHg	yld, %	NMR, δ	to prepare crown
34	126–129/0.075	72	1.1 (t, 6 H), 1.6 (b, 2 H), 2.35 (s, 6 H), 2.55 (m, 16 H), 3.7 (m, 8 H)	**1, 3, 5**
35	128–132/0.065	68	1.05 (t, 6 H), 1.10 (t, 6 H), 1.35 (b, 2 H), 2.65 (m, 16 H), 2.80 (t, 4 H), 3.55 (m, 8 H)	**2, 4**
36	176–180/0.060	64	0.9 (t, 6 H), 1.1 (t, 6 H), 1.35 (m, 10 H), 2.75 (m, 20 H), 3.5 (m, 12 H)	**6**
37	206–208/0.070	79	1.1 (t, 6 H), 1.55 (b, 2 H), 2.8 (m, 16 H), 3.50 (m, 12 H), 3.7 (s, 4 H), 7.3 (m, 10 H)	**7**
38	252–254/0.070	65	1.1 (t, 6 H), 1.6 (b, 2 H), 2.8 (m, 16 H), 3.55 (m, 16 H), 3.7 (s, 4 H), 7.3 (m, 10 H)	**8**
39	152–155/0.120	78	1.0 (m, 15 H), 1.3 (b, 2 H), 2.65 (m, 26 H), 3.5 (m, 8 H)	**9**
40	183–186/0.070	56	1.0 (m, 18 H), 1.4 (b, 2 H), 2.6 (m, 32 H), 3.6 (m, 8 H)	**10**
41	63–65/0.070	70	1.1 (t, 3 H), 1.6 (b, 2 H), 2.3 (s, 3 H), 2.45 (s, 3 H), 2.7 (m, 10 H), 3.6 (m, 4 H)	**16**
42	178–180/0.070	72	1.1 (t, 3 H), 1.5 (b, 2 H), 2.7 (m, 10 H), 3.5 (m, 8 H), 3.7 (s, 2 H), 3.8 (s, 2 H), 7.3 (m, 10 H)	**19**
43	107–108/0.120	68	1.0 (m, 12 H), 1.3 (b, 2 H), 2.6 (m, 20 H), 3.5 (m, 4 H)	**17**
44	145–147/0.120	63	1.1 (m, 15 H), 1.4 (b, 2 H), 2.65 (m, 26 H), 3.5 (m, 4 H)	**18**
46	154–156/0.060	71	1.1 (t, 6 H), 1.6 (b, 2 H), 2.75 (m, 14 H), 3.60 (m, 15 H)	**13, 14, 15**
47	150–153/0.070	73	1.1 (t, 6 H), 1.3 (b, 2 H), 2.7 (m, 12 H), 3.55 (m, 8 H), 3.7 (s, 2 H), 7.3 (m, 5 H)	**11, 12**
48[a]		82	1.7 (b, 2 H), 2.7 (m, 8 H), 3.5 (s, 8 H), 3.65 (s, 2 H), 3.8 (s, 4 H), 7.3 (m, 15 H)	**20, 21**
49[b]	234–237/0.060	41	1.05 (m, 18 H), 1.6 (b, 2 H), 2.6 (m, 32 H), 3.6 (m, 16 H)	**22, 23**

[a] Amine **48** was not distilled but was used in the next step without further distillation, the yield was of the crude product. [b] Amine **49** was distilled but it is better to use the crude product without distillation.

MS m/z 398. Anal. Calcd for $C_{22}H_{46}N_4O_2$: C, 66.29; H, 11.63. Found: C, 66.12; H, 11.49.

13,17-Diethyl-4,7-dimethyl-15-hydroxy-4,7,13,17-tetraaza-1,10-dioxacyclononadecane (3) (Scheme II). Compound **3** was prepared as **2** above from 1.65 g (5 mmol) of **34**, 1.8 g (5.7 mmol) of 2-hydroxy-1,3-diiodopropane, 10 g of sodium carbonate, 0.4 g of sodium iodide, and 200 mL of acetonitrile. The product was chromatographed on neutral alumina (toluene/ethanol, 20/1) to give 0.05 g (3%) of **3** as an oil: NMR (δ) 0.95 (t, 6 H), 2.20 (s, 6 H), 2.60 (m, 20 H), 3.20 (b, 1 H), 3.50 (m, 8 H), 3.70 (m, 1 H); IR 3400, 1100 cm^{-1}; MS m/z 374. There was not enough of **3** to obtain an elemental analysis. The NMR spectrum and MS analysis were consistent with the indicated structure.

