SOME ALKYLATION AND REDUCTIVE AMINATION STUDIES OF β-KETOMACROLIDES AS POTENTIAL METAL SPECIATION MATERIALS

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Dedicated with respect to Professor E.C.Taylor on the occasion of his 70th birthday.

Abstract– The β-ketomacrolide **(1)** was reduced and alkylated with 2-methoxy-ethoxymethyl chloride to obtain **3**. Mono and bis adducts of **1** were obtained by alkylation and reductive amination These compounds were synthesised for the metal ion binding studies. Compound **(12)** binds to potassium and cesium ions.

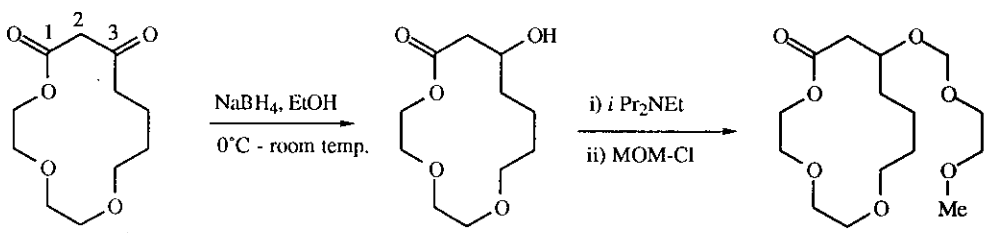
Over many years there has been an increasing effort towards the production of novel materials capable of binding metal ions or recognising other molecules through secondary interactions.[1] Also there has been increasing interest in macrocyclic substitution reactions, especially those which could lead to stereo control.[2-4]

Following our studies on the use of S-*t*-butyl 3-oxobutanethioate, which can afford efficiently β-ketomacrolides and diolides,[5] we have initiated a brief investigation of various alkylation and reductive amination sequences of the β-ketomacrolide **(1)** in the hope of generating useful structures with metal ion speciation properties.

Compound **(1)** which is readily available in quantity[5] by the alkylation of dianion derived from S-*t*-butyl 3-oxobutanethioate, has three potentially active carbon sites, *viz.* the ester carbonyl carbon (C1), the methylene carbon (C2) and the carbonyl carbon (C3). We have restricted ourselves to reactions at C2 and C3.

As **1** contains insufficient oxygen atoms in a suitable array for metal complexation, we first selected the selective reduction of the C3 carbonyl group and the subsequent alkylation with an electron rich side chain.

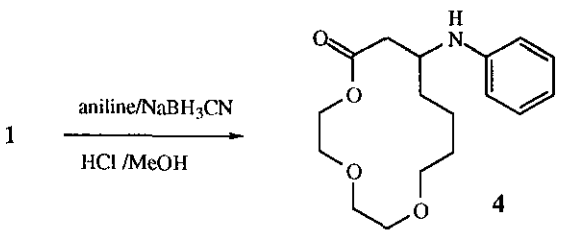
Reduction of **1** with sodium borohydride in ethanol readily affords the alcohol **(2)**. This was then treated with 2-methoxyethoxymethyl chloride to give 79% yield of the desired alkylated product **(3) (Scheme 1)**.



