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Abstract: Bisphenol-containing diaza-18-crown-6 ligands (**1-16**) were synthesized as potential membrane-forming amphiphiles *via* the one-pot Mannich reaction. Sonication of the crude products in a small amount of MeOH followed by filtration and drying proved to be an efficient method of purifying nearly all compounds. Compounds **8** and **9** were selected for assay as amphiphiles. Compared to simple, alkylated diazacrown ethers, the stability of the amphisomes formed from these monomers is lower possibly because intramolecular hydrogen bonding prevents formation of intermolecular hydrogen bonds.

Keywords: macrocycles, crown ethers, aggregation

During the past decade, a number of synthetic channel model systems have been developed and tested. For the most part, these models can be classified as "half-channel elements" or "transmembrane" structures. Systems designed and prepared in the groups of Nolte,[1] Voyer,[2] Fyles,[3] Lehn,[4] de Mendoza[5] and by one of us[6] represent the transmembrane approach. Notable examples of the "half-channel" approach have been reported from the laboratories of Tabushi[7] and Kobuke.[8] A number of other important contributions are described in a recent review.[9] In a number of these synthetic channel model systems, crown ethers have served either as head groups or as transient ion binding sites. The ability of crowns to serve as amphiphile headgroups is critical to the success of any macrocycle-based channel model that employs them as entry portals. The amphiphilic properties of alkyl-substituted crown ethers were explored by Okahara and co-workers[10] and by Kuwamura *et al.*[11] who demonstrated micelle formation with a variety of single-chained macrocycles. Our own studies of aggregate formation have focused on azacrowns having steroidal sidechains or two or more alkyl chains.[12]

In a further effort to assess the efficacy of diazacrowns as potential headgroups and cation entry portals, as well as to explore the influence of proximate phenolic donors, we developed the novel class of twin-tailed macrocycles reported here. As a part of the synthetic survey, 16 novel macrocycles were prepared that had appended a variety of sidechains. A range of sidechains was studied to assess the breadth of the synthetic approach. Clearly, not all were expected to function as amphiphiles. It should be noted, however, that recent work suggests that relatively short alkyl chains can lead to liposome formation when the headgroup is either diaza- or triaza-18-crown-6.[12i]

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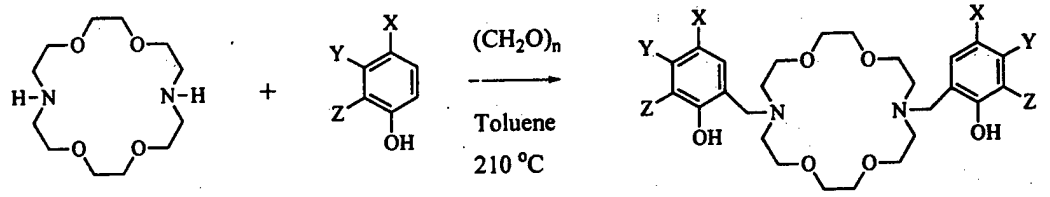
RESULTS AND DISCUSSION

The Mannich reaction is known to be a powerful method for the functionalization of azacrown ethers with additional ligating units.[13] Reaction of diaza-18-crown-6, paraformaldehyde, and the appropriate phenols in refluxing toluene gave compounds **1-16** (Figure 1) in good yields. The bisphenol-substituted azacrown ethers were purified by sonication in a small amount of MeOH, followed by filtration and drying.

Compounds **1-16** were designed to have three types of "wall units": (i) linear aliphatic chains (**1**, **3-5**, and **7-9**); (ii) bulky aliphatic chains (**2**, **6**, **10**, and **11**); and (iii) aryl groups with different types of substituents (**12-16**). All "wall units" are substituted at the positions *para* to the hydroxy groups of the phenols except the pentadecyl groups of compound **9** and the 1-adamantyl groups of compound **11** that are *meta* and *ortho* to the hydroxy groups, respectively. The methoxy groups adjacent to the hydroxy groups of compound **3** may influence its metal ion-complexing ability and selectivity. For compounds **12-16**, the two sidearms have two or more benzene rings which may provide hydrophobic interactions with a membrane.