15-Allyl-4,7,13,17-tetraethyl-4,7,13,17-tetraaza-1,10-dioxacyclononadecane (4) (Scheme II). 2-Allyl-1,3-propanediol was first prepared by reducing diethyl allylmalonate (**52**) with lithium aluminum hydride as above for **34–44**. The dimesylate of 2-allyl-1,3-propanediol was prepared by slowly adding in a dropwise fashion 10.2 g (90 mmol) of mesyl chloride in 160 mL of dichloromethane to a solution of 4.15 g (40 mmol) of the diol and 11.8 g (0.11 mol) of triethylamine in 160 ml of dichloromethane at −10 °C. The mixture was stirred at 0 °C for 1 h and diluted with 100 mL of dichloromethane. The resulting solution was washed successively with 50-mL portions of cold 5% aqueous hydrochloric acid, cold water, cold 5% aqueous sodium bicarbonate, and cold water. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure to give 9.6 g (98%) of crude dimesylate: NMR δ 1.95 (m, 1 H), 2.10 (m, 2 H), 3.00 (s, 6 H), 4.10 (m, 4 H), 5.05 (m, 2 H), 5.85 (m, 1 H). The crude dimesylate (8.5 g, 32 mmol), 30 g (200 mmol) of sodium iodide, and 10 g of sodium bicarbonate were refluxed in 200 mL of acetone for 36 h. The mixture was filtered, and the acetone was removed under reduced pressure. The residue was dissolved in 150 mL of ether. The ether solution was washed twice with 100-mL portions of 5% aqueous sodium thiosulfate and then with 100 mL of saturated brine. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed to give 8.4 g (78%) of crude **53**: NMR δ 1.95 (m, 1 H), 2.10 (t, 2 H), 3.10 (m, 4 H), 5.05 (m, 2 H), 5.70 (m, 1 H). This material was used in the next step to prepare **4** without further purification.

Crude compound **53** (1.68 g, 5 mmol), 1.73 g (5 mmol) of **35**, 15 g of sodium carbonate, and 0.1 g of sodium iodide were reacted in 200 mL of acetonitrile as above for **2** to give 0.43 g (20%) of **4** as an oil: NMR δ 0.95 (m, 12 H), 1.85 (m, 2 H), 2.20 (m, 25 H), 3.75 (m, 8 H), 5.00 (m, 2 H), 5.90 (m, 1 H); MS m/z 426. Anal. Calcd for $C_{24}H_{50}N_4O_2$: C, 67.72; H, 11.60. Found: C, 67.65; H, 11.68.

17-[(Allyloxy)methyl]-13,22-diethyl-4,7-dimethyl-4,7,13,22-tetraaza-1,10,16,19-tetraoxacyclotetracosane (5) (Scheme III). Macrocycle **5** was prepared as above for **2** using 1.6 g (5 mmol) of **34**, 2.35 g (5 mmol) of **54**,[16] 6 g of sodium carbonate, and 0.4 g sodium iodide in 200 mL of acetonitrile. The chromatography solvent was toluene/ethanol, 50/1. The reaction gave 1.2 g (48%) of **5** as an oil: NMR δ 1.00 (t, 6 H), 2.30 (s, 6 H), 2.70 (m, 20 H), 3.55 (m, 17 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS m/z 503. Anal. Calcd for $C_{26}H_{54}N_4O_5$: C, 62.11; H, 10.83. Found: C, 61.89; H, 10.67.