Scheme 1

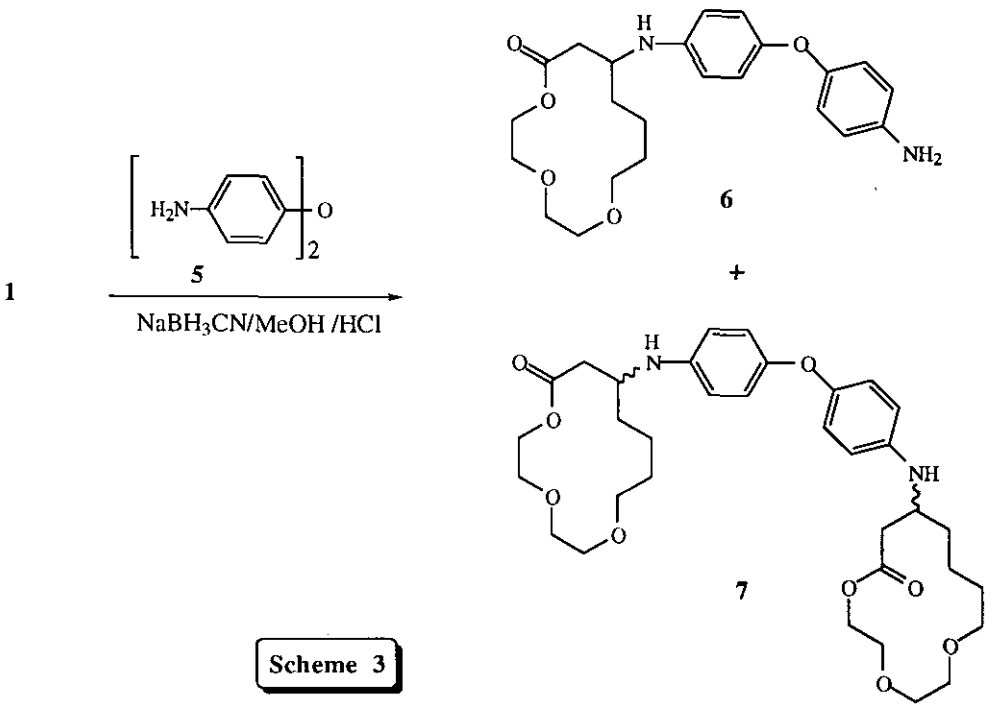
In the event, however, the appending polyether chain failed to produce a strong metal ion chelation in compound **(3)** as determined by the Cram picrate extraction procedure.[6] The lack of crystallinity of compound **(3)** also meant that we could not perform any solid state conformational studies to determine side chain orientation by X-ray methods.

In the next experiments we investigated reductive amination of β-ketomacrolide **(1)** using amines including bis-amines in the anticipation of being able to produce bis adducts. Thus **1** was reacted with a readily available and simple aromatic amine in methanol followed by the reductive treatement with sodium cyanoborohydride to obtain **4** in 67% yield **(Scheme 2)**. However this compound not too surprisingly failed to bind any of the alkali metal ions.



Scheme 2

We therefore decided to react **1** with bis amines. When **1** was reacted with 4-aminophenyl ether **(5)** in methanol followed by reductive treatment with sodium cyanoborohydride in a normal way, we obtained the mono and the bis adducts **(6)** and **(7)** in 25% and 12% yields respectively **(Scheme 3)**.

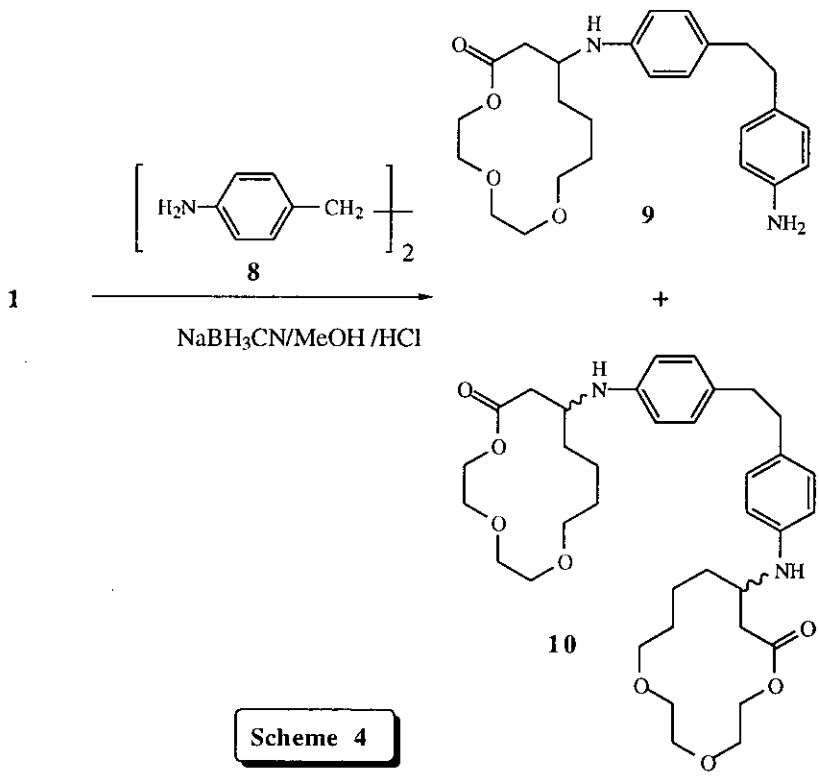


Scheme 3

No attempt was made to separate the *meso* and *dl* mixture produced in compound (**7**) as these again failed to yield good binding data.

