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An Eight-Coordinate Cage: Synthesis and Structure of the First Macrotricyclic Tetraterephthalamide Ligand

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One side effect of nuclear technology is possible actinide element dispersal, which has raised concerns about low-level nuclear contamination of humans.[1] Efficient removal of actinides, especially plutonium, from living organisms represents a significant synthetic challenge for actinide coordination chemistry, due to the constraints of physiological conditions and low ligand toxicity. We have suggested[2] that the biological and chemical similarities of Pu(IV) and Fe(III) when combined with Nature's solution to sequestering iron can yield efficient actinide sequestering agents. The most potent natural Fe(III) chelator is enterobactin, a siderophore produced by enteric bacteria with a formation constant of $K_f \approx 10^{49}$, pM $\approx$ 35.5.[3,4] It is composed of three catechoylamide groups attached to a triserine lactone backbone. The greater efficiency of enterobactin in complexing iron when compared to other similar synthetic analogues is attributed to its optimal ligand disposition around the metal center.[4-6]

We have previously reported siderophore analogues with linear,[7-9] tripodal,[10,11] and macrocyclic topologies[12] and macrobicyclic topologies.[13-15] The linear tetracatecholate ligand 3,4,3-LICAMC has been shown to be one of the most effective chelating agents for Pu(IV) that is not toxic.[16] However, at physiological pH, due to the weak acidity of the catechol hydroxy groups and the large proton dependence of the complexation reaction, only three of four catecholate subunits are coordinated to Pu(IV).[17] Therefore, a more effective tetracatecholate ligand would be one with increased acidity and a greater predisposition toward binding. We have designed a new topological class of tetracatecholate ligands based on "H-shaped" tetrapodal hexaamine backbones[18]

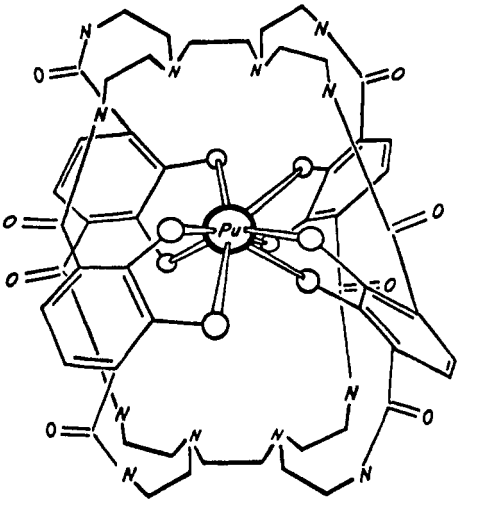
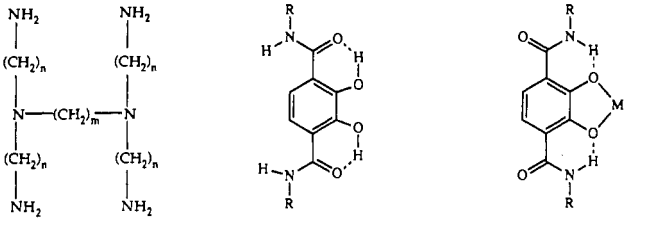


Figure 1. Schematic structure of a Pu(IV)–macrotricyclic tetraterephthalamide complex.

