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THE SYNTHESIS OF BINUCLEATING POLYAZA MACROCYCLIC AND MACROBICYCLIC LIGANDS AND THE DIOXYGEN AFFINITIES OF THEIR COBALT COMPLEXES

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Abstract. The synthesis of a new macrobicyclic (cryptand) ligand 1,4,9,12,19,20,25,30-octaazabicyclo(10.10.10)dotriacontane, C4BISTREN and improved syntheses of the ligands 7,9,30-trioxa-1,4,10,13,16,22,-27,33-octaazabicyclo(11.11.11)pentatriacontane, OBISTREN and 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane, OBISDIEN. The Co(II) complexes of these ligands are oxygen carriers. Among the six macrocyclic and six macrobicyclic ligands that are considered in this paper, the binuclear cobalt(II) complexes of OBISTREN and OBISDIEN form the most stable dioxygen complexes.

Introduction

In 1988 Motekaitis and Martell[1,2] reported that the dinuclear cobalt complex of OBISTREN is an excellent oxygen carrier which can reversibly oxygenate and deoxygenate and not undergo degradation at an appreciable rate. Therefore it is of great interest to synthesize the dinuclear cobalt complexes of other similar ligands and compare their oxygen affinities with those of the dinuclear cobalt complex of OBISTREN.

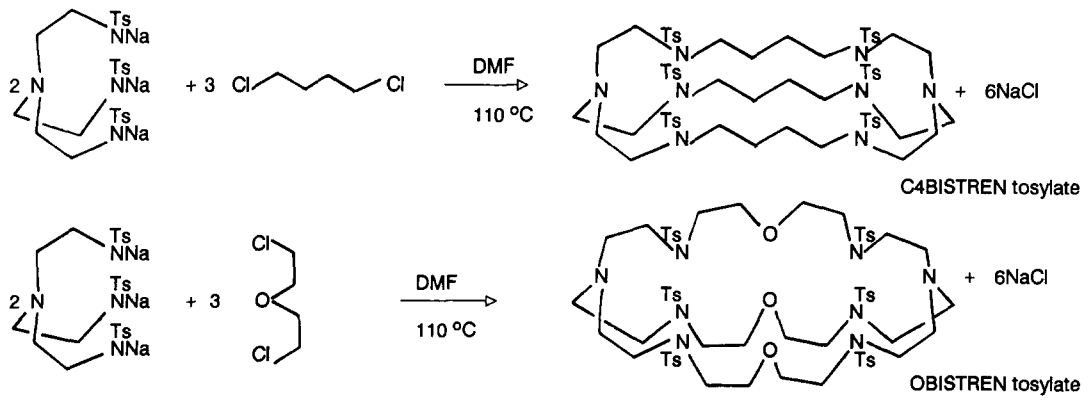
The Co(II) complex of the Schiff base bis(salicylaldehyde)ethylenediiminato was originally investigated by Tsumaki[3] more than fifty years ago. Calvin and his coworkers[4] conducted an exhaustive study of the oxygen carrying capabilities of this complex and some of its ring-substituted derivatives both in solution and in the solid state. The experiments by Calderazzo and coworkers[5,6] and by Crumbliss and Basolo[7] established the oxygen-carrying properties of several Co(II) Schiff base complexes in solution. Several cobalt "dry-cave" complexes have recently been synthesized by Busch et al.[8]

This work reports the synthesis of macrobicyclic (cryptand) ligands 1,4,9,12,19,20,25,30-octaazabicyclo(10.10.10)dotriacontane, C4BISTREN and 1,4,7,12,15,18-hexaazabicyclododocosane, C4BISDIEN. Also reported are modified syntheses of 7,9,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo(11.11.11)-pentatriacontane, OBISTREN, 1,13-dioxa-4,7,10,16,19,22-hexaazacyclotetracosane, OBISDIEN. The Co(II) complexes of these ligands are all oxygen carriers. Among the six macrocyclic and six macrobicyclic ligands that have been synthesized, the cobalt(II) complexes of OBISTREN and OBISDIEN

have the lowest rates of degradation. A brief discussion is given of the probable reasons why these two complexes are superior as oxygen carriers to other dinuclear macrocyclic and macrobicyclic complexes of cobalt(II).

Results and Discussion

Synthetic Methods. Because the C4BISTREN and OBISTREN are difficult to synthesize, an attempt has been made to synthesize these two compounds by a one step (3+2) condensation as follows:



NMR measurements of the reaction products show that a mixture is produced and no macrobicyclic compounds were found after chromatographic separation. In order to promote the cyclic condensation, some metal salts such as $La(NO_3)_3$, $Pb(SCN)_2$ and $Ag(NO_3)$ were also tried as templates but the results were not successful.

Recently Chen and Martell[9] reported the synthesis of macrocyclic and macrobicyclic Schiff bases in good yield by dipodal (2+2) and tripodal (3+2) condensations of a series of dialdehydes with diethylenetriamine or tris(2-aminoethyl)amine. The success of this kind of one-step synthesis seems to require a rigid dialdehyde, a polyamine, and a suitable solvent. The failure of the experiments described above is probably due to the fact that the 1,4-dichlorobutane and 2-chloroethyl ether are too flexible to perform the (2+3) tripodal condensation.

C4BISTREN was synthesized by the general procedure for OBISTREN and C5BISTREN[10,11] shown in Scheme 1. The OBISTREN was synthesized by a modification of the method of Dietrich et al.[10] and Murase et al.[11] (Scheme 2). The OBISDIEN was synthesized by a modification of the method of Comarmond et al.[12] The general procedure is outlined in Scheme 3.