20-[(Allyloxy)methyl]-4,10-dibutyl-16,25-diethyl-4,10,16,25-tetraaza-1,7,13,19,22-pentaoxacycloheptacosane (6) (Scheme III). Macrocycle **6** was prepared as above for **2** using 2.23 g (5 mmol) of **36**, 2.4 g (5 mmol) of **54**, 10 g of potassium carbonate, and 0.5 g of potassium iodide in 400 mL of acetonitrile. The chromatography solvent was toluene/ethanol, 100/1. The reaction gave 0.6 g (20%) of **6** as an oil: NMR δ 0.90 (t, 6 H), 1.05 (t, 6 H), 1.35 (m, 8 H), 2.60 (m, 24 H), 3.60 (m, 21 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS m/z 631. Anal. Calcd for $C_{34}H_{70}N_4O_6 \cdot 0.5H_2O$: C, 63.86; H, 11.18. Found: C, 63.95; H, 11.05.

20-[(Allyloxy)methyl]-4,10-dibenzyl-16,25-diethyl-4,10,16,25-tetraaza-1,7,13,19,22-pentaoxacycloheptacosane (7) (Scheme III). Macrocycle **7** was prepared as above for **2** using 2.52 g (5 mmol) of **37**, 2.4 g (5 mmol) of **54**, 8 g of potassium carbonate, 4 g of cesium carbonate, and 0.5 g of potassium iodide in 300 mL of acetonitrile to give 0.95 g (26%) of **7** as an oil: NMR δ 1.00 (t, 6 H), 2.70 (m, 20 H), 3.60 (m, 25 H), 4.00 (d, 2 H), 5.25 (m, 2 H), 5.90 (m, 1 H), 7.30 (m, 10 H); MS m/z 698. Anal. Calcd for $C_{40}H_{66}N_4O_6$: C, 68.73; H, 10.46. Found: C, 68.50; H, 10.29.

23-[(Allyloxy)methyl]-4,13-dibenzyl-19,28-diethyl-4,13,19,28-tetraaza-1,7,10,16,22,25-hexaoxacyclotriacontane (8) (Scheme III). Macrocycle **8** was prepared as above for **2** using 2.8 g (5 mmol) of **38**, 2.3 g (5 mmol) of **54**, 10 g of potassium carbonate, and 0.8 g of potassium iodide in 300 mL of acetonitrile. The chromatography solvent was toluene/ethanol, 100/1. The reaction gave 1.0 g (27%) of **8** as an oil: NMR δ 1.00 (t, 6 H), 2.70 (m, 20 H), 3.50 (m, 25 H), 3.70 (s, 4 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H), 7.30 (m, 10 H); MS m/z 742. Anal. Calcd for $C_{42}H_{70}N_4O_7$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.28.

20-[(Allyloxy)methyl]-4,7,10,16,25-pentaethyl-4,7,10,16,25-pentaaza-1,13,19,22-tetraoxacycloheptacosane (9) (Scheme III). Macrocycle **9** was prepared as above for **2** using 2.08 g (5 mmol) of **39**, 2.4 g (5 mmol) of **54**, 15 g of potassium carbonate, 5 g of cesium carbonate, and 0.7 g of potassium iodide in 300 mL of acetonitrile to give 1.1 g (37%) of product: NMR δ 1.00 (t, 15 H), 2.30 (m, 30 H), 3.60 (m, 17 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.95 (m, 1 H); MS m/z 602. Anal. Calcd for $C_{32}H_{67}N_5O_5$: C, 63.86; H, 11.22. Found: C, 63.83; H, 11.24.

23-[(Allyloxy)methyl]-4,7,10,13,19,28-hexaethyl-4,7,10,13,19,28-hexaaza-1,16,22,25-tetraoxacyclotriacontane (10) (Scheme III). This macrocycle was prepared as above for **2** from 0.8 g (1.6 mmol) of **40**, 0.75 g (1.8 mmol) of **54**, 5 g of potassium carbonate, 4 g of cesium carbonate, and 0.1 g of potassium iodide in 300 mL of acetonitrile to give 0.4 g (36%) of **10**: NMR δ 1.0 (t, 18 H), 2.60 (m, 36 H), 3.50 (m, 17 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS m/z 673. Anal. Calcd for $C_{36}H_{76}N_6O_5$: C, 64.25; H, 11.34. Found: C, 64.16; H, 11.29.

