Rational Design of Sequestering Agents for Plutonium and Other Actinides

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Anne E. V. Gorden was born in Kansas City, Missouri, and grew up in the north Dallas area in Texas. A National Merit Scholar (1992) and recipient of two General Electric Faculty for the Future Fellowships (1995, 1996), she graduated from Emory University in Atlanta, Georgia, in 1996, earning a B.S. in chemistry as well as completing a second major in literature. She then returned to Texas, attending graduate school at the University of Texas at Austin, where her thesis work, under the direction of Professor Jonathan L. Sessler, concerned the design and synthesis of novel expanded porphyrins and oligopyrroles for selective ion coordination, in a collaborative project with Los Alamos and Argonne National Laboratories as a Seaborg Research Fellow (1999) and as a Seaborg Institute Research Fellow (2000–2002). In 1999 and 2000, she was awarded two Delta Gamma Foundation Fellowships for Women in Science. After completing her dissertation in 2002, Dr. Gorden began a postdoctoral appointment at the University of California at Berkeley with Professor Kenneth N. Raymond, investigating the structural and solution properties of siderophore-based actinide-sequestering agents.

Professor Kenneth N. Raymond was born in 1942 in Astoria, Oregon. He attended Reed College, where he received a B.A. in 1964. His Ph.D. research at Northwestern University, under the direction of Professors Fred Basolo and James A. Ibers, concerned the synthesis and structure of five-coordinate metal complexes. Upon completing his Ph.D., he began his faculty appointment at the University of California at Berkeley in 1967, becoming Associate Professor in 1974 and Professor in 1978. His work has been recognized with several awards, including the Ernest O. Lawrence Award of the Department of Energy (1984), a Humboldt Research Award for Senior U.S. Scientists (1991), and the American Chemical Society Alfred Bader Award in Bioinorganic or Bioorganic Chemistry (1994). He has been an Alfred P. Sloan research fellow (1971–1973), a Miller research professor at the University of California (1977–1978, 1996) and Guggenheim fellow (1980–1981). He was elected to the National Academy of Sciences in 1997, and the American Academy of Arts and Sciences in 2001. In addition to his academic appointment at the University of California, he is a cofounder of Lumiphore Inc., which utilizes new luminescent agents developed in his laboratory, and Faculty Senior Scientist and Interim Director of the Seaborg Center at Lawrence Berkeley National Laboratory. He is the author of 12 patents and approaching 400 research publications.

Jide Xu was born in China. He earned the equivalent of a B.S. in chemistry in 1964 at Wannan University. After a brief period in agriculture in Anhui, China (1964–1967), he worked for Anhui Chizhou Chemical Fertilizer Factory in Anhui, China (1967–1980). After this time away from academics, he returned to Anhui University as a student and lecturer (1980–1986), completing the equivalent of a Ph.D. in 1986. At that time, he was appointed an Associate Professor and Advisor to Graduate Students at Anhui University, and for his work there he was recognized with an Outstanding Teacher Collective Award (1989) and a Significant Achievement Award of Anhui Science and Technology Commision (1989). He came to Berkeley first as a Visiting Scholar (1989–1992) and postdoctoral research fellow (1990–1992), and is currently serving as Staff Scientist working with Professor Kenneth N. Raymond, involved in all aspects of research and project development in his laboratories.

1. Introduction

Providing effective chelation therapy in response to internal human actinide contamination has been shown to reduce acute radiation damage, chemical toxicity, and late radiation effects. The recent development of improved actinide-sequestering agents for potential use in chelation therapy has been based on a body of work in several areas of coordination chemistry. Key among these is the expansion of our fundamental understanding of the structural and solution (thermodynamics) coordination of the actinides. This understanding allows lanthanide metal ions to be used as suitable models for the actinides. Described in this work is an overview of an approach toward the design and optimization of actinide-sequestering agents.

This rational approach for the design of preorganized multidentate sequestering agents for actinides was inspired by siderophores, the naturally occurring microbial iron(III)-sequestering agents. Biological evaluation of the efficacy and toxicity of these ligands has provided comprehensive data for the ongoing ligand optimization process. This has enabled the development of a class of promising highly selective agents for *in vivo* chelation of Pu(IV). In addition, several low-toxicity tetradentate linear ligands with a pentylene or diethyl ether backbones containing catecholate or hydroxypyridinonate binding groups have been found to chelate other actinides and have been identified as suitable agents for *in vivo* chelation of Am(III), Np(IV/V), or U(VI).

Patricia W. Durbin was born in Oakland, California. She received both her B.S. in chemistry (1948) and her Ph.D. in biophysics (1953) from the University of California at Berkeley. Dr. Durbin began her distinguished career in biophysics and actinide biology as a laboratory assistant and technician at Crocker Laboratory at the University of California at Berkeley in 1946 while still a student. Upon completing her Ph.D., she was an instructor in medical physics from 1953 to 1957 at the University of California at Berkeley. Concurrently, she began work as a physiologist at Lawrence Berkeley National Laboratory (LBNL), a position she held until being promoted to Staff Senior Scientist at LBNL in 1978. She has served on numerous committees for the National Council on Radiation Protection (NCRP) (1956–1991), including serving as a NCRP Councilor (1975–1991), and has been on advisory panels for the National Academy of Sciences National Research Panel (NAS–NRP) Committee on Radioactive Waste Management (CRWM) on Hanford Wastes (1976–1978), Savannah River Wastes (1978–1981), and Oak Ridge National Laboratory Wastes (1982–1985). She has been honored with the Distinguished Scientific Achievement Award from the Health Physics Society (1984), to which she was elected a Fellow in 1985. Since retiring in 1991, she has continued studies as a Participating Guest and Senior Scientist at LBNL.

2. Background

2.1. Actinides in Applications

If the development of the energy potential of the actinides ceased today, the use of actinides in both civilian energy generation and space exploration would still require further research directed toward a variety of environmental and health issues resulting from these applications.[1] Complicating the problem is the fact that, in comparison to that of the d-transition metals, our fundamental knowledge of the actinides, their basic chemistry, and coordination systems is still relatively early in its development.[2] The energy potential of the actinides first impacted the world with the invention of the atomic bomb in 1945, at the time overshadowing the scientific implications of their groundbreaking discovery. Since that first isolation of plutonium and the subsequent inception of the Atomic Age, the civilian use of actinides has primarily been to provide a large fraction of the developed world's electricity; however, this and weapons programs have generated a legacy of environmental wastes and a large worldwide inventory of actinide elements.[3,4]

All isotopes of the actinide elements are radioactive. The lengths of the half-lives of the most stable isotopes of these elements decrease across the actinide series, with the heaviest members being so unstable they can only be created and isolated a few atoms at a time.[2] Because of the wider use of nuclear fuel sources, there is an increased risk of exposure to actinides. Of these, plutonium (Pu) and uranium (U) are the elements most likely to be encountered. Plutonium has been manufactured through the irradiation of nuclear fuel to be isolated for material of a grade suitable for military use in weapons and space exploration applications, but in civilian energy production applications, plutonium is generated as a byproduct of systems that are based primarily on uranium fission.[4] Today, with close to one-third of the world's electrical power supply produced using nuclear sources,[5] the overall amount of spent nuclear fuels generated each year is in the range of 9000−10000 tons.[4] This yearly quantity of spent fuel contains about 75 tons of Pu.[4] The total amounts of plutonium produced from power reactors accumulated globally is an estimated 7000 metric tons worldwide, most of which is dilute and contained in this spent reactor fuel.[4,6] In addition, it has been estimated that, after 50 years of production, 100 metric tons of purified plutonium has been produced in the United States and presumably a similar amount in Russia.[4,6] These quantities are increasing daily, and thus the challenge of managing, safely storing, and limiting the potential environmental or injurious effects is constantly on the rise.[7]

While plutonium has been introduced into the environment via atomic weapons tests and accidents at nuclear facilities, the need for therapies to isolate ingested and/or inhaled actinide materials was previously considered an issue solely of concern for trained radiation workers working with sizable quantities of actinides.[8] Unfortunately, recent events have brought to light the potential for exposure to actinides to members of the population at large as the result of an accidental release or an intentional dissemination caused by sabotage or a so-called "dirty" bomb. Although the likelihood of the contamination of a large group or area using this method might be small because of the limits on the availability of radioactive materials and the technical knowledge required to effectively carry out such an attack,[9] the possibility exists, and there is a high potential for panic by people in the area of such a release and a limited time period in which to determine precisely who received a sufficient dose to be harmful in which to administer treatment.[10] Currently, we have limited capabilities to address such a scenario; therefore, it is important to have the means of making available safe, nontoxic, effective (preferably orally bioavailable) chelating agents for decontamination or easily synthesized, inexpensive chelating agents for new separations technologies.[1,10]

2.2. Behavior of Plutonium in Biological Systems

The rationale for actinide removal therapy is the premise that reducing the amounts of the tissue burdens and cumulative radiation doses significantly diminishes radiation-induced tissue damage and carcinogenesis, and reduces chemical damage to the kidneys and liver. The high specific activity alpha emissions of the common isotopes of the transuranic actinides make these elements potent carcinogens.[11−17] Unlike organic poisons, which the body is able to metabolize, these toxic metals are either excreted or

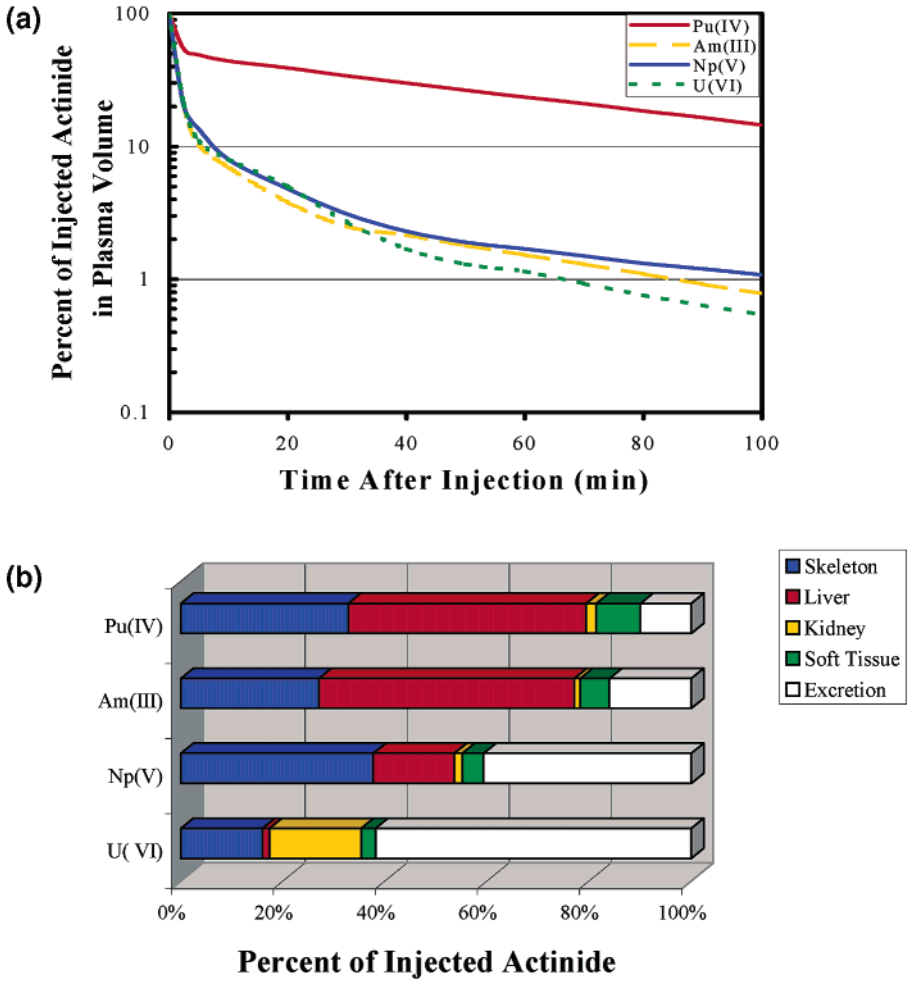


Figure 1. (a) Clearance of intravenously injected soluble actinides from the plasma volume of mice (3 ng of ^{238}Pu,[155] 8 ng of ^{241}Am,[326] 3.6 μg of $^{232+235}$U,[121] and 44 μg of ^{237}Np[122]). (b) Distribution of soluble actinides in the tisues of mice 1 day after intravenous injection (3 ng of ^{238}Pu,[155] 8 ng of ^{241}Am,[156] 3.6 μg of $^{232+235}$U,[121] and 44 μg of ^{237}Np[122]).