The greatest difficulty in the synthesis of OBISTREN is the purification of compound **12**. In this research, it was twice purified by flash chromatography with silica gel (200-400 mesh, 60 Å). The results show that this method of purification was both successful and rapid. For the preparation of OBISDIEN, compound **18** is simpler to purify than compound **12**. Compound **18** is not soluble in CH_2Cl_2 but the main impurity is soluble so that purification is thus simplified. After the reaction mixture was treated with CH_2Cl_2, pure compound **18** was obtained. Also the yield is much higher than was reported by Cormamond et al.[12]

Oxygenation of the dinuclear cobalt(II) macrocyclic and macrobicyclic complexes. Motekaitis et al.[2,13] reported that OBISTREN and OBISDIEN form dinuclear Co(II) complexes in aqueous solution, and that these complexes combine with molecular oxygen. The oxygen complexes formed contains bridging

dioxygen between the metal centers, and is sometimes represented by a peroxo group bridging two Co(III) centers. The two ligands C4BISTREN and C4BISDIEN also form analogous dinuclear cobalt complexes in solution, and the dinuclear complexes also combine with molecular oxygen to form dioxygen complexes. The oxygenations of these four dinuclear cobalt complexes are shown in Figures 1-4.

The cobalt complex of C4BISDIEN absorbs oxygen rapidly at 25.0 °C from air at pH 9.0. After the process had been carried out for about four minutes, 50% of the theoretical amount of dioxygen was absorbed. Then the rate of absorption of oxygen became slower and at about 20 minutes the absorption of oxygen ceased (Figure 1). The color of the solution changed from the beginning yellow of the dinuclear complex, to brown of the dioxygen complex, and then to a red color which is typical of inert Co(III) complexes.

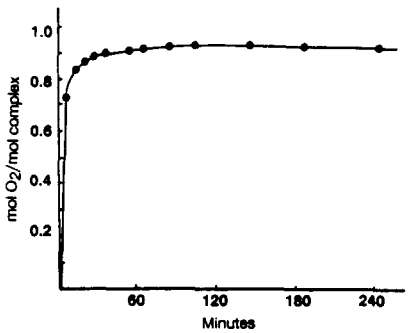


Figure 1 Oxygen absorption by the cobalt complex of C4BISDIEN (1.2 x 10^{-3} M), at 25.0 °C; P_{O_2} = 151 mm Hg and pH = 9.0; mol O_2/mole complex *vs* minutes; $t_{1/2}$ = 4 min.

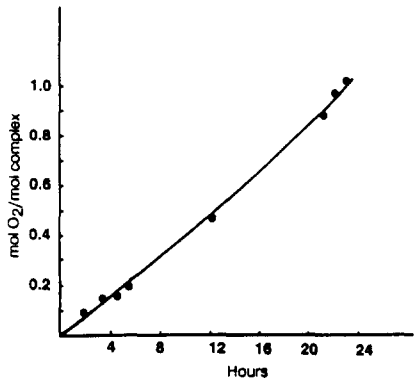


Figure 2 Oxygen absorption by the cobalt complex of C4BISTREN (1.2 x 10^{-3} M), at 25.0 °C; P_{O_2} = 153 mm Hg and pH = 10.0; mole O_2/mol complex *vs* hours; $t_{1/2}$ = 12.5 h.

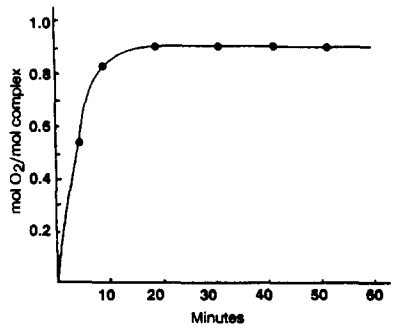


Figure 3 Oxygen absorption by the cobalt complex of OBISDIEN (1.2 x 10^{-3} M), at 25.0 °C; P_{O_2} = 151 mm Hg and pH = 8.5; mole O_2/mol complex *vs* minutes; $t_{1/2}$ = 4.5 min.

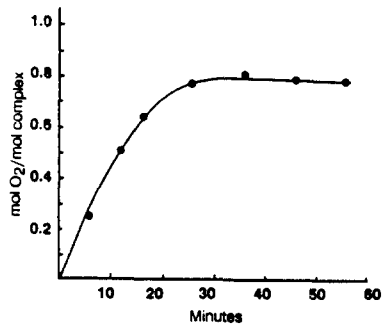


Figure 4 Oxygen absorption by the cobalt complex of OBISTREN (1.2 x 10^{-3} M), at 25.0 °C; P_{O_2} = 152 mm Hg and pH = 8.4; mole O_2/mol complex *vs* minutes; $t_{1/2}$ = 10 min.

The dinuclear cobalt complex of C4BISTREN absorbs oxygen more slowly than does the cobalt complex of C4BISDIEN at 25.0 °C from air at pH 10.0. After the oxygenation was carried out about 12.5 hr, the complex absorbed 50% of the theoretical amount of oxygen (Figure 2). The oxygen absorption, which is a measure of dioxygen complex formation is shown in Figure 2. The fact that more than the theoretical amount of dioxygen is absorbed indicates that the degradation products initially formed may also have affinity for dioxygen and thus, at least initially, begins a secondary cycle of oxygenation and degradation. This type of successive oxygenation and degradation has been observed for other cobalt polyamine oxygen-carrying complexes.[14] The color change of the solution is similar to that described above, but occurs much more slowly.