Compounds **8** and **9** have, respectively, *n*-dodecyl and *n*-pentadecyl sidechains. They were judged to be the best prospects for forming aggregates. The ability of these compounds to form amphisomes was assessed as follows. A 1 m*M* suspension of each compound was prepared in distilled, deionized water and bath sonicated. In both cases, cloudiness indicative of aggregation was apparent after 10-15 min of sonication but the bulk of the material remained on the sides of the test tubes. After the relatively long sonication time of 45 min, the mixtures were filtered and the filtrate was studied by laser light scattering (Coulter N4M). Dodecyl-chained **8** exhibited a unimodal distribution of 1750±650Å. The corresponding mean diameter distribution was 2310 ± 840Å. The formation of a precipitate began



Compound	X	Y	Z
1	Methyl	H	H
2	*t*-Butyl	H	H
3	Allyl	H	Methoxy
4	Allyloxy	H	H
5	Heptyloxy	H	H
6	*t*-Octyl	H	H
7	Octyl	H	H
8	Dodecyl	H	H
9	H	Pentadecyl	H
10	1-Adamantyl	H	H
11	Me	H	1-Adamantyl
12	4-Trifluoromethyl-phenoxy	H	H
13	Benzyloxy	H	H
14	4-Cyanophenyl	H	H
15	3,5-Dicyanophenyl	H	H
16	Trityl	H	H

Figure 1. Synthesis of bisphenol-armed diaza-18-crown-6 ligands *via* the one-pot Mannich reaction

almost immediately in the sample formed from **8** and continued until, after ~45 min, turbidity was no longer apparent in the aqueous phase. When **8** was sonicated to form aggregates, significant material remained on the test tube walls as a melt or gel even after 45 min. Coupled with the precipitation that was observed after filtration, the aggregates were judged to be unstable. The aggregates formed from **9**, which has longer alkyl chains, appeared to be more stable. Thus, some precipitate was apparent after an hour but the suspension was still turbid, suggesting qualitatively that aggregates from **9** were more stable than from **8**. This difference in stability is expected based on chain length but the difference in chain position on the phenol is a variable that precludes exact comparisons. The overall lack of stability also precluded dye entrapment, electron microscopy, or other standard characterization methods. Since the longest-chained compounds did not form stable aggregates, it was assumed that shorter-chained derivatives would be even less stable if they formed aggregates at all.

The size of the aggregates formed from **8** is somewhat smaller than previously observed for *N*-alkylated diaza-18-crown-6 derivatives.[12i] The aggregates formed from **9** are closer in size to this range. In both cases, however, they are within or not far from the 2000-3000 Å size span generally observed for related structures. The key issue is that they are less stable than are aggregates of simple, alkylated diazacrown ethers. Indeed, aggregates formed from **8** are much less stable than those formed, for example, from *N,N'*-bis(dodecyl)-4,13-diaza-18-crown-6.[12i]

In previous work, we have speculated that aggregate size in this series may be determined by a hydrogen bonded network of protonated nitrogen atoms.[12] The longer chains present in **9** would be expected to produce more stable aggregates than observed in **8** but the isomer mixture present in the latter case may be as important. The formation of intramolecular hydrogen bonds between the phenolic hydroxy group and macroring nitrogen may reduce headgroup polarity and the possibility of nitrogen protonation. This, in turn, would prevent the formation of an H-bonded network and this may account for the low stability of amphisomes formed from monomers **8** and **9**.

EXPERIMENTAL SECTION

The ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in $CDCl_3$. FAB ionization was used to record the HRMS. Starting substituted phenols were purchased from commercial sources except *p*-(4-hydroxyphenyl)isophthalonitrile[14] needed for the synthesis of **15** and 4-allyloxyphenol[15] needed for the synthesis of **4**. Those substituted phenols were prepared as reported.[14,15]

General Procedure for the Syntheses of Compounds 1-16 Using the One-Pot Mannich Reaction. An anhydrous toluene solution (180 mL) of 4,13-diaza-18-crown-6 (1.00 g, 3.82 mmol), paraformaldehyde (280 mg, 9.30 mmol), and the appropriate phenol (9.10 mmol) was refluxed at 110 °C for 20 h. The solvent was evaporated under vacuum, and a small amount of MeOH was added. The mixture was sonicated for 20 to 30 min. The resulting solid was collected by filtration and dried.