immobilized. In the case of the actinides, immobilization in the body presents the problem of localized sites of intense radiation and increasing absorbed radiation doses as the emitted alpha particles repeatedly affect limited groups of cells.[11−17] Prompt aggressive chelation therapy limits the retention of these toxic metals by preventing their coordination with and immobilization by tissue constituents and by promoting their excretion from the body. These processes serve to lessen or eliminate both acute radiation toxicity and/or chemical damage in tissues caused by the intake of actinides.[8,10,16,18,19] We have chosen to focus on plutonium as the most likely hazard presenting the greatest potential threat, as Pu has by far the greatest retention in the body after contamination by actinides.[14,16−22] Those substantial differences in actinide transport and retention in the body are demonstrated in Figure 1a, which displays the plasma clearances in mice of intravenously (iv) injected Pu(IV), Np(V), Am(III), and U(VI), and in Figure 1b, which displays the tissue distributions in mice one day after (iv) injection of Pu(IV), Np(V), Am(III), and U(VI).[19]

The hazards one typically associates with plutonium and other radionuclides are acute radiation damage and sickness caused by exposure to large quantities of radiation (as in the case of those injured in the bombing of Hiroshima), but the chemical and radioactive properties of plutonium are such that it also causes long-term damage and induces cancer in the tissues in which it is deposited.[12,14−17] Somewhat fortuitously, the viable routes of internal plutonium contamination are in large part limited to direct physical transport such as through ingestion, inhalation, or wound contamination.

Plutonium is immobilized readily in sediments in natural waters, in part due to poor solubility and the formation of polymers.[9,23] Plutonium has, however, been found to migrate in nonhumic, carbonate-rich soils, presumably because these soils lack the humic materials left by the decomposition of plant matter that retard the migration of plutonium.[23] These same humic materials also increase the solubility of plutonium in seawater. Increasing the solubility of plutonium increases the potential for environmental migration, thus increasing the bioavailability of the metal.[24]

It was long held that the inability of uncomplexed plutonium to cross physiological barriers greatly hinders its concentration in the food chain.[21,25,26] Nonetheless, there continues to be concern that naturally occurring chelating agents, in particular those that coordinate iron, might complex sufficient Pu to alter that situation.[21,23,27] Consequently, inves-

tigations using siderophores, naturally occurring iron-chelating ligands, were conducted to increase the rate of dissolution of plutonium(IV) hydroxides.[28] One siderophore, desferrioxamine-B (DFOB), was shown to facilitate the uptake of Pu(IV) into bacteria; however, in this case, uptake of Fe(III) was inhibited, and cell reproduction ceased.[29]

The ability of a complexing agent to transport actinide(IV) ions depends on many factors. These include the rate of dissolution from solid hydrolysis and polymeric products formed by the metal, the stability of the metal−ligand complex, and the ability of the complex to compete with other substrates to retain the metal. The effects of ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), citrate, humic acid, fulvic acid, nitrilotriacetic acid (NTA), and siderophores (naturally occurring iron-coordinating species) on the migration of Pu(IV) and Th(IV) have been studied.[30−36] Both EDTA and DTPA have been shown to increase the uptake of plutonium and americium into certain plants, with major implications for the introduction of actinides into the food chain.[37−41] The circumstances in which introduction of actinides into the food chain could occur require additional study of the formation constants of the actinide complexes of the substrates of concern as well as the potential for the substrates themselves to be present in high environmental concentrations.[27]

Plutonium is a potent carcinogen in mammals because of its alpha radioactivity and long-term retention of the complexes it forms with bone and tissue constituents once it is ingested, inhaled, or introduced into the blood through a wound or abrasion.[14−17,42−44] The retention of Pu in soft tissue can be attributed to the similarity of Pu(IV) and Fe(III).[21] Pu can maintain up to four oxidation states in aqueous solutions, and the most likely at physiological pH is Pu(IV). In mammals, Pu(IV) is associated to a high degree with Fe(III) transport and storage systems.[21,26] In mammalian liver, Pu(IV) becomes associated with the iron-storage protein ferritin.[45,46] In blood plasma, the small, highly charged Pu(IV) ion circulates bound to the protein, transferrin, which normally transports Fe(III), occupying one or both of the Fe-binding sites therein.[47−49] While large quantities of citric acid can displace the plutonium once it is coordinated to transferrin, these quantities are so large as to induce toxic calcium depletion *in vivo*.[50] As a consequence, once bound as a transferrin complex, Pu(IV) is not efficiently filtered by the kidneys, inhibiting renal excretion.[14−17] The Pu−transferrin complex circulating in the blood gradually dissociates, to form more stable long-lived Pu complexes with bioligands in the skeleton and liver. Plutonium accumulates in parenchymal cells of the liver, in reticuloendothelial cells in many tissues, on mineralized surfaces of bone, and in some cases it is bound by connective tissue proteins.[15,43,46,51−55]

The endosteal bone surfaces, particularly in the axial skeleton, are considered the most sensitive sites for radiation-induced bone tumors.[44] Because the actinides preferentially deposit on those sensitive endosteal bone surfaces, the most important long-term consequence of a systemic actinide intake is induction of bone tumors. The proximity of trabecular bone to well-nourished erythropoietic marrow and its inherently more rapid growth and maintenance remodeling make reduction by chelating agents of actinide deposits on these most sensitive bone surfaces particularly desirable.[52−55] Studies using mineralized bone or uncalcified matrix models for bone have demonstrated that actinides have affinities for bone mineral and also for bone proteins, such as sialoproteins, chondroitin sulfate−protein complexes, and glycoproteins, and that Pu binds at the mineral−organic interfaces of bone surfaces independently of the presence of functional bone or marrow cells.[56−58] It is still unclear whether either one alone or a combination of both ligand types (mineral or protein) constitute the long-term binding sites in intact bone; however, the central purpose of chelation therapy for internally deposited actinides must be reduction of the bone surface deposit to lessen the local radiation dose, which in turn should reduce bone tumor risk, prolong tumor latency, and increase tumor-free life expectancy.

By diverting circulating actinide to excretion, prompt chelation therapy can prevent deposition on bone surfaces and remove some loosely bound actinide already deposited. Protracted therapy can prevent bone surface deposition of actinide that is recirculated from other tissues and reservoirs (lungs or contaminated wounds) and redeposition on new bone surfaces of actinide released from bone.[19,42,55,59] Among the few investigations of the efficacy of chelation therapy for suppressing the carcinogenic effect of deposited actinides, the experimental conditions vary widely—the injected nuclide, dose, mode of exposure, animal species, and chelation treatment protocol.[19,52,53,60−69] The outcomes of the studies using injected actinides range from encouraging to quite favorable, because chelation therapy generally reduced bone tumor risk (in proportion to, or in some cases to a greater degree than the reduction of skeletal radiation dose), reduced radiation damage to soft tissues, and increased bone tumor latency and survival. Treatment efficacy appeared to be greatest when treatment was initiated within hours of exposure and then was continued over a significant fraction of the life span. Early treatment is particularly important, because it reduces both initial skeletal radiation dose rate and cumulative skeletal dose.[70]

2.3. Chelation Therapy

The potential health hazards of plutonium and the actinides were recognized early in the development of nuclear materials, and soon after the first reactor-generated plutonium was produced, the search for effective means of decorporation began.[71,72] The Health Group of the Manhattan Project assigned to this task pursued three general research goals: to quantify the metabolism of the fission products and heaviest elements, to quantify the acute and long-term toxicity of ionizing radiation from external and internal sources, and to find ways to remove internally deposited radioelements from the body.[71,73] Great

progress has been made in the ensuing years toward accomplishment of the first two research tasks,[44,74,75] but the removal of radioelements from the body has proved to be more difficult. The earliest efforts to remove actinides by means of dietary manipulation, supplements of hormones, common carboxylic acids or complexing agents, or colloidal zirconium citrate were discouraging, as these measures had little effect on the rate or quantity of plutonium excreted.[72,76−78]

From this work, it was determined that the only practical therapy to reduce the health consequences of internal actinide contamination was aggressive, and often protracted, treatment with chemical agents that would form excretable low-molecular-weight chelates.[19,21,42,76] Ideally, such agents should have greater affinity at physiological pH for actinide ions than the complexing species that bind them in tissues and body fluids; they should have low affinities for essential divalent metal ions; they must be of low chronic toxicity at effective dose.[21,59,79,80] It is also highly desirable, especially in cases requiring long-term treatment, to have a decorporation agent that is orally effective.[81,82]

Progress in developing improved agents that meet the requirements for this application has been slow, sporadically marked by serendipitous "discoveries" of industrially prepared chemicals and natural iron chelators and studies with derivatized known agents. Comprehensive reviews and progress reports chart the history and scope of chelation therapy for removing internally deposited actinides: they cover variously the chemistry of metal chelates, animal experimentation to determine chelating agent efficacy for reducing tissue actinide burdens and biological effects, development of new agents and improved treatment protocols, and clinical applications.[10,19,21,42,59,76−78,83−88] In recent years, steady progress has been made through strategies focusing on design of ligands with structural and coordination properties suitable for actinide chelation. The reviews cited above provide ample detail concerning the efficacy and clinical applications of the chelating agents that have been used or proposed for actinide decorporation as well as their use and evaluation. A brief mention of these should be made here for general comparison and to highlight the areas in which there is need for improvement on current techniques.