4-Benzyl-10,16-diethyl-4,10,16-triaza-1,7,13-trioxacyclooctadecane (11) (Scheme IV). The cyclic diamide intermediate (**11** containing two carbonyl groups) was prepared by simultaneously adding a solution of 3.37 g (10 mmol) of **47** and 6 g (20 mmol) of triethylamine in 125 mL of toluene in one addition funnel and 1.7 g (10 mmol) of diacid chloride **55** in 125 mL of toluene in another to vigorously stirred 500 mL of toluene at 0 °C over an 8-h period. The mixture was stirred for 24 h at room temperature and filtered, and the residue was washed with 50 mL of toluene. The toluene was removed under reduced pressure, and the residue was chromatographed on neutral alumina (toluene/ethanol, 20/1) to give 3.0 g (69%) of crude cyclic diamide as an oil: NMR δ 1.15 (m, 6 H), 2.70 (m, 4 H), 3.50 (m, 20 H), 4.30 (s, 2 H), 7.20 (m, 5 H); MS m/z 435.

A solution of the crude cyclic diamide (2 g, 4.6 mmol) in 20 mL of THF was slowly added to 0.4 g of lithium aluminum hydride in 20 mL of THF at 0–5 °C. The resulting mixture was refluxed for 24 h. The mixture was cooled, and 2 mL of 5% aqueous sodium hydroxide was added. After standing for 5 h, the mixture was filtered and the residue was washed several times with hot THF. The THF filtrate was evaporated under reduced pressure, and the residue was chromatographed on neutral alumina (toluene/ethanol, 50/1) to give 1.38 g (74%) of **11** as an oil: NMR δ 1.00 (t, 6 H), 2.60 (m, 4 H), 2.75 (m, 12 H), 3.55 (m, 12 H), 3.60 (s, 2 H), 7.20 (m, 5 H); MS m/z 407. Anal. Calcd for $C_{23}H_{41}N_3O_3$: C, 67.77; H, 10.14. Found: C, 67.81; H, 10.14.

14-[(Allyloxy)methyl]-4-benzyl-10,19-diethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (12) (Scheme III). Macrocycle **12** was prepared as above for **2** from 1.55 g (4.6 mmol) of **47**, 2.16 g (5 mmol) of **54**, 8 g of sodium carbonate, 2 g of potassium carbonate, and 0.3 g of sodium iodide in 400 mL of acetonitrile to give 1.72 g (72%) of the product as an oil: NMR δ 1.00 (t, 6 H), 2.70 (m, 16 H), 3.60 (m, 19 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H), 7.30 (m, 5 H); MS m/z 521. Anal. Calcd for $C_{29}H_{51}N_3O_4$: C, 66.76; H, 9.85. Found: C, 66.81; H, 9.72.

10,19-Diethyl-4-[2-(2-hydroxyethoxy)ethyl]-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (13) (Scheme IV). Macrocycle **13** was prepared as above for **2** from 3.35 g (10 mmol) of **46**, 4.0 g (11 mmol) of **56**, 5 g of potassium carbonate, 5 g of sodium carbonate, and 0.4 g of sodium iodide in 300 mL of acetonitrile to give 2.6 g (58%) of the product as an oil: NMR δ 1.00 (t, 6 H), 2.40 (b, 1 H), 2.65 (q, 4 H), 2.80 (m, 14 H), 3.60 (m, 22 H); MS m/z 449. Compound **14**, a derivative of **13**, gave a satisfactory elemental analysis.

10,19-Diethyl-4-[2-[2-(allyloxy)ethoxy]ethyl]-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (14) (Scheme IV). A

mixture of 1.2 g (2.5 mmol) of **13**, 0.4 g (3 mmol) of allyl bromide, and 0.5 g of potassium *tert*-butoxide in 50 mL of *tert*-butyl alcohol was stirred at 40–50 °C for 3 h. The mixture was evaporated under reduced pressure, and the residue was chromatographed on neutral alumina (toluene/ethanol, 50/1) to give 1 g (81%) of **14** as an oil: NMR δ 1.00 (t, 6 H), 2.60 (q, 4 H), 2.75 (m, 14 H), 3.55 (m, 22 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 490. Anal. Calcd for $C_{25}H_{51}N_3O_6$: C, 61.32; H, 10.51. Found: C, 61.27; H, 10.43.