7,16-Bis(2-hydroxy-5-methylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (1) and **7,16-bis(5-*t*-butyl-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (2).** Compounds **1** and **2** were prepared by the above procedure in 92% and 90% yields, respectively. The mp and NMR spectral data were identical to those reported.[13b]

7,16-Bis(5-allyl-2-hydroxy-3-methoxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (3). Compound **3** was prepared by the above procedure to give a white solid; mp 132-133 °C; yield 78%; ^{1}H NMR δ: 2.87 (t, J = 5.3 Hz, 8H), 3.28 (d, J = 6.6 Hz, 4H), 3.60 (s, 8H), 3.67 (t, J = 5.3 Hz, 8H), 3.79 (s, 4H), 3.85 (s, 6H), 5.07 (m, 4H), 5.94 (m, 2H), 6.42 (s, 2H), 6.62 (s, 2H); ^{13}C NMR δ: 39.9, 53.6, 56.0, 58.8, 69.3, 70.8, 111.5, 115.6, 120.6, 122.4,

130.3, 138.1, 145.6, 148.1; HRMS calcd for $C_{34}H_{50}N_2O_8$ $(M+H)^+$ 615.3646, found 615.3635. Anal. Calcd for $C_{34}H_{50}N_2O_8$: C, 66.43; H, 8.20. Found: C, 66.48; H, 8.40.

7,16-Bis(5-allyloxy-2-hydroxy-3-methoxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (4). Compound **4** was prepared by the above procedure to give a yellow solid; mp 130-131 °C; yield 85%; ^{1}H NMR δ: 2.83 (t, J = 5.4 Hz, 8H), 3.59 (s, 8H), 3.64 (t, J = 5.4 Hz, 8H), 3.74 (s, 4H), 4.34 (dt, J = 1.5, 5.1 Hz, 4H), 5.24 (qd, J = 1.5, 10.5 Hz, 4H), 5.38 (qd, J = 1.7, 17.3 Hz, 2H), 6.03 (m, 2H), 6.57 (br s, 2H), 6.72 (d, J = 1.7 Hz, 2H), 10.06 (br s, 2H); ^{13}C NMR δ: 53.9, 58.9, 69.3, 70.9, 114.7, 115.9, 116.8, 117.6, 123.3, 133.9, 151.6, 152.1; HRMS calcd for $C_{32}H_{46}N_2O_8$ $(M+H)^+$ 587.3333, found 587.3322. Anal. Calcd for $C_{32}H_{46}N_2O_8$: C, 65.51; H, 7.90. Found: C, 65.50; H, 7.88.

7,16-Bis(5-heptyloxy-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (5). Compound **5** was prepared by the above procedure to give a white solid; mp 81-83 °C; yield 70%; ^{1}H NMR δ: 0.89 (t, J = 6.8 Hz, 6H), 1.39 (m, 16H), 1.74 (p, J = 6.8 Hz, 4H), 2.84 (t, J = 5.4 Hz, 8H), 3.60 (s, 8H), 3.65 (t, J = 5.4 Hz, 8H), 3.80 (s, 4H), 3.86 (t, J = 6.6 Hz, 4H), 6.56 (s, 2H), 6.72 (s, 4H); ^{13}C NMR δ: 14.3, 22.8, 26.3, 29.3, 29.7, 32.0, 53.9, 58.9, 68.9, 69.3, 71.0, 114.4, 115.6, 116.8, 123.3, 151.8, 152.1; HRMS calcd for $C_{40}H_{66}N_2O_8$ $(M+Na)^+$ 725.4717, found 725.4726. Anal. Calcd for $C_{40}H_{66}N_2O_8$: C, 68.34; H, 9.46. Found: C, 68.50; H, 9.56.

