

0040-4020(94)E0008-H

Design and Synthesis of Actinide Specific Chelators: Synthesis of New Cyclam Tetrahydroxamate (CYTROX) and Cyclam Tetraacetylacetonate (CYTAC) Chelators

Nirmal Koshti^a, Vincent Huber^a, Paul Smith^{*b} and Aravamudan S. Gopalan^{*a}

^a Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, NM 88003-0001, USA

^b INC-1, MS-C346, Los Alamos National Laboratory, Los Alamos, NM 87545, USA

Abstract: Molecular modeling shows that two new chelators, the cyclam tetrahydroxamate, **1**, and the cyclam tetraacetylacetonate derivative, **2**, have potential for the binding of plutonium (IV). The synthesis of these chelators has been achieved using short sequences from readily available cyclam. Both the details of the molecular modeling and the synthetic route to these molecules are described.

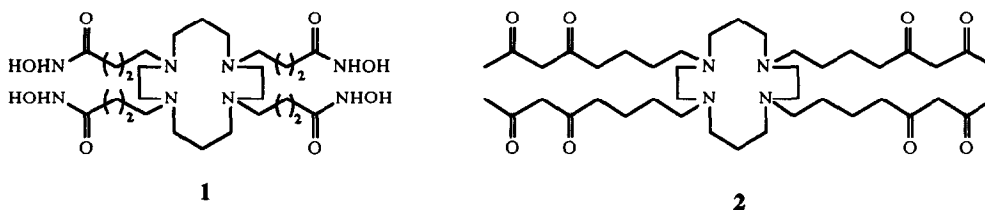
As part of our research efforts, we have been interested in the development of cost effective organic chelators for the removal of plutonium and other actinides from process waste streams and the environment.^{1,2} There have been some reports on the development of sequestering agents which are both relatively specific and strong chelating agents for Pu⁴⁺, particularly for *in vivo* clinical evaluation.³ The analogy of the chemistry of Pu⁴⁺ to Fe³⁺ in biological systems and their similar charge to ionic radius ratio (46 and 42 e nm⁻¹ respectively) has been the guiding principle in the design of actinide sequestering agents.^{4,5,6} It is generally agreed that octadentate ligands possess the appropriate denticity for selective actinide complexation. The large size and the flexible coordination geometry of the actinide ions may provide an avenue for its selective complexation in environmentally relevant situations. Chelators with hydroxamates, catecholates, and to a lesser extent hydroxypyridonates have been widely examined because these ligands are known to strongly complex highly charged metal ions such as Fe³⁺ and Pu⁴⁺.⁷ Some of the actinide chelators that have been studied are similar to enterobactin, a siderophore, and contain four sulfonated catechol groups appended onto an azamacrocyclic structural backbone.^{8,9,10} Almost all of the chelators developed so far have limitations (e.g. solubility, stability, unfavorable kinetics or selectivity) that restrict their potential use in environmental applications.

Because of the difficulties associated with handling plutonium, it is advantageous to synthesize a limited number of chelators to screen for plutonium binding. Hence, we have pursued methods which will allow us to design and model chelators with maximum potential for plutonium binding prior to execution of

their synthesis and binding studies. Molecular modeling is rapidly becoming an important tool finding use in the areas of rational drug design and structural chemistry.^{11, 12} Computer based molecular modeling is also beneficial to understanding the structures of metal-ligand complexes.¹³

The ability of molecular modeling programs to reproduce the observed coordination geometry of d and f-block complexes has been shown. Hay has found that the calculated coordination structure of 58 octa- to dodeca-coordinate aquo and nitratolanthanide(III) complexes are very close to their observed crystal structure.^{14a} This study has also been extended with some success to the calculation of the coordination structures for a number of metal acetylacetonato (acac) complexes, including plutonium.^{14b}

We have used computer modeling to identify and design chelators for plutonium(IV) based on maximization of ligand interactions with the metal ion, leading to energetically and sterically favorable complexes. In this paper, we describe both the results of our initial molecular modeling studies and the subsequent synthesis of two novel cyclam based chelators, CYTROX, **1**, and CYTAC, **2**, for selective actinide binding.