Dinuclear cobalt(II) complexes of OBISTREN and of OBISDIEN absorb oxygen quickly at 25.0 °C from air at pH about 8.5 (Figures 3 and 4). As expected, the cobalt complex of OBISDIEN absorbs oxygen more rapidly than cobalt complex of OBISTREN. The half time of oxygen absorption for the cobalt complex of OBISDIEN is about 4.5 minutes and is about 10 minutes for the cobalt complex of OBISTREN. Table 1 shows that the more open and flexible macrocyclic complexes take up dioxygen more rapidly than do the cryptands and have much higher thermodynamic stability. These factors reinforce the interpretation that steric factors reduce the stability of the cobalt bicyclic dioxygen complexes and the fact that considerable bending and distortion of the macrocyclic and macrobicyclic ligands is necessary in order to form the dioxygen complex.

UV-Visible absorbance spectra. Because of rapid degradation of the dioxygen complex of the dinuclear cobalt complex of C4BISDIEN, the absorbance must be measured quickly in order to see the absorbance peak. When air is passed through the solution for more than ten minutes, the peak (380 nm) for the dioxygen complex disappears because of the degradation of the dioxygen complex. The final dicobalt(III) complex formed by the irreversible degradation is indicated by reaction (2).

Oxygenation: $Co(II)_2L^{4+} + O_2 \longrightarrow LCo\text{-}O\text{-}O\text{-}Co^{4+}$ (1)

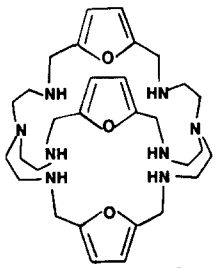
Degradation: $Co\text{-}O\text{-}O\text{-}CoL^{4+} + 2H^+ \longrightarrow H_2O_2 + Co_2L^{6+}$ (2)

The presence of H_2O_2 in the reaction mixture was confirmed by standard iodometric titration.[15]

UV-visible tests of the cobalt complex of C4BISTREN shows that after air is passed through solution of the cobalt complex of C4BISTREN for 48 hours, there appears a new peak at 370 nm. This peak, shown in Figure 5, was assigned to the dioxygen adduct, because when HCl solution was added to the reaction mixture to reduce the pH to 1.0, the 370 nm peak disappeared. The data also show that after the absorption is carried out for 48 hours, the dioxygen complex is still present.

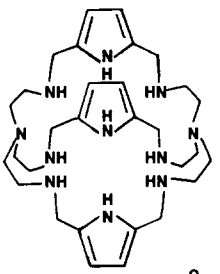
The macrocyclic ligand OBISDIEN forms a thermodynamically stable hydroxo-bridged binuclear cobalt(II) complex.[13] The complex reacts with dioxygen to form a kinetically stable peroxo-bridged complex[11] that does not undergo (metal-centered) degradation at appreciable rates (Figure 6). The loss of dioxygen from the μ-peroxo-μ-hydroxo-dicobalt(II) OBISDIEN complex is estimated to have a first order rate of about 6×10^{-8} sec^{-1}. The rate of degradation of the dioxygen complex formed from OBISTREN is kinetically even slower.[1,2]

Table 1. Macrocyclic and Macrobicyclic Ligands and the Time of 50% Dioxygenation of Their Dinuclear Cobalt(II) Complexes.



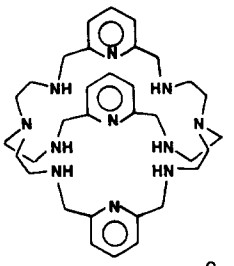
TrisfuranBISTREN[9]

no absorption



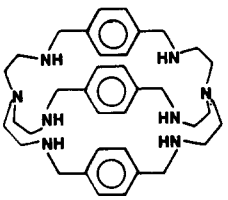
TrispyrroleBISTREN[9]

$t_{1/2}$ = 60 min



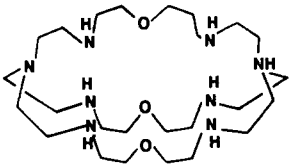
TrispyridineBISTREN[9]

$t_{1/2}$ = 34 min



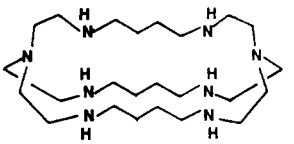
Tris-*p*-xylylBISTREN[9]

no absorption



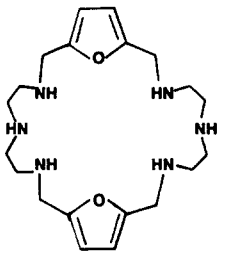
OBISTREN

$t_{1/2}$ = 10 min



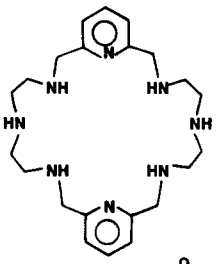
C4BISTREN

$t_{1/2}$ = 12.5 h



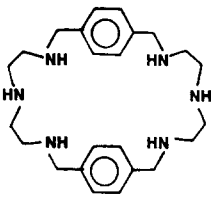
BisfuranBISDIEN[9]

$t_{1/2}$ = 40 min



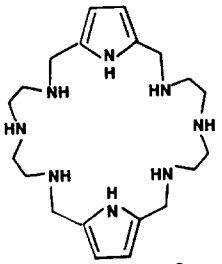
BispyridineBISDIEN[9]

$t_{1/2}$ = 29 min



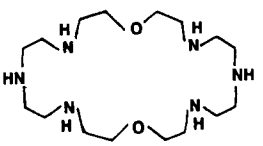
Bis-*p*-xylylBISDIEN[9]

$t_{1/2}$ = 20 min



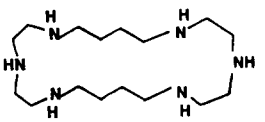
BispyrroleBISDIEN[9]