7,16-Bis(2-hydroxy-5-*t*-octylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (6). Compound **6** was prepared by the above procedure to give a white solid; mp 122-123 °C; yield 69%; ^{1}H NMR δ: 0.69 (s, 18H), 1.31 (s, 12H), 1.66 (s, 4H), 2.85 (t, J = 5.4 Hz, 8H), 3.60 (s, 8H), 3.66 (t, J = 5.4 Hz, 8H), 3.80 (s, 4H), 6.73 (d, J = 8.3 Hz, 2H), 6.93 (d, J = 2.2 Hz, 2H), 7.14 (dd, J = 2.4, 8.6 Hz, 2H); ^{13}C NMR δ: 31.9, 32.0, 32.6, 38.0, 53.9, 57.4, 59.3, 69.4, 70.9, 115.6, 121.6, 126.5, 126.6, 140.6, 155.5; HRMS calcd for $C_{42}H_{70}N_2O_6$ $(M+H)^+$ 699.5313, found 699.5303. Anal. Calcd for $C_{42}H_{70}N_2O_6$: C, 72.17; H, 10.09. Found: C, 72.38; H, 10.16.

7,16-Bis(2-hydroxy-5-octylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (7). Compound **7** was prepared by the above procedure to give a white solid; mp 74-76 °C; yield 78%; ^{1}H NMR δ: 0.88 (t, J = 6.8 Hz, 6H), 1.27 (br s, 20H), 1.54 (p, J = 6.6 Hz, 4H), 2.47 (t, J = 7.6 Hz, 4H), 2.85 (t, J = 5.4 Hz, 8H), 3.61 (s, 8H), 3.66 (t, J = 5.4 Hz, 8H), 3.77 (s, 4H), 6.72 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 1.7 Hz, 2H), 6.95 (dd, J = 2.0, 8.3 Hz, 2H); ^{13}C NMR δ: 14.3, 22.9, 29.5, 29.6, 29.7, 32.0, 32.1, 35.3, 53.9, 59.0, 69.3, 70.9, 116.2, 122.2, 128.6, 128.7, 133.5, 155.9; HRMS calcd for $C_{42}H_{70}N_2O_6$ $(M+Na)^+$ 721.5132, found 721.5124. Anal. Calcd for $C_{42}H_{70}N_2O_6$: C, 72.17; H, 10.09. Found: C, 72.07; H, 10.04.

7,16-Bis(5-dodecyl-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (8). Compound **8** was prepared by a modification of the above procedure. The reaction mixture formed a emulsion layer in MeOH and was difficult to solidify. The upper MeOH layer containing unreacted starting materials was removed by pipet. The emulsion layer was further treated by MeOH five more times and dried in vacuum to give a white solid; mp 50-52 °C; yield 40%. The starting material, 4-dodecylphenol, was only commercially-available as a mixture of isomers, so compound **8** did not give sharp ^{1}H and ^{13}C NMR spectra. Only major peaks are listed below: ^{1}H NMR δ: 0.4-1.7 (m, 50H), 2.85 (t, J = 4.8 Hz, 8H), 3.60 (s, 8H), 3.66 (t, J = 4.8 Hz, 8H), 3.79 (s, 4H), 6.74 (dd, J = 2.0, 8.3 Hz, 2H), 6.86 (m, 2H), 7.06 (m, 2H), 10.25 (br s, 2H); ^{13}C NMR δ: 8.9, 12.4 14.3, 14.7, 15.1, 17.6, 22.9, 29.4, 29.6, 37.1, 40.3, 41.0, 53.9, 59.4, 69.4, 70.9, 115.7, 121.7, 127.0, 138.5, 140.4, 155.3; HRMS calcd for $C_{50}H_{86}N_2O_6$ (M^+) 833.6384, found 833.6377. Anal. Calcd for $C_{50}H_{86}N_2O_6$: C, 74.03; H, 10.69. Found: C, 74.05; H, 10.52.

7,16-Bis(2-hydroxy-4-pentadecylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (9). Compound **9** was prepared by the above procedure to give a white solid; mp 76-77 °C; yield 90%; ^{1}H NMR δ: 0.88 (t, J = 6.8 Hz, 6H), 1.26 (br s, 48H), 1.58 (p, J = 6.6 Hz, 4H), 2.52 (t, J = 7.8 Hz, 4H), 2.85 (t, J = 5.1 Hz, 8H), 3.61 (s, 8H), 3.66 (t,

J = 5.1 Hz, 8H), 3.77 (s, 4H), 6.58 (d, J = 7.6 Hz, 2H), 6.65 (s, 2H), 6.85 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ: 14.3, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9, 31.5, 32.1, 35.9, 53.8, 58.6, 69.4, 71.0, 116.4, 119.2, 119.7, 128.6, 144.1, 157.9; HRMS calcd for $C_{56}H_{98}N_2O_6$ $(M+Na)^+$ 917.7323, found 917.7339. Anal. Calcd for $C_{56}H_{98}N_2O_6$: C, 75.12; H, 11.03. Found: C, 75.38; H, 10.87.