We have used the CAChe molecular modeling system,¹⁵ version 3.0, to model the coordination of chelators **1** and **2** with plutonium(IV). The structural coordinates for a symmetric, tetra-N-substituted cyclam moiety having substituents on the same face of the ring were obtained from a suitable model listed in the Cambridge Structural Database.^{16, 17} Tetrakis(acetohydroxamato)- and tetrakis(acetylacetonato)-Pu(IV) complexes were then constructed and minimized using the CAChe augmented force field parameters. Subsequently, the remainder of the molecule was assembled. Then, the minimized coordinates of the plutonium complexes were retained while the cyclam and carbon chains were allowed to assume a minimum energy conformation. At this point the entire structures were allowed to assume a minimum energy conformation which are shown in Figures 1 and 2. Because of the number of possible conformations of the cyclam ring and the known flexibility of the f-block coordination sphere, these illustrations show one of a number of possible complex structures. The overall structures for the Pu(IV) complexes of **1** and **2** are consistent with our expectations and indicate both chelators are viable candidates for the sequestration of the Pu(IV).¹⁸

The synthesis of CYTROX, **1**, was relatively straightforward and could be achieved in two steps from commercially available cyclam (Scheme 1). Alkylation of cyclam with ethyl 4-bromobutyrate in the presence of catalytic potassium iodide in refluxing acetonitrile gave the desired tetraester **3** in 30% yield after purification. The tetraester **3** was converted to the desired hydroxamic acid by treatment with excess hydroxylamine and potassium hydroxide in methanolic solution. Under these conditions, CYTROX **1** could be readily isolated as its potassium salt.

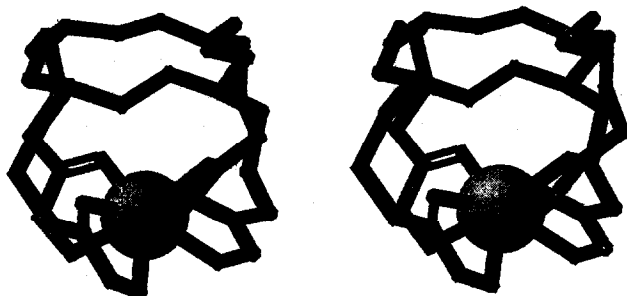


Figure 1. Stereoview of the CYTROX-Pu(IV) complex (from molecular modeling).

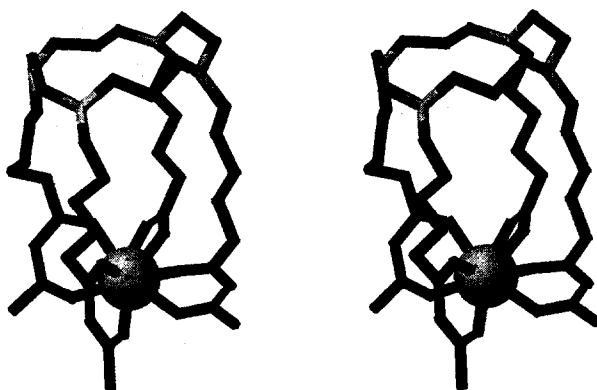
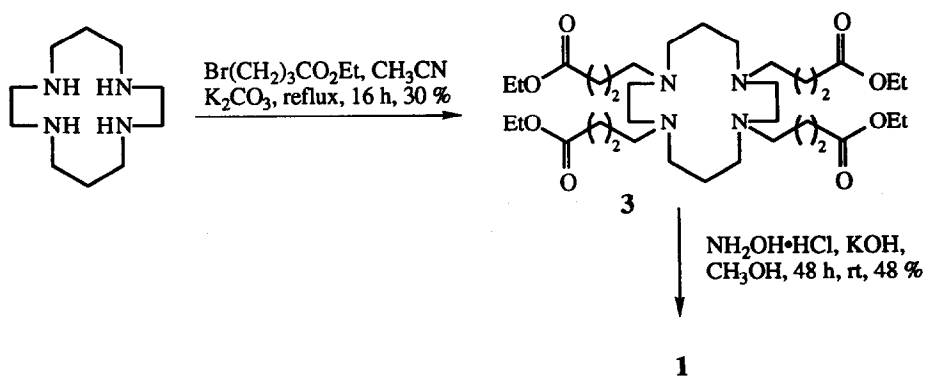
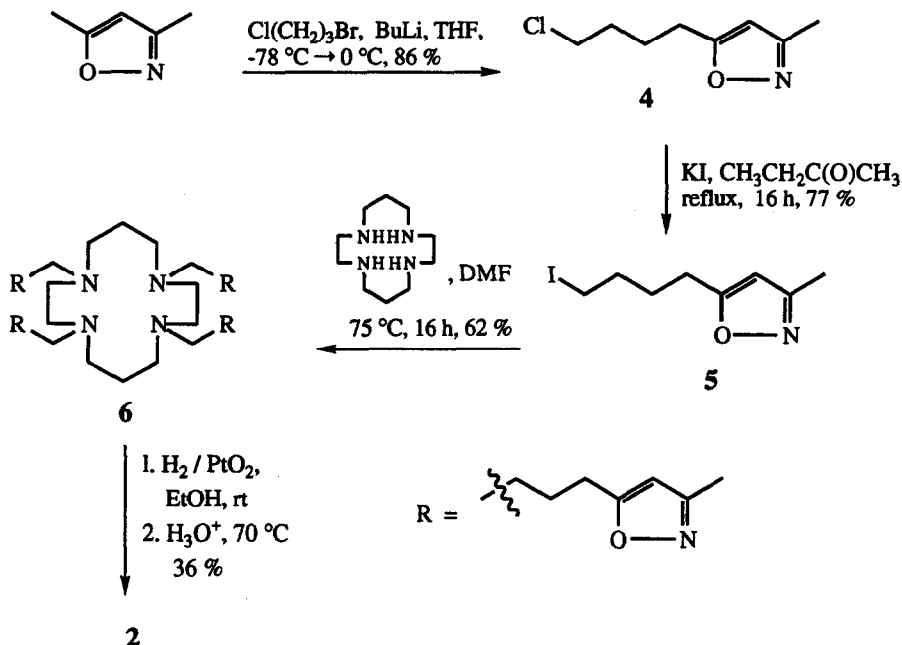


