Octadentate Ligands Containing 2,3-Dihydroxybenzamide and 2,3-Dihydroxyterephthalamide Coordinating Subunits on a Tetrapodal Amine Backbone for Chelation of Actinides

Jide Xu,[a] Anne E. V. Gorden,[a] and Kenneth N. Raymond*[a]

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The linear octadentate ligand 3,4,3-LICAM(C) (**2**) is one of the most effective chelating agents for Pu^{IV} that is not acutely toxic; 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 the four catecholate subunits are coordinated to Pu^{IV}. To overcome this disadvantage, a new topological class of octadentate ligands based on tetrapodal amine backbones and 2,3-dihydroxyterephthalamide (**3**) (TAM) binding units were designed and synthesized. The amide substituents provide a handle by which the functionality of the ligand can be readily modified, and this synthetic strategy and procedure can be extended to prepare a variety of new multidentate metal-coordination and extraction agents. A streamlined synthesis for the terephthalamides, both symmetric and asymmetric, was recently reported. In this work, the synthetic details of their incorporation into octadentate systems for use as coordination or extraction agents for Pu^{IV} or other metals in the +4 oxidation state are described.

Introduction

Nature has responded to the problem of the low bioavailability of Fe due to the insolubility of $Fe(OH)_3$ by developing selective, high-affinity Fe^{III}-sequestering agents, called siderophores.[1] The great specificity of the siderophores towards Fe^{III}, the toxicity of Pu^{IV}, and its chemical similarities to Fe^{III}, inspired the development of analogous sequestering agents for Pu^{IV}.[2] Previously, catecholate-based ligands have been investigated in the formation of metal coordination complexes in large part due to their high affinity for high-oxidation-state metals.[3−5] Ligands containing four catechol-binding subunits connected by a suitable molecular backbone were predicted to form stable eight-coordinate complexes with Pu^{IV}. This has been the foundation of an ongoing program of research resulting in the design and synthesis of numerous octadentate ligands for Pu^{IV} chelation and is the subject of a recent extensive review.[2]

The ligand of this group found to be the most effective tetracatecholate ligand for Pu^{IV} chelation, 3,4,3-LICAM(S) (**1**) (which is toxic), and the nontoxic 3,4,3-LICAM(C) (**2**) promoted as much or more Pu excretion from mice and dogs at a dosage of 30 μmol kg^{-1} as an equimolar amount of $CaNa_3$-DTPA, and at lower dosages it was much more effective than $CaNa_3$-DTPA;[6] however, 3,4,3-LICAM(C) (**2**) was only marginally effective for reducing the lung burden of inhaled Pu,[7] and treatment with 3,4,3-LICAM(C) (**2**) caused potentially radiologically damaging amounts of Pu to be transferred to and deposited in the kidneys of several species (Figure 1).[8] From this, it was determined that at physiological pH, the weak acidity of the catechol hydroxy groups and the eight-proton stoichiometry of the complexation reaction prevent 3,4,3-LICAM(C) (**2**) from forming an octadentate Pu^{IV} complex. With only three of the four catecholate subunits coordinated to Pu^{IV}, the stability of the Pu complexes at pH 7.4 only slightly exceed that of the Fe^{III} complex, and at pH lower than 7.4, the Pu^{IV} complexes with 3,4,3-LICAM(C) (**2**) are unstable.[9,10] Therefore, a more effective tetrakis catechoyl-based ligand would be one with increased acidity and a greater predisposition towards binding.

The 2,3-dihydroxyterephthalamide (TAM) ligating group **3** (see Figure 2), while similar in structure to the catecholamide groups found naturally occurring in siderophores, is substantially more acidic than the CAM ligating group, is less sensitive to oxidation, and displays the greatest affinity for the ferric ion of any catecholate derivative.[11,12] These properties are believed to be derived from the strong hydrogen bonding between the amide proton and the *ortho* hydroxy group. Structural characterizations of metal complexes of this class of ligands with iron (Fe)[13] and with thorium (Th), as an analog for plutonium (Pu),[14,15] exhibit this hydrogen-bonding motif. An eight-coordinate geometry is generally preferred by Pu^{IV}, and a preorganized

[a] Department of Chemistry and Chemical Science Division, Lawrence Berkeley Laboratory, University of California at Berkeley,
Berkeley, California, 94720 USA
Fax: (internat.) +1-510-486-5283
E-mail: Raymond@socrates.berkeley.edu

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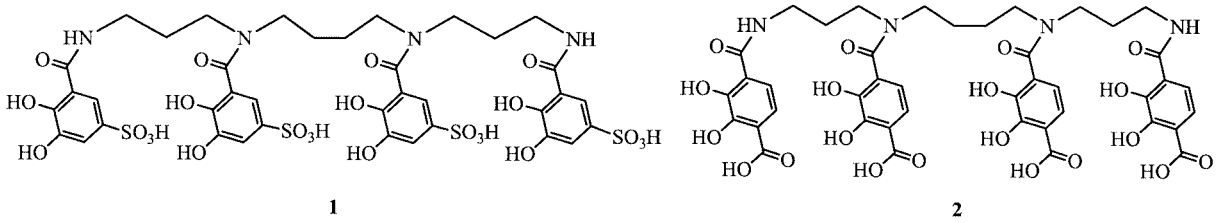


Figure 1. Tetracatecholate ligands 3,4,3-LICAM(S) (**1**) and 3,4,3-LICAM(C) (**2**)

tetrapodal tetra-terephthalamide ligand should provide a proper coordination environment for chelating Pu^{IV}. Based on this hypothesis, a new structural class of ligands was designed, incorporating "H-shaped" tetra-primary-amine backbones and the 2,3-dihydroxyterephthalamide ligating subunits (Figure 2) in both open and closed or macrotricyclic architectures.[16]

We recently reported a streamlined synthesis for the terephthalamides (e.g. **3**, Figure 2), both symmetric and asymmetric.[14] Earlier work has carefully detailed their efficiency as chelating agents for Fe^{III} [11] and more recently, the results of peripheral charge variation on the stability of the Fe^{III} complexes.[17] In this work, the synthetic details of their incorporation into octadentate systems for use as coordination or extraction agents for Pu^{IV} or other metals in the +4 oxidation state and the effects of changes in the fundamental octadentate framework are described. In order to optimize the ligand design, corresponding octadentate linear TAM ligands, H-CAM, Oxo-H-CAM, and H-CAM(C) ligands were also designed and characterized.[18–20]

Results and Discussion

The synthetic routes for different types of octadentate ligands are shown in Schemes 1–4. Methyl 4-chlorocarbonyl-2,3-dimethoxybenzoate (**9**),[21,22] 3-[(2,3-Dimethoxyphenyl)carbonyl]thiazolidine-2-thione (**22**),[23] and the terephthalamide derivative **26**[13] were prepared as described previously. TAEC [*N*,*N*′,*N*′′,*N*′′′-tetrakis(2-aminoethyl)-1,4,8,11-tetraazacyclotetradecane, **7**][24] and PENTEN [*N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)ethylenediamine, **6**][25] were synthesized following the published method. *N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)propanediamine and *N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)butanediamine were prepared by a similar method. Like the CAM ligands, TAM ligands can be used to create a wide variety of ligand sys-