In 1947, a patent for hexadentate H_4−EDTA was issued in Switzerland to Chemische Fabrik Uetikon[89] for use as an analytical agent for calcium and several other metal ions. At that time, its dissociation constants and log K_{ML} values of its Ca, Mg, and Ba chelates were reported.[90] Two years later, in late 1949, Foreman, who was investigating radioelement decontamination at the University of California Radiation Laboratory in Berkeley, learned by chance of this new complexing agent, then under the trade name Versene (Bersworth Chemical Co.). Foreman postulated, if an aqueous solution of Versene dissolved lead phosphate at pH ≥ 7, as claimed by the distributor, it might also form stable lanthanide and actinide complexes that could be excreted. He sought to examine this premise, beginning with studies using yttrium (in the form of ^{91}Y) and later cerium (using ^{144}Ce) as models for Pu. The ^{91}Y−EDTA chelate injected intravenously (iv) in rats proved to be sufficiently stable that 70% of the ^{91}Y was recovered in urine in 24 h. At the time, this was a notable achievement.[91]

The acute toxicity of Na_4−EDTA was detected almost immediately, and $CaNa_2$−EDTA was used in the demonstration of enhanced excretion and some mobilization of injected ^{91}Y, ^{144}Ce, and ^{239}Pu in rats.[92−94] Simultaneously, in a separate study, Catsch obtained similar results.[95] While $CaNa_2$-EDTA promoted some excretion, its shortcomings as an actinide decorporation agent were soon recognized.[57] When administered over prolonged periods, it is renally toxic (500 μmol kg^{-1} d^{-1} for 16 days in rats).[85] $CaNa_2$−EDTA depletes vital divalent trace metals (e.g., zinc) with greater chelate stabilities.[85] Finally, and most importantly, the efficacy of the chelate is only improved by increasing dose, due to the limits of actinide chelation imposed by the need to use the Ca salt.[76]

2.4. Current Chelation Methods Using DTPA

It became apparent that new ligands with greater affinities than EDTA for multivalent cations and with at least the same or preferably smaller affinities for divalent metals were needed. In 1954, octadentate H_5−DTPA was patented by the Geigy Chemical Co.[96] In late 1955, shortly after the dissociation constants and log K_{ML} values for its alkaline earth and lanthanide chelates were measured,[90] its potential as a therapeutic agent for heavy metal poisoning was noted.[77] The *in vivo* stability of ^{91}Y−DTPA and ^{140}La−DTPA (urinary excretion nearly quantitative in 24 h) was reported by Kroll et al.,[97] and the *in vivo* chelation of ^{144}Ce in rats was reported by Catsch and Lê in 1957.[98] The predicted efficacy of DTPA for *in vivo* chelation of Pu(IV) was verified by V. H. Smith the following year.[99]

H_5−DTPA and Na_5−DTPA were found to be acutely toxic, but this toxicity could be suppressed by use of the Ca chelate, which has a stability similar to that of $CaNa_2$−EDTA.[85,90] $CaNa_3$−DTPA is also about as renally toxic as $CaNa_2$−EDTA, but because the log K_{ML} values for the DTPA chelates with lanthanide and actinide ions are 10^2−10^3 times greater than those for EDTA, $CaNa_3$−DTPA is an effective removal agent at a much lower, clinically acceptable dose (30 μmol kg^{-1}).[42,85,90] In some species, $CaNa_3$−DTPA is toxic if injected frequently, due to depletion of essential divalent metals.[100] Substitution of $ZnNa_3$−DTPA (log K_{ML} 7 orders of magnitude greater than that for $CaNa_3$−DTPA)[90] reduces overall effectiveness for Pu decorporation, but the lower toxicity allows daily treatment over an extended time.[52,101] Polyaminocarboxylic acids (PACAs) with longer central bridges or additional carboxylic acid groups were synthesized and tested. The ratios of the affinities of these ligands for trivalent lanthanides and Ca are not more favorable than those of DTPA. None was more effective than $CaNa_3$−DTPA for *in vivo* chelation of Y or Ce; in fact, some were less effective, and these investigations were discontinued.[42,85,102]

Other PACAs have been investigated for their ability to remove incorporated actinide deposits.[103] An assortment of PACAs with alkyl chains of various lengths were found to reduce Am deposits when given orally.[104] One of these, docosyl-triethylenetetraminepentaacetic acid (or C_{22}TT), reduced plutonium from liver cytosol *in vitro* and was moderately effective when added to the diet of rats 14 days after injection of ^{239}Pu−citrate. The rats were fed 50 μmol per day for 10 days, resulting in 71% reduction in liver Pu and modest reductions in the spleen and kidney Pu—16.7% and 13.8%, respectively. The differences in bone Pu, however, were negligible. This compound is still under study.[104]

Hydrophilic $CaNa_3$−DTPA and $ZnNa_3$−DTPA, which distribute only in extracellular water, cannot react directly with intracellular actinide deposits.[42,85] Attempts were made to facilitate transport of $CaNa_3$−DTPA across cell membranes to improve actinide removal of cellularly deposited actinides by encapsulation of $CaNa_3$−DTPA into liposomes,[105] which accumulate intracellularly in liver. Liposomal encapsulation prolonged DTPA retention in tissues in the body, mobilized somewhat more Pu (injected as a colloid) from liver, and prevented redistribution of liver Pu to bone more efficiently than injected $CaNa_3$−DTPA; however, dosage-dependent splenic hypertrophy was an unacceptable side effect.[42,105]

A lipophilic derivative of H_5−DTPA incorporating two decane chains, colloquially called Puchel, was synthesized at the National Radiation Protection Board, UK, to produce a chelator that penetrated cells.[106] Injected Puchel reduced liver Pu as anticipated, and when inhaled, it accelerated Pu clearance from the lung but did not reduce Pu in the liver.[26,107,108] Protracted weekly or monthly inhalations of Puchel caused lung inflammation, and with the finding that unacceptable liver damage occurred when it was given by injection, its further development was abandoned.[109]

Despite its ability to chelate soluble trivalent actinides and Pu(IV) in body fluids, conventional DTPA therapy has deficiencies.[21,57,59,90,110,111] For example, the log K_{ML} of Pu(IV)−DTPA is not great enough to affect solubilization of plutonium hydroxides at physiological pH.[90] Thus, while DTPA can remove much of soluble actinide complexes in body fluids, it is much less effective for removing lanthanides or actinides after metal hydrolysis and the subsequent formation of colloids or polymers.[60,86,102,112] Once Pu is bound in tissues and bone, DTPA has little effect on its mobilization.[42,111] Although octadentate, DTPA appears not to coordinate fully with tetravalent actinides, possibly not forming the optimal 1:1 chelate with Pu(IV) because some of the electron donor groups are sterically hindered from proper orientation around the metal ion.[21,90] DTPA is not specific for metals of high ionic charge, and the less potent Ca or Zn chelates must be used to avoid hypocalcemia and depletion of essential divalent metal ions such as Zn, Co, Cu, and Mn.[42,57,110,113−116] This effect was extreme enough to cause death in dogs due to Zn(II) depletion, in which high levels of DTPA were maintained by multiple injections, and it limits the frequency of doses that can safely be administered.[100]

Derivatizations and modest modifications of DTPA were not found to sufficiently improve Pu chelation.[42,85,117,118] Hydrophilic DTPA does not penetrate cells and is therefore unable to act on aggregated actinides in phagocytic cells[60,94,119,120] and does not compete for actinides already incorporated into bone.[54,111] These factors also understandably limit the efficacy of decorporation if the chelating agent is not administered immediately after the intake of radionuclides. The current FDA-approved drug, $CaNa_3$−DTPA or $ZnNa_3$−DTPA, is also not orally effective at the recommended clinical dose and is administered by injection or inhalation. Oral bioavailability is potentially a most desirable property of an actinide-sequestering agent, especially if repeated doses are considered necessary or if a large number of people require treatment.[19] Finally, DTPA is not an effective therapeutic agent for some other actinides, such as Th(IV), Np(IV), or U(VI). This may be an issue if more than one metal is present in an accident or if there are questions about the contaminant.[59,121,122] With these limits on the current treatment using DTPA, there remains a great deal of room for improved decorporation methods, and there continues to be a need for more powerful, less toxic, orally active chelating agents with increased specificity for actinide(IV) ions and U(VI).

3. Designing a Model System

3.1. Actinide Coordination Chemistry

3.1.1. Characteristic Features

Fifty years of investigations of actinide coordination chemistry make it possible to describe some general trends in their chemistry. Actinides form easily hydrolyzed acidic metal ions that form strong complexes with common chelating agents.[3,7] These hard ions preferentially interact with hard acid donors, such as oxygen or carboxylate, alkoxide, and fluoride anions, but have been known to demonstrate some covalency in interactions with softer donor atoms, such as chloride, nitrogen, and sulfur. Unlike the elements of the lanthanide group (abbreviated Ln), which are primarily found in a characteristic trivalent oxidation state, the lighter weight actinides, those preceding americium in the periodic table, exhibit a diverse redox chemistry.[2]

While actinium (Ac) maintains a stable trivalent state in solution, the typical characteristic thorium (Th) oxidation state is tetravalent, that of protactinium (Pa) is pentavalent, and the most stable oxidation state for uranium (U) is hexavalent. The actinides between uranium and americium (Am) possess four principal oxidation states, III, IV, V, and VI, in addition to a heptavalent state for neptunium (Np) and possibly for plutonium (Pu). The penta- and hexavalent oxidation states exist as linear ("-yl") dioxocations in most solutions and many solid media.[2,123,124] Common methods for the chemical separation of actinides from reactor fuels take advantage of the unique differences in redox chemistry across

Table 1. Bite Angle, Coordination Number, and Geometry of Actinide(IV) Complexes

metal	complex	coordination number	bite angles (deg)	idealized geometry	ref
Pu	$NH_4Pu(NO_3)_6$	12	50.9	icosohedron	307
Pu	$[Na_6Pu(CO_3)_5]\cdot 2Na_2CO_3\cdot 33H_2O$	10	52.2	pseudohexagonal bipyramid	303
Pu	$Pu(DFOE)\cdot 3H_2O$	9	65.6	tricapped trigonal prism	24
Pu	$Pu(thenoyltrifluoroacetylacetone)_4$	8		trigonal-faced dodecahedron	*a*
Th	$NH_4Th(NO_3)_6$	12	49.8	icosohedron	307
Th	Th(*N*-isopropyl pivalohydroxamate)$_4$	8	62.3	cube	80
Th	Th(*N*-isopropyl-3,3-dimethylbutanohydroxamate)$_4$	8	63.0	trigonal-faced dodecahedron	80
Th	$Th(catechol)_4$	8	66.8	trigonal-faced dodecahedron	310
Th	$Th(1,2\text{-}HOPO)\cdot H_2O$	9	63.8	monocapped square antiprism	313
Th	$Th(PR\text{-}Me\text{-}3,2\text{-}HOPO)_4$	9	63.4	monocapped square antiprism	322
Th	$Th(acac)_4$	8	70.7	trigonal-faced dodecahedron	*b*
Th	$Th(thenoyltrifluoroacetylacetone)_4$	8	70.5	trigonal-faced dodecahedron	*c*
Th	$Th(salicylaldehyde)_4$	8		trigonal-faced dodecahedron	*d*
Np	$Np(acac)_4$	8	71.8	trigonal-faced dodecahedron	*e*
U	$U(salicylaldehyde)_4$	8		trigonal-faced dodecahedron	*d*
U	$U(bipyridyl)_4$	8		cube	*f*

[a] Baskin, Y.; Prasad, N. S. K. *J. Inorg. Nucl. Chem.* **1963**, *25*, 1011. [b] Reeves, P. J.; Smith, A. J. *Inorg. Chim. Acta* **1987**, *139*, 51. [c] Lenner, M.; Lindquist, O. *Acta Crystallogr.* **1979**, *B35*, 600. [d] Hill, R. J.; Rickard, C. E. F. *J. Inorg. Nucl. Chem.* **1977**, *39*, 1593. [e] Allard, B. *J. Inorg. Nucl. Chem.* **1976**, *38*, 2109. [f] Piero, G. D. *Cryst. Struct. Commun.* **1975**, *4*, 521.

the group.[125−127] The transamericium actinides have fewer oxidation states and behave quite similarly to the trivalent lanthanides.[128]

In complexes, the actinide(III) and actinide(IV) ions generally display variable and high (8, 9, 10, or higher) coordination numbers. The energy differences between the various coordination geometries are small; therefore, they show low stereochemical preferences. Although the actinyl ions prefer to retain their linear di-oxo structure, they also display variable coordination numbers (6, 7, 8). This combination of factors serves to make the rational design of specific actinide-sequestering agents quite challenging. Better control of the coordination environment can be imposed by using structurally predisposed ligands. The large size and flexible coordination geometry of the actinide ions should provide clues to the design of actinide-specific chelating agents, and two fundamental questions in the designing are the determination of which coordination number and geometry are, indeed, preferred by a given actinide metal ion with a given ligand. Because of the large ionic radii of actinides, the preferred coordination number is 8 for actinide complexes, with bidentate chelating agents forming five- or six-membered chelate rings. In general, the coordination number depends on the bite angles of the chelating units, as well as the steric bulk of the ligands. Higher coordination numbers are often encountered with ligands having small bite angles or by the incorporation of solvent molecules, as shown in Table 1.

