Contribution from the Department of Chemistry,
Texas A&M University, College Station, Texas 77843

New Multidentate Ligands. 28. Synthesis and Evaluation of New Macrocyclic Ligands Containing Bidentate Endocyclic Catechol Donor Groups

Yizhen Sun, Arthur E. Martell,* and Ramunas J. Motekaitis

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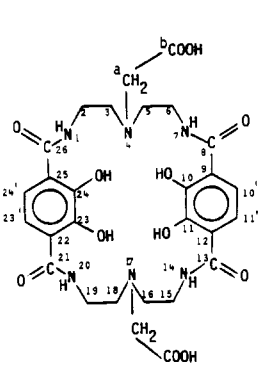
Synthetic pathways are described for the preparation of 26- and 30-membered macrocyclic ligands containing two endocyclic catechol groups and two aminoacetate donor groups: 5,20-bis(carboxymethyl)-12,13,27,28-tetrahydroxy-10,15,25,30-tetraoxo-11,12,13,14:26,27,28,29-dibenzena-1,5,9,16,20,24-hexaazacyclotriacontane (DA-BDHT[30]N_6) and 4,17-bis(carboxymethyl)-10,11,23,24-tetrahydroxy-8,13,21,26-tetraoxo-9,10,11,12:22,23,24,25-dibenzena-1,4,7,14,17,20-hexaazacyclohexacosane (DA-BDHT[26]N_6). A combination of spectrophotometric and potentiometric measurements was employed to determine six protonation constants for each ligand, the stability constants of the iron(III) chelates, and protonation constants of the iron(III) chelates. The Fe(III) stability constants were determined by competition reactions with ethylenediaminetetraacetic acid (EDTA), whereby the EDTA chelate formed at low pH was converted to the more stable macrocyclic complexes at high pH.

Introduction

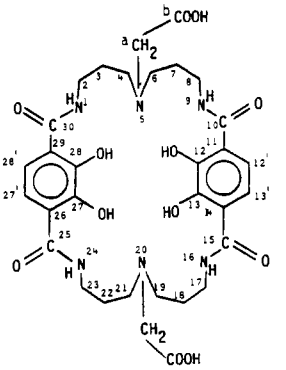
New selective ligands for the formation of highly stable complexes of Fe(III), Ga(III), In(III), and Gd(III) are of considerable interest because of their potential applications for the treatment of iron overload disease (Cooley's anemia),[1-4] for the imaging of organs and tumors in the human body,[5] and as NMR contrast agents.[6] The natural and synthetic siderophores containing catecholates and hydroxamate donor groups have been of interest in this connection because of their high affinity for the ferric ion and for other trivalent metal ions. Many synthetic ligands containing catechol donor groups have been reported recently by Raymond and co-workers.[4]

The natural siderophores show considerable variation with respect to their molecular structures and placement of the bidentate catecholate and hydroxamate donor groups, which interestingly seem never to occur together in the same ligand. The hydroxamate siderophores contain the bidentate donor moiety, which is always secondary, in endocyclic, exocyclic, and acyclic arrangements in the ligand molecules. Of these, the endocyclic ligands show the highest metal ion affinities, because they are associated with stronger macrocyclic effects on complex formation. A recent report of the first synthetic endocyclic hydroxamate macrocyclic ligand[7] indicates a similar increase in metal complex stability relative to the acyclic and exocyclic analogues. Thus far natural endocyclic catecholate ligands have not been discovered although the potential superiority of this type of ligand structure has been recognized for some time.[2] Recently, however, reports on synthetic macrocyclic and cryptand catecholate siderophores with endocyclic donor groups have appeared.[8-10] Preliminary stability constant determinations on a macrocyclic tricatecholate have shown that it effectively binds Fe(III). Quantitative measurements on the more elaborate but potentially more selective cryptand-type tricatecholate[8] have not yet appeared.

Macrocyclic ligands containing endocyclic donor groups are of special interest because of the specificity that can be built into the complexing agent by varying the size of the ring. For the natural and synthetic tricatecholates, however, the presence of six negative charges close to the central metal ion may be a disadvantage because of the mutual repulsions of the six negative charges, thus considerably mitigating the chelate or macrocyclic effect on metal ion affinity.[2] It was therefore decided for the present investigation to design and synthesize macrocycles with only two catechol moieties, but with additional softer donor groups to satisfy coordination requirements of six or more. The present investigation describes two new macrocyclic ligands each containing two endocyclic catecholate donor groups, but with different ring sizes, in order to explore the importance of the fit in determining metal chelate stability and selectivity. The formulas of these ligands and the numbering system employed for naming them are indicated by formulas **1** and **2**.



1
DA-BDHT[26]N_6



2
DA-BDHT[30]N_6

Experimental Section

Proton NMR were measured with an EM-390 spectrometer, and ^{13}C NMR spectra were measured on a Varian XL-200 spectrometer operating at 200 MHZ. Unless otherwise specified, the solvent is deuteriochloroform with tetramethylsilane (Me_4Si) as standard. The shifts are given in ppm from Me_4Si.

C, H, N, and S analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

The chromatographic separation described below was effected by the dry-column procedure (using neutral alumina A-950 from Fisher Co.) or by flash chromatographic separation[11] (silica gel, Merck, grade 60, 230-400 mesh, from Aldrich Chemical Co.). TLC was performed with a commercially prepared silica gel 60 F_{254} purchased from Merck (layer thickness 0.2 mm).

All solvents and reagents were purchased commercially and used as supplied except for tetrahydrofuran, which was refluxed with sodium and distilled before use, and benzene and bromoacetic acid, which were purified by conventional methods.[12]