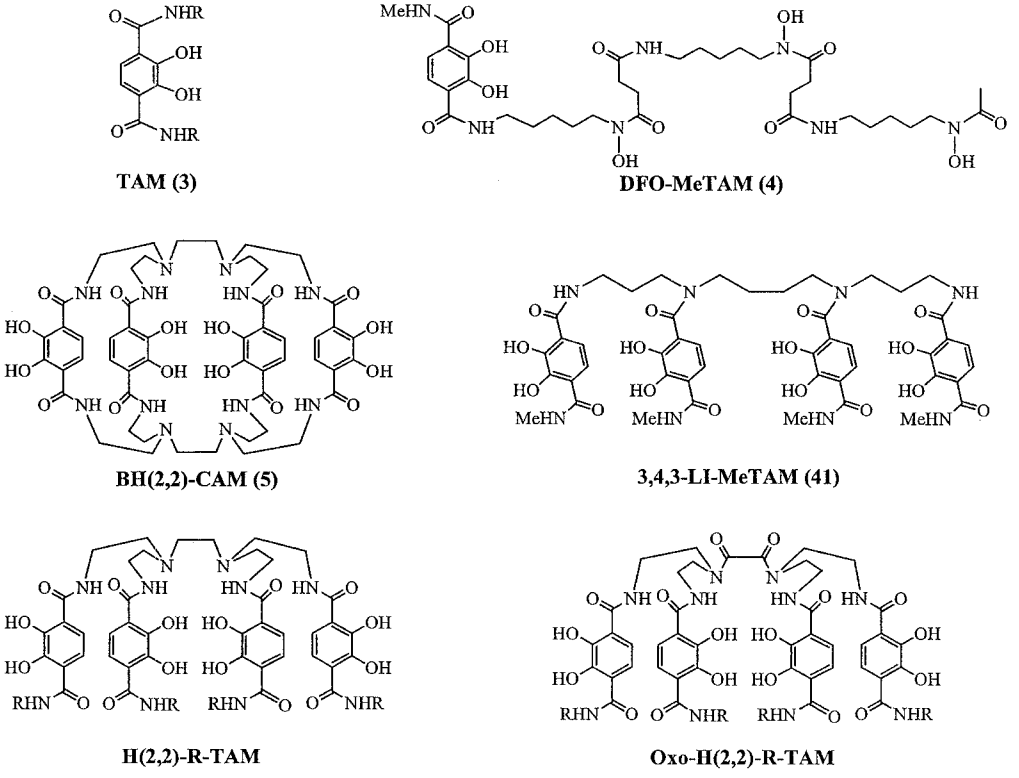


Figure 2. Octadentate terephthalamide ligands

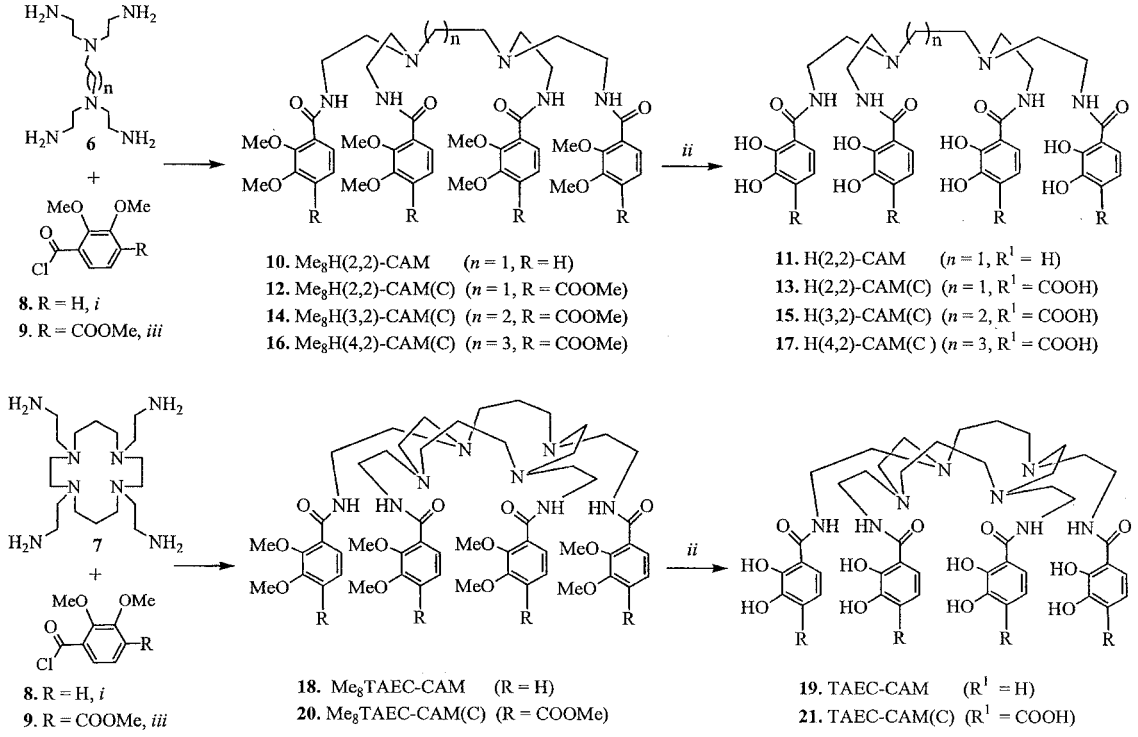
tems by attaching them to various backbones. This strategy can be extended to prepare a variety of multidentate sequestering agents with unique geometries using other amines or modified chelating subunits or combinations of subunits.

The synthetic scheme for the TAM chelating subunits begins with the inexpensive, commercially available catechol. The carboxylation of catechol is followed by conversion of these carboxy groups to methyl esters, then methyl protection of the catecholate oxygen atoms and saponification of the esters to the carboxylic acid, which can then be converted into the acyl chloride or thiazolamide. This procedure differs from the synthesis of CAM ligands in that it requires the saponification of both the esters as opposed to one in the case of the CAM ligands. The acid chloride- or thiazolamide-activated TAM provides the required functionalization to treat the ligand with a variety of amines to serve as the backbone for the higher denticity system. After amidation to add a chelating unit to the backbone, aminolysis of the second with an excess of amine results in the TAM ligand. The hydroxyl-protecting groups can then be cleaved by treatment with an excess of BBr_3. In the alternative streamlined methodology, the protection of the phenolic oxygen atoms is not required as the direct activation of the 2,3-dihydroxyterephthalic acid with sulfuryl chloride is followed directly by reaction with an amine.[26]

The general procedure for the synthesis of the octadentate CAM ligands H(2,2)-CAM (**11**) and TAEC-CAM (**19**) (Scheme 1) begins with the addition of a solution of the desired tetraamine, PENTEN H(2,2)-amine (**6**) or TEAC (**7**), in CH_2Cl_2 to the acyl chloride, 2,3-dimethoxybenzoyl chloride (**8**).[23] Purification by flash chromatography on silica gel (1−6% MeOH gradient in CH_2Cl_2 as eluent) provides the methoxy-protected H(2,2)-CAM **10** (75% yield) or the methoxy-protected TAEC-CAM **18** (80% yield) as a pale yellow oil. This product was deprotected with the addition of BBr_3 by syringe to the above methoxy-protected ligand **10** or **18** in anhydrous CH_2Cl_2 at −78 °C. The slurry was warmed to room temperature and stirred continuously for four days. After returning the reaction mixture to −78 °C, methanol was added. The mixture was then heated to boiling with water to hydrolyze the remaining borate ester. The H(2,2)-CAM (**11**) (100% yield) or TAEC-CAM (**19**) (65% yield) that precipitated upon cooling was collected by filtration and dried under vacuum at 60 °C overnight.

When a solution of the appropriate H(*n*,2)-tetraamine and NEt_3 in anhydrous THF was added to 4-chlorocarbonyl-2,3-dimethoxybenzoic acid methyl ester (**9**),[21] a white precipitate immediately formed. This reaction mixture was stirred overnight at room temperature and filtered. Evaporation of the filtrate in vacuo yielded a viscous oil, which was purified by flash chromatography on silica gel (2−4% MeOH gradient in CH_2Cl_2 as eluent) to give the fully methoxy-protected product [H(*n*,2)-CAM(C) **12**, **14**, **16** or TAEC-CAM(C) (**20**)] as a yellow oil, which, when deprotected with BBr_3 as described above, resulted in the carboxylated CAM product **13**,**15**,**17**, or **21** in good yield (Scheme 1).

