Facile Synthesis of Mono and Dibenzo *N*,*N*'-Disubstituted Diaza 18-Crown-6 Derivatives

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This study represents a facile synthesis of building blocks (**1-3**) of crown ethers and amine precoursers (**4a-d**). The study also involves synthesis of mono and dibenzo *N*,*N*'-disubstituted diaza 18-crown-6 derivatives with high yield without chromatographic purification and high vacuum distillation. The complex ability of host the ethers was evaluated in terms of structural modification.

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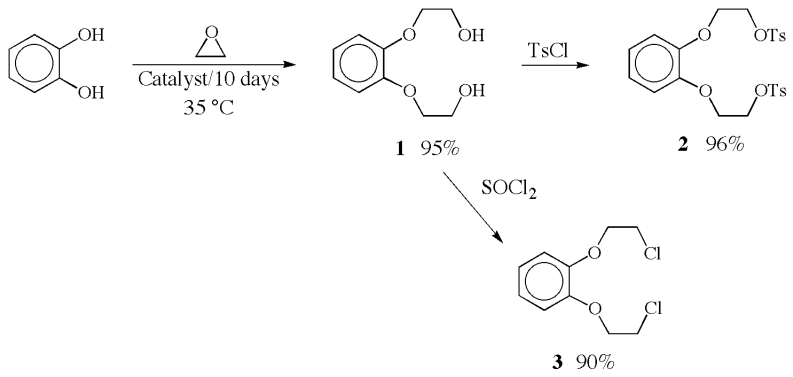
Introduction.

The remarkable ability of crown ethers, such as 18-crown-6, to form complexes with alkali metal cations and a wide range of other cations including primary alkylammonium cations, was discovered by Pedersen [1]. This observation has been studied by several groups [2], and crown ethers have been designed and synthesised that show high chiral selectivity in complexe formation [3] and also in the catalysis of chemical reactions [4].

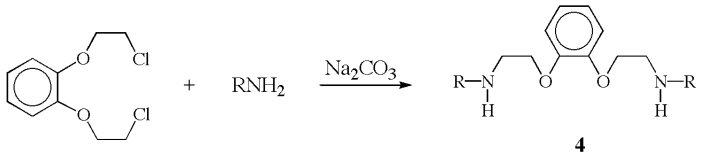
It has been shown [5,6] that benzo-derivatives of crown ethers have an ability to form complexes with primary alkylammonium salts that are similar to that of the parent crown ethers. The advanteges of benzo- substitution include potentially ease of synthesis, increased solubility of host compounds in organic solvents, and simpler nmr spectra of the host macrocycles and their complexes [7].

In general, complexes formed with saturated crown ethers are more soluble and stable in aliphatic solvent than are those formed with aromatic crown ethers. On the other hand, the presence, in the crown compounds, of aromatic nuclei carries with it certain advantages. For example, complex formation with aromatic crowns can be followed commercial using ultra-violet spectrophotometers [8].