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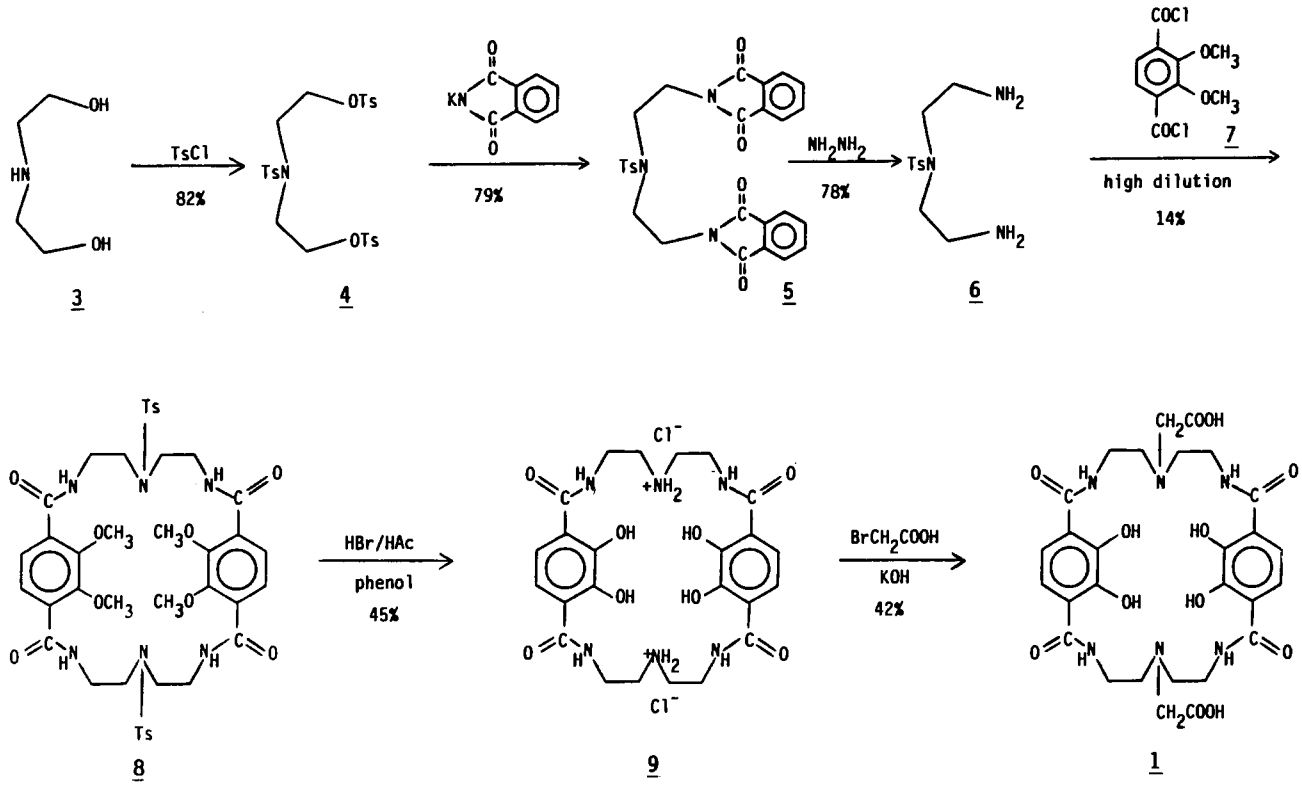
Scheme I. Synthetic Scheme for BDHT[26]N_6



Potentiometric equilibrium measurements were carried out in a 75-mL double-walled reaction vessel under an atmosphere of purified nitrogen, maintained at 25.00 °C by circulation of thermostated water. The hydrogen ion concentration was measured with a Corning Model 145 research pH meter fitted with high pH glass and standard calomel electrodes calibrated with standard HCl and NaOH solutions to read hydrogen ion concentration directly. For the purposes of this paper the negative logarithm of the hydrogen ion concentration is defined as $-\log [H^+]$. All potentiometric (and spectrophotometric) equilibrium measurements were carried out on aqueous solutions maintained at 0.100 M ionic strength with KNO_3 as the inert supporting electrolyte. Under the conditions employed the value of $K_w = [H^+][OH^-]$ was found to be $10^{-13.79}$. The potentiometric data were processed with the use of program BEST[13] on a PDP 11/44 computer. Values of pM were calculated at pH 7.4 with a program written in Basic and with the use of Micromation Z-80 microcomputer.

Spectrophotometric data were measured on a Perkin-Elmer Model 553 UV–visible spectrophotometer in a thermostated cell compartment. In pH ranges below and above the range 2–12, within which reasonably accurate potentiometric measurements can be made, concentrations of hydrogen and hydroxide ion were determined from the measured amounts of added acid or base.

2,3-Dimethoxyterephthaloyl Chloride. The acid chloride **7**, Scheme I, used in the high dilution reaction was prepared in three steps by using modifications of procedures described in the literature.[14,15] Methyl esterification and hydroxyl methylation of 2,3-dihydroxyterephthalic acid were carried out in one step by treatment with dimethyl sulfate in accordance with procedures described by Dallacker and Korb.[14] The ester was then converted to the dicarboxylic acid by the procedure of Dallacker and Korb[14] and finally to the diacid chloride as described by Dietrich et al.[16] and by Adams and Ulich.[17]

4-(*p*-Tolylsulfonyl)-1,4,7-triazaheptane (6). Diethanolamine (**3**) Scheme I, was tritosylated by the method of Eisleb.[18] The terminal tosyl groups were converted to primary amino groups by the Gabriel synthesis, as described by Dietrich et al.[19] for the synthesis of a somewhat more complex polyamine.

10,11,23,24-Tetramethoxy-8,13,21,26-tetraoxo-4,17-bis(*p*-tolylsulfonyl)-9,10,11,12:22,23,24,25-dibenzena-1,4,7,14,17,20-hexaazacyclohexacosane, $(Ts)_2(Me)_4$BDHT[26]N_6 (8). A 9-g (34-mmol) sample of 2,3-dimethoxyterephthaloyl chloride was dissolved in 500 mL of dry tetrahydrofuran while 9.2 g (34 mmol) of 4-(*p*-tolylsulfonyl)-1,4,7-triazaheptane and 7.0 g (68 mmol) of triethylamine were dissolved in a second 500 mL of dry tetrahydrofuran. These two solutions were added to 1.2 L of dry THF dropwise with vigorous stirring over a period of 12 h. After the addition, the reaction mixture was allowed to stand for 36 h. Insoluble material was filtered out, and the solvent was removed by evaporation under reduced pressure at 40 °C. The residue was dissolved in 250 mL of chloroform, which was washed two times with 100 mL of 1.2 M HCl and once with 150 mL of a saturated NaCl solution. The organic phase was filtered and dried with $MgSO_4$. After removal of the solvent, the remaining yellow oil was dissolved in a small amount of $CHCl_3$ and loaded on 100 g of neutral alumina (A-950 Fisher Co. Grade III). The loaded alumina was placed on the top of 50 g of alumina in a 45/900 mm column and washed with $CHCl_3$. The approximately 500 mL of eluate that was collected contained the desired product (relative R_f 0.36, developed with 95:5 $CHCl_3$–MeOH), with a small amount of impurity having a higher relative R_f of 0.43 (developed by the same mixed solvent). The impurity was separated from the product by flash chromatography; 2.2 g of pure product was obtained after recrystallization from $CHCl_3$–MeOH (v/v = 1:10). Yield: 14%.