14-[(Allyloxy)methyl]-10,19-diethyl-4-[2-(2-hydroxyethoxy)ethyl]-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (15) (Scheme III). Macrocycle **15** was prepared as above for **2** from 3.35 g (10 mmol) of **46**, 4.24 g (10 mmol) of **54**, 10 g of potassium carbonate, and 0.4 g of sodium iodide in 400 mL of acetonitrile to give 2.9 g (56%) of the product as an oil: NMR δ 1.05 (t, 6 H), 2.70 (m, 18 H), 3.60 (m, 23 H), 3.90 (b, 1 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 519. Anal. Calcd for $C_{26}H_{53}N_3O_7$: C, 60.09; H, 10.28. Found: C, 59.88; H, 10.09.

11-(or 12)-[(Allyloxy)methyl]-16-ethyl-4,7-dimethyl-4,7,16-triaza-1,10,13-trioxacyclooctadecane (16) (Scheme III). Macrocycle **16** was prepared as above for **2** from 1.95 g (4.7 mmol) of **41**, 2.15 g (4.7 mmol) of **54**, 6 g of sodium carbonate, and 0.2 g of sodium iodide in 200 mL of acetonitrile to give 1.2 g (66%) of the product as an oil: NMR δ 1.00 (t, 3 H), 2.30 (2 s, 6 H), 2.65 (m, 14 H), 3.60 (m, 13 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 387. Anal. Calcd for $C_{20}H_{41}N_3O_4$: C, 61.98; H, 10.66. Found: C, 61.92; H, 10.70.

14-(or 15)-[(Allyloxy)methyl]-4,7,10,19-tetraethyl-4,7,10,19-tetraaza-1,13,16-trioxacycloheneicosane (17) (Scheme III). Macrocycle **17** was prepared as above for **2** from 0.72 g (2.4 mmol) of **43**, 1.1 g (2.6 mmol) of **54**, 10 g of potassium carbonate, and 1 g of potassium iodide in 250 mL of acetonitrile to give 0.65 g (56%) of the product as an oil: NMR δ 1.00 (t, 12 H), 2.60 (m, 24 H), 3.60 (m, 13 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 486. Anal. Calcd for $C_{26}H_{54}N_4O_4$: C, 64.16; H, 11.18. Found: C, 64.10; H, 10.96.

17-(or 18)-[(Allyloxy)methyl]-4,7,10,13,22-pentaethyl-4,7,10,13,22-pentaaza-1,16,19-trioxacyclotetracosane (18) (Scheme III). Macrocycle **18** was prepared as above for **2** from 0.4 g (1.1 mmol) of **44**, 0.50 g (1.2 mmol) of **54**, 4 g of potassium carbonate, and 0.1 g of potassium iodide in 150 mL of acetonitrile to give 0.3 g (37%) of the product as an oil: NMR δ 1.00 (t, 15 H), 2.60 (m, 30 H), 3.60 (m, 13 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (s, 1 H); MS *m/z* 558. Anal. Calcd for $C_{30}H_{63}N_5O_4$: C, 64.59; H, 11.38. Found: C, 64.72; H, 11.19.

14-(or 15)-[(Allyloxy)methyl]-4,10-dibenzyl-19-ethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (19) (Scheme III). Compound **19** was prepared as above for **2** from 1.9 g (4.8 mmol) of **42**, 2.12 g (5 mmol) of **54**, 6 g of sodium carbonate, 4 g of potassium carbonate, and 0.3 g of sodium iodide in 300 mL of acetonitrile to give 1.4 g (51%) of the product as an oil: NMR δ 1.00 (t, 3 H), 2.70 (m, 14 H), 3.60 (m, 21 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H), 7.3 (m, 10 H); MS *m/z* 583. Anal. Calcd for $C_{34}H_{53}N_3O_5$: C, 69.94; H, 9.15. Found: C, 70.05; H, 9.05.