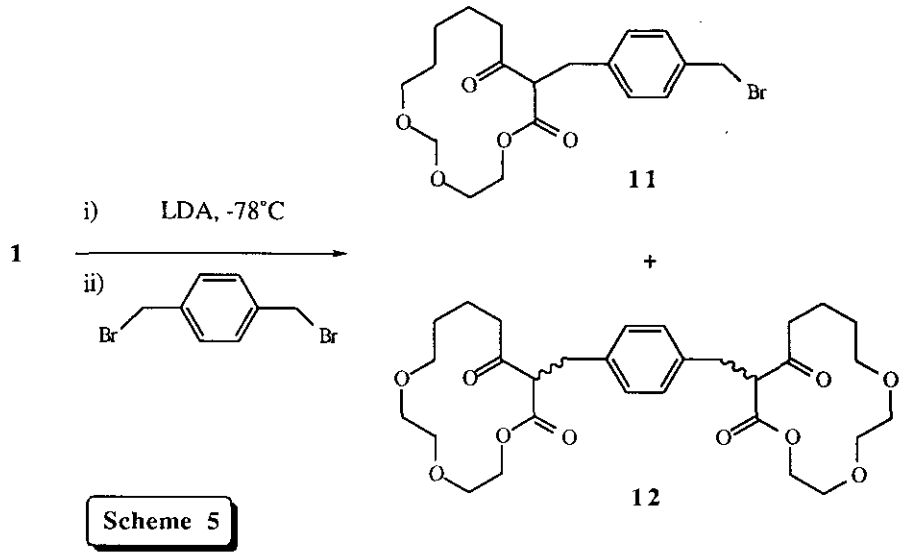
We therefore decided to link the β-ketomacrolide (**1**) *via* a more flexible spacer diamine grouping. Compound (**1**) was reductively aminated with the methylene bridged diamine 4,4'-ethylenedianiline (**8**) as above, to obtain the mono and bis adducts (**9**) and (**10**) in 23% and 17% yields respectively (**Scheme 4**).

As the mono and bis adducts of **1** obtained by the reductive amination using the bis amines, the anilino derivative (**4**) and the 2-methoxyethoxymethyl derivative (**3**) failed to produce good binding data, we then studied the compounds obtained by the alkylation at C2 position in the hope that suitable metal ion speciation compounds would be produced. Alkylation of the anion derived from **1** by treatment with lithium diisopropylamide at -78°C gave two compounds which could be readily characterised as the mono and bis adducts (**11**) and (**12**) in 11% and 16% yield respectively (**Scheme 5**).



Scheme 4

Pleasingly the bis adduct (**12**) was proved to be reasonably effective as a metal ion complexing agent, especially to potassium ions (K_a for $K^+ = 3.84 \times 10^4$). It also binds to Cs^+ ions (K_a for $Cs^+ = 5.7 \times 10^3$). This compound therefore shows acceptable selectivity for potassium ions over cesium ions. Further studies of this compound and other binding data will be reported later.



Scheme 5

The above reactions constitute some of the first examples of chemistry at the C2 and C3 sites in β-keto-macrolides. The dimerisation of β-ketomacrolides through alkylation can produce promising metal ion binding compounds which in turn could be suitable for further studies.

EXPERIMENTAL

^{1}H Nmr spectra were recorded in $CDCl_3$ using Bruker WM250 or AM500 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 983G spectrophotometer. Mass spectra were obtained using VG-7070B, VG 12-253 and VG ZAB-E instruments. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated. All the solvents used were freshly distilled following standard drying procedures. Analytical thin layer chromatography was performed using pre-coated glass backed plates (Merck Kieselgel 60 F254) and visualised by ultra-violet, acidic ammonium molybdate (IV) or iodine as appropriate. All the compounds were racemic mixtures unless otherwise stated.

8,11-Dioxa-3-hydroxytetradecan-14-olide (2).