Chart I



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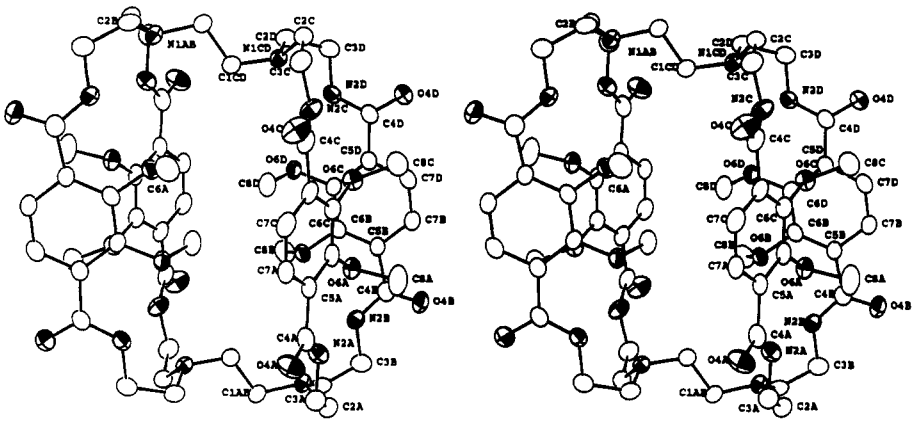
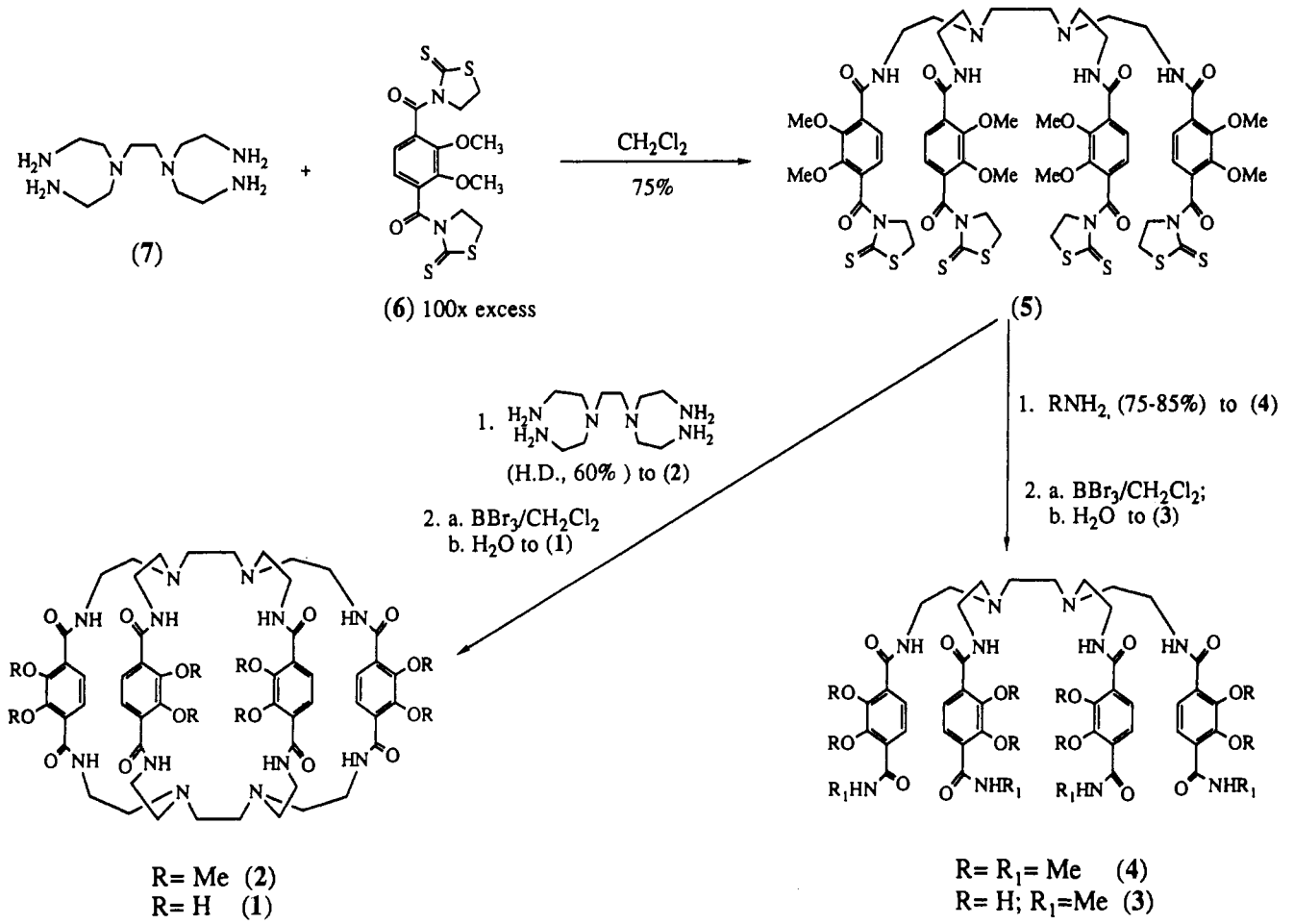


Figure 2. Stereoview (ORTEP) of the structure of the Me_8BHCAM molecule.

Scheme I



and the 2,3-dihydroxytetraphthalamide ligating subunits (Chart I) in both an open and a closed (macrotricyclic) architecture.