$t_{1/2}$ = 24 min



OBISDIEN

$t_{1/2}$ = 4.5 min



C4BISDIEN

$t_{1/2}$ = 4.0 min

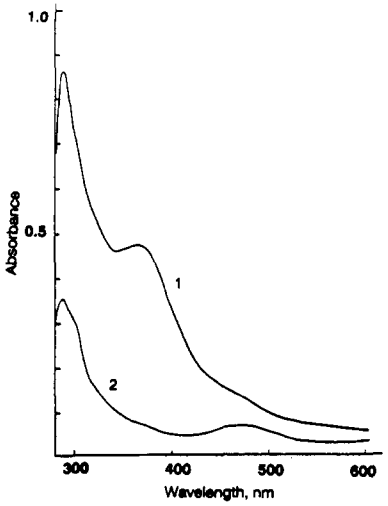


Figure 5 Uv-visible spectra of cobalt complex of C4BISTREN (2.4 x 10^{-4} M), measured at 25.0 °C and pH 10.0. 1, Solution after treatment with air for 48 h; 2, cobalt complex of C4BISTREN.

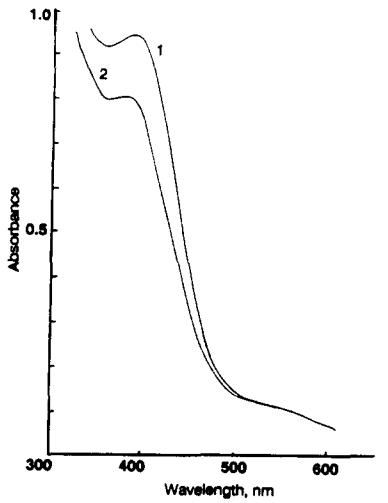


Figure 6 Uv-visible spectra of cobalt complex of OBISDIEN (2.4 x 10^{-3} M), measured at 25.0 °C and pH 8.5. 1, Dioxygen complex; 2, measured after standing at 25.0 °C for 30 days..

Because the two ligands OBISDIEN and OBISTREN are difficult to synthesize, an attempt has been made to form dioxygen complexes of dinuclear cobalt(II) complexes from macrocyclic ligands that are readily prepared. A number of macrocyclic and macrobicyclic ligands are formed in good yield by a two-step process: (2+2 and 3+2) condensation of a dialdehyde with a bis or tris-primary amine to form the macrocyclic or macrobicyclic Schiff base, respectively, followed by hydrogenation to give the macrocyclic hexamine or the macrobicyclic octamine (Table 1).[9] Of these ten dioxygen complexes (Table 1), all were found to undergo metal-centered degradation reactions (with the release of hydrogen peroxide) at appreciable rates; in fact none were found to have a half-life longer than one day (besides C4BISTREN). These findings indicate that the binuclear cobalt(II) complexes of OBISDIEN and OBISTREN are the best oxygen carriers.

The fact that cobalt complexes of both OBISTREN and OBISDIEN form tremendously stable (against degradation) dioxygen complexes compared with other complexes is possibly due to the flexible ether oxygens as bridging groups, which the other ligands do not have. Although the bisfuran BISDIEN[9] contains an oxygen bridge it is not strictly an ether oxygen, is part of a rigid aromatic structure, and is not flexible. It seems that the flexible ether oxygen plays a very important role in stabilizing the dioxygen complex. This information may be important for the design and synthesis of good oxygen carriers and deserves further investigation.

Experimental

Materials. The following materials were obtained in the highest purity available and were used without further purification: tris(2-aminoethyl)amine (97%, Aldrich); *p*-toluenesulfonyl chloride (98%, Aldrich); 3,4-dihydro-2H-pyran (97%, Aldrich); sodium hydride (60% dispersion in mineral oil, Aldrich);

2-(2-chloroethoxy)ethanol (99%, Aldrich); methanesulfonyl chloride (98%, Aldrich); diethylenetriamine (99%, Aldrich); $CoAc_2 \cdot 4H_2O$ (Baker Analyzed Reagent).

NMR Spectra. The proton and carbon-13 NMR spectra were measured with a Varian XL-200 NMR spectrometer, operating at 200 MHz and the chemical shifts are reported in ppm relative to tetramethylsilane.

Mass spectra. The mass spectra were obtained with a VG analytical 70S high-resolution double-focusing mass spectrometer with an attached VG analytical 11/250J data system, in the Center for Chemical Characterization and Analysis, Texas A&M University.

Elemental Analysis for carbon, hydrogen, and nitrogen was carried out by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Uv-vis spectrophotometric measurements were performed with a Perkin-Elmer Model 553 fast scan UV-vis spectrophotometer.

Preparation of dicobalt complexes. The complexes were self-assembled by the addition of 28.6 mg (0.12 mmol) of $CoCl_26H_2O$ to 50 ml ligand solution (1.2×10^{-3} M, pH 8.4-10.0) in a reaction flask and stirred until dissolved.

Oxygen uptake measurements. The oxygen absorption of the dicobalt complexes was measured by determining the volume of gaseous dioxygen taken up by the complexes in aqueous solution with the apparatus and procedure described previously.[16]

Synthetic procedures

1,4,9,12,15,20,25,30-octaazabicyclo(10.10.10)dotriacontane, C4BISTREN.

N,N′,N′′-Tritosyl-2,2′,2′′-nitrilotriethylamine, 1. Tris(2-aminoethyl)amine, 25.2 g, was dissolved in 350 ml of water containing 22 g NaOH. To this was added dropwise 100g p-toluenesulfonyl chloride in 300 ml ether with vigorous stirring at room temperature. Stirring was continued for 2 hr after the addition and the reaction mixture as allowed to stand for 12 hr. The white solid which separated out was collected by filtration, washed with water and recrystallized from methanol: 88 g, yield 84%. ^{1}H NMR $CDCl_3$ (ppm) 7.7, 7.3 (m, 12H, arom); 6.1 (t, 3H, -NH); 2.9 (br, 6H, NCH_2); 2.46 (br, 6H, NCH_2); 2.40 (s, 9H, CH_3).