Sodium borohydride (18.9 mg, 0.5 mmol) was added to a cooled (0°C) magnetically stirred solution of 8,11-dioxa-3-oxo-tetradecan-14-olide (**1**) (115.1 mg, 0.5 mmol), in ethanol (2 ml). The solution was stirred for 30 min at 0°C, then allowed to come to room temperature and stirred for 4 h when tlc showed that no starting material remained. The solvent was removed under reduced pressure. To the residue was added ethyl acetate (5 ml) and the solution was washed with water (2 ml) and brine (2 ml). The organic extract was dried over anhydrous sodium sulphate and solvent was removed under reduced pressure to obtain colourless thick gum. Silica gel column chromatography (5-20% ethyl acetate-ether, gradient elution) of the oil afforded **2** as colourless crystals which were crystallised from ethyl acetate-petroleum ether (40-60) ; yield: 70 mg (64%); mp 78°C; ir (film): ν max = 3395, 2975, 1646, 1598, 1298, 1087, 1047, 875 cm^{-1}; ^{1}H nmr (500 MHz, $CDCl_3$): δ= 1.50-1.80 (m, 6H), 2.60 (d, J 5.0 Hz, 2H), 3.45-3.70 (m, 9H), 3.90-3.95 (m, 1H), 4.22-4.25 (m, 2H); ms: m/z (%)

= 232 (M^+)(7.6), 214(20.4), 171(13.5), 142(14.9), 127(25.4), 115(52.6), 108(25.3), 98(31.1), 89(30.2), 85(100), 81(24.1), 71(28.5), 57(30.6), 45(92); hrms: m/z Calcd for $C_{11}H_{20}O_5$: 232.131. Found 232.130; Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.89; H, 8.62. Found C, 56.85; H, 8.86.

3-(2-Methoxyethoxymethyl)-8,11-dioxatetradecan-14-olide (3).

2-Methoxyethoxymethyl chloride (28.5 µl, 0.25 mmol) was added to a cooled (0°C) magnetically stirred solution of **2** (58.6 mg, 0.25 mmol) and di-*iso*propylethylamine (48 µl, 0.27 mmol) in dichloromethane (2 ml). Stirring was continued for 30 min and the solution was then allowed to come to room temperature. Tlc showed no starting material after 3 h. The solvent was then removed to obtain faint yellow coloured oil. To the oil was added dichloromethane (5 ml). The solution was then washed with water (2x3 ml) and brine (3 ml). The organic phase was dried over anhydrous sodium sulphate and solvent was then removed under reduced pressure to obtain faint yellow coloured liquid. Silica gel column chromatography (3-6% ethyl acetate-ether, gradient elution) of the faint yellow liquid afforded **3** as colourless liquid; yield: 61 mg (79%); ir (film): ν max = 2960, 2930, 1740, 1110, 1048 cm^{-1}; ^1H nmr (500 MHz, $CDCl_3$): δ = 1.50-1.85 (m, 6H), 2.50 (q, J 15.0 Hz, 1H), 2.80 (q, J 7.5 Hz, 1H), 3.38 (s, 3H), 3.45-3.75 (m, 12H), 4.00 (m, 1H), 4.25-4.28 (m, 2H), 4.77 (q, J 10.0 Hz, 2H); ms: m/z (%) = 245(3.8), 231(6.3), 215(6.3), 125(4,3), 119(6.9), 105(10.1), 89(100), 59(98.5); Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.25; H, 9.00. Found: C, 56.25; H, 8.75.

3-Anilino-8,11-dioxatetradecan-14-olide (4).