The terephthalamide ligating group displays the greatest affinity for ferric ion of any catecholate derivatives. The increased acidity and stronger metal complexation of the 2,3-dihydroxyterephthalamide ligands are attributed to the strong hydrogen bonding between the amide proton and the ortho hydroxyl group;[19] structures of all metal complexes of this class of ligands exhibit this.[15,20] The macrotricyclic tetraterephthalamide ligands are expected to be predisposed to coordination and hence display a high affinity toward Pu(IV). Figure 1 illustrates the schematic structure of a Pu(IV)–macrotricyclic tetraterephthalamide complex.

Entry into the chemistry of highly-predisposed catecholamide ligands has been restricted by synthetic methodology. Two routes to bicapped tricatecholate ligands have been devised,[13,21] yet each suffers limiations of generality or low yields. A high-yield route to various bicapped tricatecholate ligands[22] couples the bis(thiazolidine-2-thione) derivative of 2,3-dimethoxyterephthalic acid with a tripodal amine; preparation of gram quantities of this class of ligands with significant reduction in effort results. The previous nontemplate route required five steps and gives only

(18) "H-shaped" amines are based on *N,N,N',N'*-tetrakis(2-aminoethyl)-ethylenediamine (penten) and its homologues and derivatives.
(19) Garret, T. M.; Miller, P. W.; Raymond, K. N. *Inorg. Chem.* **1989**, *28*, 605.
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20–30% of the macrobicyclic product in the final cyclization step, while the new route has only three steps and much higher final cyclization yield (50–60%). This route was used to develop the novel topological class of H-tetrakis(catechoylamide) and bicapped H-terephthalamide macrotricycle ligands as shown in Scheme I.

The monocapped H-terephthalamide intermediate **5** is prepared in high yield by the presence of a large excess of **6**, which is readily separated from the product **5** by flash chromatography on silica. The methyl-protected macrotricyclic terephthalamide ligand, Me_8BHCAM, was prepared in a 60% yield via a high-dilution coupling cyclization.[23] This compound exists as two isomers, as indicated by TLC and NMR.[24] Recrystallization from acetone gives a white crystalline product[25] of only isomer B, which is relatively stable and does not convert to isomer A at room temperature in chloroform solution. The ^{1}H NMR and ^{13}C spectra of these isomers indicated that both of them have effective D_{2h} symmetry.[26]

Removal of the protecting groups (BBr_3/CH_2Cl_2) gives a 90% yield of impure product **1**, which is purified via formation of the Fe(III) complex, followed by demetalation with an acidic EDTA solution. The sparingly soluble ligand is filtered to give pure **1** as a light tan powder.[27] The simplicity of the ^{1}H NMR spectrum is indicative of a single species of D_{2h} symmetry.[28]

The free octadentate ligand H_8BHCAM reacts with $Ce(acac)_4$ in the presence of KOH as base to give the dark-brown complex K_4CeBHCAM, which can be purified on a polyacrylamide gel column. Its ^{1}H NMR suggests the formation of a high-symmetry eight-coordinated cage complex species.[29]

Only about 10% of absorbed Pu is removed spontaneously from mice[30] (with no chelating agent). In contrast, the macrotricycle **1** can remove 56% injected Pu(IV). This percentage is lower than that of the noncyclic analogue compound **3**, which can remove 77% injected Pu(IV) from mice. We suggest that the slower coordination kinetics of the macrocyclic ligand under physiological conditions is the reason for its relative performance.

The structural analysis of Me_8BHCAM·$4CH_2Cl_2$ shows the macrotricycle has idealized D_{2h} symmetry[31] and is most easily understood as a collection of two capping moieties and four terephthalamide units. The molecule is positioned on a crystallographic inversion center in the space group $P2_1/c$. An ORTEP stereodrawing of the entire molecule is in Figure 2.

The topology of this compound inherently generates a central cavity which is defined by the two capping units and the four nearly planar terephthalamide units. The lone pairs of the four tertiary amines on the caps are directed inward. Two methoxymethyl groups are also directed inward, filling the cavity of the molecule. All the amide protons are hydrogen bonded to their respective *o*-methoxy oxygens. This motif of hydrogen bonding in 2,3-dimethoxyterephthalamide units is well documented[32] and results in the nearly planar terephthalamide groups, as found.

By variation of the length or type of the central bridge of the H-amine, asymmetric or symmetric macrotricyclic tetraterephthalamide ligands with differing size of central cavity can be made by this synthetic route. Further work on the synthesis and coordination chemistry of H_8BHCAM, H-terephthalamide, and related compounds is in progress.