Scheme 1



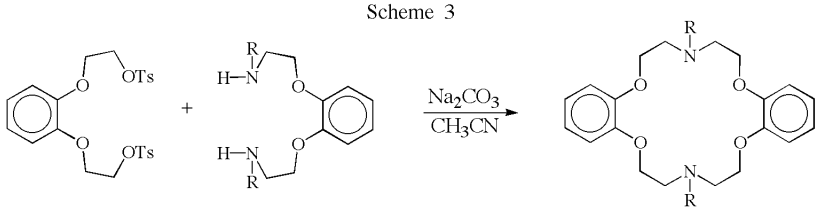
Scheme 2



4

a; R : Hexyl	72%
b; R : Octyl	56%
c; R : Benzyl	70%
d; R : Dodecyl	70%

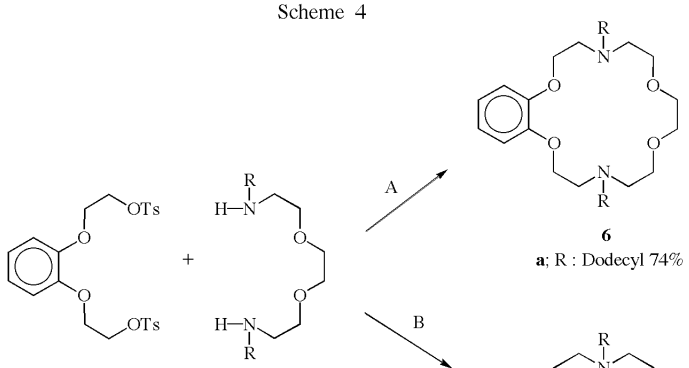
Scheme 3



5

a; R : Hexyl 75%
b; R : Octyl 73%
c; R : Benzyl 72%

Scheme 4



A = Na_2CO_3/CH_3CN
B = Tripropylamine/Xylene

6

a; R : Dodecyl 74%

6

b; R : Benzyl 76%

It is known that the most stable complex is formed with a cation which fits well into the molecule cavity of a given ligand, whereas a stable complex is not formed if the ion is too large or to small to lie in the cavity. Hence in order to investigate the effect of benzo substitution on complex formation of diaza crown ethers with alkali metal and primary alkyl-aryl ammonium cations five different crown ethers with various lipophilic character were synthesized.

Result and Discussion.

The versatile building blocks of crown ethers (**1-3**) and amine precursours (**4a-d**) were prepared as shown in scheme-1 and scheme-2 respectively. The advantage of our procedure, in synthesis of **1**, compared with those in litaratüre is summarized as follows; it is a single step reaction of catechol with ethelene oxide at mild temperature in high yield. Sutherland and co-workers synthesised **1** using more than one step with a low overall yield. Another method is recorded in a patent [8]. Synthesis of diamine (**4a-d**) was accomplished by the reaction of **3** with four different aryl and alkyl amine in the presence of sodium carbonate (Na_2CO_3) as base in a Dean-Stark apparatus to remove water formed at 100-110 °C in good yield.

Cyclization of **2** with **4a-c** in refluxing acetonitrile (CH_3CN) gave macrocycles **5a-c** in yields of 75%, 73% and 72% respectively. An interesting result was obtained in the synthesis of **5a-c**. Although sodium perchlorate ($NaClO_4$) was added to the reaction medium to promote cyclization, the product analysis revealed that macrocycles existed as free ligand, no complexation was observed. Cyclization of **2** with an appropriate diamine in refluxing xylene or CH_3CN gave macrocycles **6a-b** in yields of 74% and 76% respectively.

Macrocycles **6a-b** were isolated as $NaClO_4$ and barium perchlorate ($Ba(ClO_4)_2$) complexes respectively. This result showed that benzo substitution on diaza crown ethers enhances selectivity. On the other hand dibenzo substitution, due to steric hindrence of the benzene units on the ring, diminished the selectivity of crown ethers on alkali metals.

EXPERIMENTAL

General Information.

The ^{1}H nmr spectra were obtained at 400 MHz on a BRUKER DPX-400 High Perpormance Digital FT-NMR in deuterio-chloroform ($CDCl_3$) with TMS as the internal standard. The ^{13}C nmr spectra were obtained at 100 MHz on a BRUKER DPX-400 High Perpormance Digital FT-NMR. The elemental analyses were obtained with CARLO-ERBA 1108 Model. Infrared Spectra were obtained on a MIDAC-FTIR Model 1700 Spectrophotometer. Melting points were obtained on a GALLENKAMP Model apparatus with open capillaries. All chemicals were reagent grade unless otherwise stated.

1,2-Bis-(2-hydroxy ethoxy)benzene (**1**).

Catechol (11.0 g, 100 mmol) and diethylamine hydrochloride (as catalyst) were cooled to -80 °C in a sealed container. Ethylene Oxide (9.8 ml, 200 mmol) was added to the mixture at the same temperature, and the mixture was kept at 30-35 °C for 10 days. The product distilled under reduced pressure for further purification to give 18.81 g (95 %) of **1**, mp 81-83 °C. (Lit. [7]: mp 93-94 °C) ir: ν 3495, 3396, 3314, 3082, 3068, 2957, 2939, 2926, 1594, 1510, 1454, 1426, 1320, 1248, 1213, 1112, 1089, 1070, 1042 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.63 (bs, 2H); 3.93 (t, *J* 4.27 Hz, 4H); 4.12 (t, *J* 4.32 Hz, 4H); 6.95 (s , 4H); ^{13}C nmr ($CDCl_3$): δ 61.4, 71.8, 115.3, 122.4, 149.3.

Anal. Calcd. for: $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.42; H,7.43.

1,2-Bis-(2-*p*-tolylsulphonylethoxy)benzene (**2**).