Following a similar procedure (Scheme 2), diethylenetriamine in CH_2Cl_2 was added to **22**.[23] The crude product



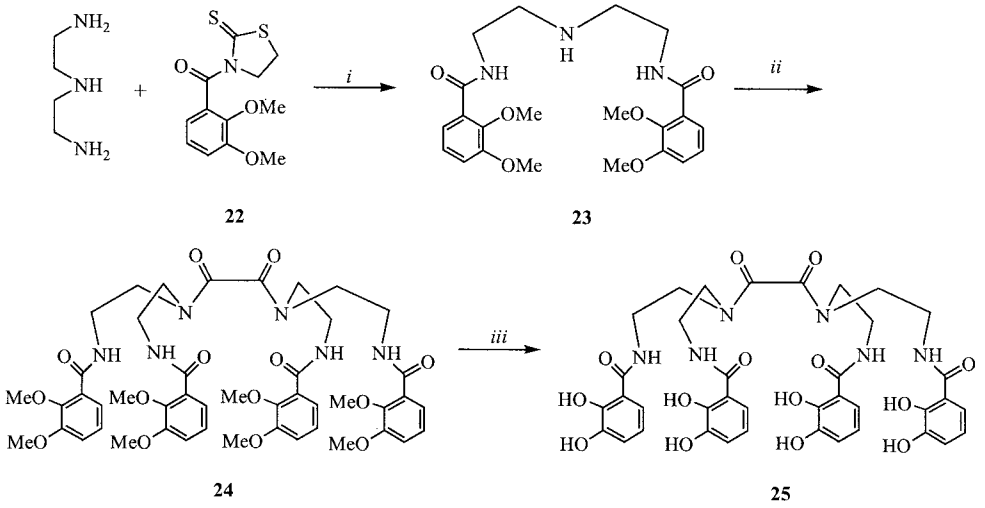
Scheme 1. Synthesis of octadentate catecholamide ligands; reagents and conditions: (i) CH_2Cl_2, room temp., 24 h; (ii) 1. BBr_3, CH_2Cl_2, −78 °C, under Ar; 2. MeOH, −78 °C; 3. H_2O, 100 °C (iii) anhydrous THF, Et_3N

was purified by chromatography on silica gel (1−3% MeOH gradient in CH_2Cl_2 as eluent) to give pure **23** (87% yield) as a pale yellow oil. Compound **23**, Et_3N, and oxalyl chloride were combined in anhydrous THF at −78 °C, and the reaction mixture was stirred at 25 °C for 4 hours and before being evaporated to dryness and an aqueous work up. The crude product was purified by chromatography on silica gel (3−6% MeOH gradient in CH_2Cl_2 as eluent) to give the methoxy-protected oxo-H(2,2)-CAM **24** as a pale yellow oil (63% yield), which, after deprotection with an excess of BBr_3 as described above, yielded **25** as a white powder (89% yield).

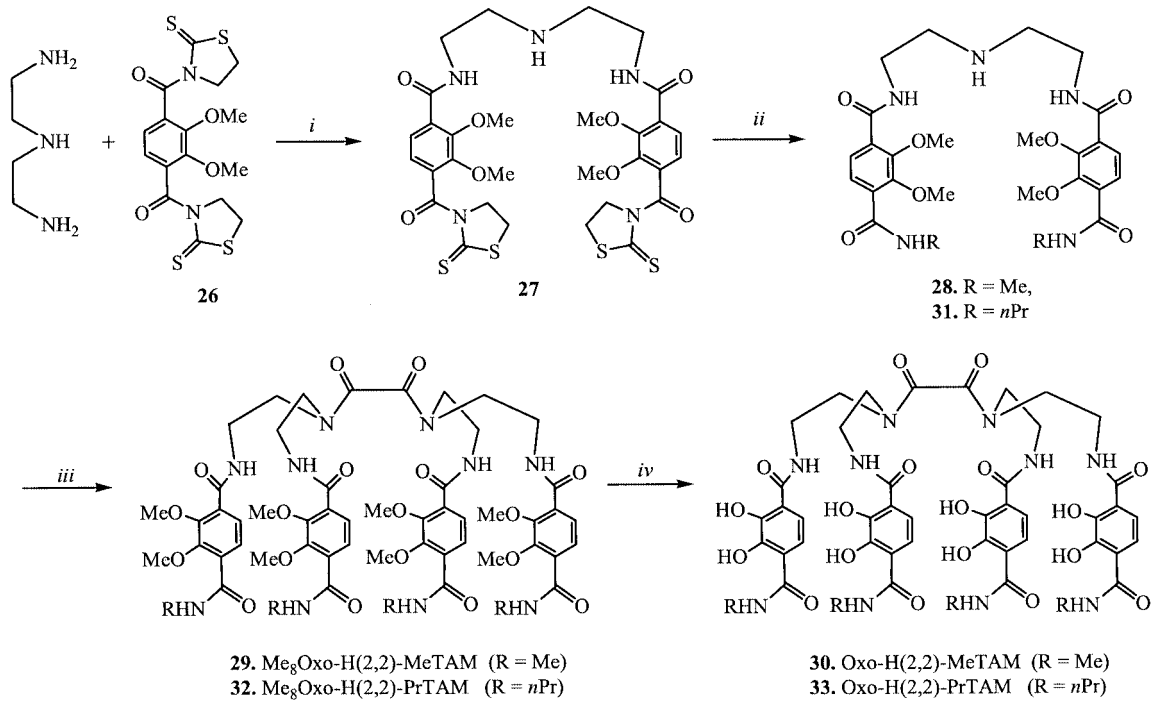
Scheme 3 depicts the synthesis of the Oxo-TAM ligands beginning from the diethylenetriamine derivative **27**. This intermediate product can be produced through the slow addition of a solution of diethylenetriamine in CH_2Cl_2 to a solution of terephthalamide derivative **26**[13] in CH_2Cl_2 containing 2% MeOH. After the addition, the reaction mixture was passed through a silica gel column, and eluted with 2% MeOH in CH_2Cl_2 to remove most of the excess terephthalamide derivative **26**, while **27** was retained on the silica column. The appropriate fractions of a gradient elution (5−10% MeOH in CH_2Cl_2) were collected and concentrated to produce **27** (75% yield) as a white foam. A solution of **27** in CH_2Cl_2 was reacted with methylamine in MeOH. The crude product, isolated by column chromatography on silica gel (6−12% MeOH +0.2% Et_3N in CH_2Cl_2), yielded the **28** as a white solid (85% yield). The methoxy-protected Oxo-H(2,2)-MeTAM **29** was then synthesized by coupling two molecules of **28** with oxalyl chloride by adding the reagent with stirring to a solution of **28** and Et_3N in anhydrous THF at −30 °C. The reaction mixture was stirred at 25 °C for 4 hours and concentrated by evaporation. The residue was dissolved in dichloromethane and washed successively with aqueous 1 M HCl and water. The crude product was purified by column chromatography on silica gel (6−12% MeOH + 0.2% Et_3N in CH_2Cl_2) to give a white solid (63% yield). The methoxy-protected oxo-H(2,2)-MeTAM **29**, deprotected with excess BBr_3 as described for the deprotection of CAM ligands, yielded **30** as a beige powder in 85% yield.

Following the same procedure using *n*-propylamine in place of the methylamine solution, yields compound **33**. The pure product was obtained as a white foam (89% yield). Preparation of Me_8Oxo-H(2,2)-PrTAM (**32**) was carried out in a procedure similar to the synthesis of Me_8Oxo-H(2,2)-MeTAM (**29**), except that **29** was used as the starting material instead of **28**. Purification by column chromatography (4−10% MeOH in CH_2Cl_2) gave Me_8Oxo-H(2,2)-PrTAM (**32**) as a white solid (71%). Me_8Oxo-H(2,2)-PrTAM (**32**), deprotected with excess BBr_3 as described for the deprotection of the other CAM ligands, yielded **33** as a beige powder in 78% yield.