Sodium cyanoborohydride (12.56 mg, 0.2 mmol) was added to a magnetically stirred solution of **1** (57.5 mg, 0.25 mmol) and aniline (23.2 mg, 0.25 mmol) in methanol (2 ml). *p*-Nitrophenol (1 mg) was added as an indicator and hydrochloric acid in methanol (1N, 2-3 drops) was added to maintain pH 5. Tlc showed no starting material after 24 h. The solvent was then removed under reduced pressure. To the oil was added ethyl acetate (5 ml). The solution was then washed with water (2x2 ml) and brine (2 ml). The organic layer was dried over anhydrous sodium sulphate and the solvent was then evaporated to obtain faint yellow liquid. It was then applied to 20x20 cm silica gel plates (x2, 60 F 254 precoated, Merck). The plates were run twice in 5% ethyl acetate-petroleum ether(40-60). The appropriate bands were cut, the silica gel was washed with ethyl acetate (5x5 ml) and the solvent was then removed under reduced pressure to obtain **4** as faint yellow crystals, which were recrystallised from petroleum ether(40-60)-ethyl acetate, yield: 41 mg, (67%), mp 77°C; ir (film): ν max = 3379, 2858, 1723, 1600, 1509, 1355, 1284, 1133, 750, 693 cm^{-1}; ^1H nmr: (500 MHz, $CDCl_3$) δ = 1.50-1.90 (m, 6H), 2.43 (dd, J 12.0, 7.5 Hz, 1H), 2.74 (dd, J 6.0, 2.5 Hz, 1H), 3.45-3.70 (m, 8H), 3.78 (s, 1H), 4.00 (s, 1H), 4.29-4.40 (m, 2H), 6.59-6.70 (m, 3H), 7.10-7.20 (m, 2H); ms: m/z (%) = 307 (M^+)(100), 207(10.6), 191(11.2), 177(22.0), 160(50.1), 146(34.8), 132(66.3), 119(76.7), 104(29.6), 93(65.3); Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.19; N, 4.55. Found: C, 66.22; H, 8.33; N, 4.48.

***N*-3-(8,11-Dioxatetradecan-14-olidyl)-4-aminophenyl ether (6) and *N*,*N*'-bis-3,3-(8,11-dioxatetradecan-14-olidyl)-4-aminophenyl ether (7).**

Sodium cyanoborohydride (25.1 mg, 0.4 mmol) was added to a magnetically stirred solution of **1** (115.0 mg, 0.5 mmol) and 4-aminophenyl ether (**5**) (50.1 mg, 0.25 mmol) in methanol (4 ml). *p*-Nitrophenol (1 mg) was added as an indicator and hydrochloric acid in methanol (1N, 2-3 drops) was added to maintain pH 5. Tlc showed no starting material after 24 h. The solvent was then removed under reduced pressure. To the oil was added ethyl acetate (5 ml) and the solution was then washed with water (2x2 ml) and brine (2 ml) The organic layer was dried over anhydrous sodium sulphate and the solvent was then evaporated to obtain faint yellow liquid. It was then applied to 20x20 cm silica gel plates (x2, 60 F 254 precoated, Merck). The plates were run twice in 5% ethyl acetate-petroleum ether(40-60). Appropriate bands were cut, silica gel was washed with ethyl acetate (5x5 ml) and the solvent was then removed under reduced pressure to obtain mono and bis adducts (**6**) and (**7**) as faint yellow coloured viscous liquids, yields: 51 mg (25%) and 39 mg (12%) respectively.

Monoadduct of 4-aminophenyl ether (6):

Ir: (film) ν max = 3355, 2922, 2881, 1723, 1645, 1490, 1380, 1284, 1250, 1166, 1086, 918, 875, 829, 750cm^{-1}; ^{1}H nmr: (500 MHz, $CDCl_3$) δ = 1.50-1.90 (m, 6H); 2.45 (dd, J 7.5, 5.0 Hz, 1H); 2.75 (dd, J 7.0, 2.5 Hz, 1H); 3.45-3.78 (m, 12H); 4.35 (m, 2H); 6.75 (d, J 7.5 Hz, 4H); 6.81 (d, J 7.5 Hz, 4H); ms: m/z (%) = 414(M^+)(32.2), 322(19.6), 293(10.2), 226(26.1), 211(25.3), 167(27.3), 150(10.2), 149(91.2), 127(11.2), 113(11.2), 108(12.6), 97(18.0), 85(34.1), 71(57.5), 57(100), 43(61.5); hrms: Calcd for $C_{23}H_{30}N_2O_9$: 414.2154. Found 414.2159.