^{1}H NMR: 7.9 (t, 4 H, H-1,7,14,20), 7.7 and 7.4 (d, 8 H, H-b,c), 7.5 (s, 4 H, H-10′,11′,23′,24′), 3.9 (s, 12 H, H-f), 3.7 (q, 8 H, H-2,6,15,19), 3.2 (t, 8 H, H-3,5,16,18), 2.5 (s, 6 H, H-e). ^{13}C NMR: 164 (C-8,13,21,26), 150 (C-10,11,23,24), 144 (C-a), 132 (C-d), 129, 128, 126.5, 125 (C-9,12,22,25, C-10′,11′,23′,24′, C-c,b), 62 (C-f), 49 (C-3,5,16,18), 39 (C-2,6,15,19), 21 (C-e). MP = 269–271 °C.

Anal. Calcd for $C_{42}H_{50}N_6O_{12}S_2 \cdot H_2O$: C, 55.25; H, 5.74; N, 9.21. Found: C, 55.22; H, 5.66; N, 9.89.

4,13-Bis(*p*-tolylsulfonyl)-19,20-dimetboxy-8,9,17,22-tetraoxo-18,19,20,21-benzena-1,4,7,10,13,16-hexaazacyclodocosane, $(Ts)_2$-$(Me)_2$DHT (16). The impurity described in the procedure for the synthesis of $(Ts)_2(Me)_4$BDHT[26]N_6 has a melting point of 280–282 °C; yield 3.8%. ^{1}H NMR: 8.2 (t, 2 H, H-1,16), 7.7 and 7.3 (d, 4 H and 4 H, H-b and H-c), 7.6 (s, 2 H, H-19′,20′), 7.2 (t, 2 H, H-7,10), 4.1 (s, 6 H, H-f), 3.8 (q, 4 H, H-2,15), 3.3 (t, 4 H, H-3,14), 3.4 (q, 4 H,

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H-6,11), 3.0 (t, 4 H, H-5,12), 2.5 (s, 6 H, H-e). ^{13}C NMR: 165 (C-17,22), 159 (C-8,9), 151 (C-19,20), 144 (C-a), 134 (C-d), 130, 129.8, 127, 125 (C-18,19′,20′,21, C-b,c), 62 (C-f), 50 and 49 (C-3,5,12,14), 40 and 39 (C-2,6,11,15), 21 (C-e).

Anal. Calcd for $C_{34}H_{42}N_6O_{10}S_2$: C, 53.83; H, 5.54; N, 11.08. Found: C, 53.47; H, 5.55; N, 10.77.

10,11,23,24-Tetrahydroxy-8,13,21,26-tetraoxo-9,10,11,12:22,23,-24,25-dibenzena-1,4,11,14,17,20-hexaazacyclohexacosane Dihydrochloride Salt, BDHT[26]N_2·2HCl (9). A 6.6-mL amount of 30% HBr–HAc and 0.33 g (3.5 mmol) of phenol were added to 0.49 g (0.55 mmol) of the $(Ts)_2(Me)_4$BDHT[26]N_6 in a 25-mL round-bottom flask. The reaction mixture was kept at room temperature for 5 days, with exclusion of moisture. The flask was then chilled in ice, and the mixture was poured into 44 mL of cold dry ether. The colloidal suspension that formed was stirred at 2–3 °C for 1 h until the supernatant solution became completely clear. After the pale yellow precipitate obtained was filtered and washed with cold dry ether, the crude product was dissolved in 18 mL of 20% KOH, and 0.3 g of activated charcoal was added to absorb the oily insoluble material. The clear filtrate was added to 36 mL of 6N HCl, and 30–40 mL of dry ether was added to extract other organic impurities. The insoluble material was filtered off, washed with ether and water (adjusted to pH 2 with HCl), and vacuum dried over P_2O_5 for 16 h at room temperature, and 0.15 g of product was obtained. ^1H NMR (D_2O–NaOD): 2.9 (b, 8 H, H-3,5,16,18), 3.6 (b, 8 H, H-2,6,15,19), 7.0 (s, 4 H, H-10′,11′,23′,24′). Yield: 45%.

4,17-Bis(carboxymethyl)-10,11,23,24-tetrahydroxy-8,13,21,26-tetraoxo-9,10,11,12:22,23,24,25-dibenzena-1,4,7,14,17,20-hexaazacyclohexacosane, DA-BDHT[26]N_6 (1). A 0.15-g (0.25-mmol) sample of BDHT-[26]N_6·2HCl and 2.5 mL of 0.2 M KOH were mixed with a solution of 0.139 g (1.0 mmol) bromoacetic acid in 5 mL of 0.2 M KOH in an ice–water bath. A 0.2 M KOH solution was added dropwise to maintain the pH at 11.2, and the temperature was kept at 40–42 °C. After approximately 2.5–3 mL of 0.2 M KOH solution had been added, all the insoluble starting material had dissolved and the pH of the solution became steady. Then 2.5 M HCl was added to the clear solution until the pH reached 2.8. A nearly colorless precipitate was filtered off and washed with water. The product was redissolved in dilute KOH and precipitated with 7.5 M HCl. After it was filtered and dried over P_2O_5 at room temperature under reduced pressure for 6 h, 85 mg of pale yellow product was obtained. Yield: 42%.

^1H NMR (D_2O–NaOD): 2.9 (b, 8 H, H-3,5,16,18), 3.3 (s, 4 H, H-a), 3.5 (b, 8 H, H-2,6,15,19), 6.9 (b, 4 H, H-10′,11′,23′,24′). ^{13}C NMR: (D_2O–NaOD): 179 (C-b), 172 (C-10,11,23,24), 166 (C-8,13,21,26), 116 (C-10′,11′,23′,24′), 111 (C-9,12,22,25), 57 (C-a), 54 (C-3,5,16,18), 37 (C-2,6,15,19). Peaks in the ^1H and ^{13}C NMR spectrum for toluenesulfonic acid were also found.