The H(2,2)-MeTAM (**37**), H(2,2)-EtTAM (**38**), and H(2,2)-PrTAM (**39**) ligands can be obtained using a general procedure based on that for the CAM(C) ligands (Scheme 4). A solution of PENTEN H(2,2)-amine (**6**) and NEt_3 in anhydrous THF was added to the benzoate **9**[21] in anhydrous THF by cannula under nitrogen, immediately forming a white precipitate. The reaction mixture was stirred overnight under nitrogen at room temperature, and the triethylamine hydrogen chloride-precipitate by-product was collected by filtration. Concentration of the filtrate in vacuo yielded a viscous oil, which was purified by chromatography on silica gel (2−4% MeOH in CH_2Cl_2) to give the methoxy-protected CAM(C) species **34** as pale yellow oil. Compound **34** was mixed with methanol and a 1 M aqueous NaOH solution. The reaction mixture was heated to reflux temperature for 4 hours and then evaporated to dryness. The residue was dissolved in H_2O and acidified to pH 2 using 6 M HCl. The methoxy-protected CAM(C) tetraacid species **35** settled as a pale yellow oil. The crude product was dissolved in dry THF, filtered, and coevaporated with anhydrous THF three times to remove water.



Scheme 2. Synthesis of octadentate oxo-catecholamide ligands **1**, Oxo-H(2,2)-CAM; reagents and conditions: (i) anhydrous THF, Et_3N; (ii) 1. Et_3N, anhydrous THF, oxalyl chloride, −78 °C; 2. 25 °C, 4 h; 3. CH_2Cl_2, aqueous workup, 1 M HCl; (iii) 1. BBr_3, CH_2Cl_2, −78 °C, under Ar; 2. MeOH, −78 °C; 3. H_2O, 100 °C



Scheme 3. Synthesis of octadentate oxo-catecholamide ligands; reagents and conditions 2: (i) CH_2Cl_2 containing 2% MeOH; (ii) NH_2Me, MeOH, room temp., 4 h; (iii) Et_3N, anhydrous THF, oxalyl chloride, −30 °C; (iv) 1. BBr_3, CH_2Cl_2, −78 °C, under Ar; 2. MeOH, −78 °C; 3. H_2O, 100 °C

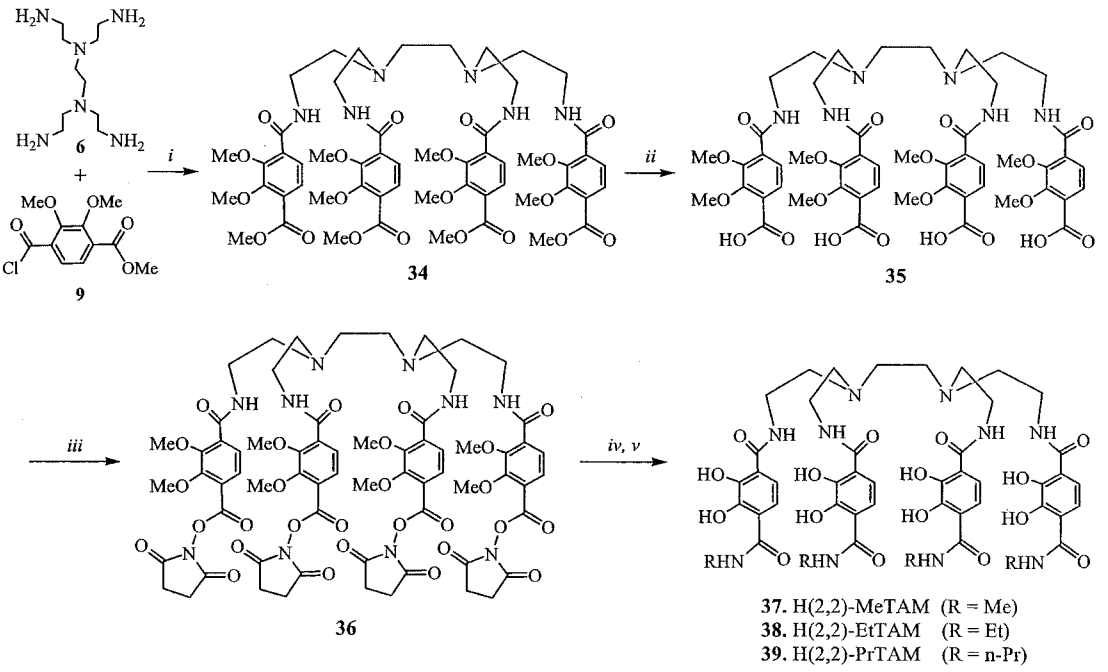
At −10 °C, under argon, *N*-hydroxysuccinimide and 1,3-dicyclohexylcarbodiimide were added to **35** in THF. After stirring for 24 hours, an appropriate backbone amine in THF was added with stirring. The dichlorourethane solids were removed by filtration, and the filtrate was evaporated to dryness and purified by chromatography on silica gel (4−6% MeOH in CH_2Cl_2) to give the corresponding octadentate 2,3-dimethoxyterephthalamide ligand as a pale yellow oil, which was then deprotected with BBr_3 as above to give **37**, **38**, or **39**. The linear octadentate terephthalamide ligand 3,4,3-LIMeTAM (**41**) was synthesized and purified by the same procedure as for the H(2,2)-TAMs, except that spermine (**40**) was used instead of PENTEN **6** (Scheme 5).

The isolated ligands are white to pale yellow in color. In general, they are not very hygroscopic and are obtained as micro-crystalline or amorphous solids. While DFO-MeTAM and 3,4,3-LIMeTAM melt sharply, the other octadentate compounds having tertiary nitrogen atoms decompose slowly upon heating. The most distinctive feature of the ^{1}H NMR spectra of H-CAMs and Oxo-H-CAM is the presence of two doublets and one triplet in the aromatic region arising from the catechoylamide ring protons: the triplet appears at δ = 6.4−6.7 ppm, the two doublets appear at δ = 6.9−7.0 and 7.2−7.4 ppm. The infrared spectra of the isolated compounds display a strong band at 1610−1640 cm^{-1} due to the amide groups. These octadentate ligands are in general slightly soluble in water. They have pKa_1′s in range of 6−8, and the pH of a saturated solution is typically neutral. These compounds should form stable complexes with metal ions having high charge-to-radius ratio, such as Fe^{3+}, Ce^{4+}, Pu^{4+}, and so forth.

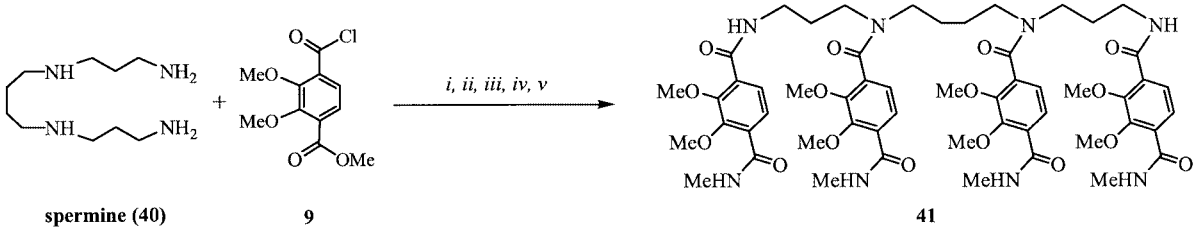
The crystal structure, ^{1}H and ^{13}C NMR spectra of the protected Me_8BH(2,2)-CAM, previously reported, indicated that it has effective D_{2h} symmetry both in the solid state and in solution. The ^{1}H NMR spectra taken of the related free macrotricyclic octadentate ligand, BH(2,2)-CAM (**5**), and its stable complex, K_4CeBH(2,2)-CAM, also revealed that they have effective D_{2h} symmetry, suggesting some predisposition of the ligand for the expected highly symmetrical eight-coordinated cage-complex formation, although this cannot be concluded definitively without structural evidence.[19]