Acknowledgment. We thank Dr. P. W. Durbin and Ms. B. Kullgren for animal testing. T.D.P.S. thanks the National Science Foundation for a postdoctoral research fellowship (Grant CHE-8809111). This research was supported by the Director, Office of Energy Research, Office of Basic Energy Science, Chemical Sciences Division of the U.S. Department of Energy, under Contract No. DE-AC03-76SF00098.

Supplementary Material Available: For Me_8BHCAM, Tables I–IX, listing crystallographic data, positional parameters, bond lengths, bond angles, anisotropic thermal factors, least-squares planes, and dihedral angles (9 pages). Ordering information is given on any current masthead page.

(23) 4 L of CH_2Cl_2; 35 °C; duration of addition 100 h; yield 2 g of **2**.
(24) 10% MeOH in CH_2Cl_2; R_f = 0.66 and 0.73, respectively.
(25) Anal. Calcd (found) for $C_{60}H_{80}N_{12}O_{16}\cdot 2H_2O$: C, 57.13 (57.34); H, 6.71 (6.66); N, 13.33 (13.24). +FAB-MS: *m/e* 1226 $(MH)^+$.
(26) ^{1}H NMR (250 MHz, $CDCl_3$) for isomer A: δ 7.700 (br s, 8 H, amide), 7.038 (s, 4 arom H), 3.581 (br s, 16 H, NCH_2), 3.558 (s, 12 H, CH_3O), 2.93–3.04 (br m, 8 H, NCH_2), 2.65–2.75 (br m, 8 H, NCH_2), 2.630 (s, 8 H, NCH_2). ^{1}H NMR (250 MHz, $CDCl_3$) for isomer B: δ 7.707 (br s, 8 H, amide), 7.211 (s, 4 arom H), 3.609 (br s, 16 H, NCH_2), 3.506 (s, 12 H, CH_3O), 2.97–3.06 (br m, 8 H, NCH_2), 2.65–2.79 (br m, 8 H, NCH_2), 2.637 (s, 8 H, NCH_2). ^{13}C NMR (500 MHz, $CDCl_3$) for isomer A: δ 165.4, 151.3, 131.4, 124.7, 61.5, 53.8, 50.3, 37.3. ^{13}C NMR (500 MHz, $CDCl_3$) for isomer B: δ 165.2, 151.2, 131.1, 124.9, 61.5, 52.6, 49.0, 37.2.
(27) Anal. Calc (found) for $C_{52}H_{64}N_{12}O_{16}\cdot H_2O$: C, 55.21 (55.11); H, 5.88 (5.70); N, 14.86 (15.09). +FAB-MS: *m/e* 1113 $(MH)^+$.
(28) ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.92 (br s, phenol), 8.21 (s, 8 H, amide), 6.91 (s, 8 arom H), 3.41 (br s, 16 H + H_2O, NCH_2), 2.83 (br s, 8 H, NCH_2), 2.61 (br s, 8 H, NCH_2), 2.37 (s, 8 H, NCH_2).
(29) ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.81 (br s, 8 H, amide), 6.721 (br s, 8 arom H), 3.710 (br s, 16 H, NCH_2), 2.742 (br s, 24 H, NCH_2).
(30) 30 μmol/kg ligands were administered at 1 h, and mice were killed 24 h after injection of plutonium(IV)-238 citrate: Durbin, P. W.; Xu, J.; Raymond, K. N. Unpublished results.
(31) Me_8BHCAM ($C_{60}H_{80}O_{16}N_{12}\cdot 4CH_2Cl_2$), M = 1565.11, monoclinic, space group $P2_1/c$, a = 15.400 (3) Å, b = 11.225 (2) Å, c = 21.659 (6) Å, β = 98.50 (2)°, V = 3703 (3) Å^3, D_m = 1.37 g cm^{-3}, D_c = 1.40 g cm^{-3}, Z = 2, Mo Kα radiation (λ = 0.710 73 Å), μ(Mo Kα) = 3.74 cm^{-1}. 5354 reflections collected at −114 (5) °C on a CAD-4 diffractometer in the 2θ range between 3 and 45°. Redundant and systematically absent data were removed, leaving 4825 unique reflections. The structure was solved by direct methods and refined by full-matrix least squares to R = 0.046, R_w = 0.050 for 3282 reflections [$F_o^2 > 3\sigma(F_o^2)$].
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