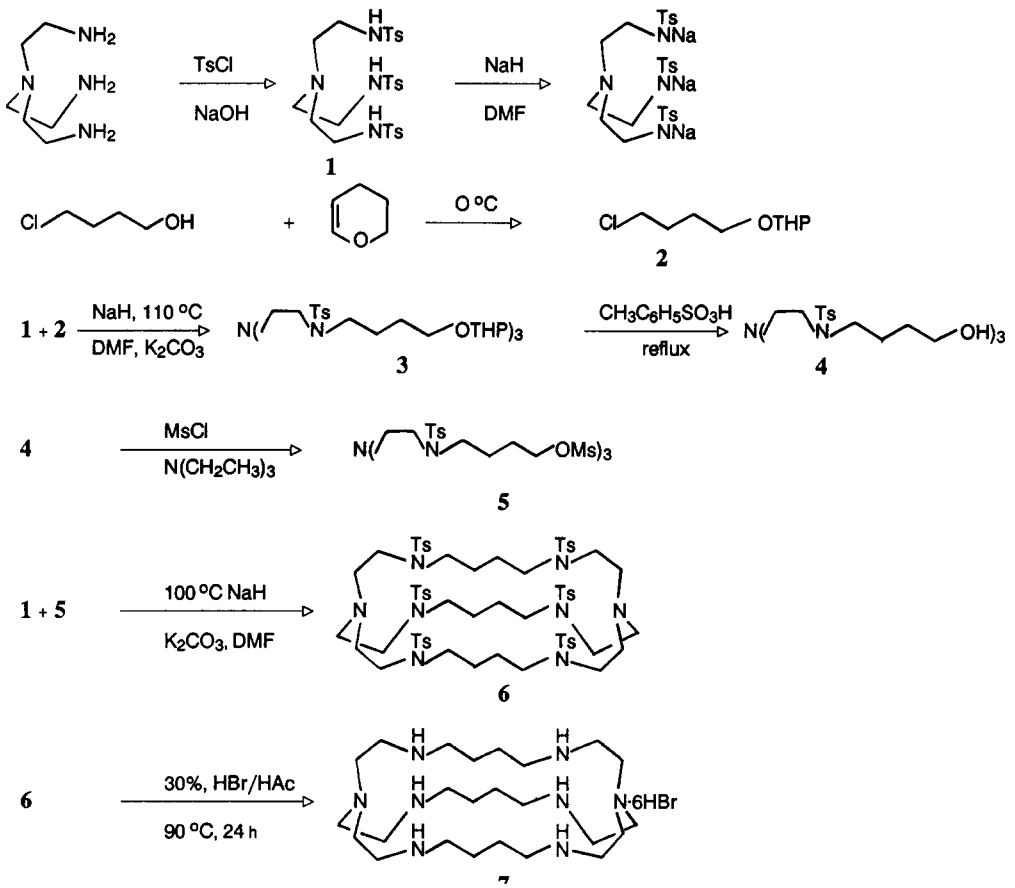
1-Chloro-4-((tetrahydro-2H-pyran-2yl)oxy)butane, 2. To a solution of 4-chloro-1-butanol (16.3 g) in 50 ml CH_2Cl_2, a solution of 2H-dihydropyran (14.1 g) in CH_2Cl_2 (15 ml)was added over 30 minutes, with stirring. After the addition was complete, 3 drops of concentrated HCl were added and the solution was heated for 1 h at 40 °C. The mixture was cooled and dried over anhydrous K_2CO_3, and the solvent was evaporated off. The product was obtained as 29 g of oil, which was used directly for the next step. ^{1}H NMR ($CDCl_3$): 1.56 (br, 4H, $-CH_2$); 1.7-2.0 (br, 6H, tetrahydropyran); 3.4-3.6 (br, 4H, $ClCH_2$, CH_2O); 4.62 (m, 1H, OCHO).

N,N,N-Tris(7-tetrahydro-2-pyranyl)oxy)-3-tosyl-3-azaheptyl)amine, 3. A 29.6 g sample of **1** was dissolved in 400 ml DMF and 5.2 g NaH was added. This reaction mixture was stirred at room temperature for 1.5 hr, 10 g of K_2CO_3 was added, and the solution was heated to 110 °C. A solution of 28.1 g compound **2** in 100 ml DMF was then added dropwise over 1 hr. Heating was continued for another 6 hr. The NaCl was filtered off, and the solvent was removed by evaporation. The residue was dissolved in 250 ml ether, washed with two 100 ml batches of water, and dried over Na_2SO_4. Separation from Na_2SO_4 hydrate and removal of the ether left an oil which was eluted on a silica gel column with CH Cl . After removal of the solvent, an oil was obtained which was used directly in the next step.

N,N,N-Tris(7-hydroxy-3-tosyl-3-azaheptyl)amine, 4. Compound **3** and *p*-toluenesulfonic acid monohydrate (15 g) were refluxed in 95% EtOH (420 ml) for 12 hr. The solvent was evaporated off and the resulting oil was extracted with 300 ml CH_2Cl_2, washed with 150 ml 2 M NaOH, 150 ml water, and dried over K_2CO_3. After separation of the solid and evaporation of the CH_2Cl_2, the residue was chromatographed on silica gel (200-400 mesh, 60 Å, 550 g). Compound **4** was eluted with 1.5% MeOH/CH_2Cl_2 as a viscous oil (21 g, 52%). ^{1}H NMR $CDCl_3$: 7.7, 7.3 (m, 12H, arom); 3.1-3.6 (br, 12H, CH_2O, $TsNCH_2$); 2.4 (s, 9H, CH_3); 1.4-1.8 (br, 12H, CH_2CH_2).