Conclusion

The Pu^{IV} complexes with tetracatechoylate ligands are functionally hexadentate at physiological pH.[8,10] In the case of 3,4,3-LICAM(C), the Pu complex becomes progressively less stable as the pH is reduced below pH 7.4. In vivo, hexadentate binding, whether structural or functional, is manifested by retention of Pu in the mouse of 30 to 35% of control, and instability of the Pu complexes at pH lower than 7.4 causes large Pu residues (> 150% of control) to be deposited in kidneys and soft tissue.[8,10] In separate studies using Pu^{IV}-injected mice, none of the ligands described in this report [composed of CAM, CAM(C), or TAM metal-binding groups] promoted significantly more Pu excretion than an equimolar amount of 3,4,3-LICAM(C), from



Scheme 4. Synthesis of octadentate 2,3-dihydroxyterephthalamide ligands; reagents and conditions: (i) 1. anhydrous THF, Et_3N, under N_2; 2. under N_2, room temp., 12 h; (ii) 1. aqueous workup, MeOH, 1 M NaOH; 2. 100 °C, 4 h; 3. H_2O, 6 M HCl; (iii) THF, −10 °C, under Ar, *N*-hydroxysuccinimide, 1,3-dicyclohexylcarbodiimide; (iv) 24 h, room temp., THF, RNH_2; (v) 1. BBr_3, CH_2Cl_2, −78 °C, under Ar; 2. MeOH, −78 °C; 3. H_2O, 100 °C



Scheme 5. Synthesis of 3,4,3-LIMeTAM; reagents and conditions: (i) 1. anhydrous THF, under N_2; 2. under N_2, room temp., 12 h; (ii) 1. aqueous workup, MeOH, 1 M NaOH; 2. 100 °C, 4 h; 3. H_2O, 6 M HCl; (iii) THF, −10 °C, under Ar, *N*-hydroxysuccinimide, 1,3-dicyclohexylcarbodiimide; (iv) 24 h, room temp., THF, $MeNH_2$; (v) 1. BBr_3, CH_2Cl_2, −78 °C, under Ar; 2. MeOH, −78 °C; 3. H_2O, 100 °C

which it is inferred that these are also functionally hexadentate for Pu^{IV} chelation at physiological pH. All but four of this related series of ligands [3,4,3-LIMeTAM, BH(2,2)-CAM, DFO-MeTAM, and its Fe^{III} complex] were found to deposit Pu^{IV} in the kidneys in excess of the control value, indicating that their Pu^{IV} complexes are not stable at reduced pH. This deposition of the heavy metal at the reduced pH of the kidney is held to be the cause of some toxicity found with other CAM ligands previously studied,[27,28] and is one reason for ongoing research and the continued development of new ligand systems.[29−31]

Several conclusions on the desirable characteristics for an in vivo, chelating ligand for Pu^{IV} can now be drawn. In comparison to the 3,4,3-LICAM(C) system, the attachment of the TAM functional group to the spermine backbone improved the stability of the Pu chelate at the low pH of renal tubular urine somewhat, diminishing the problem of dissociation of the Pu^{IV} complex within the kidneys. In vivo, the MeTAM binding group was found to be almost equally effective in tetrameric ligands based on spermine or PENTEN, and replacement of the ethylene bridge by Oxo-H(2,2)- or by propylene or butylene bridges reduced the stability of the Pu complexes, supporting the usefulness of the PENTEN backbone for octadentate ligands.[29]

Previously, the synthesis and, in some cases, evaluation of in vivo Pu^{IV} chelation by siderophore analogs with linear,[6,30,32−34] tripodal[34−36] macrocyclic,[6] and macrobicyclic topologies have been reported,[13,37] including an approach similar to this using "H-shaped" tetrapodal hexaamine backbone systems in the design of hydroxypyridinone-based chelating ligands for actinides. The hydroxypyridinonate or HOPO (2-hydroxy-1-methyl-3- or 1-hydroxy-2-pyridinone abbreviated as Me-3,2-HOPO or 1,2-HOPO) ligands possesing increased acidity and solubility, were found to further improve Pu^{IV} chelation in mice while still maintaining the stability of the Pu^{IV} complex at the reduced

pH of the kidney.[36] Recently, mixed TAM-HOPO systems have been investigated as Pu^{IV} decorporation agents.[30] These mixed systems have also been used to prepare complexes with Gd^{III} for the development of higher relaxivity-contrast agents for MRI.[38,39]

As shown in Schemes 1−4, various approaches were designed to prepare octadentate ligands bearing CAM, CAM(C), and TAM chelating subunits. Amide substituents provide a handle by which the functionality of the ligand can be readily modified, and this synthetic strategy has been extended to prepare a variety of new multidentate ligand systems. Although Pu complexes of the TAM ligands were found to be more stable at reduced pH than the previously described CAM-based ligands, the increase in acidity from CAM-based ligands to TAM-based systems did not markedly increase the coordination of Pu^{IV}, as there was no dramatic increase in Pu^{IV} excretion seen in in vivo testing in the mouse model.[29] These systems remain attractive for use as actinide-selective extraction agents in environmental applications or waste-remediation systems due to their relative ease of synthesis and comparative stability.

Experimental Section

General Remarks: Unless otherwise noted, materials were used as obtained commercially without further purification. Benzoate **9**,[21,22] benzamide derivative **22**[23] and terephthalamide derivative **26**[13] were prepared as described in previous publications. TAEC [*N*,*N*′,*N*′′,*N*′-tetrakis(2-aminoethyl)-1,4,8,11-tetraazacyclotetradecane, **7**][24] and PENTEN [*N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)ethylenediamine, **6**][25] were synthesized following the published method, *N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)propanediamine and *N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)butanediamine were prepared by a similar method. Syntheses of macrotricyclic DFO-MeTAM (**4**, Figure 2) and BH(2,2)-CAM (**5**) have been published in earlier works.[19,20]

The synthetic routes for different types of octadentate ligands are shown in Schemes 1−4. Mass spectroscopic data were obtained with an Atlas MS-12, a consolidated 12−110B, or a Kratos MS50 spectrometer. The ^1H and ^{13}C NMR spectra were recorded with a UCB-250, a Bruker AM-400 or a Bruker DRX500 spectrometer. Elemental analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

Synthesis of Octadentate CAM Ligands H(2,2)-CAM and TAEC-CAM (11, 19)

General Procedure: See Scheme 1. A solution of the appropriate tetraamine, PENTEN [H(2,2)-amine) or TEAC, (0.5 mmol) in CH_2Cl_2(50 mL) was added to benzamide derivative **22**[23] (0.60 g, 2.2 mmol) with stirring. The mixture was stirred at 25 °C for 24 h and the solvent was removed. The crude product was purified by flash chromatography on silica gel (1−6% MeOH gradient in CH_2Cl_2 as eluent) to give the methoxy-protected H(2,2)-CAM **10** (75% yield) or the methoxy-protected TAEC-CAM **18** (80% yield) as a pale yellow oil. The product was deprotected as follows: Under argon, BBr_3 (1.5 mL, neat) was added dropwise by a syringe, with stirring, to the above methoxy-protected ligand **10** or **18** (0.4 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C. The slurry was warmed to 25 °C and stirred continuously for 4 days. After returning the reaction mixture to −78 °C, methanol (20 mL) was added. The mixture was then warmed to 25 °C; then heated to boiling with water (100 mL) to hydrolyze the remaining borate ester. The H(2,2)-CAM (**11**) (100% yield) or TAEC-CAM (**19**) (65% yield) that precipitated upon cooling was collected by filtration and dried under vacuum at 60 °C overnight.