Anal. Calcd for $C_{28}H_{34}O_{12}N_6$·$C_7H_8O_3S$: C, 51.34; H, 5.13; N, 10.27; S, 3.91; 0, 29.34. Found: C, 51.71; H, 5.05; N, 10.48; S, 3.48; 0, 29.28 (by difference).

5-(*p*-Tolylsulfonyl)-1,5,9-triazanonane (13). Dipropylenetriamine (1,5,9-triazanonane, **10**) was converted to the diphthaloyl derivative in the usual way by following the procedure described by Ng.[20] The product, **11**, was obtained in 84% yield; mp 151–154 °C.

^1H NMR ($(CD_3)_2SO$): 1.6 (q, 4 H, $CH_2CH_2CH_2$), 2.4 (t, 4H, CH_2NHCH_2), 3.4 (t, 4H, $PhthNCH_2$); 7.7 (s, 8 H, aromatic H); 3.9 (br, NH).

To a solution of 24 g (125 mmol) of tosyl chloride in 150 mL of dry pyridine, was added 39 g (100 mmol) of dry diphthaloyldipropylenetriamine (**11**) in small portions over a 2-h period, while the solution was maintained at 3–5 °C. After the reaction mixture was allowed to stand for 12 h, half of the solvent was removed by evaporation under reduced pressure, the remaining solution was poured over 600 mL of crushed ice, and the reaction mixture was allowed to stand for 2 h. The colorless precipitate was filtered off and dried at 60 °C. The crude product was dissolved in 250 mL of $CHCl_3$ and the solution was filtered and allowed to stand for 12 h. The solvent was evaporated under reduced pressure to reduce the volume to 100 mL, and the precipitation was completed by the addition of 80 mL of methanol. The pure product thus obtained weighed 20.7 g.

^1H NMR ($CDCl_3$): 1.9 (q, 4 H, $CHCH_2CH_2$), 3.2 (t, 4 H, $PhthNCH_2$), 3.7 (t, 4 H, $TsNCH_2$); 7.2 and 7.8 (d, 4 H, tosyl aromatic), 7.7–7.8 (m, 8 H, Ph aromatic).

The 20.7-g (38-mmol) sample of the phthalimido compound was suspended in 160 mL of absolute ethanol, and 3.5 mL (3.0 g, 90 mmol) of 97% hydrazine was added. The reaction mixture was refluxed for 14 h and cooled, and 40 mL of 6 M HCl was added to reduce the pH to 1.0. The reaction mixture was refluxed for 1 h, cooled, and filtered to remove phthalhydrazide. The solution was evaporated to remove ethanol and finally dried under reduced pressure (ca. 1 Torr). The crude product was treated with excess 25% NaOH solution and extracted with chloroform three times. The extracts were filtered and dried with $MgSO_4$, the solvent was evaporated off, and the residue was dried under reduced pressure. The product weighed 9.6 g (86%).

^1H NMR ($CDCl_3$): 1.3 (s, 4 H, NH_2), 1.7 (q, 4 H, $CH_2CH_2CH_2$), 2.4 (s, 3 H, CH_3), 2.75 (t, 4 H, CH_2NH_2), 3.2 (t, 4 H, $TsNCH_2$), 7.3 and 7.7 (d, 4 H, tosyl aromatic).

12,13,27,28-Tetramethoxy-10,15,25,30-tetraoxo-5,20-bis(*p*-tolylsulfonyl)-11,12,13,14:26,27,28,29-dibenzena-1,5,9,16,20,24-hexaazacyclotricontane, $(Ts)_2(Me)_4$BDHT[30]N_6 (14). A solution of 6.0 g (23 mmol) of 2,3-dimethoxyterephthaloyl chloride in 400 mL of dry THF and 6.7 g (23 mmol) of 5-(*p*-tolylsulfonyl)-1,5,9-triazanonane and 4.6 g (44 mmol) of triethylamine in 400 mL THF were added simultaneously and dropwise to 1.2 L of dry THF at the rate of one drop per 5 s, with rapid stirring. The addition of reactants was completed in 11.5 h, and the solution was allowed to stand at room temperature for 24 h. The insoluble triethylamine hydrochloride was filtered off and the filtrate was evaporated to near dryness to give 11 g of a glasslike solid.

The crude product was loaded on 100 g of Al_2O_3 (activity III prepared by equilibration of Fisher A-950 activity I Al_2O_3 with 6% water for 3 h). Washing the loaded Al_2O_3 with 95:5 $CHCl_3$–MeOH and evaporation of solvent from the extract produced 5.5 g of product, which formed four spots on a TLC plate. This material was loaded on 60 g of neutral Al_2O_3 and air-dried. The loaded Al_2O_3 was placed on the top of 250 g of Al_2O_3 in a 24-mm-diameter column and eluted with $CHCl_3$ (CX1055-9, MCB reagent), and 1.7 g of the compound identified as the first spot was obtained. Another fraction consisting of 1.8 g contaminated with some of the second spot material was purified by elution from 80 g of Al_2O_3 with $CHCl_3$ to give 1.24 g of pure compound. A third fraction gave 0.31 g of pure product by the same chromatographic procedure, making the combined extracts of purified material 3.25 g or 30%.

The product was recrystallized by dissolving 0.7 g in 3 mL of $CHCl_3$, filtering, and adding 30 mL of ethanol. The colorless crystalline material that formed on standing at approximately −10 °C was filtered and dried under reduced pressure to give 0.57 g of pure product (mp 252–253 °C).

^1H NMR ($CDCl_3$): 1.95 (m, 8 H, H-3,7,18,22), 2.5 (s, 6 H, H-e), 3.2 (t, 8 H, H-4,6,19,21), 3.5 (q, 8 H, H-2,8,17,23), 3.8 (s, 12 H, H-f), 7.1 (s, 4 H, H-12′,13′,27′,28′), 7.2 and 7.7 (d, 8 H, H-b,c), 8.0 (t, 4 H, H-1,9,16,24). ^{13}C NMR: 165.0 (C-10,15,25,30), 151 (C-12,13,27,28), 148 (C-a), 135 (C-d), 130, 129, 127, 125 (C-12′,13′,27′,28′,b,c); 62 (C-f), 47, 38, 29 (C-2,3,4,6,7,8,17,18,19,21,22,23), 21 (C-e).