Figure 2. Stereoview of the CYTAC-Pu(IV) complex (from molecular modeling).



Scheme 1

CYTAC, **2** was prepared using the route shown in Scheme 2. 3,5-Dimethylisoxazole was metallated¹⁹ with butyllithium followed by alkylation with 1-bromo-3-chloropropane to give the chloroisoxazole **4** in high yields. The chloride **4** was readily converted to the corresponding iodide **5** using standard procedures. Alkylation of cyclam in DMF at 70°C with iodide **5** gave the cyclam tetraisoazole derivative **6**, which could be isolated in moderate yields. Catalytic hydrogenation of **6** with PtO₂ as the catalyst led to the cleavage of the isoxazole ring²⁰ to give the corresponding β aminoenone which was not purified but directly hydrolyzed with aqueous ethanolic hydrochloric acid to obtain CYTAC, **2**, as its tetrahydrochloride salt.²¹ The free ligand, CYTAC, could be obtained by neutralization of the tetrahydrochloride salt with sodium bicarbonate.



Scheme 2

Based on our molecular modeling studies, we believe that both CYTAC and CYTROX are viable targets for the sequestration of the Pu(IV) ion. Our modeling indicates the alkyl chain length of CYTROX and CYTAC are sufficient to allow complete coordination of the plutonium ion. It is our expectation that the flexibility of the cyclam backbone and the carbon chains will allow both chelators to effectively coordinate tetravalent actinides. Both chelators **1** and **2** were synthesized by a route that is amenable for ready modification for the preparation of analogous ligands with varying carbon chain lengths. The reagent **5** has the potential to be particularly useful for the incorporation of the acetylacetyl ligand into a variety of substrates. Currently we are initiating the binding studies of these chelators and hope to establish the validity of our models with actual evaluation of binding properties.

Experimental

General Procedures. Infrared spectra were recorded on a Perkin Elmer 283B Spectrophotometer. ^1H NMR spectra were obtained on a Varian XL 200 MHz spectrometer unless otherwise noted and ^{13}C NMR spectra were obtained on a Varian Unity 400 MHz Spectrometer. ^1H NMR and ^{13}C NMR spectra were usually obtained in CDCl_3 which contained tetramethylsilane as an internal standard. For ^1H NMR spectra taken in D_2O , the HOD peak was set to 4.67 ppm. For ^{13}C NMR spectra taken in D_2O , TMS was used as an external reference. Analytical and preparative thin layer chromatography was done on silica 60/F254 plastic or glass backed plates obtained from E. M. Science. Column chromatography was performed on silica gel Merck (230-400 mesh) obtained from Aldrich Chemical Company. All solvents were HPLC grade and were obtained from Fisher Scientific Company or VWR Scientific Company. Elemental analyses were performed by Desert Analytics, Tucson, Arizona. THF was freshly distilled from sodium/benzophenone. Cyclam (1,4,8,11-tetraazacyclotetradecane) was obtained from Lancaster Chemical Company. Reagents were usually obtained from Aldrich Chemical Company and were used without purification unless indicated.