H(2,2)-CAM (11): M.p. 215 °C, total yield 75%. $C_{38}H_{44}N_6O_{12}$; $[M + H]^+$ calcd. 776.81; found 777. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 3.53 (s, 8 H, CH_2N), 3.82 (s, 8 H, CH_2N), 3.88 (s, 4 H, CH_2N), 6.70 (t, *J* = 7.8 Hz, 4 H, Ar H), 6.97 (d, *J* = 7.6 Hz, 4 H, Ar H), 7.41 (d, 4 H, Ar H), 9.2 (s, 4 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 34.1, 51.8,115.3, 117.9, 118.3, 119.2, 146.2, 149.2, 170.2 ppm.

TAEC-CAM (19): M.p. 186°C, total yield 52%. $C_{46}H_{60}N_8O_{12}$; $[M + H]^+$ calcd. 917.04; found 917. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.80 (br., 4 H, CH_2), 2.80−3.00 (br., 16 H, CH_2), 3.35, 3.54 (br., 16 H, CH_2), 6.70 (t, *J* = 7.8 Hz, 4 H, Ar H), 6.90 (d, *J* = 7.7 Hz, 4 H, Ar H), 7.30 (d, *J* = 8.0 Hz, 4 H, Ar H), 8.90 (s, 4 H, NH) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 37.4, 46.6, 48.2, 51.2, 55.0, 115.7, 119.5, 120.1, 146.5, 150.4, 170.8 ppm.

Synthesis of Octadentate CAM(C) Ligands H(*n*,2)-CAM(C) 13, 15, 17 and TAEC-CAM(C) (21)

General Procedure: See Scheme 1. A solution of the appropriate H(*n*,2)-tetraamine (0.3 mmol) and NEt_3 (0.2 mL, 1.5 mmol) in anhydrous THF (10 mL) was added to the benzoate derivative **9**[21] (0.39 g, 1.5 mmol) in anhydrous THF (20 mL). A white precipitate immediately formed. The reaction mixture was stirred at room temperature overnight in a stoppered flask and filtered. Evaporation of the filtrate in vacuo yielded a viscous oil, which was purified by flash chromatography on silica gel (2−4% MeOH gradient in CH_2Cl_2 as eluent) to give the fully methoxy-protected product as a pale yellow oil in good yield (65−85% yield). It was deprotected with BBr_3 as described for octadentate CAM ligands (60−85% yield).

H(2,2)-CAM(C) (13): M.p. 220°C, total yield 54%. $C_{42}H_{44}N_6O_{20}$; $[M + H]^+$ calcd. 952.85; found 953.5. ^1H NMR (400 MHz, [D$_6$]DMSO: δ = 3.10 (s, 4 H, CH_2), 3.15 (s, 8 H, CH_2), 3.60 (s, 16 H, CH_2), 7.10 (s, 8 H, Ar H), 8.90 (br. s, 4 H, NH), 12 (br., 8 H, phenol H) ppm. ^{13}C NMR (125 MHz, D_2O-NaOD): δ = 37.5, 51.8, 53.3, 115.0, 118.2, 119.8, 120.0, 153.7, 157.4, 171.2, 176.9 ppm.

H(3,2)-CAM(C) (15): M.p. 237°C. $C_{43}H_{46}N_6O_{20}$; $[M + H]^+$ calcd. 966.88; found 967.1 . ^1H NMR (400 MHz, [D$_6$]DMSO: δ = 2.02 (br., 2 H, NCH_2CH_2), 3.12 (br. s, 12 H, NCH_3), 3.54 (br. s, 8 H, $NHCH_2$), 7.19 (br. s, 8 H, Ar H), 8.97 (br. s, 4 H, NH) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 23.7, 37.2, 52.5, 53.2, 116.7, 117.7, 119.3, 120.5, 152.7, 154.5, 170.9, 176.3 ppm. (Total yield 55%).

H(4,2)-CAM(C) (17): M.p. 245°C. $C_{44}H_{48}N_6O_{20}$; $[M + H]^+$ calcd. 980.91; found 981.4 $[M + H]^+$, 1003 $[M + Na]^+$. ^1H NMR (400 MHz, [D$_6$]DMSO: δ = 1.76 (br. s, 4 H, CH_2), 3.26 (br. s, 4 H, NCH_2), 3.36 (br. s, 8 H, NCH_2), 3.69 (br. s, 8 H, $NHCH_2$), 7.22 (d, *J* = 8.5 Hz, 4 H, Ar H), 7.31 (d, *J* = 8.5 Hz, 4 H, Ar H), 9.15 (br. s, 4 H, NH), 12.0 (br., 4 H, phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 24.4, 37.1, 53.1, 54.3, 113.1, 117.4, 119.4, 121.2, 155.8, 161.7, 171.6, 178.0 ppm. (Total yield 56%).

TAEC-CAM(C) (21): M.p. 256 °C. $C_{50}H_{60}N_8O_{20}$; $[M + H]^+$ calcd. 1093.08; found 1093.3 $[M + H]^+$, 1115.0 $[M + Na]^+$. ^1H NMR (400 MHz, [D$_6$]DMSO: δ = 1.81 (br. s, 4 H, CH_2), 3.04 (br. s, 24

H, CH_2N), 3.54 (br. s, 8 H, CH_2N), 7.23 (d, J = 8.6 Hz, 4 H, Ar H), 7.32 (d, J = 8.7 Hz, 4 H, Ar H), 9.01 (br. s, 4 H, NH), 12.1 (br., 4 H, phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 36.9, 47.3, 48.4, 51.0, 54.3, 113.4, 118.6, 119.7, 120.0, 154.8, 160.3, 171.5, 177.2 ppm. (Total yield 50%).

Synthesis of Oxo-H-CAM (25)

***N*,*N*"-Bis(2,3-dimethoxybenzamidoethyl)amine (23):** (Scheme 2); Diethylenetriamine (0.3 g, 3 mmol) in CH_2Cl_2 (50 mL) was added to benzamide derivative **22** (1.89 g, 6.4 mmol),[23] and the yellow solution was stirred at 25 °C for 12 h. The crude product was purified by chromatography on silica gel (1−3% MeOH gradient in CH_2Cl_2 as eluent) to give pure **23** (1.06 g, 2.61 mmol, 87% yield) as a pale yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.64 (br., 2 H, NH), 2.92 (t, J = 6.0 Hz, 4 H, NCH_2), 3.59 (q, J = 5.8 Hz, 4 H, NCH_2), 3.88 (s, 12 H, OCH_3), 7.02 (d, J = 8.1 Hz, 2 H, Ar H), 7.13 (t, J = 8.0 Hz, 2 H, Ar H), 7.66 (d, J = 7.9 Hz, 2 H, Ar H), 8.32 (br. s, 2 H, NH) ppm.

Me_8Oxo-H(2,2)-CAM (24): Compound **23** (815 mg, 2 mmol), Et_3N (1 mL, 10 mmol) in anhydrous THF (25 mL), and oxalyl chloride (130 mg, 1.03 mmol) were combined at −78 °C, and the reaction mixture was stirred at 25 °C for 4 h and the solvents evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed successively with aqueous HCl (1M) and water. The crude product was purified by chromatography on silica gel (3−6% MeOH gradient in CH2Cl2 as eluent) to give methoxy-protected Oxo-H(2,2)-CAM as a pale yellow oil (519 mg, 0.45 mmol, 63% yield). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.4−3.6 (br. m, 8 H, NCH_2), 3.74 (br. s, 8 H, CH_2N), 3.8−3.9 (m, 24 H, OCH_3), 7.06 (tt, J = 7.94 Hz, 4 H, Ar H) 7.45 (d, J = 7.73 Hz, 4 H, Ar H), 7.59 (d, J = 7.73 Hz, 4 H, NH), 8.14 (t, J = 5.0 Hz, 4 H, NH), 8.37 (br. s, 4 H, NH) ppm. +FAB MS (TG/G): m/z = 917.3 $[M + H]^+$. $C_{46}H_{56}N_6O_{14}\cdot 0.5H_2O$ (926.004): calcd. C 59.67, H 6.20, N 9.07; found C 60.07, H 6.02, N 8.61.