12,13,27,28-Tetrahydroxy-10,15,25,30-tetraoxo-11,12,13,14:26,-27,28,29-dibenzena-1,5,9,16,20,24-hexaazacyclotriacontane Dihydrochloride, BDHT[30]N_6·2HCl (15). A 1.89 g (20 mmol) sample of the ditosyl tetramethyl macrocyclic compound, **14**, was mixed with 24.2 mL of a 30% solution of HBr in acetic acid and 1.2 g (13 mmol) of phenol. The reaction mixture was kept at ambient room temperature for 7 days. The reaction mixture was then chilled and was poured into 160 mL of cold dry ether at 2–3 °C. The mixture was stirred at this temperature for 0.5 h, filtered, and washed three times with 15 mL of cold dry ether. The crude product obtained (after being vacuum-dried at 0.5 mmHg for 1.5 h) consisted of 1.4 g of a pale yellow solid. The crude product (1.33 g) was dissolved in 66 mL of 20% KOH and filtered. This solution was added to 132 mL of cold HCl. The colorless precipitate was filtered and dried at 0.5 mmHg 50–60 °C for 5 h. The yield of recrystallized product (1.01 g) was 77%.

^1H NMR ($(CD_3)_2SO$): 1.5, 2.5, 3.0 (m, 8 H, 8 H, 8 H, H-2,3,4,6,7,8,17,18,19,21,22,23), 5.7 (br, H-5,20), 7.0 (s, 4 H, H-12′,13′,27′,28′), 8.1 (m, 4 H, H-1,9,16,24); 8.6 (br, 4 H, catechol OH).

5,20-Bis(carboxymethyl)-12,13,27,28-tetrahydroxy-10,15,25,30-tetraoxo-11,12,13,14:26,27,28,29-dibenzena-1,5,9,16,20,24-hexaazacyclotriacontane, DA-BDHT[30]N_6 (2). A 0.264-g (0.4-mmol) sample of the macrocyclic dicatechol diamine tetraamide compound (hydrochloric acid salt), **15**, was suspended in 8 mL of water and mixed with 0.33 g (2.4 mmol) of bromoacetic acid in 7.5 mL of water, which had been neutralized to ca. pH 8. To the resulting solution (ca. pH 5). A 2.5 M NaOH solution was added dropwise while the solution had been kept at 40–45 °C and thoroughly stirred. Whenever the pH of the solution dropped below 10, more NaOH solution was added. When a stoichiometric amount of NaOH solution was added, the pH of the solution reached 11. The reaction mixture was cooled, and 2.5 M HCl was added slowly until the pH was lowered to 2.5. The precipitate that formed was filtered off and washed with dilute cold HCl and was then vacuum-dried at 0.5 mmHg at room temperature under P_2O_5 for 24 h. The product obtained (0.218 g, yield 78%) was purified by acid–base precipitation. A 110-mg sample was dissolved in NaOH solution (pH >12), filtered, and acidified with 2.5 M HCl to pH 2–3. The precipitate was filtered and washed with cold water (3 drops of 2.5 M HCl was added to about

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Table I. Logarithms of the Protonation Constants of Sexadentate Macrocyclic Ligands with Endocyclic Catechol Donor Groups

	log K		
concn quotient	DA-BDHT-[26]N_6[a,b] (1)	DA-BDHT-[30]N_6[a,b] (2)	TRIMER[a,c]
$[HL^{5-}]/[H^+][L^{6-}]$	11.8 (1)	11.22 (5)	11.61
$[H_2L^{4-}]/[H^+][HL^{5-}]$	10.7 (2)	9.94 (2)	11.18
$[H_3L^{3-}]/[H^+][H_2L^{4-}]$	10.4 (1)	9.57 (2)	10.83
$[H_4L^{2-}]/[H^+][H_3L^{3-}]$	9.9 (2)	8.87 (4)	7.98
$[H_5L^-]/[H^+][H_4L^{2-}]$	7.8 (1)	6.51 (4)	6.97
$[H_6L]/[H^+][H_5L^-]$	6.9 (2)	5.88 (3)	6.33
$[H_7L^+]/[H^+][H_6L]$		2.40 (3)	

[a] t = 25.00 °C; μ = 0.100 M. [b] This research. [c] TRIMER = ((*p*-$C_6H_4(OH)_2)(CO)_2)_3(NHCH_2CH_2NH)_3$; see ref 9.

Table II. Logarithms of the Formation Constants of Fe(III) Macrocyclic Complexes Containing Endocyclic Catechol Donor Groups

	log K		
concn quotient	DA-BDHT-[26]N_6[a,b] (1)	DA-BDHT-[30]N_6[a,b] (2)	TRIMER[a,c]
$[FeL^{3-}]/[Fe^{3+}][L^{6-}]$	37.6 (5)	36.0 (2)	38.7
$[FeHL^{2-}]/[FeL^{3-}][H^+]$	10.20 (5)	9.69 (4)	7.63
$[FeH_2L^-]/[FeHL^{2-}][H^+]$	7.54 (5)	6.76 (4)	4.80
$[FeH_3L]/[FeH_2L^-][H^+]$	4.86 (5)	3.32 (4)	
p[M] at p[H] 7.4, $[H_NL_t]/[Fe_t]$ = 10	28.0	29.3	27.4

[a] t = 25.00 °C; μ = 0.100 M. [b] This research. [c] TRIMER = ((*p*-$C_6H_4(OH)_2)(CO)_2)_3(NHCH_2CH_2NH)_3$; see ref 9.

15 mL of water). After being vacuum-dried at room temperature under P_2O_5 for 20 h, 77 mg of pure product was obtained (yield 70%).

^{1}H NMR (D_2O–NaOD, pH 12–13): 1.8 (m, 8 H, H-3,7,18,22), 2.8 (m, 8 H, H-2,8,17,23) 3.2 (s, 4 H, H-a), 3.4 (t, 8 H, H-4,6,19,21), 6.9 (s, 4 H, H-12′,13′,27′,28′). ^{13}C NMR (D_2O–NaOD): 179 (C-b), 172 (C-12,13,27,28), 166 (C-10,15,25,30), 116 and 114 (C-11,12′,13′,14,26,27′,28′,29), 57 (C-a), 53, 37, 26 (C-2,3,4,6,7,8,17,18,19,21,22,23).

Anal. Calcd for $C_{32}H_{42}N_6O_{12}$: C, 54.62; H, 5.97; N, 11.95. Found: C, 54.32; H, 5.53; N, 11.65.