N,N',N'',N''' -tetra (3-ethoxycarbonylpropyl)-1,4,8,11-tetraazacyclotetradecane (3).

A mixture of cyclam (0.800 g, 4.00 mmol), ethyl 4-bromobutyrate (3.12 g, 16.0 mmol), potassium carbonate (1.10 g, 8.00 mmol) and potassium iodide (10 mg) in acetonitrile (40 mL) was refluxed under nitrogen for 24 h. The reaction mixture was then cooled and filtered. The residue obtained on removal of acetonitrile was stirred with hexane (40 mL) for an hour. The hexane soluble portion was removed and the colorless liquid that remained was heated under reduced pressure (Kugelrohr, $80^\circ\text{C}/1$ torr) to remove any unreacted 4-bromobutyrate. The desired tetraester (0.810 g, 30.0 %) was obtained as a colorless and viscous liquid. IR (neat): 1733, 2802, 2940 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.26(t, 12 H, $J=6.8$ Hz), 1.56 (m, 4 H), 1.72 (m, 8 H), 2.32 (t, 8 H, $J=6.8$ Hz) 2.40 (t, 8 H, $J=6.8$ Hz) 2.50 (m, 16 H), 4.12 (q, 8 H, $J=6.8$ Hz); ^{13}C NMR (400 MHz, CDCl_3): δ 14.2, 22.7, 23. 6, 32.0, 51.1, 51.5, 54.4, 60.1, 173.7. Anal. calc'd for $\text{C}_{34}\text{H}_{64}\text{O}_8\text{N}_4$: C, 62.19; H, 9.75; N, 8.53; Found C, 62.27; H, 9.95; N, 8.24.

CYTROX 1. To a solution of hydroxylamine hydrochloride (0.556 g, 8.00 mmol) in methanol (15 mL), potassium hydroxide (0.672 g, 12.0 mmol) was added while maintaining the temperature below 20°C and the mixture stirred for 1 h at room temperature. The potassium chloride precipitate was filtered off. The methanolic filtrate was added to tetraester **3** (0.656 g, 1.00 mmol) and stirred at rt for 48 h. The white solid which separated out from the reaction was filtered, washed with methanol (40 mL) and dried in vacuo. The hydroxamate salt was finally isolated as a white solid (0.315 g, 48.0%). IR (neat): 1631 cm^{-1} ; ^1H NMR (400 MHz, D_2O): δ 1.5 - 1.7 (m, 12 H), 2.0 (t, 8 H, $J=6.8$ Hz), 2.43 (improperly resolved t, 8 H,), 2.56 (improperly resolved t, 8 H), 2.67 (s, 8 H); ^{13}C NMR (400 MHz, D_2O): δ 22.4, 25.0, 33.5, 49. 5, 52.7, 57.0, 172.4. Anal calc'd for dipotassium salt $\text{C}_{26}\text{H}_{50}\text{O}_8\text{N}_8\text{K}_2$: C, 45.88; H, 7.35; N, 16.47. Found: C, 46.24; H, 7.48; N, 16.50.

5-(4-chlorobutyl)-3-methylisoxazole (4). To a solution of 3,5-dimethylisoxazole (6.20 g, 64.0 mmol) in freshly distilled dry THF (75 mL) under N_2 at -78°C was added n-butyllithium (44.2 mL of a 1.6 M solution in hexane, 70.4 mmol). The solution was stirred at -78°C for 3 h. To this solution, 1-chloro-3-bromopropane (10.1 g, 64.0 mmol) was added dropwise and stirred at -78°C for another 6 h and then warmed up to room