The most common coordination number encountered in actinide(III) and -(IV) complexes is 8. Calculations of ligand−ligand repulsions indicate that either the square-antiprism (D_{4d}) or the trigonal-faced dodecahedron (D_{2d}) is the expected geometry for the coordination polyhedra of eight-coordinate complexes.[129] The Coulombic energy differences between these polyhedra are small, and the preferred geometry is largely determined by steric requirements and small ligand field effects.[130]

Eight-coordinate complexes are known in a variety of coordination geometries in which the assignment

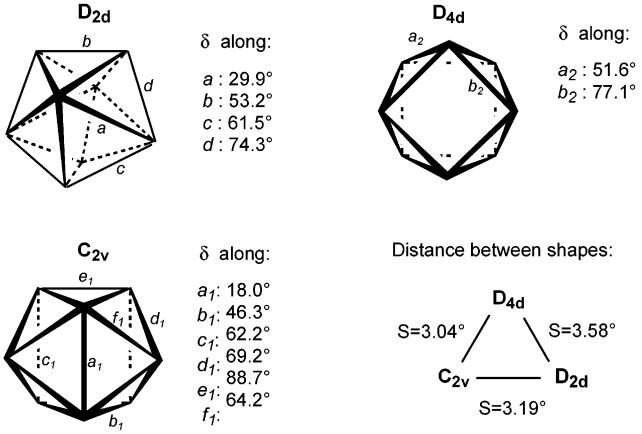


Figure 2. Examples of the three idealized eight-coordinate polyhedra geometries: trigonal dodecahedron (D_{2d}), bicapped trigonal prism (C_{2v}), and square antiprism (D_{4d}) with shape measure *S* (deg) and the distance between the shapes given for each pair. Reprinted with permission from ref 130. Copyright 2000 American Chemical Society.

of a closest idealized polyhedron is not straightforward. An analysis of the shape is usually expressed in terms of three high-symmetry polyhedra. These three are shown Figure 2: the trigonal dodecahedron, the bicapped trigonal prism, and the square antiprism.[131−133] Subsequent to that of Porai-Koshits and Aslanov,[133] another approach was suggested by Muetterties and Guggenberger[134] for determining the polyhedral shape by comparing chosen ideal and observed pertinent dihedral angles and the nonplanarity of the trapezoidal-type atoms. Ideal coordination geometries were in turn proposed by Kepert,[129,135] taking into account a repulsive potential of the form of eq 1 to optimize the ideal coordination geometry of a given symmetry.

$$\left(\sum_{i\neq j}^{m} R_{ij}^{-n}\right) \qquad (1)$$

We will refer to this as the Kepert model and have chosen $n = 8$. Dihedral angles along edges are defined as the angles between the normals to adjacent

bounding faces of the polyhedron, where the vertices of that polyhedron are the ligand donor atoms around the metal. This "shape analysis" is then independent of the size of the polyhedron and allows for the comparison of complexes formed by various metal ions and ligands. Recently, another approach to a continuous symmetry measure was proposed by Pinsky and Avnir, in which a least-squares method is used to fit all of the vertices of the observed polyhedron to those of idealized values.[136]

In previous approaches to shape analysis,[129,131−136] only specific dihedral angles were used; however, if the symmetry of the complex deviates significantly from an idealized geometry, it becomes difficult to decide which dihedral angles to choose. In an alternative approach, one can compare the dihedral angles, as these are intrinsically connected to the notion of shape and are the basis of symmetry. From this, it can be suggested that the geometry of complexes be analyzed using *all* the dihedral angles (one for each pair of adjacent triangular planes) in the polyhedron. All observed dihedral angles in a given structure could then be compared with the corresponding ideal values. To this end, following general error theory, we suggest the use of S, the "shape measure", to evaluate the degree of distortion from an ideal geometry; S is the minimal mean deviation of dihedral angles along all edges, defined as

$$S(\delta,\theta) = \min\left[\frac{1}{m}\sqrt{\sum_{i=1}^{m}(\delta_i - \theta_i)^2}\right] \qquad (2)$$

where m is the number of all possible edges (here $m = 18$), δ_i is the observed dihedral angle (angle between normals of adjacent faces) along the ith edge of the experimental polyhedron, and θ_i is the same angle of the corresponding ideal polytopal shape (D_{2d}, D_{4d}, or C_{2v} structures shown in Figure 2).[129] The minimization is carried out by looking at all possible orientations of the observed structure (δ) relative to the reference polyhedron (θ). The value $S(\delta,\theta)$ is a measure (a metric in the strict mathematical sense) of structural resemblance to an ideal polytopal shape.

Based on this method, the shape analysis of a coordination polyhedron is performed in three steps. The first step is the calculation of all the dihedral angles of each pair of adjacent planes in the polyhedron. The second step in this analysis is to find which superposition of the polyhedron on the targeted ideal polyhedron gives the smallest deviation for that idealized shape. Finally, eq 2 is used to compare S for the different ideal coordination geometries. A computer program that incorporates this algorithm has been developed, and the shape measures for the idealized polytopal shapes are given in Figure 2.[130]

3.1.2. Lanthanides as Models for Actinides

Because of the hazards and expense associated with working with actinide metals, it is often convenient to use other less hazardous metals as analogous models. This enables the development of experimental techniques while requiring less material and producing less hazardous waste, as well as providing access to a wider range of available analytical tools. The lanthanides have been found to be useful as actinide analogues for the purpose of structural investigation and modeling studies, because of their chemical similarities and reduced radioactivity. It is important to remember, as the capabilities of computer-generated modeling systems expand and their makers promote said capabilities, that while computer modeling may be a useful tool, many systems still lack the capability to model actinide systems consistently and accurately, due in large part to limited data. Many of these systems use other metals to approximate parameters for actinide (and lanthanide!) systems. Thus, while computer modeling is a useful tool, there is still no substitute for quality experimental data.

Lanthanides and actinides have several properties in common. Both groups act as Lewis acids, have large ionic radii, possess flexible coordination geometries, and prefer high coordination numbers (especially the coordination numbers 8 and 9), and both groups prefer interactions with hard acid donor atoms such as oxygen or carboxylate, alkoxide, and fluoride anions.[3,124] Although transuranium actinides have a wide variety of oxidation states available, in their trivalent state they exhibit ionic radii similar to those of the trivalent lanthanides in the same column of the periodic table or one column to the left.[137] A division exists within the actinide group, in which the early actinides have multiple oxidation states and demonstrate some covalent character, while the late actinides (Am and beyond) are even closer in their similarities to the chemistry of the lanthanides and are found in the +3 oxidation state.[123] While this has made the separation of americium from lanthanides another pressing nuclear waste management issue, one of the most challenging in separation science,[126,128,138] it also serves as a prime example of how lanthanides function as useful models.

The redox potentials of the catechol complexes (the metal IV/III oxidation state couple), combined with the stability constants of the metal(III) complexes, allow indirect thermochemical determination of the metal(IV) stability constants.[22] Since the stability and coordination chemistry of metal catecholate complexes are largely determined by the metal's charge-to-ionic radius ratio,[21,139,140] the lanthanide(III) catecholates are excellent models for corresponding transuranium catecholate complexes. This has made them particularly useful in modeling the behavior of americium(III) catecholates and in the development of americium decorporation agents.[22,87] Europium is in the same column of the periodic table as americium, and gadolinium is immediately to the right of europium. The eight-coordinate ionic radii are 1.066 Å for Eu, 1.053 Å for Gd, and 1.090 Å for Am.[137]

Plutonium presents a more complex problem. Although Pu has been found in each of the oxidation states from III to VI in aqueous solution, the Pu(IV) state is preferred. Biological evidence indicates that most, if not all Pu exists as Pu(IV) *in vivo*.[43] Cerium is the only lanthanide for which the +4 oxidation

state is important and long-lived, stable for several weeks, in aqueous solutions.[124] For this reason, Ce(IV) has been chosen for studies in systems for investigating Pu coordination.[141,142] The problem of selectivity for Pu over Ce in decorporation or sequestering applications is limited; however, systems developed using lanthanides as models would have difficulties for waste management applications where quantities of Ce might become an issue.[128] Further examples of modeled systems will be discussed in the context of the particular actinide later in this review.

3.2. Requirements for an Effective Sequestering Agent

In general, the requirements for an effective sequestering agent are high selectivity toward metal binding, low toxicity, and preferably high oral activity and low cost. There are several factors to be considered in the design of an actinide-sequestering agent, and key among these is designing a ligand that combines a high affinity for the target metal with a low affinity for other biologically significant metal ions. Thus, the electronic properties of the target metal and ligand must match. The chelate must also be able to assume the appropriate coordination cavity size and geometry for the desired metal.[143] As discussed above, the actinide ions are "hard" cations, have large charge-to-radius ratios, and prefer "hard" oxygen and negatively charged oxygen donors. Preferring a coordination number of 8 or greater, actinide ions have a tendency to form stable complexes with ligands of high denticity.[2] For a given chelating unit, the denticity and topology of a sequestering agent play important roles in complexation, and these should be matched to the coordination number and the geometry requirements of the actinide ion, respectively. A well-preorganized sequestering agent can achieve many orders of magnitude of additional stability (up to 6 in the case of iron-sequestering agents) upon metal complex formation.[144,145]

High selectivity toward actinide ions is critical. The effective but nonselective amino-carboxylic acid ligands such as DTPA can deplete essential biological metal ions from patients, thus causing serious health problems.[42,57,90,110,113−116] Selecting the correct type of chelating unit is the most decisive factor in achieving high selectivity toward the specific metal ion. The binding subunits found in siderophores—catecholates, catecholamide, amino-carboxylic acids, hydroxamates, or hydroxypyridinonates (HOPOs)—tend to be extremely specific for Fe(III) as well as Pu(IV). Hence, sequestering agents bearing these binding units usually form highly stable complexes with actinide metal ions.[21] Although the strongly basic catecholamide ligands should exhibit high affinity toward actinide ions, they also show strong affinity to protons and are likely to be protonated under physiological conditions, which decreases their ability for metal binding. The fact that the amino-carboxylic acids, 1,2-HOPOs, and 3,2-HOPOs have pK_a values below or close to physiological pH, that is, they are deprotonated at pH 7.4, makes them very effective under physiological conditions.[19]

The bioavailability of a sequestering agent is also important, as with increased bioavailability it is possible to decrease the required drug dose. An excellent selective coordinating ligand is of limited use as a sequestering agent if it is not readily absorbable into the bloodstream. However, predicting which characteristics serve to improve bioavailability can be difficult.[146,147] Although lipophilic compounds tend to be largely absorbed when administered orally, the fraction of chelator orally absorbed for a range of the bidentate 3,4-HOPOs in the rabbit was found to be insensitive to the lipophilicity of the iron-sequestering agent.[148]

Low toxicity is another essential requirement of a metal-sequestering agent.[149] Type of chelating unit, ligand multidenticity, and topology are important influencing factors. In general, for the ligands with the same chelating units, those of low denticity are less toxic than those of high denticity, and linear ligands are less toxic than branched ligands. We have also observed that the scaffold structures could be a crucial factor. For example, in the bis (bidentate) Me-3,2-HOPO ligands with different lengths of methylene-linking bridges, the observed toxicity sequence is C4 ≫ C3 > C6 > C5, while that with a 5-LIO scaffold ($-CH_2CH_2OCH_2CH_2-$) is the least toxic.[150]

Good oral effectiveness is a very desirable property of a sequestering agent. To have good oral activity, a sequestering agent should have a reasonably high lipophilicity to penetrate the biomembrane, and the resulting actinide complexes should be excreted via both urine and feces. Topology could also be an important factor influencing oral activity; for example, linear octadentate HOPO ligands seem to have much greater oral activity than their branched analogues, such as those with *N*1-(2-aminoethyl)-*N*1-(2-[bis(2-aminoethyl)amino]ethyl)ethane-1,2-diamine (PENTEN)-based backbones.[150]

Good water solubility for both the sequestering agent and its metal complex is a desirable property; however, this is not always the case. The neutral metal complexes with monoanion binding unit ligands, such as hydroxamate or hydroxypyridinone, often have poor solubility in water and are most likely to be excreted via feces.[150] Last, but not least, low cost is an important measure for practical application.