N,N,N-Tris(7-methanesulfonate-3-tosyl-3-azaheptyl)amine, 5. To a stirred solution of **4** (10.1 g) and Et_3N (16.3 ml in 220 ml CH_2Cl_2) at 0 °C, MsCl (5.7 g) was slowly added. The mixture was stirred for 1 hr at 0 °C and 2 hr at room temperature. The solution was washed successively with 1 M HCl (250 ml), 1 M NaOH (50 ml), and water (50 ml), dried (Na_2SO_4), separated, and evaporated. The residue was dried in vacuum for 3 hr. The product was a yellow oil **5** (10.1 g, 78%). ^{1}H NMR $CDCl_3$: 7.7, 7.3 (m, 12H, arom); 4.2 (br, 6H, CH_2O); 3.2 (br, 18H, NCH_2, $TsNCH_2$); 3.1 (s, 9H, SCH_3); 2.5 (s, 9H, CH_3); 1.7 (br, 12H, CH_2CH_2).

Scheme 1. The Synthesis of C4BISTREN, 7



4,9,15,20,25,30-Tosyl-1,4,9,12,15,20,25,30-octaazabicyclo(10.10.10)dotriacontane, 6. A 3.6 g sample of **1** was dissolved in 120 ml DMF and 0.72 g of NaH was added. This mixture was stirred at room temperature for 1.5 hr until no further H_2 evolved, and 5.0 g of K_2CO_3 was then added. The reaction mixture was heated to 100 °C while a solution of 6.9 g of compound **5** in 30 ml DMF was added dropwise over 1 hr. Heating was continued for another 6 hr. The solid (sodium methanesulfonate) was filtered off, and the solvent was removed by evaporation. The residue was dissolved in 120 ml CH_2Cl_2, and the organic layer was washed successively with 60 ml 1.2 M NaOH, 60 ml 1.2 M HCl, 60 ml H_2O, and was finally dried over Na_2SO_4. The CH_2Cl_2 was evaporated leaving a viscous oil which was absorbed at the top of silica gel column and eluted with 2% ether/CH_2Cl_2. The white solid obtained on evaporation of the solvent was further purified one more time with silica gel (same eluant). The pure product, **6** (2.1 g, 28%), was obtained as a white solid. ^{1}H NMR $CDCl_3$: 7.7, 7.3 (m, 24H, arom); 3.1 (br, 24H, $TsNCH_2$); 2.8 (br, 12H, NCH_2); 2.4 (s, 18H, CH_3); 1.6 (br, 12H, CH_2CH_2).

1,4,9,15,20,25,30-Octaazabicyclo(10.10.10)dotriacontane, 7. A 0.8 g sample of compound **6**, 1.6 g of phenol and 66 ml of HBr-HAc (30%) were mixed and heated to 90 °C for 24 hr. After the reaction mixture was cooled to room temperature, the solid residue was filtered off and washed with ether. The product was recrystallized from EtOH. The yield was 0.42 g (73%). ^{1}H NMR D_2O: 3.2, 3.1 (t, 24H, NCH_2); 2.6 (t, 12H, NCH_2); 1.9 (s,12H, CH_2). ^{13}C NMR: 48.4, 44.4, 29.4 and 23.1 ppm. Ms gave the molecular ion 455. Anal. Calcd. for $C_{24}H_{54}N_8.6HBr.3H_2O$: C, 28.99; H, 6.69; N, 11.27. Found: C, 28.95; H, 6.92; N, 11.03.

7,19,30-Trioxo-1,4,10,13,16,22,27,33-octaazabicyclo(11.11.11)pentatriacontane, OBISTREN.

Compounds 8 and 11 were synthesized by the method of Dietrich et al.[10]

N,N′,N′′-Tris(8-tetrahydro-2H-pyran-2yl)oxy-3-tosyl-6-oxa-3-azaoctyl)amine, 9. This compound was synthesized by a modification of the method of Dietrich et al.[10]

A 30.9 g sample of compound **1** was dissolved in 400 ml DMF and 6.1 g NaH was added. This reaction mixture was stirred at room temperature for 1.5 hr, 10 g of K_2CO_3 was added, and the solution was heated to 100 °C. A solution of 33.5 g of compound **8** in 100 ml DMF was then added dropwise over 1 hr. Heating was continued for another 18 hr. The NaCl was filtered off, and the solvent was removed by evaporation. The residue was dissolved in 300 ml ether, washed twice with 100 ml water, and dried over Na_2SO_4. Separation from Na_2SO_4 hydrate and removal of ether left an oil which was used directly for the next step.