temperature. The reaction mixture was poured into saturated ammonium chloride solution (200 mL) and extracted with ethyl acetate (2 X 125 mL). The combined organic extracts were washed with saturated sodium chloride solution (100 mL), dried (MgSO_4) and the solvent removed in vacuo to give the product as a pale yellow liquid. Kugelrohr distillation (90-100°C/450 mtorr) afforded the chlorobutyl isoxazole **4** as a colorless liquid. (8.88 g, 86.0%). IR (neat): 1418, 1605, 2956 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.81-1.80 (m, 4 H), 2.26 (s, 3 H), 2.75 (t, 2 H, $J=7$ Hz), 3.56 (t, 2 H, $J=6$ Hz) 5.84 (s, 1 H). Anal calc'd for $\text{C}_8\text{H}_{12}\text{ONCl}$: C, 55.32; H, 6.62; N, 8.00 Found: C, 55.33; H, 6.91; N, 8.06.

5-(4-iodobutyl)-3-methylisoxazole (5). A solution of the chloroisoxazole **4** (1.73 g, 10.0 mmol), and sodium iodide (1.80 g, 12.0 mmol) in methyl ethyl ketone (10 mL) was refluxed under N_2 for 18 h. The reaction mixture was cooled and sodium chloride was filtered off. Methyl ethyl ketone was removed under reduced pressure, and the residue was extracted with ether (40 mL). Removal of ether afforded a yellow oil which was purified by Kugelrohr distillation (120°C/450 mtorr) to give **5** as a colorless liquid (2.04 g, 77.0%). IR (neat): 1605, 2934 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.75-1.88 (m, 4 H), 2.26 (s, 3 H), 2.76 (t, 2 H, $J=7$ Hz), 3.20 (t, 2 H, $J=6.4$ Hz), 5.85 (s, 1 H); ^{13}C NMR (400 MHz, CDCl_3): δ 6.0, 11.4, 25.5, 28.3, 32.5, 101.7, 159.6, 172.2; Anal calc'd for $\text{C}_8\text{H}_{12}\text{ONI}$: C, 36.20; H, 4.52; N, 5.2. Found: C, 36.46; H, 4.58; N, 4.94.

Cyclam tetraisoxazole 6. A mixture of iodoisoxazole **5** (2.12 g, 8.00 mmol), cyclam (0.400 g, 2.00 mmol) and potassium carbonate (1.66 g, 12.0 mmol) in DMF (20 mL) was stirred at 75° C under nitrogen for 18 h. The reaction mixture was cooled and inorganic solids were filtered off. The residue obtained after removal of DMF was extracted with ether (2 x 20 mL). The crude product obtained after removal of ether was heated under reduced pressure (Kugelrohr, 130°/1 torr to remove DMF and unreacted iodoisoxazole). The remaining residue was purified by silica gel chromatography (5% methanol/ CHCl_3) to give **6** as a pale yellow oil (0.940 g, 62.8%). IR (neat): 1605, 2799, 2932 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 1.47-1.79 (m, 20 H), 2.25 (s, 12 H), 2.36-2.57 (m, 24 H), 2.74 (t, 8 H, $J=7.2$ Hz), 5.81 (s, 4 H); ^{13}C NMR (400 MHz, CDCl_3): δ 11.4, 23.2, 25.4, 26.5, 50.9, 51.4, 54.7, 101.6, 159.6, 173.0; Anal calc'd for $\text{C}_{42}\text{H}_{68}\text{O}_4\text{N}_8$: C, 67.3; H, 9.09; N, 14.9; Found: C, 66.98; H, 9.01; N, 15.14.

CYTAC 2. A mixture of the tetra N-alkylated cyclam **6** (0.650 g, 1.00 mmol) and platinum oxide (0.050 g) in absolute ethanol was stirred at room temperature under an atmosphere of hydrogen until there was no further absorption of gas. The catalyst was filtered off. Distilled water (1.4 mL) was added to the ethanolic solution and made acidic to litmus by adding concentrated HCl dropwise followed by stirring at 70°C for 7 h. Removal of solvent and drying under reduced pressure gave the tetrahydrochloride of CYTAC **2** as a white solid. This was further washed with methanol (30 mL) and dried under vacuum to give a white solid (0.501 g, 63.7%). IR (KBr): 1702, 1725 cm^{-1} ; ^1H NMR (200 MHz, D_2O): δ 1.59-1.72 (20 H, m) 2.20 (12 H, s), 2.65 (8 H, t, $J=6.4$ Hz), 3.28-3.74 (32 H, m); ^{13}C NMR (400 MHz, D_2O): δ 16.6, 19.1, 19.2, 23.3, 30.5, 42.2, 42.5, 46.8, 55.4, 208.3, 209.7.