1,2 Bis-(2-hydroxyethoxy)benzene (26.73 g, 135 mmol) was dissolved in pyridine (110 ml) at -10 °C. *p*-Toluene sulphonyl chloride (51.43, 270 mmol) was added to the mixture over three hours and then stirred at -10 °C for four hours. The mixture was kept overnight at 4 °C. The product crystallised from methanol to give 65.48 g (96%) of **2**, mp. 95-95.5 °C. (Lit. [7]: mp 95.5-97 °C, Lit.[8]: mp 95-96 °C) ir: ν 3093, 3070, 3046, 2938, 2877, 1601, 1501, 1454, 1355, 1253, 1224, 1170, 1123, 1100, 1062, 1015, 921, 811, 773 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.46 (s, 6H); 4.18 (t, *J* 4.83 Hz, 4H); 4.34 (t, *J* 4.85 Hz, 4H); 6.82-6.94 (dq, 4H); 7.34-7.83 (dd , 8H); ^{13}C nmr ($CDCl_3$): δ 22.0, 67.8, 68.8, 116.8, 123.1, 128.3, 130.3, 133.3, 145.4, 148.9.

Anal. Calcd. for: $C_{24}H_{26}O_8S_2$: C, 56.9; H, 5.2; S, 12.65. Found: C, 57.2; H, 5.3; S, 12.60**.**

1,2-Bis-(2-chloroethoxy)benzene (**3**).

A solution of 1,2-bis-(2-hydroxyethoxy)benzene (16.43 g, 83 mmol) and pyridine (13.38 g , 170 mmol) in absolute benzene (200 ml) was stirred at 80 °C. Thionyl chloride ($SOCl_2$) (20.15 g, 170 mmol) was added to the solution dropwise in three hours and then left for 18 hours. The mixture was cooled to the room temperature and 10 ml concentrated hydrochloric acid (HCl) and 10 ml water was added. The resulting organic phase was washed twice with water. The benzene extract was dried with potassium carbonate (K_2CO_3) and evaporated. The product crystallised from methanol to give 17.55 g (90%) of **3**, mp 55-56 °C; ir: ν 3072, 3018, 2963, 2917, 2869, 1593, 1456, 1422,1257, 1196, 1126, 769, 746, 666 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.76 (t, *J* 5.86 Hz, 4H); 4.21(t, *J* 5.86 Hz, 4H); 6.91 (s, 4H); ^{13}C nmr ($CDCl_3$): δ 42.7, 70.4, 116.9, 123.1, 149.2.

Anal. Calcd. for: $C_{10}H_{12}Cl_2O_2$ C, 51.08; H, 5.14. Found: C, 51.64; H, 5.06.

1,2-Bis-[2-(*N*-Hexylamino)ethoxy]benzene (**4a**).

1,2-Bis-(2-chloroethoxy)benzene (8.62 g, 36.68 mmol), sodium carbonate (Na_2CO_3) (15.55 g, 146.7 mmol) and hexylamine (29.69 g, 293.44 mmol) was stirred at 100-110 °C under dry nitrogen with a Dean-Stark apparatus to remove water from the reaction medium. The benzene extract was dried (Na_2CO_3) and evaporated. The product distilled to give 9.64 g (72.2 %) bp 181-182 °C at 0.1 mm-Hg; ir: ν 3335, 3274, 3063, 3036, 2927, 2894, 1593, 1502, 1454, 1377, 1328, 1255, 1120, 1112, 1042, 933, 741 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.89 (t, *J* 6.87 Hz, 6H); 1.28-1.38 (m, 12H); 1.52 (p, *J* 7.21 Hz, 4H); 1.8 (bs, 2H); 2.67 (t, *J* 7.29 Hz, 4H); 3.01 (t, *J* 5.31 Hz, 4H); 4.11 (t, *J* 5.32 Hz, 4H); 6.90-6.94 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 14.2, 22.9, 27.3, 30.5, 32.1, 49.2, 50.2, 69.3, 115.1, 121.8, 149.5.

Anal. Calcd. for: $C_{22}H_{40}N_2O_2$•2HCl: C, 60.39; H, 9.68; N, 6.40. Found:C, 60.6; H, 9.57; N, 6.47.

1,2-Bis-[2-(*N*-Octylamino)ethoxy]benzene (**4b**).