3.3. Biological Means for Evaluation

3.3.1. Initial Assessment

Chemical properties, molecular modeling, and *in vitro* measurements may produce leads, but the efficacy and toxicity of a new drug must be established in living animals. From its beginnings, research and development of siderophore-based actinide-sequestering agents included biological evaluation as a guide to ligand design. The stabilities of the actinide chelates in the range of physiological pH would need to be great enough to displace the actinide from their complexes with bioligands in the blood, soft tissues, and bone; any new chelating agent for the actinides, particularly for Pu(IV), would also need to be demonstrably more effective for promoting actinide excretion than clinically accepted $CaNa_3$−DTPA or desferrioxamine (DFO).[79]

Good results from chemical *in vitro* studies of competitive binding, for example removal of actinides

from their transferrin complexes in blood, are insufficient because a reaction vessel cannot be made to include the complexities of a living host. These complicating factors include selective cell membranes and structural barriers in tissues, the rapid shift of actinides from blood to stably binding bioligands in soft tissues and bone, and the rapid excretion of the ligand. The results discussed here are all the product of testing of the *in vivo* complexation and enhancement of actinide excretion. The biological evaluation protocols that were adopted and used, with minor modifications and additions, throughout the Berkeley collaboration agree with consensus recommendations for evaluating new chelating agents for the actinides.[79]

Many of the new ligands described here were costly and/or difficult to synthesize, at least initially, and as only a small amount of each new ligand was expected to be prepared, it was necessary to miniaturize the biological procedures. Mice are commonly used for metabolic and toxicity studies, because they are appropriate small-scale acute models for larger mammals. Mice were used in part because plutonium metabolism and chelate action had already been studied in that animal,[149,151,152] but there were other factors to consider as well. The animal chosen for the primary investigations was the young adult female Swiss-Webster mouse, an outbred strain of stable size and docile behavior. The mice were used at 12−14 weeks of age and 33 ± 2 g body weight. At that age, the female mouse skeleton is nearly mature, and the long bones have attained 98% of their maximum length.[153] An animal model with a mature skeleton more closely resembles a human adult with respect to the degree and extent of bone remodeling. These are important considerations in interpreting the results of chelation therapy, as they will significantly affect the retention of actinides deposited in the skeleton. The mouse model as described here provided an effective screening method to determine which ligand systems warrant further study. The last important advantage, unique to the study of actinide chelators, is the generation of much smaller amounts of radioactively contaminated wastes.

Ligands were prepared for animal administration in 0.14 M NaCl (normal saline), and the pH was adjusted with NaOH to 7.4; however, some of the ligands required a pH as high as 8.5 for complete dissolution. All ligands were administered initially at a standard dose of 30 μmol kg^{-1}, the dose of $CaNa_3$−DTPA most often used clinically. Those standard ligand solutions were 0.002 M, and a 35-g mouse was given 0.5 mL. The desired dose for each mouse was obtained by adjusting the injected volume to its body weight. For a ligand of molecular weight 1000 g/mol, 30 μmol kg^{-1} in a 35-g mouse is 1.05 mg. Thus, with the small amount of ligand needed for each mouse, groups of five similarly treated mice could be used for each evaluation procedure, providing reasonable statistical measures of ligand efficacies.[149,154]

All newly synthesized ligands were initially evaluated for *in vivo* chelation of Pu(IV). Initial biological evaluation of ligands for *in vivo* chelation of Pu in mice consisted of three screening protocols for the introduction of the ligands into the animal: prompt injection—ip injection of groups of five mice with the standard ligand dose given 1 h after the iv injection of Pu (killed after 24 h); delayed injection—ip injection of groups of five mice with the standard ligand dose given at 24 h after the iv injection of Pu (killed after 48 h); or oral administration—groups of five fasted mice treated via gastric intubation with the standard ligand dose at 3 min after the iv injection of Pu (killed after 24 h). Prompt ligand injection measures the ability of a ligand to compete for Pu with the bioligands that transport it in the circulating fluids (mainly as a complex with the iron-transport protein, transferrin) and to compete for Pu newly bound by bioligands in the skeleton and liver. At 1 h after an iv injection in the mouse, about 50% of the injected Pu is still circulating in the blood and extracellular water, and 20% and 30%, respectively, has already been deposited in the blood-free skeleton and liver.[153,155] Deposition of iv-injected actinides in the skeleton and target soft tissues of mice is nearly complete within a few hours; thus, the delayed injection ligand treatment at 24 h assesses its ability to compete for actinide recently deposited in the target tissues.[121,122,156]

Oral administration studies serve to demonstrate the bioavailability of the ligand. This is key in the development of orally effective ligands for the actinides, an ultimate goal in the area of actinide decorporation agents, and is a very important attribute that would enable the initiation of treatment for actinide exposure within minutes without requiring medical assistance. Ligands were administered orally to mice by stomach tube at 3 min after the iv injection of an actinide to ensure that, even if only a small fraction of the ligand were absorbed, sufficient actinide would still be circulating and readily available to react with the incoming ligand. The mice in these investigations were fasted for 14−16 h before injection of the actinides and administration of ligands to optimize gastrointestinal (GI) absorption by suppressing physical interference of the GI contents and chemical interference by ligand loss to complexation with dietary iron. [146,147]

The dose−effectiveness (D−E) relationships of several ligands for Pu removal were investigated to establish minimally effective doses and to determine the dependence of effective doses on ligand denticity and the properties of its functional groups. In the D−E studies, ligand doses in the prompt ip injection protocol were adjusted to range from 0.001 to 100 μmol kg^{-1}.

In addition to Pu(IV), some ligands were also evaluated for *in vivo* chelation of other actinides. This enables comparison of how the different preferred coordination states are chelated by the various chelating structures, and the results underscore the deficiency of DTPA to adequately chelate all of the actinides that might commonly be found in nuclear fuel systems. In some accident situation a worker may be contaminated only with Pu; exposure to a mixture of metals generated during uranium fission energy production is also a likely scenario. Actinides other than ^{238}Pu used in these investigations include

^{241}Am, ^{237}Np, and U as ^{233}U or ^{232,234,235}U.[121,122,156,157]

Pu(IV). A stock solution of ^{238}Pu(IV) in 0.08 M sodium citrate pH 3.5 was prepared according to a published method[158] and stored frozen. Aliquots were thawed as needed, diluted 10:1 with sterile normal saline, and filtered (0.22 μm Millipore). Each mouse received 0.2−0.4 mL of the diluted Pu solution (0.008 M sodium citrate, 0.14 M NaCl, pH 3.5) containing 925−1850 kBq (0.0014−0.0028 μg) of ^{238}Pu(IV) by iv injection into a warmed lateral tail vein. The molar ratio ligand:Pu is (0.9−1.8) × 10^5 for 30 μmol kg^{-1} of administered ligand. That dose in a 35-g mouse is the equivalent of 2.8−5.6 μg of ^{238}Pu(IV) in a 70-kg Reference Man, an amount of any Pu isotope that, if taken into the body, would require rapid, aggressive chelation therapy.

Am(III). Mice were given iv injections of 0.2 mL of a solution (0.008 M sodium citrate, 0.14 M NaCl, pH 4) containing 1.1 kBq and 0.008 μg of ^{241}Am. The ligand:Am molar ratio was 3.1 × 10^4 for 30 μmol kg^{-1} of ligands.

Np(V). Mice were injected iv with a solution of $^{237}NpO_2Cl$ (0.14 M NaCl, pH 4) containing 121−1153 Bq and 5−44 μg of ^{237}Np, respectively. The respective molar ratios ligand:Np were 50−5.6 for 30 μmol kg^{-1} of a ligand.

U(VI). Mice were injected iv with 0.2 mL of a solution of $^{232,234,235}UO_2Cl_2$ (0.14 M NaCl, pH 4) containing 1240 Bq of ^{232}U and 3.2 μg of uranium. The molar ratio ligand:U was 77 for 30 μmol kg^{-1} of a ligand. Alternatively, mice were injected with 0.2 mL of a solution (0.14 M NaCl, pH 4) containing 933 Bq and 2.6 μg of ^{233}U as $^{233}UO_2Cl_2$. The ligand:U molar ratio was 94 for 30 μmol kg^{-1} of ligand.

The effectiveness of a promptly injected ligand for *in vivo* chelation of Am, Np, or U was evaluated by ip injection of ligands 5 min after the iv actinide injection, because all three of these actinides are rapidly cleared from the circulating fluids of mice (Figure 1a) and deposited in skeleton and liver and, in the case of U, also in the kidneys.[121,122,156]

Each experimental or control group of mice consisted of five individuals that were housed together in a cage with a liner for collecting excreta. At the end of the time interval judged necessary for nearly complete excretion of the chelated metal and the excess free ligand (24 or 48 h in most cases), the mice were killed by cervical dislocation. Samples taken for radioactivity measurement included liver, kidneys, gastrointestinal tract plus contents, carcass (which was separated after dry ashing into bone and soft tissue ash), and excreta (separated into urine and feces). The tissues and excreta samples were dry ashed and dissolved in 6 M HNO_3, and their radioactivity was determined by scintillation counting. The result for each sample was reported as a percent of the amount of radioactivity injected as determined from aliquots of the injection solution (100 × radioactivity sample/radioactivity injected). Details of the methods of managing the animals, processing the samples, and radioactivity detection are available.[121,149,159−161]

In all of the biological evaluation protocols, the actinide distributions and excretion in ligand-treated mice were compared with actinide-injected controls. The efficacies of the new ligands were compared with that of an equimolar amount of clinically accepted $CaNa_3$−DTPA in all of the test protocols and, in some cases, also with desferrioxamine. These studies were done over a period of years while maintaining the same protocols, enabling direct comparisons over the entire range of ligands prepared. The internal distribution and excretion of the iv-injected ^{238}Pu was the same for more than 50 groups of untreated Pu-injected controls, providing evidence for the reproducibility and stability of the ^{238}Pu preparations and the animals.[18,19,82,121,122,147,149,150,156,157,159−170]

The design of these studies of *in vivo* actinide chelation differs from those of studies conducted in other laboratories in several important respects. The actinide content of the whole skeleton was measured directly.[149,159] Total GI excretion was measured by taking account of the actinide present in the GI contents at death.[159] Separated urine and feces were collected at 4 h and daily from each group of five mice. Each group of five mice was managed as an individual material balance study, and all injection procedures, sample taking and processing, and radioactivity detection methods were refined to obtain material recoveries of 95 ± 5% of the injected radioactivity.