Neutral CYTAC was obtained by treating the tetrahydrochloride salt (0.100g) with an aqueous solution of saturated sodium bicarbonate (3 mL). The solution was extracted with CHCl_3 (3 x 10 mL) and the combined organic extracts were washed with water (3 mL), dried (MgSO_4), and the solvent removed in vacuo. The

crude product was purified by filtering through a short silica gel column (CHCl_3) to give pure CYTAC (30.5 mg, 36.3%) as a pale yellow oil. IR (neat): 1710, 1720, 3425 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.44-1.58 (m, 20 H), 2.05 (s, 12 H), 2.84 (t, 12 H, $J = 6.4$ Hz), 2.37-2.50 (m, 24 H), 3.59 keto and 5.49 enol (s, 8 H); ^{13}C NMR (400 MHz, CDCl_3): δ 23.1, 23.7, 25.7, 26.8, 38.1, 50.7, 51.5, 55.0, 99.9, 191.5, 194.1; Anal calcd for $\text{C}_{42}\text{H}_{72}\text{O}_8\text{N}_4$: C, 66.31; H, 9.47; N, 7.36; Found C, 66.14; H, 9.30; N, 6.96.

Acknowledgments

The Waste-management Education and Research Consortium and the Department of Energy are thanked for their financial support. Dr. Richard Barrans and Dr. Hollie Jacobs are thanked for their helpful discussions.

References

1. Gopalan, A. S.; Huber, V.; Zincircioglu, O.; Smith, P. H. *J. Chem. Soc. Chem. Commun.* **1992**, 1266.
2. Gopalan, A.; Zincircioglu, O.; Smith, P. *Radioactive Waste Management and the Nuclear Fuel Cycle*, **1993**, 17(3-4), 161.
3. a) Xu, J.; Stack, T. D. P.; Raymond, K. N. *Inorg. Chem.* **1992**, 31, 4903. b) Uhlir, L. C.; Durbin, P. W.; Jeung, N.; Raymond, K. N. *J. Med. Chem.* **1993**, 36, 504.
4. Raymond, K. N. *Coord. Chem. Rev.*, **1990**, 105, 135.
5. a) Durbin, P. W.; White, D. L.; Jeung, N.; Weitl, F. L.; Uhlir, L. C.; Jones, E. S.; Bruenger, F. W.; Raymond, K. N. *Health Physics*, **1989**, 56 (6), 839. b) Sofen, S. R.; Abu-Dari, K.; Freyberg, D. P.; Raymond, K. N. *J. Am. Chem. Soc.*, **1978**, 100, 7882. c) Evers, A.; Hancock, R. D.; Martell, A. E.; Motekaitis, R. J. *Inorg. Chem.* **1989**, 28, 2189. d) Ali, S. A.; Ache, H. J. *Radiochimica Acta*, **1984**, 36, 89. e) Manchanda, V. K. *Radiochimica Acta*, **1989**, 48, 213. f) Raymond, K. N.; Freeman, G. E.; Kappel, M. J. *Inorg. Chim. Acta*, **1984**, 94, 193. g) White, D. L.; Durbin, P. W.; Jeung, N.; Raymond, K. N. *J. Med. Chem.*, **1988**, 31, 11. i) Kappel, M. J.; Nitsche, H.; Raymond, K. N. *Inorg. Chem.* **1985**, 24, 605.
6. a) Raymond, K. N.; Smith, W. L. *Struct. Bonding* (Berlin), **1981**, 43, 159. b) Raymond, K. N.; Garrett, T. M. *Pure and Appl. Chem.*, **1988**, 60, 1807.
7. a) Yakirevitch, P.; Rochel, N.; Albrecht-Gary, A. M.; Libman, J.; Shanzer, A. *Inorg. Chem.* **1993**, 32, 1779. b) Dayan, I.; Libman, J.; Agi, Y.; Shanzer, A. *Inorg. Chem.* **1993**, 32, 1467. c) Tor, Y.; Libman, J.; Shanzer, A.; Felder, C. E.; Lifson, S. *J. Am. Chem. Soc.* **1992**, 114, 6661. d) Ng, C. Y.; Rodgers, S. J.; Raymond, K. N. *Inorg. Chem.* **1989**, 28, 2062. e) Martell, A. E.; Motekaitis, R. J.; Murase, I.; Sala, L. F.; Stoldt, R.; Ng, C. Y.; Rosenkrantz, H.; Metterville, J. J. *Inorg. Chim. Acta*, **1987**, 138, 215. f) Akiyama, M.; Katoh, A.; Ogawa, T. *J. Chem. Soc. Perkin Trans. II*, **1989**, 1213. g) Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem.* **1985**, 28, 317. h) Bergeron, R. J.; Kline, S. J.; Navratil, J. D.; Smith, C. M. *Radiochimica Acta*, **1984**, 35, 47. i) Streater, M.; Taylor, P. D.; Hider, R. C.; Porter, J. *J. Med. Chem.*, **1990**, 33, 1749. j) Dobbin, P. S.; Hider, R. C. *Chemistry in Britain*, **1990**, 565.
8. Miller, M. J. *Chem. Rev.*, **1989**, 89, 1563.