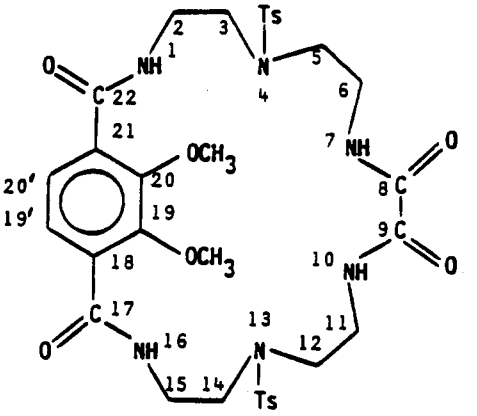
Results and Discussion

The synthetic routes that in our hands proved to be the most efficient for the preparation of macrocycles **1** and **2** are illustrated in Schemes I and II, respectively. The crucial step in each reaction sequence is the high-dilution reaction, **6** → **8** in Scheme I and **13** → **14** in Scheme II. One of the main requirements for a successful high-dilution reaction is that the compounds involved combine extremely rapidly so that there can be no buildup of unreacted materials in the reaction mixture. The type of reaction employed—the acylation of an amine with an acid chloride—meets these requirements very well.

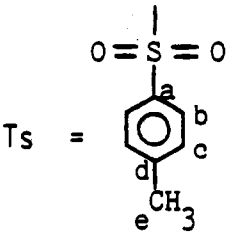
The large difference in the yields of the high-dilution reaction in forming the 30- and 26-membered macrocycles (30% and 14%, respectively) indicates that formation of the smaller ring is the more difficult. This is believed due to the steric effects of the ring substituents, two tosyl and four methoxy groups, which would be much greater for the more crowded smaller ring.

The diamines employed as starting materials in the high-dilution reactions, though very similar in structure, were prepared by quite different reaction pathways. Synthesis from a triamine such as **10** involves tosylation of the bisphthaloyl derivative, **11** → **12**, a reaction that is made difficult because of the low solubility of the diphthaloyl compound, resulting in a low yield. This problem is even greater in the case of the diethylenetriamine derivative, requiring the use of another synthetic route, illustrated in Scheme I, sequence **3** → **6**.

It is interesting to note that a small amount of impurity, oxalyl chloride, used in synthesizing the acid chloride **7** also reacted with the diamino intermediate **6** to form another macrocycle, **16**, containing only one catechol function. Because of its low molecular weight and high reactivity as an acid chloride, only a small amount



16

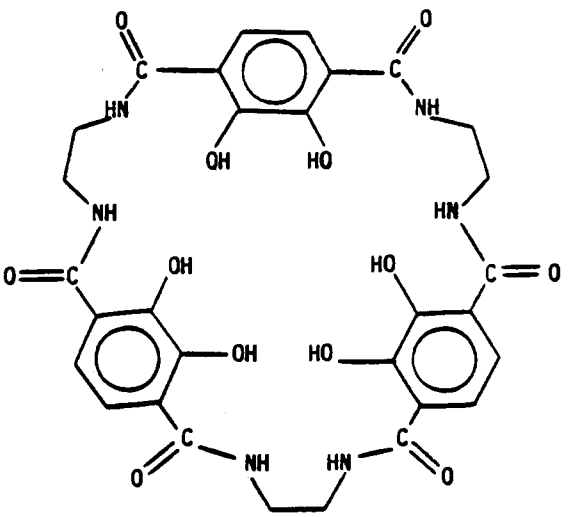


$(Ts)_2(Me)_2DHT$

$(Ts)_2(Me)_2$DHT
4,13-bis(*p*-tolylsulfonyl)-19,10-dimethoxy-8,9,17,22-tetraoxo-18,19,20,21-benzena-1,4,7,10,13,16-hexaazacyclodocosane

of oxalyl chloride was needed to produce an isolatable amount of **16**.

Protonation Constants. The protonation constants of **1** and **2** are listed in Table I, along with those of the tricatecholate macrocycle **17** recently described by Raymond and co-workers.[9]