Oxo-H(2,2)-CAM (25): The methoxy-protected compound **24** (500 mg, 0.44 mmol), deprotected with an excess of BBr_3 as described earlier in the deprotection of **10** and **18**, yielded **25** as a white powder (371 mg, 89% yield). M.p. 145°C. $C_{38}H_{40}N_6O_{14}$ $[M + H]^+$; calcd. (804.78); found 805.1. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 3.55,3.58 (s+s, 16 H, NCH_2), 6.46 (t, J = 7.93 Hz, 4 H, Ar H), 6.90 (d, J = 7.78 Hz, 4 H, Ar H), 7.22 (d, J = 7.41 Hz, 8 H, Ar H), 8.78 (s, 2 H, NH), 8.92 (s, 2 H, NH), 8.94 (br. s, 2 H, phenol H), 12.55 (br. s, 2 H, phenol H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 36.3, 37.5, 43.2, 46.4, 114.8, 115.0, 117.2, 118.1, 119.0, 146.2, 149.6, 165.3, 170.1, 170.2 ppm.

Synthesis of Octadentate Oxo-2,3-dihydroxyterephthalamide Ligands 30, 33

Compound 27: See Scheme 3.

A solution of diethylenetriamine (520 mg, 3 mmol) in CH_2Cl_2 (250 mL) was added over the course of 16 h to a stirred solution of terephthalamide derivative **26**[13] (50 g, 0.125 mol) in 98% CH_2Cl_2/2% MeOH (3 L). The reaction mixture was passed through a silica gel column, and eluted with 2% MeOH in CH_2Cl_2 to remove most of the **26**, while **27** was retained on the silica column. The appropriate fractions of a gradient elution (5−10% MeOH in CH_2Cl_2) were collected and the solvents evaporated to dryness to produce **27** as a white foam (1.63 g, 75% yield). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.95 (t, J = 5.8 Hz, 4 H, CH_2N), 3.44 (t, J = 7.3 Hz, 4 H, CH_2N), 3.63 (q, J = 5.7 Hz, 4 H, CH_2N), 3.89 (d, 12 H, OCH_3), 4.65 (t, J = 7.3 Hz, 4 H, CH_2S), 7.10 (d, J = 8.2 Hz, 2 H, Ar H), 7.80 (d, J = 8.2 Hz, 2 H, Ar H), 8.23 (br., 2 H, NH) ppm.

Compound 28: A solution of **27** (721 mg, 1 mmol) in CH_2Cl_2 (50 mL) was added to methylamine (4 mmol) in MeOH (2 mL) and stirred for 4 h. The crude product, isolated by column chromatography on silica gel (6−12% MeOH +0.2% Et_3N in CH_2Cl_2), gave **28** as a white solid (442 mg, 85% yield). ^1H NMR (250 MHz, $CDCl_3$) δ = 2.96 (t, J = 5.9 Hz, 4 H, NCH_2), 3.03 (d, J = 4.8 Hz, 6 H, $NHCH_3$), 3.64 (q, J = 5.7 Hz, 4 H, CH_2N), 3.87 (s, 6 H, OCH_3), 3.91 (s, 6 H, OCH_3), 7.77 (s, 4 H, Ar H), 7.81 (s, 2 H, NH), 8.12 (t, J = 5.1 Hz, 2 H, NH) ppm.

Me_8Oxo-H(2,2)-MeTAM (29): The methoxy-protected Me_8Oxo-H(2,2)-MeTAM (**29**) was synthesized by coupling two molecules of **28** with oxalyl chloride as follows: oxalyl chloride (100 mg, 0.79 mmol) was added with stirring to **28** (840 mg, 1.54 mmol) and Et_3N (1 mL, 10 mmol) in anhydrous THF (25 mL) at −30 °C. The reaction mixture was stirred at 25 °C for 4 h and the solvents evaporated to dryness. The residue was dissolved in dichloromethane and washed successively with aqueous HCl (1M) and water. The resultant crude product was purified by column chromatography on silica gel (6−12% MeOH + 0.2% Et_3N in CH_2Cl_2) to give a white solid (519 mg, 63% yield). ^1H NMR (250 MHz, $CDCl_3$) δ = 3.03 (d, J = 4.8 Hz, 12 H, NCH_3), 3.45−3.65 (br. m, 8 H, NCH_2), 3.76 (br. s, 8 H, CH_2N), 3.87−3.93 (m, 24 H, OCH_3), 7.55−7.75 (m, 8 H, Ar), 7.75−7.95, (m, 4 H, NH), 8.231 (br. t, J = 5.27 Hz, 2 H, NH), 8.29 (br., 2 H, NH) ppm. +FAB MS (TG/G): m/z = 1145.8 $[M + H]^+$.

Oxo-H(2,2) MeTAM (30): The methoxy-protected Me_8Oxo-H(2,2)-MeTAM (**29**) (500 mg, 0.44 mmol), deprotected with excess BBr_3 as described for the deprotection of CAM ligands, yielded **30** as a beige powder in 85% yield. M.p. 271 °C. $C_{46}H_{52}N_{10}O_{18}$; $[M + H]^+$ calcd. 1032.99; found 1033.6. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 2.79 (d, J = 4.0 Hz, 12 H, NCH_2), 3.41 (br. s, 8 H, NCH_2), 3.56 (br. s, 8 H, $NHCH_2$), 7.19 (s, 4 H, Ar H), 7.24 (s, 4 H, Ar H), 8.82 (br. q, J = 4.3 Hz, 4 H, NH), 9.00 (br. s, 4 H, NH), 12.44 (d, J = 6.7 Hz, 2 H, phenol H), 12.85 (d, J = 9.0 Hz, 2 H, phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 25.1, 37.4, 40.9, 43.1, 46.4, 108.7, 115.8, 115.9, 117.2, 117.4, 149.9, 150.1, 150.2, 165.3, 168.7, 168.8, 169.2 ppm.

Compound 31: Compound **31** was prepared by the same procedure as **28**, with one exception: *n*-propylamine was used in place of the methylamine solution. The pure product was obtained as a white foam (535 mg, 89% yield). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.4 Hz, 6 H, CH_3), 1.69 (br. q, J = 7.2 Hz, 4 H, CH_2), 2.958 (t, J = 5.9 Hz, 4 H, NCH_2), 3.44 (q, J = 5.9 Hz, 4 H, CH_2N), 3.61 (q, J = 5.8 Hz, 4 H, CH_2N), 3.88 (s, 6 H, OCH_3), 3.93 (s, 6 H, OCH_3), 7.83 (br. s, 4 ArH + 2 NH), 8.14 (br., 2 H, NH) ppm.

Me_8Oxo-H(2,2)-PrTAM (32): Preparation of Me_8Oxo-H(2,2)-PrTAM (**32**) was carried out on a 1.5 mmol scale in a procedure similar to the synthesis of Me_8Oxo-H(2,2)-MeTAM (**30**), except **31** was used as the starting material instead of **28**. Purification by column chromatography (4−10% MeOH in CH_2Cl_2) gave Me_8Oxo-H(2,2)-PrTAM (**32**) as a white solid (667 mg, 71% yield). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.015 (tt, J = 7.4 Hz, 12 H, CH_3), 1.67 (sext., J = 7.2 Hz, 8 H, CH_2), 3.42 (q, J = 6.6 Hz, 8 H, NCH_2), 3.47−3.65 (br. m, 8 H, NCH_2), 3.76 (br. s, 8 H, CH_2N), 3.85−3.95 (m, 24 H, OCH_3), 7.55−7.75 (m, 8 H Ar H), 7.75−7.95, (m, 4 H, NH), 8.23 (t, J = 5.2 Hz, 2 H, NH), 8.29 (br., 2 H, NH) ppm. +FAB MS (NBA): m/z = 1257.6 $[M + H]^+$. $C_{62}H_{84}N_{10}O_{18}$ (1257.424): calcd. C 59.25, H 6.73, N 11.13; found C 59.49, H 6.85, N 11.03.