9. a) Weitz, F. L.; Raymond, K. N.; Smith, W. L.; Howard, J. R. *J. Am. Chem. Soc.*, **1978**, *100*, 1170. b) Weitz, F. L.; Raymond, K. N. *J. Am. Chem. Soc.*, **1980**, *102*, 2289.
10. a) Lindoy, L.F. "The Chemistry of Macrocyclic Ligand Complexes," Cambridge University Press, Cambridge, 1989. b) Hancock, R.D.; Martell, A. E. *Chem. Rev.*, **1989**, *89*, 1875. c) Bernhardt, P. V.; Lawrance, G.A.; *Coord. Chem. Rev.* **1990**, *104*, 297.
11. Krieger, J. H. *C and EN*, **1992**, *70(19)*, 40.
12. Matteis, C. I.; Jackson, D. E. *Annual Reports on the Progress of Chemistry Section B*, **1990**, *87*, 27.
13. a) Hancock, R. D., *Acc. Chem. Res.* **1990**, *23*, 253. b) Hay, B. P. *Coord. Chem. Rev.* **1993**, *126*, 177.
14. a) Hay, B.P. *Inorg. Chem.* **1991**, *30*, 2876. b) Hay, B.P. unpublished results.
15. For some recent reports on the use of CAChe system see: a) Purvis III, G.D. *J. Computer Aided Molecular Design*, **1991**, *5*, 55; b) Hofmeister, G. E., Zhou, Z.; Leary, J. A.; *J. Am. Chem. Soc.*, **1991**, *113*, 5964. c) Rzepa, H. S., Yi, M. Y. *J. Chem. Soc. Perkin. II*, **1991**, 531. d) Karpishin, T. B.; Stack, T. D. P.; Raymond, K. N. *J. Am. Chem. Soc.*, **1993**, *115*, 182.
16. Allen, F. H.; Davier, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Mitchell, G. F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comp. Sci.*, **1991**, *31*, 187.
17. Mikuriya, M.; Kida, S.; Kohzuma, I.; Murase, I. *Bull. Chem. Soc. Jpn*, **1988**, *61*, 2666.
18. The overall formation constant ($\log \beta$) for the Pu(acac)₄ complex is approximately 34. The overall formation constant ($\log \beta$) for the Pu(PhCON(OH)Ph)₄ complex is 41.3. See Katz, J. J.; Seaborg, G. T.; Morss, L. R. "The Chemistry of the Actinide Elements", 2nd ed. Chapman and Hall, London, 1986 and references cited therein.
19. Brunelle, D.J. *Tetrahedron Lett.* **1981**, *22*, 3699.
20. a) Kobuke, Y.; Satoh, Y. *J. Am. Chem. Soc.* **1992**, *114*, 789. b) Auricchio, S.; Ricca, A.; Vajna de Pava, O. *Gazz. Chim. Ital.*, **1980**, *110*, 567.
21. For some reports on macrocyclic acetylacetonate chelators for metal ions see: a) Alberts, A.H.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3545. b) Tabushi, I.; Kobuke, Y.; Nishiya, T. *Tetrahedron Lett.*, **1979**, 3515.

(Received in USA 1 October 1993; accepted 13 December 1993)