The acute toxicities of some ligands were also determined. The detailed protocols have been published[121,163,150,171] but can be summarized briefly. Groups of 20 mice were injected daily for 10 days (ip or subcutaneously, s.cut.) with 100 μmol kg^{-1} of a ligand or twice in 8 h with 500 μmol kg^{-1} of a ligand. Toxicity was assessed from mortality and several toxicity indices, which were determined for one-half of the survivors on day 11 and the remaining mice on day 21. The toxicity indices included body, kidney, liver, and spleen weights, blood urea nitrogen (BUN) determination, gross pathology of internal organs and the s.cut. injection site, if applicable, and by microscopic pathology of liver, kidneys, and the s.cut. injection site.

3.3.2. Collaborative Studies

Reinvestigation in other laboratories of the efficacies of several siderophore-based ligands for decorporation of ^{238}Pu confirmed the initial assessments in mice of their effectiveness for *in vivo* and *in vitro* chelation of Pu(IV) relative to that of $CaNa_3$−DTPA.[117,118,171−183] These partnerships allowed for studies with other isotopes of Pu[180,184−188] in addition to ^{238}Pu(IV) and other actinides, Am(III),[117,118,171−181,184,187] Np(IV),[189] Np(V),[189−191] U(VI),[181,185,192] and Th(IV),[193] as well as actinides in chemical forms other than the soluble citrate complex, such as the nitrate[174−180] and tri-*N*-butyl phosphate complexes[194−198] or as MOX particles (a refractory solid solution of UO_2 and PuO_2 and the ingrown ^{241}Am daughter),[187] compounds that might be commonly found in nuclear fuel processing and waste remediation systems. The collaborative efforts

included animal models in addition to mice: rats,[117,118,172−183,187−191,193−196] hamsters,[172,174] baboons (*Papio papio*),[188,197−199] and beagle dogs,[184,185,200] each providing a unique insight in modeling the potential human subject response. Subsequent studies with the other animal models provided the opportunity to explore other methods of exposure to actinides, i.e., inhalation[117,174−176,179,195,196,198] or wound contamination.[177−180,187,193,194] The collaborative projects also explored a variety of ligand administration regimens in addition to parenteral injection:[117,118,172−191,193−200] local injection (either im or s.cut.) at a wound site,[177−180,187,193,194] by means of an s.cut. implanted osmotic pump,[118,175,178,182] and oral administration by gavage[118,172,177] or in drinking water.[177,182] Finally, new *in vitro* and *ex vivo* model systems were also the subject of continued investigations, measuring the abilities of some siderophore-based ligands to remove Pu from transferrin[201,202] or mouse liver ferritin,[203] to remove Pu and Am sorbed to bone mineral,[171] and to remove U from kidney cytosol proteins.[204] As a group, these studies take advantage of the expertise and different instrumentation for actinide measurements available in other research groups while simultaneously providing confirmation of the findings in the mouse model. More importantly, the studies of other actinides and other exposure modes in several species revealed some ligand defects and some deleterious side effects that were not disclosed by the initial evaluation procedures in mice.[172−175,183−185,188,197,198,200]

One important aspect of the new studies with alternative animal models is the opportunity to change the mode of administration of actinides, enabling simulation of various accident-based scenarios. Experiments to test the effects of chelating ligands on inhaled actinides involved the administration of a mixture of Pu and Am as a nitrate aerosol generated from nitric acid solutions through the use of a nebulizer over the period of 1 h. As one might imagine, the use of such a nebulizer on an animal as small as a mouse is very difficult; hence, 3-month-old female rats of the HMT strain, NRPB, weighing 180−200 g at the time of exposure, were used for studies determining the effects of inhaled actinides.[117,174−176,179] Similar studies followed using a nebulizer to administer the Pu as a tri-*N*-butyl phosphate (TBP) complex. TBP is commonly used in extractions to limit waste produced using nuclear fuels.[5,195,196,198] This simulates the inhalation exposure of the 1971 americium accident victim.[205]

Other studies in the rat model explored introduction of actinides into the body as the result of wound contamination. In these, the rats received an s.cut. or im injection of an actinide solution containing Np, Th, or Pu plus Am, to simulate a contaminated wound. In all cases, the chelators were injected directly into the wound site 30 min later to simulate on-the-scene accident conditions, and, in some cases, the chelators were injected ip one or more times during the next 7 days. The animals were killed at 7 days and autopsied to obtain measurements of the actinide retained in the wound site, liver, kidney, and remaining carcass. All of the excreta were collected for radioanalysis. Organ samples were retained for detailed histological examination.[177−180,187,193,194]

Unlike the mouse model system, adult rats have slowly but continuously growing skeletons. This means that the direct comparison of rats to larger mammals in terms of the efficacy of a chelating agent may be masked by a decrease in the amount of actinide retained in rat bone, making a chelator tested in rats appear better for the removal of actinides from bone than it would be when applied to other mammals.

Work with larger mammals, such as dogs[184,185,200] and baboons,[188,197−199] allows a closer approach to human physiology. The studies with dogs were done in collaboration with the Radiobiology Laboratory at the University of Utah School of Medicine. This allowed the use of animals from their beagle colony with physical characteristics nearly identical to those dogs under continuous study since 1951. Pairs of dogs were given ligands by iv injection 30 min after injection of actinide solutions. The animals were monitored for 7 days prior to sacrifice, and all excretions were collected. Blood was compared with samples taken prior to the introduction of actinides to measure any chelator-related changes in the blood chemistry. Complete gross autopsies were performed and specimens taken of multiple tissues for histopathological studies, in addition to the radioactivity counting studies done on the whole body and selected organs. Dogs will be useful for future work in areas such as the long-term effects of continuous treatment over periods of years, longer than the mouse lifespan.

The beagle dog studies,[184,185,200] which were confirmed in rats,[172−175] hamsters,[172,174] and baboons,[188,197−199] showed that the carboxy-catecholamide-based chelating ligands had potentially toxic side effects. Unlike the rodents, the hamster liver does not spontaneously excrete heavy metals. In this respect, the hamster model is somewhat more like the larger mammals than mice or rats. Within this set of studies, a wide variety of animal models with different kidney pH was investigated, and in the mammals eating a protein-rich diet (lower kidney pH), renal toxicity due to redistributed deposited metals makes certain ligands unsuitable for continued drug development. Repeating studies in different animal models enabled this determination. All of this work is necessary in the development of a drug to ensure its safety and efficacy before it can be made available to people, or replace current treatments. Highlights of the results of the chelation efficacy studies are presented in appropriate sections later in this review.

4. A Biomimetic Approach toward Actinide-Sequestering Agents

4.1. Similarities between Fe(III) and Pu(IV)

As discussed in detail above, the actinide ions have large charge-to-radius ratios; they belong to the group of "hard" cations (strong Lewis acids) and prefer hard electron donors such as oxygen.[3,7] The remarkable similarities in the chemical and the biological trans-

Table 2. Similarities of Pu(IV) and Fe(III)[21,139]

	Pu(IV)	Fe(III)
charge/ionic radius (Z/r)	$4/0.93 = 4.3$	$3/0.65 = 4.6$
hydrolysis	$Pu(OH)_4 \rightarrow Pu^{4+} + 4OH^-$ $K = 10^{-55}$ (10^{-14} per OH^-) $Pu^{4+} + H_2O \rightarrow Pu(OH)^{3+} + H^+$ $K = 0.031$ (in $HClO_4$)	$Fe(OH)_3 \rightarrow Fe^{3+} + 3OH^-$ $K = 10^{-38}$ (10^{-13} per OH^-) $Fe^{3+} + H_2O \rightarrow Fe(OH)^{2+} + H^+$ $K = 0.0009$
biological behavior	Pu^{4+} is transported in the blood plasma of mammals as a complex of transferrin, the normal Fe^{3+} transport agent. The Pu^{4+} binds at the same sites as Fe^{3+}. In liver, Pu^{4+} is bound to ferritin, the iron storage protein.[21,139]	

port and distribution properties of Fe(III) and actinides, especially Pu(IV) (Table 2), were recognized some time ago.[18,21] These similarities, which explain much of the biological behavior of plutonium, include the ion potentials (the charge-to-ionic radius ratios) for Fe(III) and Pu(IV) (4.6 and 4.2 e/Å, respectively), formation of highly insoluble hydroxides,[83,90] and similar transport and storage properties in mammals.[15−17,21,37,45−50,59,152,206] It was recognized early on that much could be learned about the behavior of Pu(IV) through the study of the more benign Fe(III), and this suggested that a biomimetic approach to development of sequestering agents for Pu(IV), based on highly selective Fe(III)-sequestering agents, might be advantageous.[18,21,207−209]

4.2. Complexes with Naturally Occurring Ligands—Siderophores

Because of the essential role of iron in most biological systems and its unavailability under aqueous environmental conditions, there are naturally produced Fe(III)-specific ligands that select for size, charge, and coordination number. Although iron is the most abundant of the transition elements in the earth's crust and is essential for all plants and animals and most microbes, it is highly inaccessible under atmospheric conditions because of the insolubility of $Fe(OH)_3$.[209−216] Nature has responded to the challenge of the unavailability of iron by developing selective, high-affinity iron-binding compounds. These compounds, termed siderophores (Greek for "iron bearers"),[211] are sequestering agents of low molecular weight (200−1000 Da) produced by plants and bacteria in order to obtain growth-limiting iron.[215] The siderophores have very high affinities for Fe(III). Their Fe(III) formation constants range from 10^{25} to 10^{49}, and their function is to solubilize ferric iron and enable it to be transported into cells. They constitute the largest group of compounds containing iron found in living material.[217]

More than 400 naturally occurring siderophores have been isolated and characterized.[145,215] Some representative structures are given and described in detail in recent reviews.[218,219] The first of these iron-sequestering agents to be isolated, ferrichrome, a cyclic hexadentate trishydroxamic acid, was isolated from the fungus, *Ustilago sphaerogena*, in 1952 by Neilands, who identified it as a cellular transport cofactor.[220] Ferrioxamine B, a stable chelate of ferric iron with a linear hexadentate trishydroxamic acid moiety, was isolated from *S. pilosus* in 1960, and its structure and function were characterized.[221] The affinities of iron-free desferrioxamine ("Desferal," DFOM) are 100 times greater for Fe and 10^{-7} less for Ca than those of DTPA.[90] The selectivity of DFOM for highly charged metal ions and its clinical effectiveness and acceptance for iron removal[222] stimulated investigation of DFOM as a decorporation agent for the actinides. Removal of Pu from plasma proteins *in vitro* was similar for DFOM and Na_5−DTPA, but the amount of Pu mobilized by delayed injection of DFOM in mice was disappointingly small.[223] Injection of high doses (>100 μmol kg^{-1}) of DFOM within minutes or hours reduced liver and bone Pu in rats to about the same degree as an equimolar amount of $CaNa_3$−DTPA, but Pu residues were left in the kidneys.[224] Moderate doses of DFOM (<100 μmol kg^{-1}) are only about one-third as effective as equal amounts of $CaNa_3$−DTPA.[165] DFOM is ineffective for *in vivo* chelation of trivalent actinides and lanthanides.[224,225]