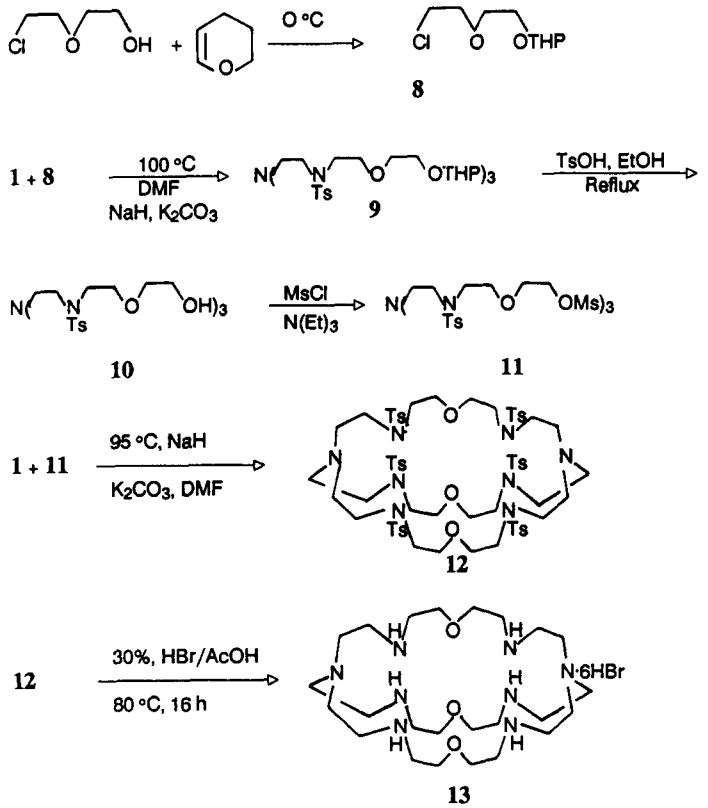
6,6′,6′′-Tritosyl-8,8′,8′′-nitrilo(3-oxa-6-azaoctanol), 10. This compound was synthesized according the procedure described above for the preparation of **4**.

Compound **9** and *p*-toluenesulfonic acid monohydrate (11 g) were refluxed in 95% EtOH for 12 hr. The solvent was evaporated off, the resulting oil was extracted with 300 ml CH_2Cl_2 washed with 150 ml water, and dried over K_2CO_3. After separation of the solid and evaporation of the CH_2Cl_2, the residue was chromatographed on silica gel (200-400 mesh, 60 Å, 550 g). Compound **10** was eluted with 3% MeOH/CH_2Cl as a viscous oil (25 g, 57%). ^{1}H NMR ($CDCl_3$): 7.7, 7.3 (m, 12H, arom); 3.1-3.8(br, m, 33H, 30H, $6CH_2NTs$, $9CH_2$); 2.82 (br, 6H, $3NCH_2$); 2.40 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$): 143.5, 136.4, 129.9, 127.2 (arom); 72.6, 70.3, 62.5 (CH_2O); 53.6, 49.1, 47.4 (CH_2N); 21.6 (CH).

4,10,16,22,27,33-Hexatosyl-7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo(11.11.11)pentatriacontane, 12. This compound was synthesized by a modification of the method of Dietrich et al.[10] The

mixture of compound **1** (8.8 g) and NaH (1.7 g) in 400 ml DMF was stirred at room temperature for an hr, 10 g K_2CO_3 was added, and the solution was heated to 95 °C. A solution of compound **11** (16 g) in 120 ml DMF was then added dropwise over 1 hr. Heating was continued for another 24 hr. The solid was filtered off and the solvent was removed by evaporation. The residue was dissolved in 300 ml CH_2Cl_2, washed twice with 100 ml water and dried over Na_2SO_4. It was then separated from Na_2SO_4 hydrate and most of the solvent was removed by evaporation. The crude product was chromatographed on silica gel (200 g). Compound **12** was eluted with 5% ether/CH_2Cl_2. The white solid obtained on evaporation of the solvent was further purified one more time with silica gel (same eluant). The pure compound **12** (5.8 g, 28%) was obtained as a white solid. ^{1}H NMR ($CDCl_3$): 7.71, 7.33 (m, 24H, arom); 3.47 (br, 12H, CH_2O); 3.24 (br, 24H, CH_2NTs); 2.70 (br, 12H, CH_2N); 2.41 (s, 18H, CH_3); ^{13}C NMR ($CDCl_3$): 143.7, 136.9, 130.1, 127.3 (arom); 70.6 (CH_2O); 53.7, 49.1, 48.1 (CH_2N); 21.5 (CH_3).