7,16-Bis(5-(1'-adamantyl)-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (10). Compound **10** was prepared by the above procedure to give a white solid; mp 156-158 °C; yield 95%; ^{1}H NMR δ: 1.75 (s, 12H), 1.86 (s, 12H), 2.07 (s, 6H), 2.86 (t, J = 4.8 Hz, 8H), 3.61 (s, 8H), 3.66 (t, J = 4.8 Hz, 8H), 3.80 (s, 4H), 6.76 (d, J = 8.3 Hz, 2H), 6.93 (s, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.36 (s, 2H); ^{13}C NMR δ: 29.2, 35.6, 37.0, 43.7, 53.8, 59.4, 69.4, 71.0, 115.9, 121.8, 125.1, 125.2, 128.5, 142.3, 155.7; HRMS calcd for $C_{46}H_{66}N_2O_6$ $(M+Na)^+$ 765.4819, found 765.4816. Anal. Calcd for $C_{46}H_{66}N_2O_6$: C, 74.36; H, 8.95. Found: C, 74.42; H, 8.80.

7,16-Bis(3-(1'-adamantyl)-2-hydroxy-5-methylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (11). Compound **11** was prepared by the above procedure to give a yellow solid; mp 183-184 °C; yield 73%; ^{1}H NMR δ: 1.77 (s, 12H), 2.05 (s, 6H), 2.15 (s, 12H), 2.23 (s, 6H), 2.83 (t, J = 5.7 Hz, 8H), 3.63 (s, 8H), 3.66 (t, J = 5.7 Hz, 8H), 3.74 (s, 4H), 6.64 (d, J = 1.5 Hz, 2H), 6.92 (d, J = 1.5 Hz, 2H), 10.59 (br s, 2H); ^{13}C NMR δ: 21.0, 29.4, 36.9, 37.5, 40.5, 53.7, 59.2, 69.4, 71.1, 122.7, 126.6, 127.2, 127.5, 136.8, 154.9; HRMS calcd for $C_{48}H_{70}N_2O_6$ $(M+Na)^+$ 793.5132, found 793.5132. Anal. Calcd for $C_{48}H_{70}N_2O_6$: C, 74.77; H, 9.15. Found: C, 74.59; H, 8.98.

7,16-Bis(5-(4'-trifluoromethylphenoxy)-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (12). Compound **12** was prepared by the above procedure to give a yellow solid; mp 109-111 °C; yield 60%; ^{1}H NMR δ: 2.87 (t, J = 5.4 Hz, 8H), 3.64 (s, 8H), 3.69 (t, J = 5.4 Hz, 8H), 3.80 (s, 4H), 6.73 (s, 2H), 6.87 (m, 4H), 6.96 (d, J = 8.5 Hz, 4H), 7.53 (d, J = 8.5 Hz, 4H); ^{13}C NMR δ: 53.9, 58.6, 69.2, 71.0, 116.9, 117.6, 121.0, 124.0, 127.2 (q, J_{CF} = 3.5 Hz), 147.3, 155.3, 161.9; HRMS calcd for $C_{40}H_{44}F_6N_2O_8$ $(M+Na^+)$ 817.2900, found 817.2908. Anal. Calcd for $C_{40}H_{44}F_6N_2O_8$: C, 60.45; H, 5.58. Found: C, 60.63; H, 5.44.

7,16-Bis(5-benzyloxy-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (13). Compound **13** was prepared by the above procedure to give a white solid; mp 116-117 °C; yield 77%; ^{1}H NMR δ: 2.84 (t, J = 5.4 Hz, 8H), 3.60 (s, 8H), 3.65 (t, J = 5.4 Hz, 8H), 3.75 (s, 4H), 4.97 (s, 4H), 6.64 (d, J = 2.7 Hz, 2H), 6.76 (m, 4H), 7.37 (m, 10H); ^{13}C NMR δ: 53.9, 58.9, 69.3, 71.0, 114.8, 116.0, 116.8, 123.4, 127.7, 128.0, 128.7, 137.6, 151.8, 152.2; HRMS calcd for $C_{40}H_{50}N_2O_8$ $(M+Na)^+$ 709.3465, found 709.3475. Anal. Calcd for $C_{40}H_{50}N_2O_8$: C, 69.95; H, 7.34. Found: C, 69.97; H, 7.12.