4,10,19-Tribenzyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (20) (Scheme IV). Macrocycle **20** was prepared as above for **2** from 1.15 g (2.5 mmol) of **48**, 0.93 g (2.5 mmol) of **56**, 10 g of potassium carbonate, and 0.1 g of sodium iodide in 150 mL of acetonitrile to give 0.7 g (49%) of the product as an oil: NMR δ 2.75 (m, 12 H), 3.60 (m, 22 H), 7.25 (m, 15 H); MS *m/z* 575. Anal. Calcd for $C_{35}H_{49}N_3O_4$: C, 73.01; H, 8.57. Found: C, 72.88; H, 8.43.

4,10,14-Tribenzyl-12-methylene-4,10,14-triaza-1,7-dioxacyclohexadecane (21) (Scheme II). Macrocycle **21** was prepared as above for **2** from 1.15 g (2.5 mmol) of **48**, 0.32 g (2.5 mmol) of **50**, 10 g of sodium carbonate, and 0.5 g of sodium iodide in 150 mL of acetonitrile to give 0.8 g (63%) of the product as an oil: NMR δ 2.55 (t, 4 H), 2.80 (t, 4 H), 3.20 (s, 4 H), 3.55 (m, 14 H), 5.10 (s, 2 H), 7.30 (m, 15 H); MS *m/z* 513. Anal. Calcd for $C_{33}H_{43}N_3O_2$: C, 77.15; H, 8.43. Found: C, 77.32; H, 8.35.

4,10,13,19,25,29-Hexaethyl-27-methylene-4,10,13,19,25,29-hexaaza-1,7,16,22-tetraoxacyclohentriacontane (22) (Scheme II). Macrocycle **22** was prepared as above for **2** from 0.46 g (0.8 mmol) of **49**, 0.1 g (0.8 mmol) of **50**, 3 g of potassium carbonate, and 0.5 g of cesium carbonate in 100 mL of acetonitrile to give 0.04 g (8%) of the product as an oil: NMR δ 1.00 (m, 18 H), 2.60 (m, 32 H), 3.00 (s, 4 H), 3.50 (m, 16 H), 5.00 (s, 2 H); MS *m/z* 628. Anal. Calcd for $C_{34}H_{72}N_6O_4$: C, 64.92; H, 11.53. Found: C, 64.72; H, 11.71.

7,13,19,22,28,34-Hexaethyl-7,13,19,22,28,34-hexaaza-1,4,10,16,25,31-hexaoxacyclohexatriacontane (23) (Scheme IV). Macrocycle **23** was prepared as above for **2** from 0.4 g (0.8 mmol) of **49**, 0.33 g (0.9 mmol) of **56**, 3 g of sodium carbonate, 3 g of potassium carbonate, and 2 g of cesium carbonate in 200 mL of acetonitrile to give 0.06 g (11%) of the product as an oil: NMR δ 1.00 (t, 18 H), 2.65 (m, 36 H), 3.50 (m, 24 H); MS *m/z* 691. Anal. Calcd for $C_{36}H_{78}N_6O_6$: C, 62.57; H, 11.38. Found: C, 62.44; H, 11.22.

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Conformations of *N*,*N*-Bis(2-fluorophenyl)carbamoyl Chloride

Maria Kairi,[1a] Nancy L. Keder,[1b] and J. T. Gerig*,[1c]

Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece, and Department of Chemistry, University of California, Santa Barbara, California 93106

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The structure of the title compound has been examined by X-ray crystallographic and fluorine NMR methods. In the solid state the planes of the fluorophenyl rings are oriented at angles of 98° and 64° relative to the plane through the atoms of the carbamoyl chloride group. Fluorine NMR studies indicate that the conformational properties of the molecule in solution are similar to this. Fluorine NMR lineshape data were used to estimate the rates of rotation of the fluorophenyl rings and the rate of rotation about the carbamoyl nitrogen–carbon bond. Observation of a large fluorine–fluorine coupling constant, likely the result of a through-space interaction, supports the conclusions regarding the conformations of this compound in solution.

Erlanger and co-workers have shown that diphenylcarbamoyl chloride (I) efficiently inactivates serine proteases.[2] For example, this compound reacts rapidly with α-chymotrypsin, even at a solution pH far from the op-

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