The poor efficacy of hexadentate DFOM for *in vivo* Pu chelation may be attributable in part to its lesser denticity and to its metabolic destruction *in vivo*.[42,226] The hydroxamic acid metal-binding groups are not ionized at pH < 8;[90] DFOM can only be deprotonated at pH 7 by "hard" Lewis acids like Fe(III) and Pu(IV), and the reaction is slow.[227] Instability at low pH is also the likely cause of partial dissociation of the Pu−DFOM chelate in the kidneys and the deposition of Pu residue.[227] Therapy with DFOM and $CaNa_3$−DTPA in combination, however, offers the advantages of both reduced toxicity and improved efficacy over treatment with either ligand alone.[228,229] Other natural iron-sequestering agents, tetradentate rhodoturulic acid and bidentate 2,3-dihydroxybenzoyl-*N*-glycine, complex Pu *in vitro*, but neither was effective for *in vivo* mobilization of deposited Pu.[106]

Bidentate Tiron (*o*-dihydroxy-1,5-benzenedisulfonic acid), with a structure similar to that of chelating subunits found in some siderophores, was patented in 1929 for medicinal uses.[230] Tiron has been used for many years as an analytical reagent,[231] because it is an efficient chelator of Fe and other highly charged cations.[90,232] High doses (1500 μmol kg^{-1}) of Tiron reduced tissue and bone Pu in rats to the same degree as an equimolar amount of octadentate $CaNa_3$−DTPA.[233] *In vivo* Pu chelation at lower doses was determined when Tiron was used as the baseline bidentate ligand of a set of multidentate sulfocatecholate ligands in an investigation of *in vivo* Pu chelation efficacy as a function of ligand denticity.[159,167] Tiron reduces kidney retention and toxicity of U(VI), but only in doses greater than 300 μmol kg^{-1}, amounts that were considered to be impractical for clinical applications.[234−236]

Enterobactin (EB) is a siderophore secreted by *Escherichia coli* to extract iron from the nearly neutral contents of the mammalian intestine. It contains three catechol binding subunits attached through amide linkages to a metabolically unstable cyclic L-serine backbone in such a fashion that it is preorganized for iron coordination.[21,213,237−240] The properties and chemical behavior of enterobactin, which are now well characterized,[215,219,237,238,240−247] formed the basis for the rational design of multidentate actinide-sequestering agents. Specifically, similarities in the coordination properties of tetravalent actinide ions and ferric ion, the great specificity of the siderophores for ferric ion, and the great stability of Fe(III)−EB led to its use as a model for the creation of strong specific chelators for iron and other "hard" metal ions.[240,248−252] Ligand systems based on siderophores and the chelating subunits of which they are comprised, for example hydroxypyridinones derived from maltol[253,254] or kojic acid,[255] have been studied extensively as Fe(III)-chelating agents for the purpose of developing treatments for disorders in which the body becomes overloaded with iron, such as thalassemia, in which iron in the form of ferritin and hemosiderin accumulates in the liver, spleen, heart, and other tissues.[251,252,255−257] This same biomimetic approach, using EB as a structural and functional model, has been particularly efficacious in the development of synthetic actinide-sequestering agents.[18,20,21,208,212,217,220]

4.3. Design of Ligand Scaffolds

4.3.1. Chelating Groups in Siderophores

Common features of ligand design schemes using this approach for the design of actinide-sequestering agents are the use of anionic oxygen donors in functional groups such as catechols (from enterobactin), hydroxamic acids (from alcaligin), and hydroxypyridinones (from cepabactin). It is important that the molecular scaffold is attached to the catechol moiety in an ortho position relative to the phenolate oxygens via an amide linkage. This is essential so that the ligands can adopt the correct geometry for metal binding, and also so that the amides are able to contribute to the stability of the iron complex via hydrogen bonding. Another common feature is the presence multidentate donor groups that are preorganized for metal binding. Thus, alcaligin is tetradentate while enterobactin is hexadentate. The preorganization of these two ligands has been demonstrated.[21] The most potent siderophores (in terms of their iron coordination abilities) are hexadentate and contain three hydroxamate or catecholate groups attached to molecular backbones that allow formation of a coordination cavity suitable for ferric ion.[21]

The three types of binding subunits found in siderophores are catecholates (CAM), hydroxamates, and hydroxypyridinonates (HOPO). All form five-membered chelate rings in which the metal ion is bound by two ortho oxygen donor atoms. Both catechols and hydroxamates have separate properties that cause them to be attractive subunits for the rational design of an effective actinide chelator. Although not as common a functional group as either hydroxamate or CAM groups, the HOPO functional groups are also found in siderophores. With varying positions of the nitrogen in the ring, there are three prototypes of hydroxypyridinones. They can be viewed as either an aromatic hydroxamic acid (for the 1,2-isomer) or as catechol (for the 3,2- and 3,4-isomers) analogues. These abbreviations and structures are shown in Figure 3. The imine resonance form of the HOPO ligands is isoelectronic and isostructural with the catecholate dianion. Thus, HOPO ligands share the high selectivity of catecholates for ferric as well as actinide ions by virtue of their two anionic oxygen donors and their ability to form $d\pi-p\pi$ bonds. These features are combined with a substantially lowered base strength (i.e., lower pK_a values) so that HOPO-based ligands have the greatest advantage at low pH and remain competitive even at physiological pH.

4.3.2. Multidentate Coordination Systems

The similarities between Pu(IV) and Fe(III) end with their coordination numbers. Given that the preferred coordination number for Pu(IV) will be 8 rather than 6 as in the case of Fe(III), part of the challenge in developing selective actinide-chelating agents is modifying the siderophores such that they are of the preferred octadentate system.[18,20,21,82] This was the inspiration for selecting siderophore-chelating subunits to develop macrocyclic or multidentate coordination systems. For example, hydroxamates (in the form of desferrioxamine B) have been proven successful in iron removal. Catechols and hydroxypyridinones have been shown to be more effective for iron removal from transferrin than hydroxamates. Thus, the attachment of a catecholamide to the amine terminus of desferrioxamine B makes a logical progression in improving its iron removal properties.[227] Such molecules are octadentate ligands and possess a high affinity for actinide ions as well.[117,118,157,161,165,182] Taking a ligand demonstrated to have high affinity and selectivity and modifying it to increase the denticity and improve the geometry is the method used here for developing ligand systems with both high affinity and high selectivity.

The determination of thermodynamic equilibrium constants provides a quantitative measurement of the affinity of a particular ligand for actinide ions (or for any other metal). Some representative formation constants for several related actinide(IV) complexes are shown in Table 3. Unfortunately, the definition of such constants is dependent on the metal-to-ligand stoichiometry of the complex. Thus, the equilibrium constants for a bidentate ligand (e.g., catechol) cannot be directly compared with those for a hexadentate ligand (e.g., DFO). The calculation of pM, the negative logarithm of the free metal ion concentration in the same way that pH is the negative logarithm of free proton concentration, provides a convenient value by which one can compare such systems. This value can be calculated for a given metal/ligand system for any chemical conditions (e.g. of metal/ligand concentration and pH) if the equilibrium constants are known. A set of standard refer-

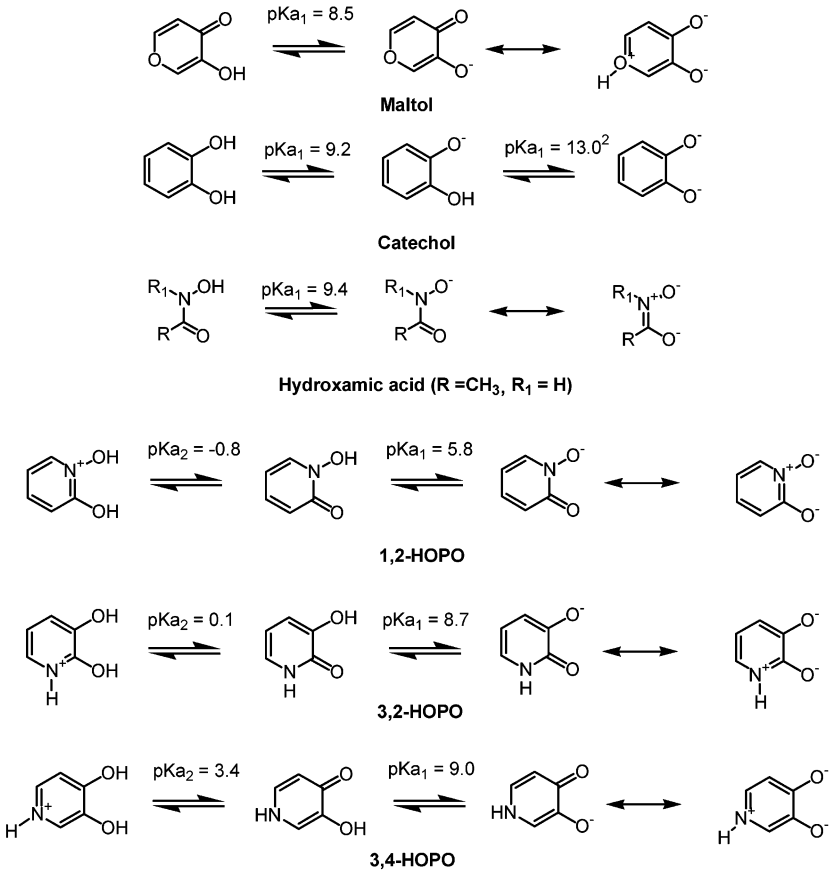


Figure 3. Prototypical binding units from siderophores and their pK_a values.[469,470]

Table 3. Formation Constants for Some Actinide(IV) Complexes as an Index of Metal Binding Affinity

ligand/metal ion	temp, °C	log β_{110}	log β_{111}	log β_{112}	log β_{113}	ref
catechol						
Th(IV)	30	17.72				*a*
benzohydroxamic acid						
U(IV)	25	9.89	18	26.32	32.94	*b*
Th(IV)	25	9.6	19.81	28.76		*b*
Pu(IV)	25	12.73				*b*
N-phenylbenzohydroxamic acid						
Th(IV)	25				37.8	*c*
Pu(IV)	22	11.5	21.95	31.85	41.35	*d*
N-phenylcinnamohydroxamic acid						
Th(IV)	20	12.76	24.7	35.72	45.72	*e*
EDTA						
Pu(IV)	20	29.4				*f*
DTPA						
Pu(IV)	20	29.4				*g*
DFO[i]						
Th(IV)	25	26.5	28.5			27
Pu(IV)	22	30.8				*h*
DFOMTA[j]						
Th(IV)	25	38.55	44.24			27
Pu(IV)	23	41.7	47.6			27
Th(IV)	25	33				27
DFOCAMC[k]						
Th(IV)	25	37.2	46.1			27
ETAM						
Th(IV)	25	17.5	30.7	39	45.57	338, 339

[a] Agrawal, R. P.; Mehrotra, R. C. *J. Inorg. Nucl. Chem.* **1962**, *24*, 821. [b] Barocas, A.; Baroncelli, F.; Biondi, G. B.; Grossi, G. *J. Inorg. Nucl. Chem.* **1966**, *28*, 2961. [c] Dyrssen, D. *Acta Chem. Scand.* **1956**, *10*, 353. [d] Chimutova, M. K.; Zolotov, Y. A. *Sov. Radiochem.* **1964**, *6*, 625. [e] Zharovskii, F. G.; Sukhomlin, R. I.; Ostrovskaya, M. S. *Russ. J. Inorg. Chem.* **1967**, 12. [f] Cauchetier, P.; Guichard, C. *Radiochim. Acta* 1973, *19*, 137. [g] Piskunov, E.; Rykov, A. *Radiokhimiya* **1972**, *14*, 260. [h] Jarvis, N. V.; Hancock, R. D. *Inorg. Chim. Acta* **1991**, *182*, 229. [i] Desferrioxamine B. [j] *N*-(2,3-Dihydroxy-4-(methylamido)benzoyl)desferrioxamine B. [k] *N*-(2,3-Dihydroxy-4-carboxybenzoyl)desferrioxamine B.

ence conditions is often used for the purposes of comparing iron chelation drugs. These conditions are pH 7.4 and total concentrations of 10 μM ligand and 1 μM metal ion.