This compound was prepared using a method similar to that used for the 1,2-bis-[2-(*N*-hexylamino)ethoxy]benzene (**4a**), from 1,2-bis-(2-chloroethoxy)benzene (7.62 g, 32.42 mmol), Na_2CO_3 (13.74 g, 129.7 mmol) and octylamine (33.52 g, 259.7 mmol). The product yield was 56%, (7.64 g) bp 190-192 °C at 0.1 mmHg; ir: ν 3316, 3064, 3033, 2921, 2848, 1587, 1501, 1447, 1250, 1124, 1040, 737cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.89 (t, *J* 6.86 Hz, 6H); 1.29-1.32(m, 20H); 1.52 (p, *J* 7.15 Hz, 4H); 1.8 (bs, 2H); 2.68 (t, *J* 7.3 Hz, 4H); 3.02 (t, *J* 5.31 Hz, 4H); 4.12 (t, *J* 5.31 Hz, 4H); 6.91-6.95 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 14.4, 23.0, 27.8, 29.6, 29.9, 32.2, 49.4, 50.3, 69.4, 115.2, 122.0, 149.5.

Anal. Calcd. for: $C_{26}H_{48}N_2O_2$•2HCl: C, 63.26; H, 10.21; N, 5.67. Found: C, 63.58; H, 10.69; N, 5.63.

1,2-Bis-[2-(*N*-Benzylamino)ethoxy]benzene (**4c**).

This compound was prepared using a method similar to that used for 1,2-bis-[2-(*N*-Hexylamino)ethoxy]benzene (**4a**), from 1,2-bis-(2-chloroethoxy)benzene (8.62 g, 36.68 mmol), Na_2CO_3 (15.55 g, 146.7 mmol) and benzylamine (31.44 g, 292.2 mmol). The product yield was 70% (9.65 g), bp 200-202 °C at 0.1 mmHg; ir: ν 3318, 3067, 3029, 2928, 2874, 2836, 1643, 1589, 1496, 1458, 1249, 1218, 1118, 1041, 910, 740, 694 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.10 (bs, 2H); 3.03 (t, *J* 5.25 Hz, 4H); 3.86 (s , 4H); 4.15 (t, *J* 5.23 Hz, 4H); 6.95 (s, 4H); 7.32-7.38 (m, 10 H); ^{13}C nmr ($CDCl_3$): δ 48.7, 54.1, 69.7, 115.4, 122.2, 127.4, 128.6, 128.9, 140.9, 149.7.

Anal. Calcd. for: $C_{24}H_{28}N_2O_2$·2HCl: C, 64.14; H, 6.73; N, 6.23. Found: C, 64.06; H, 6.74; N, 6.160.

1,2-Bis-[2-(*N*-dodecylamino)ethoxy]benzene (**4d**).

This compound was prepared using a method similar to that used for the 1,2-bis-[2-(*N*-hexylamino)ethoxy]benzene (**4a**), from 1,2-bis-(2-chloroethoxy)benzene (8.62 g, 36.68 mmol), Na_2CO_3 (15.55 g, 146.7 mmol) and dodecylamine (54.28 g, 293.44 mmol). The product was 10.7 g (70%), bp 220-222 °C at 0.1 mmHg; ir: ν 3326, 3076, 3057, 2960, 2913, 2852, 1582, 1496, 1473, 1442, 1270, 1255, 1208, 1115, 1038, 835, 733 cm^{-1}; ^{1}H ($CDCl_3$): δ 0.90 (t, *J* 6.69 Hz, 6H); 1.28-1.33 (m, 40H); 1.58 (bs, 2H); 2.71 (t, *J* 7.33 Hz, 4H); 2.90 (t, *J* 5.02 Hz, 4H); 4.09 (t, *J* 5.02 Hz, 4H); 6.78-7.00 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 14.5, 23.1, 27.6, 29.7, 29.9, 29.9, 29.9(5), 29.9(9), 30.0, 30.0, 32.3, 48.7, 49.8, 72.1, 117.7, 119.9, 150.7.

Anal. Calcd. for: $C_{34}H_{64}N_2O_2$•2HCl: C, 67.40; H, 10.98; N, 4.62. Found: C, 67.81; H, 11.23; N, 4.23.

N,N'-Dihexyl-7,16-diaza-1,4,10,13-tetraoxa-2,3,11,12-dibenzocyclooctadeca-2,11-diene (**5a**).