Bisadduct of 4-aminophenyl ether (7):

Ir (film) ν max = 3467, 2910, 2809, 1729, 1644, 1608, 1496, 1440, 1381, 1282, 1192, 1167, 1134, 1086, 918, 876, 850, 761 cm^{-1}; ^{1}H nmr: (500 MHz, $CDCl_3$) δ = 1.50-1.59 (m, 12H), 2.45 (dd, J 7.5, 5.0 Hz, 2H), 2.75 (dd, J 7.0, 2.5 Hz, 2H), 3.45-3.74 (m, 24H), 4.35 (m, 4H), 6.76 (d, J 7.5 Hz, 4H), 6.80 (d, J 7.5 Hz, 4H) ms: m/z (%) = 628(M^+)(0.4), 414(100), 267(16.9), 252(22.4), 239(12.5), 226(26.6), 200(23.6), 108(26.7); hrms: m/z Calcd for $C_{42}H_{48}N_2O_9$: 628.335. Found: 628.337.

***N*-3-(8,11-Dioxatetradecan-14-olidyl)-α,α'-bi-*p*-toluidine (9) and *N,N'*-bis-3,3-(8,11-dioxatetradecan-14-olidyl)-α,α'-bi-*p*-toluidine (10).**

Sodium cyanoborohydride (6.2 mg, 0.1 mmol) was added to a magnetically stirred solution of **1** (115 mg, 0.5 mmol) and 4,4'-ethylenedianiline **(8)** (53 mg,0.25 mmol) in methanol (4 ml). *p*-Nitrophenol (1 mg) was added as an indicator and hydrochloric acid in methanol (1N, 2-3 drops) was added to maintain pH 5. Tlc showed no starting material after 24 h. The solvent was then removed under reduced pressure. To the oil was added ethyl acetate (5 ml). The solution was then washed with water (2x2 ml) and brine (2 ml).The organic layer was dried over anhydrous sodium sulphate and the solvent was then evaporated to obtain faint yellow liquid. It was then applied to 20x20 cm silica gel plates (x2, 60 F 254 precoated, Merck). Plates were run twice in 5% ethyl acetate-petroleum ether(40-60). The appropriate bands were cut, the silica gel was washed with ethyl acetate (5x5 ml) and ethyl acetate was then removed under reduced pressure to obtain mono and bis adducts **(9)** and **(10)** as faint yellow coloured viscous liquid and faint yellow crystals respectively. The crystals were crystallised from ethyl acetate-petroleum ether (40-60) mixture; yields: 50 mg (23%) and 55 mg (17%), mp 147°C.

Monoadduct of 4,4'-ethylenedianiline (9):

Ir: (film) ν max = 3365, 2918, 1720, 1610, 1514, 1448, 1355, 1257, 1183, 1135, 824 cm^{-1}; ^{1}H nmr: (500 MHz, $CDCl_3$) δ = 1.50-1.90 (m, 6H), 2.42 (dd, J 7.5, 5.0 Hz, 1H), 2.78 (dd, J 7.0, 2.5 Hz, 1H), 3.40-3.82 (m, 16H), 4.35 (m, 2H), 6.77 (d, J 7.5 Hz, 4H), 6.83 (d, J 7.5 Hz, 4H); ms: m/z (%) = 415(M^++H) (25.4), 414(M^+)(100), 267(17), 252(24.4), 239(14.4), 226(30.8), 200(27.9), 108(33.2), 45(11.6); hrms: Calcd for $C_{23}H_{30}N_2O_5$: 414.2154. Found: 414.2157.

Bisadduct of 4,4'-ethylenedianiline (10):

Ir: (film) ν max = 3368, 2922, 1722, 1610, 1514, 1355, 1250, 1183, 1150, 824 cm^{-1}; ^{1}H nmr:(500 MHz, $CDCl_3$) δ= 1.50-1.90 (m, 12H), 2.45 (dd, J 7.5, 5.0 Hz, 2H), 2.75 (dd, J 7.0, 2.5 Hz, 2H) 3.45-3.80 (m, 24H), 4.35 (m, 4H), 6.77 (d, J 7.5 Hz, 4H), 6.83 (d, J 7.5 Hz, 4H); ms: m/z (%) = 640(M^+) (0.4), 426(4.6), 320 (100), 106(63.8); Anal. Calcd for: $C_{36}H_{52}N_2O_8$, C, 67.48; H, 8.18; N, 4.37. Found C, 67.56; H, 8.23; N, 44.26.