7,16-Bis(5-(4'-cyanophenyl)-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane (14). Compound **14** was prepared by the above procedure to give a yellow solid; mp 175-177 °C; yield 84%; ^{1}H NMR δ: 2.90 (t, J = 4.8 Hz, 8H), 3.64 (s, 8H), 3.71 (t, J = 4.8 Hz, 8H), 3.90 (s, 4H), 6.92 (d, J = 8.5 Hz, 2H), 7.25 (s, 2H), 7.42 (dd, J = 1.6, 8.2 Hz, 2H), 7.65 (q, J = 8.3 Hz, 8H); ^{13}C NMR δ: 53.9, 58.8, 69.1, 71.0, 109.9, 117.3, 119.4, 123.3, 127.0, 127.6, 127.8, 130.0, 132.7, 145.6, 159.2; HRMS calcd for $C_{40}H_{44}N_2O_6$ $(M+Na)^+$ 699.3159, found 699.3163. Anal. Calcd for $C_{40}H_{44}N_2O_6$: C, 70.99; H, 6.55. Found: C, 70.77; H, 6.48.

7,16-Bis(5-(3',5'-dicyanophenyl)-2-hydroxybenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (15). Compound **15** was prepared by the above procedure to give a yellow solid; mp 191-193 °C; yield 68%; ^{1}H NMR δ: 2.90 (t, J = 5.4 Hz, 8H), 3.64 (s, 8H), 3.71 (t, J = 5.4 Hz, 8H), 3.91 (s, 4H), 6.95 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 2.2 Hz, 2H), 7.38 (dd, J = 2.2, 8.5 Hz, 2H), 7.80 (t, J = 1.5 Hz, 2H), 8.00 (d, J = 1.5 Hz, 4H); ^{13}C NMR δ: 54.0, 59.0, 69.1, 71.1, 114.6, 117.1, 117.8, 123.8, 127.5, 127.7, 132.5, 133.8, 144.0, 160.0; HRMS calcd for $C_{42}H_{42}N_2O_6$ $(M+Na)^+$ 749.3064, found 749.3072. Anal. Calcd for $C_{42}H_{42}N_2O_6$: C, 69.41; H, 5.82. Found: C, 69.17; H, 5.83.

7,16-Bis(2-hydroxy-5-tritylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (16). Compound **16** was prepared by the above procedure to give a white solid; mp 205-207 °C; yield 94%; ^{1}H NMR δ: 2.79 (t, J = 5.4

Hz, 8H), 3.57 (s, 8H), 3.62 (t, J = 5.4 Hz, 8H), 3.67 (s, 4H), 6.68 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 2.2 Hz, 2H), 6.95 (dd, J = 2.2, 8.5 Hz, 2H), 7.20 (m, 30H); ^{13}C NMR δ: 53.8, 59.1, 64.5, 69.2, 70.9, 115.4, 121.3, 126.0, 127.6, 131.3, 131.5, 131.7, 137.4, 147.4, 156.0; HRMS calcd for $C_{64}H_{66}N_2O_6$ $(M+Na)^+$ 981.4819, found 981.4827. Anal. Calcd for $C_{64}H_{66}N_2O_6$: C, 80.14; H, 6.94. Found: C, 79.94; H, 6.72.