Oxo-H(2,2)-PrTAM (33): Me_8Oxo-H(2,2)-PrTAM (**32**) (500 mg, 0.44 mmol), deprotected with excess BBr_3 as described for the deprotection of the other CAM ligands, yielded **33** as a beige powder in 78% yield. M.p. 276°C. $C_{54}H_{68}N_{10}O_{18}$; $[M + H]^+$ calcd. 1145.20; found 1145.7. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 0.91 (t, *J* = 7.4 Hz, 12 H, CH_3), 1.50 (m, 8 H, CH_2), 3.21 (br. s, 8 H, NCH_2), 3.42 (br. s, 8 H, NCH_2), 3.58 (br. s, 8 H, NCH_2), 7.20 (m, 8 H, Ar H), 8.70−9.10 (m, 8 H, NH), 12.4 (br. s, 4 H, phenol H), 12.8 (br. s, 4 H, phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 11.4, 22.0, 36.3, 37.5, 40.8, 43.0, 46.3, 108.7, 115.5, 115.7, 117.2, 117.3, 149.9, 150.1, 150.3, 165.2, 168.7, 168.9, 169.1 ppm.

Synthesis of Octadentate H(2,2)-MeTAM (37), H(2,2)-EtTAM (38), and H(2,2)-PrTAM (39) Ligands. General Procedure: See Scheme 4. A solution of PENTEN [**6**, H(2,2)-amine) (0.6 mmol) and NEt_3 (0.4 mL, 3 mmol] in anhydrous THF (30 mL) was added to 4-chlorocarbonyl-2,3-dimethoxybenzoic acid methyl ester (**9**)[21] (0.78 g, 3 mmol) in anhydrous THF (40 mL) by a Teflon cannula under nitrogen. A white precipitate immediately formed upon addition. The reaction mixture was stirred at room temperature overnight under N_2, and the triethylamine hydrogen chloride precipitate was collected by filtration. Evaporation of the filtrate in vacuo yielded a viscous oil, which was purified by chromatography on silica gel (2−4% MeOH in CH_2Cl_2) to give the fully methoxy-protected CAM(C) species **34** as pale yellow oil.

Compound **34** (0.5 mmol) was mixed with methanol (20 mL) and aqueous NaOH (1M) solution (5 mL). The reaction mixture was heated to reflux temperature for 4 h and then evaporated to dryness. The residue was dissolved in H_2O (15 mL) and acidified to pH 2 using 6 M HCl. The methoxy-protected CAM(C) tetraacid species **35** settled as a pale yellow oil. It was dissolved in dry THF, filtered, and coevaporated with anhydrous THF three times to remove any water left as an azeotrope, then carried directly to the next reaction procedure.

At −10 °C, under argon, *N*-hydroxysuccinimide (0.23 g, 2 mmol) and DCC (0.41 g, 2 mmol) were added to the above tetraacid species **35** in anhydrous THF (20 mL). After stirring for 24 h, an appropriate backbone amine (4 mmol primary amine) in anhydrous THF (10 mL) was added with stirring. The DCU solids were removed by filtration, and the filtrate was evaporated to dryness and purified by chromatography on silica gel (4−6% MeOH in CH_2Cl_2) to give the corresponding octadentate 2,3-dimethoxyterephthalamide as a pale yellow oil. It was deprotected with BBr_3 as described for the octadentate CAM ligands.

H(2,2)-MeTAM (37): M.p. 173−175°C. $C_{46}H_{56}N_{10}O_{16}$; $[M + H]^+$ calcd. 1005.02; found 1005 $[M + H]^+$, 1027 $[M + Na]^+$. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.81 (d, *J* = 4.0 Hz, 12 H, $NHCH_3$), 3.4 (br., 12 H, NCH_2), 3.7 (br., 8 H, NCH_2), 7.30 (d, *J* = 8.7 Hz, 4 H, Ar H), 7.37 (d, *J* = 8.7 Hz, 4 H, Ar H), 8.93 (br. d, *J* = 4.0 Hz, 4 H, terminal NH), 9.13 (br. s, 4 H, NH), 12.2 (br., phenol H), 13.1 (br., phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 26.3, 37.2, 51.8, 53.8, 112.8, 112.9, 117.4, 117.5, 163.9, 164.2, 172.4, 173.0 ppm.

H(2,2)-EtTAM (38): M.p. 178−180°C. $C_{50}H_{64}N_{10}O_{16}$; $[M + H]^+$ calcd. 1061.13; found 1061.7. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.04 (t, *J* = 7.1 Hz, 12 H, NCH_3), 3.22 (quin., *J* = 6.7 Hz, 8 H, NCH_2), 3.54 (br. s, 12 H, NCH_2), 3.64 (br. s, 8 H, NCH_2), 7.22 (s, *J* = 8.8 Hz, 8 H, Ar H), 7.29 (s, *J* = 8.8 Hz, 8 H, Ar H), 8.85 (t, *J* = 5.3 Hz, 4 H, NH), 9.08 (br. s, 4 H, NH), 12.2 (br., phenol H), 12.9 (br., phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 15.0, 34.9, 37.2, 51.9, 53.8, 112.8, 112.9, 117.4, 117.6, 163.9, 172.0, 172.4 ppm.

H(2,2)-PrTAM (39): M.p. 186−188°C. $C_{54}H_{72}N_{10}O_{16}$; $[M + H]^+$ calcd. 1117.24; found 1117. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 0.87 (t, *J* = 7.18 Hz, 12 H, NCH_3), 1.5 (m, 8 H, CH_2), 2.74 (br. s, 8 H, CH_2N), 3.2 (br. s, 12 H, NCH_2), 3.4 (br. s, 8 H, NCH_2), 7.26 (s, *J* = 8.85 Hz, 8 H, Ar H), 8.82 (s, 8 H, NH), 13.0 (br., phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 12.0, 23.2, 37.0, 51.8, 53.9, 112.3, 112.4, 117.2, 117.4, 166.2, 166.4, 172.5, 172.9 ppm.

Synthesis of Octadentate 3,4,3-LIMeTAM (41): See Scheme 5. This linear octadentate terephthalamide ligand was synthesized and purified by the same procedure as for the H(2,2)-TAMs, except spermine (**40**) was used instead of PENTEN (**6**). Unlike the highly symmetric PENTEN derivatives, the NMR spectra of compound **41** shows a complicated mode, probably due to the existence of several conformers in the solution. M.p. 223−225°C. $C_{46}H_{54}N_8O_{16}$ $[M + H]^+$; calcd. 974.99 found 975.2. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.2−2.0 (br. m, 8 H, CH_2), 2.7−2.8 (m, 12 H, NCH_3), 3.0−3.6 (br. m, 12 H, $NHCH_2$), 6.6−7.4 (br. m, 8 H, ArH), 8.6−9.3 (br. m, 6 H, NH), 12.0−13.0 (m, 4 H, phenol H) ppm. ^{13}C NMR (100 MHz, D_2O-NaOD): δ = 25.3, 26.2, 26.3, 28.4, 29.2, 37.2, 37.3, 37.6, 44.9, 48.5, 50.3, 111.6, 111.8, 112.0, 112.1, 112.2, 112.3, 112.4, 113.2, 113.3, 116.7, 116.8, 117.0, 117.1, 117.2, 125.5, 125.6, 125.7, 157.5, 157.6, 157.9, 164.9, 165.0, 165.2, 165.9, 166.1, 166.2, 166.4, 171.6, 171.9, 172.1, 172.4, 172.5, 172.6, 173.2, 173.3, 173.4, 176.4, 176.5, 176.6 ppm.

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