To the mixture of Na_2CO_3 (20 g, 188.6 mmol) and sodium perchlorate monohydrate ($NaClO_4$•H_2O) (6.74 g, 48.0 mmol) in tetrahydrofuran-acetonitrile (THF-CH_3CN) (800 ml) 1,2-bis-(2-*p*-tolylsulphonylethoxy)benzene (8.67 g, 17.14 mmol) and 1,2-bis-[2-(*N*-hexylamino)ethoxy]benzene (6.24 g, 17.14 mmol) was added simultaneously. The mixture was stirred at 80 °C for 36 hours. The THF-CH_3CN extract was evaporated to give a white solid. The product crystallised from ether-ethyl acetate to give 8.33 g (75%) mp 130-131 °C; ir: ν 3063, 2954, 2925, 2854, 2799, 1594, 1112, 1049, 1022 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 6.86-6.90 (m, 8H); 4.09 (t, *J* 6.23 Hz, 8H); 3.29 (t, *J* 6.23 Hz, 8H); 2.63 (t, *J* 7Hz, 4H); 0.49-1.50 (m, 4H); 1.33-1.35 (m, 12H) 0.92 (t, *J* 6.64 Hz,6H); ^{13}C nmr ($CDCl_3$): δ 6.28, 24.88, 29.31, 30.31, 34.06, 56.03, 56.59, 69.24, 114.31, 122.80, 150.91.

Anal. Calcd. for: $C_{32}H_{50}N_2O_4$: C,72.96; H, 9.57; N, 5.32. Found: C, 72.71; H, 9.76; N, 5.10.

N,N'-Dioctyl-7,16-diaza-1,4,10,13-tetraoxa-2,3,11,12-dibenzocyclooctadeca-2,11-diene (**5b**).

This compound was prepared using a method similar to that used for *N,N'*-dihexyl-7,16-diaza-1,4,10,13-tetraoxa-2,3,11,12-dibenzocyclooctadeca-2,11-diene (**6a**), from 1,2-bis-(2-*p*-tolylsulphonylethoxy)benzene (6.02 g, 12 mmol),1,2-bis-[2-(*N*-Octylamino)ethoxy]benzene (5 g, 12 mmol), Na_2CO_3 (5 g, 47 mmol) and $NaClO_4.H_2O$ (1.67 g, 12 mmol). The product was crystallised from CH_3CN to give 5.1 g (73%) mp 135.5-137 °C; ir: ν 3063, 2919, 2848, 1595, 1505, 1469, 1454, 1337, 1256, 1229, 1122, 1046, 1022, 775, 735 cm^{-1} ;^{1}H nmr ($CDCl_3$): δ 0.91 (t, *J* 6.76 Hz, 6H); 6.84-6.90 (m, 8H); 4.09 (t, *J* 6.21 Hz, 8H); 3.29 (t, *J* 6.21 Hz, 8H); 2.63 (t, *J* 7.49 Hz, 4H); 1.51 (bs, 4H); 1.32 (s, 20H); ^{13}C nmr ($CDCl_3$): δ 14.5, 23.1, 27.8, 28.5, 29.7, 30.0, 32.3, 54.2, 54.7, 67.4, 112.4, 121.0, 149.1.

Anal. Calcd. for: $C_{36}H_{58}N_2O_4$: C, 74.22; H, 9.96; N, 4.81. Found: C, 74.30; H, 10.44; N, 4.55.

N,N'-Dibenzyl-7,16-diaza-1,4,10,13-tetraoxa-2,3,11,12-dibenzocyclooctadeca-2,11-diene (**5c**).

This compound was prepared using a method similar to that used for *N,N'*-dihexyl-7,16-diaza-1,4,10,13-tetraoxa-2,3,11,12-dibenzocyclooctadeca-2,11-diene (**6a**), from 1,2-bis-(2-*p*-tolylsulphonylethoxy)benzene (7.63 g,15 mmol) 1,2-bis-[2-(*N*-benzylamino)ethoxy]benzene (5.67 g, 15 mmol), Na_2CO_3 (6.4 g, 60 mmol) and $NaClO_4$•H_2O (2.12 g, 15 mmol). The product was crystallised from CH_3CN to give 6.28 g (72%) mp 178-180 °C (Lit. [8]: m 176 °C); ir: ν 3061, 3027, 2976, 2909, 2860, 1595, 1513, 1467, 1447, 1377, 1334, 1255, 1229, 1120, 1039, 1022, 777, cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.34 (t, *J* 6.1 Hz, 8H); 4.12 (t, *J* 6.1 Hz, 8H), Ph CH2-3.85 (s, 8H); 6.81-7.43 (m, 18H); ^{13}C nmr ($CDCl_3$): δ 55.8, 60.9, 69.3, 114.3, 122.8, 129.3, 131.0, 142.0, 150.9.