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REFERENCES

1. Roks, M. F. M.; Nolte, R. J. M. *Macromolecules* **1992**, *25*, 5398.
2. (a) Voyer, N.; Robitaille, M. *J. Am. Chem. Soc.* **1995**, *117*, 6599. (b) Meillon, J.-C.; Voyer, N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 967.
3. (a) Carmichael, V. E.; Dutton, P. J.; Fyles, T. M.; James T. D.; Swan, J. A.; Zojaji, M. *J. Am. Chem. Soc.* **1989**, *111*, 767. (b) Fyles, T. M.; Loock, D.; Zhou, X. *J. Am. Chem. Soc.* **1998**, *120*, 2997.
4. Pregel, M. J.; Jullien, L.; Canceill, J.; Lacombe, L.; Lehn, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 417.
5. DeMendoza, J.; Cuevas, F.; Prados, P.; Meadows, E. S.; Gokel, G. W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1534.
6. (a) Nakano, A.; Xie, Q.; Mallen, J.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1990**, *112*, 1287. (b) Murillo, O.; Watanabe, S.; Nakano, N.; Gokel, G. W. *J. Am. Chem. Soc.* **1995**, *117*, 7665.
7. Tabushi, I.; Kuroda, Y.; Yakota, K. *Tetrahedron Lett.* **1982**, 4601.
8. (a) Kobuke, Y.; Ueda, K.; Sokabe, M. *J. Am. Chem. Soc.* **1992**, *114*, 7618. (b) Tanaka, Y.; Kobuke, Y.; Sokabe, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 693.
9. Gokel, G. W.; Murillo, O. *Acc. Chem. Res.* **1996**, 29, 425.
10. Okahara, M.; Kuo, P. L.; Yamamura, S.; Ikeda, I. *J. Chem. Soc., Chem. Commun.* **1980**, 586.
11. (a) Kuwamura, T.; Kawachi, T. *Yukagaku*, **1979**, *28*, 195; *Chem. Abstr.* **1979**, *90*, 206248d. (b) Kuwamura, T.; Yoshida, S. *Nippon Kagaku Kaishi* **1980**, 427; *Chem. Abstr.* **1980**, *93*, 28168e.
12. (a) Echegoyen, L. E.; Hernandez, J. C.; Kaifer, A.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc. Commun.* **1988**, 836. (b) Echegoyen, L. E.; Portugal, L.; Miller, S. R.; Hernandez, J. C.; Echegoyen, L.; Gokel, G. W. *Tetrahedron Lett.* **1988**, *29*, 4065. (c) Fasoli, H.; Echegoyen, L. E.; Hernandez, J. C.; Gokel, G. W.; Echegoyen, L. *J. Chem. Soc. Commun.* **1989**, 578. (d) Lauricella, T. L.; Lopez, M.; Miller, S. R.; Gokel, G. W.; Echegoyen, L. *J. Org. Chem.* **1991**, *56*, 1524. (e) Kishore, N. S.; Lu, T.; Knoll, L. J.; Katoh, A.; Rudnick, D. A.; Mehta, P.; Devades, B.; Atwood, J. L.; Adams, J. L.; Gokel, G. W.; Gordon, J. I. *J. Biol. Chem.* **1991**, *266*, 8835. (f) Muñoz, S.; Mallén, J. V.; Nakano, A.; Chen, Z.; Echegoyen, L.; Gay, I.; Gokel, G. W. *J. Chem. Soc. Commun.* **1992**, 520. (g) Lynn, B. C.; Mallén, J. V.; Muñoz, S.; Kim, M.; Gokel, G. W. *Supramolecular Chem.* **1993**, *1*, 195. (h) Muñoz, S.; Mallén, J. V.; Nakano, A.; Chen, Z.; Echegoyen, L.; Gay, I.; Gokel, G. W. *J. Am. Chem. Soc.* **1993**, *115*, 1705. (i) DeWall, S. L.; Wang, K.; Berger, D. R.; Watanabe, S.; Hernandez, J. C.; Gokel, G. W. *J. Org. Chem.* **1997**, *62*, 6784.
13. (a) Bordunov, A. V.; Bradshaw, J. S.; Pastushok, V. N.; Izatt, R. M. *SynLett.* **1996**, 933. (b) Chi, K.-W.; Wei, H-C.; Kottke, T.; Lagow, R. J. *J. Org. Chem.* **1996**, *61*, 5684.
14. Malik, A.; Reese, S. L.; Morgan, S.; Bradshaw, J. S.; Lee, M. L. *Chromatographia* **1997**, *46*, 79.
15. (a) Nikiforova, I. S.; Mel'kanovitskaya, S. G. *Zh. Organ. Khim.* **1966**, *2*, 1459; *Chem. Abstr.* **1967**, *66*, 46168b.