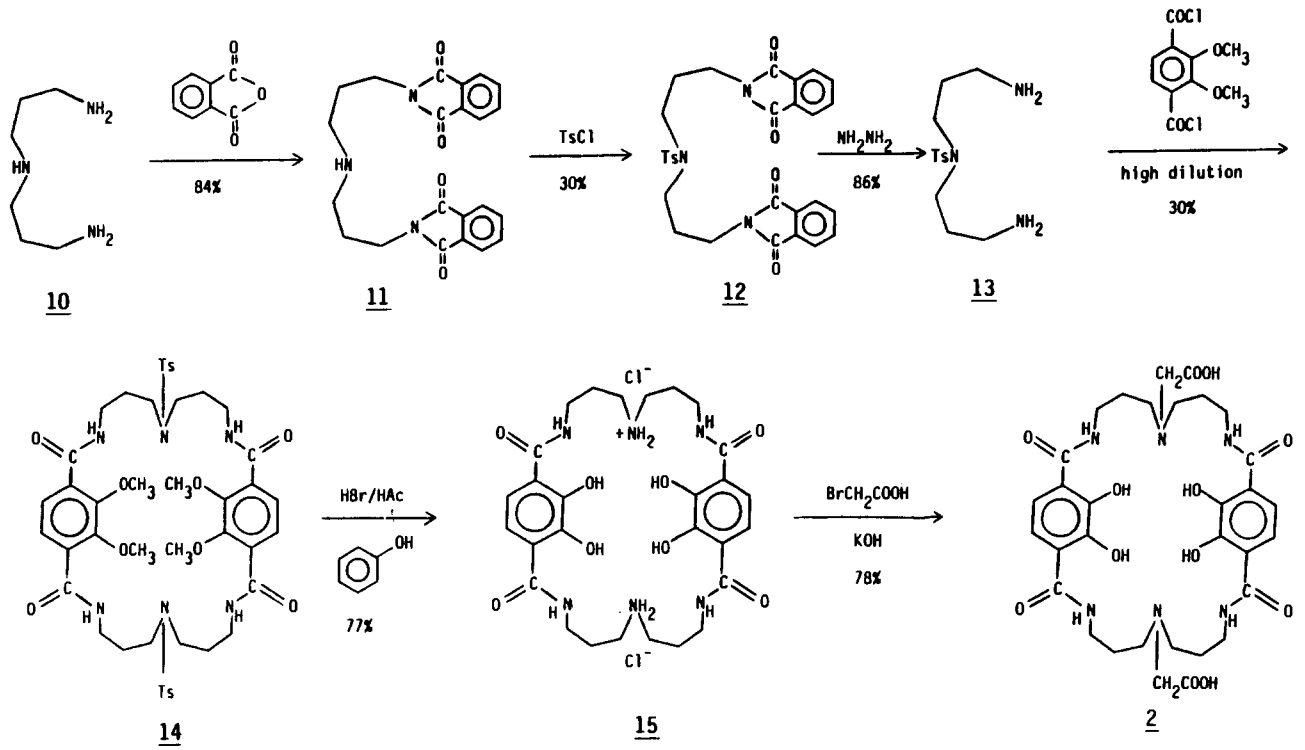
17

7,8,17,18,27,28-hexahydroxy-5,10,15,25,29-hexaoxo-6,7,8,9:16,17,18,19:26,27,28,29-benzena-1,4,11,14,21,24-hexaazacyclotriacontane

The first three overlapping protonation constants of the completely deprotonated anion of **1** were determined spectrophotometrically by a previously developed iterative method.[21-23] The remaining

(21) Anderegg, G.; L'Elpattenier, F. *Helv. Chim. Acta* **1964**, *47*, 1067.

Scheme II. Synthetic Scheme for BDHT[30]N_6



protonation constants for **1**, and all of the protonation constations of **2**, were determined potentiometrically. While the internal fit parameter was good (0.0035σ in absorbance units), the rather similar peaks for dianionic, anionic, and neutral catecholate groups result in a very large estimate of the accuracy for **1**. Similarly both the above inaccuracies and the problem of insolubility below p[H] ca. 7.5 precluded the ability to obtain a high degree of accuracy in the determination of higher protonation constants determined at low p[H].

As expected, **1** and **2** have a series of very high pK values corresponding to the presence of catecholate oxygens and aliphatic amino nitrogens. On the basis of the structures of these macrocycles alone it is not possible to predict which of the high protonation constants correspond to the protonation of the aminoacetate nitrogens. Spectral data, however, can be interpreted that the two highest pKs are phenolic in nature, and that the third and fourth involves the aliphatic amino nitrogens with partial though minor mixing with the remaining negative catecholate oxygens. The break between the fourth and fifth protonation constants for both ligands suggests that the fifth and sixth protonations involve catecholate oxygens. This conclusion is strengthened by the fact that these protonation constants are in the same range (ca. 6–8 log units) as the lower three of **17**.

It is noteworthy that the log K^H values of the smaller macrocyclic ring are higher than those of the larger ring. This is the reverse of what is usually observed in simpler molecules whereby the inductive effects across saturated ethylene bridging groups tend to lower the protonation constants (as in ethylenediamine vs. trimethylenediamine). The higher basicities in the smaller ring may be due to greater ease of hydrogen bonding to two or more donor groups in the protonated forms, thus increasing proton affinity.

Fe(III) Stability Constants. The stability constants of the Fe(III) chelates of **1**, **2**, and **17** are compared in Table II, along with the successive protonation constants of the iron(III) chelates. It is seen that Fe(III) affinities of the most basic forms of all three ligands are very high and are of comparable magnitude. The protonation constants of **1** and **2**, however are higher than those of **17**. This is probably due to the protonation of the aminoacetate nitrogens, indicating the removal of these donor groups from the coordination sphere of the metal ion and retention of the more strongly bound catecholate donor groups. The protonated complexes thus formed could have the carboxylate groups coordinated to the metal ion, so that the ligand could still supply six donor groups to the coordination sphere of the metal ion. The lower protonation constants of the Fe(III) chelate of **17** indicates somewhat greater difficulty in breaking up the coordination sphere formed by three bidentate catecholate moieties.

The visible spectra of the iron(III) chelates with absorption bands near 440 and 550 nm, do not change significantly with p[H]. The λ_{max} values shift somewhat depending on pH, which is not surprising in view of the fact that both complexes form protonated species at lower pH values. However, the basic diphenolate absorption due to charge transfer to Fe(III) appears to be intact. For example Murakami and Nakamura[24] pointed out that for some iron(III) catecholates, the absorbance shifts from 680 through 560 to 480 nm as 1:1, 2:1, and 3:1 catecholate:Fe(III) complexes are formed. Inspection of the data in Table III supports the suggestion that for the Fe(III) complex of **2** the catecholate donor groups are fully coordinated to Fe(III) throughout the p[H] range investigated. While a complete p[H] profile was not obtained for the UV–visible absorption bands of the Fe(III) complex of **1**, the pattern observed in this case was similar (i.e., peaks at 440 and 520 nm). However, a prominent additional shoulder at 350 nm would suggest a somewhat different, perhaps strained, conformation of the catecholate in the coordination sphere of Fe(III).

In both cases the presence of the 440- and 520–560-nm bands made the analysis of the EDTA competition experiments possible. The Fe(III)–EDTA complex is relatively colorless compared to the catecholate complexes.

A comparison of the effectiveness of coordination of Fe(III) by these three ligands at physiological pH is indicated by the pM values in Table II. It is seen that in spite of the fact that the stability constants for **1** and **2** are somewhat lower than that of **17**, they are as effective, or more effective, in binding Fe(III) at physiological pH. This is explained by the compensating effects of lower protonation constants for the more basic forms of the

(22) MacMillan, D. T.; Murase, I.; Martell, A. E. *Inorg. Chem.* **1975**, *14*, 468.
(23) Yoshida, I.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1983**, *22*, 2795.
(24) Murakami, Y.; Nakamura, K. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1408.

Table III. Principal Electronic Absorption Bands[a] of Fe(III)-DA-BDHT[30]N_6 (Fe^{III}(2)) as a Function of p[H]

p[H]	λ, nm	ε, M^{-1} cm^{-1}	λ, nm	ε, M^{-1} cm^{-1}	comments
2.90	440	2400	572	3500	a = 0, "MH_3L"
4.09	442	2879	565	4070	a = 4, "ML_2L"
9.03	448	4050	552	3680	a = 6, "ML"
10.60	440	4420	520	3500	a = 7, "MLOH"

[a] In H_2O at 25.0 °C; μ = 0.100 M.