α-Bromo-α'-2-(8,11-dioxa-3-oxotetradecan-14-olidyl)-*p*-xylene (11) and α,α'-bis(8,11-dioxa-3-oxotetradecan-14-olidyl)-*p*-xylene (12).

LDA (2 eq) was added dropwise to a magnetically stirred cooled (-78°C) solution of **1** (46 mg, 0.2 mmol) in THF (2 ml). The solution stirred for 15 min, then allowed to come to room temperature slowly and stirred for 15 min. It was then cooled to -78°C and a solution of α,α'-dibromo-*p*-xylene (26.4 mg, 0.1 mmol) in THF (0.5 ml) was added dropwise to the former and stirring continued for 30 min. The solution was then allowed to come

to room temperature slowly and stirring continued overnight. The solvent was then evaporated under reduced pressure. The residue was taken up in ethyl acetate (5 ml), washed with water (2x2 ml) and brine (2 ml) and ethyl acetate layer was then dried over anhydrous sodium sulphate. The solvent was then evaporated to obtain faint yellow coloured viscous liquid. This was then loaded onto a silica gel column and chromatographed (0-50% ethyl acetate-ether gradient solution) to obtain mono and bis alkylated products **(11)** and **(12)** as colourless crystals which were crystallised from ethyl acetate - petroleum ether (40-60) mixture; yields: 9 mg (11%), mp 98-99°C and 18 mg (16%), mp 112-114°C respectively.

Monoalkylated product of α,α'-dibromo-*p*-xylene (11):

Ir (film): ν max = 2925, 2890, 1742, 1707, 1462, 1305, 1201, 1185, 803 cm^{-1}; ^1H nmr (500 MHz, $CDCl_3$) δ= 1.65-1.80 (m, 4H), 2.50-2.60 (m, 1H), 3.05-3.22 (m, 3H), 3.44-3.71 (m, 8H), 3.75 (t, J 5.0 Hz, 1H), 4.00-4.05 (m, 1H), 4.45 (s, 2H), 4.52-4.58 (m, 1H), 7.12 (d, J 7.5 Hz, 2H), 7.20 (d, J 7.5 Hz, 2H); ms: m/z (%) = 412(M^+)(6.8), 333(35.9), 304(51.0), 223(27.5), 189(85.8), 145(100), 117(88.1), 104(80.5); hrms: m/z Calcd for $C_{19}H_{25}O_5Br^{79}$: 412.0887. Found 412.0885.

Dialkylated product of α,α'-dibromo-*p*-xylene (12):

Ir (film): ν max = 2922, 2881, 1740, 1705, 1472, 1308, 1200, 1188, 802 cm^{-1}; ^1H nmr: (500 MHz, $CDCl_3$) δ= 1.50-1.80 (m, 8H), 2.48-2.58 (m, 2H), 3.00-3.20 (m, 6H), 3.43-3.70 (m, 18H), 3.73 (t, J 5.0 Hz, 2H), 3.98-4.50 (m, 2H), 4.48-4.55 (m, 2H), 7.02 (s, 4H); ms: m/z (%) = 562 (M^+)(16.6), 534(11.9), 418(12.5), 400(10.9), 374(14.4), 373(54.4), 372(11.8), 333(12.5), 332(48.9), 305(16.1), 304(70.9), 267(27.0), 188(26.0), 157(22.6), 144(100), 117(27.0), 101(52.1), 89(27.8), 55(61.4), 45(95.8); Anal. Calcd for $C_{30}H_{42}O_{10}$: C,64.04; H,7.52. Found: C,64.30; H,7.63.

X Ray Crystal Structure Determination for 2:

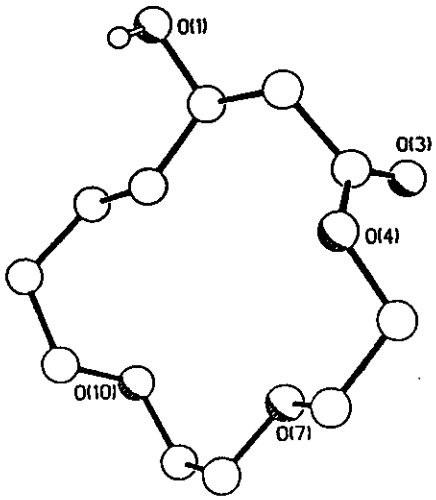
Crystal Data: $C_{11}H_{22}O_5$, M = 232.3, monoclinic, a = 5.175(1), b = 28.783(8), c = 8.552(2)Å, β = 106.25(2)0, V=1223Å^3, space group P21/a, Z = 4 , Dc = 1.26gcm^{-3}, Cu radiation, λ = 1.54178Å, m(Cu-Kα) = 8cm^{-1}, F(000) = 504. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω scans. The structure was solved by direct methods and refined anisotropically to give R = 0.073, Rw = 0.093 for 1545 independent observed reflections [($|F_o| > 3a(|F_o|)$, θ ≤ 58°]. The structure reveals severe disorder in the macrocycle indicating many overlapping partial occupancy conformations. The figure illustrates the major occupancy conformation.

X Ray Crystal Structure Determination for 4:

Crystal Data: $C_{17}H_{25}NO_4$, M = 307.4, triclinic, a = 12.389(3), b = 12.514(2), c = 12.617(4)Å, α = 61.61(2), β = 79.50(2), γ = 86.64(2)0, V=1691Å^3, space group PI, Z = 4 (2 crystallographycally independent molecules), Dc = 1.21gcm^{-3}, Cu radiation, λ = 1.54178Å, m(Cu-Kα) = 7cm^{-1}, F(000) = 664. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω scans. The structure was solved by direct methods and refined anisotropically to give R = 0.058, Rw = 0.069 for 3933 independent observed reflections [($|F_o| > 3a(|F_o|)$, θ ≤ 58°]. The structure reveals severe disorder in the macrocycle indicating many overlapping partial occupancy conformations. The figure illustrates the major occupancy conformation.

X Ray Crystal Structure Determination for 12:

Crystal Data: $C_{30}H_{42}O_{10}$, M = 367.4, monolinic,a = 5.444(1), b = 15.777(4), c = 17.145(4)Å, α = 61.61(2), β = 90.12(3), V=1473Å^3, space group PZ1/c, Z = 2 (the molecule is positioned about a center of symmetry), Dc = 1.27gcm^{-3}, Cu radiation, λ = 1.54178Å, m(Cu-Kα) = 9cm^{-1}, F(000) = 604. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω scans. The structure was solved by direct methods and refined anisotropically to give R = 0.21 for 1534 independent observed reflections. [($|F_o| > 3a(|F_o|)$, θ ≤ 58°] The structure reveals severe disorder in the macrocycle indicating many overlapping partial occupancy conformations. The figure illustrates the major occupancy conformation.



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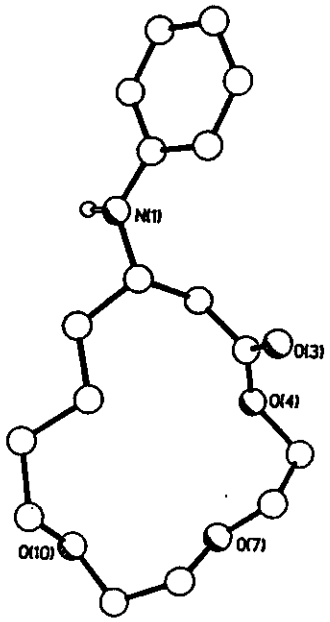

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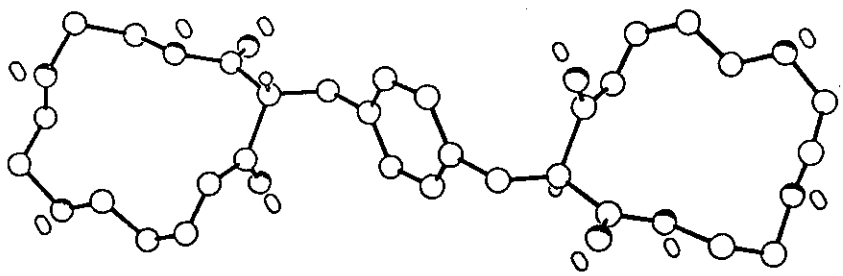

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Figure: Computer generated drawings of **2**, **4** and **12** derived from X-ray coordinates with hydrogens omitted for clarity.

ACKNOWLEDGEMENT

We wish to thank SERC for the financial support.

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Received, 2nd October, 1992