Anal. Calcd. for: $C_{34}H_{38}N_2O_4$: C, 75.80; H, 7.06; N, 5.20. Found: C, 75.56; H, 7.42; N, 5.46.

N,N'-Didodecyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-benzocyclooctadec-2-ene (**6a**).

To the mixture of Na_2CO_3 (20 g, 188.6 mmol) and $NaClO_4.H_2O$ (6.74 g, 48.0 mmol) in THF-CH_3CN (800 ml) 1,2-bis-(2-*p*-tolylsulphonylethoxy)benzene (24.27 g, 48.0 mmol) and 1,10-didodecyl-4,7-dioxa-1,10-diazadecane (23.23 g, 48.0 mmol) was added simultaneously. The mixture was stirred at 80 °C for 36 hours. The THF-CH_3CN extract was dried and evaporated and the residue crystallised from ethyl acetate to give the $NaClO_4$•H_2O complex of *N,N'*-didodecyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-benzocyclooctadec-2-ene mp 71-72 °C. The free ligand was recovered by passing the complex through a column on basic alumina (Al_2O_3) to give 22.94 g (74%), mp 43-45 °C; ir: ν 3311, 3186, 3114, 2955, 2918, 2851, 2804, 1586, 1505,1472, 1253, 1121, 1087, 758, 716, 625 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 0.86 (t, *J* 6.71 Hz, 6H); 6.89-7.02 (m, 8H); 3.65 (s, 4H); 4.16 (t, *J* 4.69Hz, 4H); 2.87 (t, *J* 4.59 Hz, 4H); 2.72 (t, *J* 4.53 Hz, 4H); 2.56 (t, *J* 8.01 Hz, 4H); 4.16 (t, *J* 4.69 Hz, 4H); 3.60 (t, *J* 4.66 Hz, 4H); 1.10-1.45 (m, 42H); ^{13}C nmr ($CDCl_3$): δ 14.0, 22.7, 24.8, 27.5, 29.3, 29.6, 29.7, 31.9, 52.3, 52.4, 53.8, 64.8, 66.3, 68.8, 113.6, 122.0, 147.0.

Anal. Calcd. for: $C_{40}H_{74}N_2O_4$•$NaClO_4$•H_2O: C, 62.40; H, 9.69; N, 3.64. Found: C, 62.70; H,10.70; N, 3.56.

Anal. Calcd. for: $C_{40}H_{74}N_2O_4$; C, 74.25; H, 12.64; N, 4.33. Found: C, 74.57; H,12.76; N, 4.28.

N,N'-Dibenzyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-benzocyclooctadec-2-ene (**6b**).

To a mixture of *n*-tripropylamine (8.1 g , 56.5 mmol) in xylene (200 ml) 1,2-bis-(2-*p*-tolylsulphonylethoxy)benzene (5.7 g, 11.3 mmol) and 1,10-dibenzyl-4,7-dioxa-1,10-diazadecan (3.7 g, 11.3 mmol) was added simultaneously. The mixture was stirred at 110 °C for 16 hours. The mixture was then cooled to the room temperature, was washed with hot methanol to remove unreacted amine and tosylate. The xylene was then evaporated and the product was dissolved in ethanol and equimolar $Ba(ClO_4)_2$ in ethanol was added to the solution. After crystallisation, the product was filtered and washed twice with methanol to give 7.1 g (76%) of the $Ba(ClO_4)_2$ complex of *N,N'*-dibenzyl-7,16-diaza-1,4,10,13-tetraoxa-2,3-benzocyclooctadec-2-ene mp 300 °C dec; ir: ν 3438, 3085, 3061, 3029, 2952, 2887, 2860, 1594, 1505,1458, 11364, 1245, 1193, 1121, 1049, 731, 634 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.79 (t, *J* 5.80 Hz, 2H); 2.96 (t, *J* 5.80 Hz, 2H); 3.54 (t, *J* 5.80 Hz, 2H); 4.02 (t, *J* 5.81 Hz, 2H); 3.69 (s, 4H); 3.46 (s, 4H); 6.81-7.34 (m, 14 H); ^{13}C nmr (DMSO-d_6): δ 53.4, 54.2, 59.4, 68.2, 70.1, 70.8, 114.4, 121.7, 127.6, 128.9, 129.4, 140.4, 149.3.

Anal. Calcd. for:$C_{30}H_{38}N_2O_4$•$Ba(ClO_4)_2$: C, 43.58; H, 4.60; N, 3.39. Found: C, 43.27; H,4.82; N, 3.64.

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