Scheme 2. The Synthesis of OBISTREN, **13**



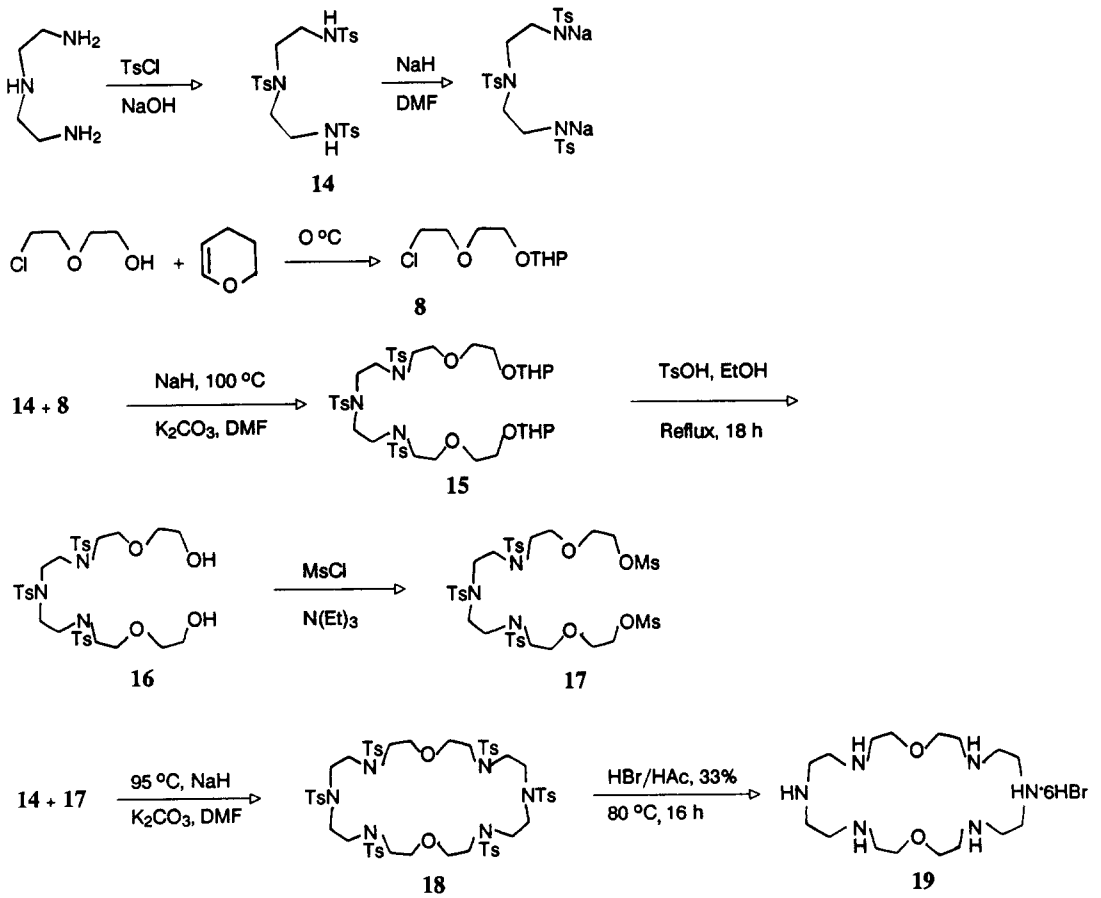
7,19,30-Trioxa-1,4,10,13,16,22,27,33-octaazabicyclo(11.11.11)pentatriacotane, 13. This compound was synthesized by a modification of the method of Dietrich et al.[10] A mixture of compound **12** (5.8 g), phenol (10.1 g) and 160 ml HBr-HAc (30%) was heated at 80 °C for 16 hr. After cooling the residue was filtered off and washed with ether and the solid was then dissolved in a minimum of water. The solution was filtered and the EtOH was added to the filtrate until the solution became cloudy. Compound **13**

crystallized out on standing. The product was recrystallized from H_2O/EtOH mixed solvent. The product weighed 2.7 g (68%). ^1H NMR (D_2O) 3.80 (t, 12H,CH_2O); 3.33 (br, 12H, $NHCH_2$); 2.91 (t, 24H, NCH_2CH_2). Anal. Calcd. for $C_{24}H_{54}N_8O_3{\cdot}6HBr{\cdot}2H_2O$: C, 28.14; H, 6.30; N, 10.94. Found: C, 28.34; H, 6.29; N, 10.92.

1,13-dioxa-4,7,10,16,19-22-hexaazacyclotetracosane, OBISDIEN.

N,N′,N″-Tris-(p-tosylsulfonyl)diethylenetriamine, 14. A 1.25 L aqueous solution of 21.7 g of diethylenetriamine and 76 g $K_2CO_3{\cdot}1.5H_2O$ was stirred vigorously at 60 °C. Tosyl chloride (130 g) was added in batches over 1 hr. Stirring was continued at 60 °C for 3 more hr and the mixture was allowed to stand for 16 hr at room temperature. The residue was washed with water and EtOH and was then refluxed with 500 ml EtOH for 24 hr. After the reaction mixture was cooled to room temperature, the residue which separated out was filtered off and washed with EtOH. After the product was dried over P_2O_5 under high vacuum at 60 °C for 12 hr, 98 g of compound **14** was obtained (82%). ^1H NMR $(CD_3)_2SO$: 7.5, 7.3 (m, 12H, arom); 2.9, 2.7 (m, 8H, NCH_2, $NHCH_2$); 2.26 (s, 9H, CH_3).

Scheme 3. The Synthesis of OBISDIEN, **19**



Compounds **15** and **16** were synthesized by the same procedure as that described for the preparation of compounds **9** and **10**. Compound **17** was synthesized by the method of Dietrich et al.[10]

1,13-Dioxa-4,7,10,16,19,22-hexatosyl-1,4,7,16,19,22-hexaazacyclotetracosane, 18. Compound **14** (9 g) and NaH (1.2 g) in 400 ml DMF was stirred at room temperature for 1 hr, K_2CO_3 (10 g) was added and the solution was heated to 95 °C. A solution of compound **17** (14.7 g) in 120 ml DMF was then added dropwise over 1 hr. Heating and stirring were continued for 24 hr. The solution was filtered and the solvent was removed by evaporation. The residue was mixed with 250 ml CH_2Cl_2 and vigorously stirred for 24 hr to extract the impurity. Pure compound **18** was obtained by filtration and was washed with CH_2Cl_2 (yield of **18** was 10g, 50%). ^{1}H NMR ($CDCl_3$) 7.7, 7.3 (m, 24H, arom); 3.62 (m, 8H, CH_2O); 3.39 (br, 24H, $NTsCH_2$); 2.41 (s, 18H, CH_3).

1,13-Dioxa-4,7,10,16,19,22-hexaazacyclotetracosane, 19. This compound was synthesized by the procedure described for the preparation of compound **13**. ^{1}H NMR (D_2O): 3.74 (t, 8H, CH_2O); 3.52 (br, 16H, NCH_2); 3.31 (t, 8H, NCH_2). ^{13}C NMR (D_2O): 64.10, 46,74, 43.48, 42.41. Anal. Calcd. for $C_{16}H_{38}N_6O_2{\cdot}6HBr{\cdot}2H_2O$: C, 22.14; H, 5.57; N, 9.68. Found: C, 22.12; H, 5.18; N, 9.57.

1,4,7,12,15,18-Hexaazacyclodocosane, C4BISDIEN. This compound was synthesized by following the method of Martin and Bulkowski.[17] The compound was characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis.

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