Table IV. Logarithms of the Formation Constants of Protonated Macrocyclic Complexes of Fe(III)

formation equilibrium	DA-BDHT-[26]N_6 (1)	DA-BDHT-[30]N_6 (2)	TRIMER[a]
$Fe^{3+} + HL^{5-} \rightleftharpoons FeHL^{2-}$	36.0	34.52	34.7
$Fe^{3+} + H_2L^{4-} \rightleftharpoons FeH_2L^{-}$	32.8	31.34	28.7
$Fe^{3+} + H_3L^{3-} \rightleftharpoons FeH_3L$	27.1	25.09	

[a] TRIMER = $((p\text{-}C_6H_4(OH)_2)(CO)_2)_3(NHCH_2CH_2NH)_3$; see ref 9.

ligands, and greater metal binding by the protonated forms of the ligand that are predominant at physiological pH. Table IV shows the formation constants derived from the corresponding values of the equilibrium constants listed in Tables I and II.

The question has been raised[9] as to why the stability constant of the Fe(III) chelate of **17** turns out to be so much lower than that of enterobactin (log K ca. 52), in view of the fact that models show that Fe(III) coordination by all three catechol moieties can readily take place. The same questions might be raised for ligands **1** and **2**; however it should be pointed out that these sexadentate and octadentate ligands cannot conform to the octahedral coordination sphere of the metal ion without considerable distortion, involving twisting of the connecting bridges between the bidentate donor groups, which are made somewhat rigid by the trigonal amide pairs that extend the planarity of the aromatic rings. Such twisting would cost energy arising from the internal repulsions of the flexible ethylene groups of **17**, as well as **1**. The more flexible trimethylene bridge of **2** should provide some advantage in this respect. Another factor that would tend to lower the metal ion stability constants of **1**, **2**, and **17** would be the considerable loss of entropy associated with the conversion of a flexible macrocyclic ring to a relatively rigid distorted conformation when it is completely coordinated to a central metal ion.

The stabilizing influence of the so-called "macrocyclic effect" does not seem to be operating effectively for the iron(III) chelates of ligands **1**, **2**, and **17**. It should be noted, however, that the macrocyclic effect applies only when the fit between the metal ion and the cavity of the macrocycle is reasonably close, and the macrocyclic stability increment falls off very rapidly when the ring is too large or too small. Presumably this is the situation for all three ligands discussed here.

Because of the fact that the use of CPK space-filling models indicates that the structure of the iron(III) chelate of **1** is somewhat crowded, it had been thought that its stability constant for Fe(III) would be somewhat lower than that of **2**. That such is not the case indicates that the macrocyclic ring of **2** may be too large, and that the optimum size may be somewhere in between (i.e., a ring with 28 atoms). The difference of four atoms between the ring sizes of **1** and **2** is seen to be a matter of convenience in synthesis. Nevertheless, an attempt should be made to devise a convenient synthetic scheme for a 28-membered macrocyclic ring containing two catechols and two additional donors, and work along these lines is currently being planned.

In order to design sexadentate ligands with six donor groups that closely conform to an octahedral structure without considerable twisting and distortion, cryptand type ligands similar in design to the one reported by Wolfgang and Vogtle[8] are needed. With the cryptates, however, the preciseness of fit between the metal ion and the cryptand cavity is even more important than for the simpler macrocyclic ligands. Thus the synthetic problems for such ligands may be more severe, but the rewards in terms of high stability and selectivity would seem to make the required synthetic efforts very worthwhile.

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Registry No. **1**, 105103-80-8; **2**, 105103-79-5; **3**, 111-42-2; **4**, 16695-22-0; **5**, 23538-91-2; **6**, 23539-15-3; **7**, 7169-12-2; **8**, 105139-38-6; **9**, 105103-82-0; **10**, 111-40-0; **11**, 56-18-8; **12**, 56642-94-5; **13**, 105103-83-1; **14**, 105103-84-2; **15**, 105103-85-3; **16**, 105103-81-9.

Contribution from the Laboratoire de Synthèse et d'Electrosynthèse Organométallique associé au CNRS (UA 33), Faculté des Sciences "Gabriel", Université de Dijon, 21100 Dijon, France, and Centre d'Etudes Nucléaires de Saclay, Laboratoire associé au CNRS (UA 331), 91191 Gif sur Yvette Cedex, France

Thorium and Uranium Porphyrins. Synthesis and Crystal Structure of Bis(acetylacetonato)(2,3,7,8,12,13,17,18-octaethylporphyrinato)thorium(IV)

A. Dormond,[1a] B. Belkalem,[1a] P. Charpin,[1b] M. Lance,[1b] D. Vigner,[1b] G. Folcher,[1b] and R. Guilard*[1a]

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The action of thorium tetrachloride or uranium tetrachloride with porphyrins affords the dichloro complexes (Por)MCl_2 (M = Th or U). The latter derivatives react with sodium acetylacetonate giving rise to bis(acetylacetonato) complexes (Por)$M(acac)_2$. The two series of complexes are characterized on the basis of mass spectral, IR, UV-visible, and NMR data. The crystal structure of the title compound has been determined by X-ray diffraction methods: (OEP)$Th(acac)_2$, $C_{46}H_{58}N_4O_4Th$; M_r = 963; triclinic, $P\bar{1}$; a = 9.493 (7), b = 21.185 (5), c = 24.331 (7) Å; α = 104.18 (2), β = 96.11 (4), γ = 92.35 (4)°; V = 4705 Å^3; d_{calcd} = 1.359 g cm^{-3}; Z = 4; T = 298 K. A total of 9019 intensities were measured on a CAD 4 Enraf-Nonius diffractometer in the ω-2θ scan mode with monochromatized Mo Kα radiation ($1.5 < \theta < 20°$). The crystal structure was refined to a conventional $R(F)$ = 0.047 for 5323 reflections having $\sigma(I)/I < 0.33$. The thorium atom is octacoordinated by the four porphyrin nitrogen atoms and by the four oxygen atoms of the two acetylacetonato groups.

Introduction

There has recently been considerable work in metalloporphyrin chemistry because some complexes are of great interest as model compounds for understanding the function and relationships of several biological macromolecules. The chemical reactivity of this family of compounds has also attracted interest from their potential use in the activation of small molecules.[2-4] However, complexes

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(2) Smith, K. M., Ed. *Porphyrins and Metalloporphyrins*; Elsevier: Amsterdam, 1975.

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