A higher pM value indicates a lower concentration of free metal and therefore a more competitive (stronger) ligand. The pM value is proportional to the chemical free energy (ΔG) released by metal−ligand binding and remains a useful parameter for the comparison of binding abilities of ligands. The pM values may be used to guide ligand design and to rationalize biological testing results for a particular ligand. For example, these pM calculations can therefore provide rationalization for increasing ligand denticity and the effect of this on biological efficacy.[22,121,145,249]

Ligand denticity is defined as the number of chelating units in a discrete ligand. For example, a HOPO-based ligand bearing only one HOPO unit is bidentate, one with two units is tetradentate, one with three units is hexadentate, and one with four units is an octadentate ligand. It is generally agreed that octadentate ligands possess the appropriate denticity for selective actinide complexation.[129,134,143] Clearly, from the following equilibrium, given the same ligand concentrations, the octadentate ligand has the highest pM value and, therefore, it is the most competitive ligand for actinide ions.

bidentate An(IV) complex:

$$\mathrm{An} + 4\mathrm{L}^{\mathrm{B}} = \mathrm{AnL}_4^{\mathrm{B}} \quad (3)$$

$$\beta_{140} = \frac{[\mathrm{AnL}_4^{\mathrm{B}}]}{[\mathrm{An}][\mathrm{L}_4^{\mathrm{B}}]^4} \quad (4)$$

tetradentate complex: $\mathrm{An} + 2\mathrm{L}^{\mathrm{T}} = \mathrm{AnL}_2^{\mathrm{T}}$ (5)

$$\beta_{120} = \frac{[\mathrm{AnL}_2^{\mathrm{T}}]}{[\mathrm{An}][\mathrm{L}^{\mathrm{T}}]^2} \quad (6)$$

hexadentate complex: $3\mathrm{An} + 4\mathrm{L}^{\mathrm{H}} = \mathrm{An}_3\mathrm{L}_4^{\mathrm{H}}$ (7)

$$\beta_{340} = \frac{[\mathrm{An}_3\mathrm{L}_4^{\mathrm{H}}]}{[\mathrm{An}]^3[\mathrm{L}^{\mathrm{H}}]^4} \quad (8)$$

octadentate complex: $\mathrm{An} + \mathrm{L}^{\mathrm{O}} = \mathrm{AnL}^{\mathrm{O}}$ (9)

$$\beta_{110} = \frac{[\mathrm{AnL}^{\mathrm{O}}]}{[\mathrm{An}][\mathrm{L}^{\mathrm{O}}]} \quad (10)$$

Of equal importance is the stoichiometry of the metal−ligand complexes. Thus, four equivalents of the bidentate ligand are required to fully coordinate an actinide ion, and the cumulative formation constant for this ligand, β_4, has a fourth-order dependence on ligand concentration, $[L]^4$. In contrast, the octadentate ligand forms a 1:1 complex with an actinide ion; its formation constant, β, has only a first-order dependence on ligand concentration. It is clear that increasing ligand denticity is an important design criterion. Once the selection of the particular type of binding unit has been made, the effect of ligand denticity on the coordination chemistry of a substrate becomes particularly important at low ligand concentrations. Hence, the disparity between the pM curve of a bidentate ligand and the curves for its multidentate ligands is increasingly important with increasing dilution. This observation is critical for drug design, since low clinical doses are desirable for avoiding possible toxic side effects.

A negative aspect of increasing ligand denticity is that it is likely to decrease the solubility of the drug since it increases the molecular weight. An octadentate chelator will have a molecular weight in the range of 800−1200 Da and thus is often either too large or just within the range for oral availability. Other factors such as solubility and ionization may be equally or more important in affecting the bioavailability of a particular drug. A positive aspect of decreased membrane permeability is that it will help prevent passage of a drug across the blood−brain barrier, avoiding possible neurotoxicity. It is also interesting to note that the tetradentate ligand has a lower concentration dependence $[L]^2$ than that of a bidentate ligand. Given a large enough stability constant, a tetradentate actinide chelator may be expected to be effective at low clinical dose. Thus, affinity and denticity should be included among several key factors that must be carefully considered in combination with other factors such as pK_a or solubility, when designing systems for potential medical applications.

4.3.3. Ligand Geometry and Denticity

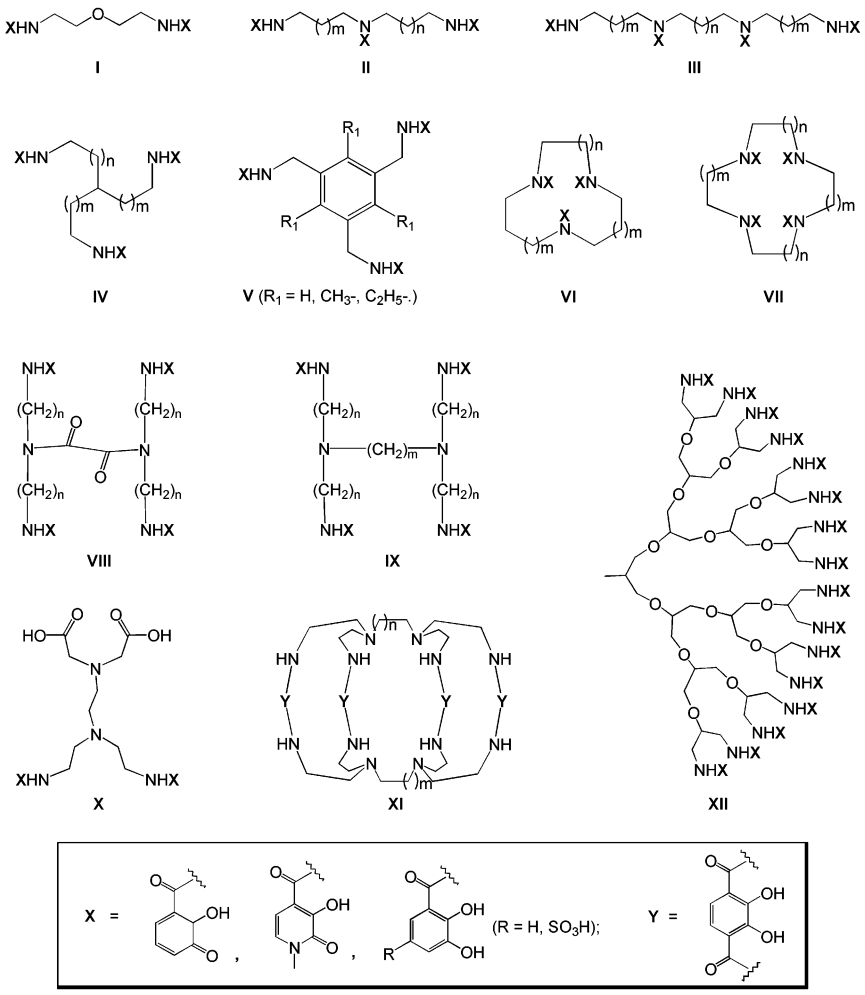
After chelating units and ligand denticity have been chosen, the next task in ligand design for a specific metal ion is to select the appropriate ligand topology by choosing a molecular scaffold for the ligand.[36] A number of ligand topologies are available, including linear, tripodal, tetrapodal, exo-macrocyclic, macrobicyclic, macrotricyclic, and even dendritic. Examples of these five representative topologies are shown in Figure 4.

Linear. Since linear multiamines are commercially available, ligands with linear backbones are easily synthesized and, in general, have less cross-area and thus are better suited to penetrate biomembranes, an important factor in bioavailability.

Tripodal. Trisbidentate tripodal ligands, such as enterobactin, generally provide six coordination sites for metal ions; however, for high-coordinate f-elements, tripodal ligands generally fail to occupy all the coordination sites. Therefore, a tripodal topology is rare among strong actinide-sequestering agents.

Tetrapodal. Molecular modeling studies on actinide complexes suggested that tetrapodal ligands might be good choices for actinide sequestration.[258] Since the most favored coordination number for most actinide ions is 8, PENTEN was chosen as the scaffold for several tetrabidentate tetrapodal octadentate ligands.

Macrocyclic. Due to the macrocycle effect in complex formation, macrocyclic topologies have been studied, often using azamacrocyclic structural scaffolds.[20,259−262] Although macrocyclic ligands may form very stable complexes with actinides, they have unfavorable kinetics in the formation of "inert complexes" that restrict their potential use in sequestering actinide *in vivo*.[149,159,161]



I, II, III Linear; **IV, V** Tripodal; **VI, VII** Exo-macrocyclic; **VIII, IX, X** Tetrapodal; **XI** Macrotricyclic; **XII** Dendritic.

Figure 4. Representative geometries.

Dendritic. Recently, water-soluble dendrimers have been investigated for potential uses in drug delivery,[263−266] and a variety of these have contained metals either at the core[267−269] or in the dendritic branches.[265,266,270] As yet, there are no dendritic actinide-sequestering agents reported and studies on the use of dendrimers specifically for sequestering metal ions from the environment are limited.[271] However, based on a preliminary study in our group, it should be possible to design and synthesize water-soluble dendritic actinide-sequestering agents.[272]

5. Ligand Synthesis

5.1. Ligand Systems

Table 4 contains a listing of the Raymond group chelator ligands. References cited for the specific ligands in Table 4 are primarily the reports of their syntheses. For some of the ligands shown, the synthetic method is incompletely published or unreported, and in those cases, the citations refer to the reports of their biological testing for chelation of actinides or related equivalent cations. We have reported the synthesis and, in many cases, also the evaluation of *in vivo* chelation of actinides by siderophore analogues with the following topologies: linear,[82,149,150,159,165−167,170,248,259,273] tripodal,[150,156,159,160,163,167,248,259,273−275] tetrapodal (PENTEN),[116,161,160,169] macrocyclic,[20,149,159,274,276] and macrobicyclic.[277,278] A few of these ligands have also been studied as chelators of iron and other trivalent cations.

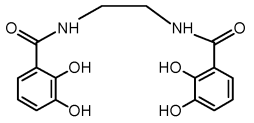
5.2. Catecholamide (CAM) Ligands

Various approaches were used to develop novel ligands based on the siderophores. Two major considerations in the preparation of these ligand systems are the protection/deprotection of the hydroxyl groups whose oxygens are ultimately the donor atoms in the metal ion−ligand complex and the functionalization of the chelating subunit for attachment to the amine backbone. The basic synthetic scheme for all of these types of ligands involves the synthesis of the functionalized protected ligand, followed by activation of the carboxylic acid usually by conversion to an acyl chloride, which can then be reacted with a variety of amines to serve as the backbone for a higher denticity system. After the amidation, hydroxyl-protecting groups are cleaved by hydrolysis, hydrogenolysis, or treatment with BBr_3.[279]

This strategy and procedure can be extended to prepare a variety of multidentate sequestering agents

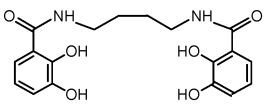
Table 4. Molecular Structures and Abbreviated Nomenclature of Ligands Designed and Synthesized by the Raymond Group

CAM Ligands:



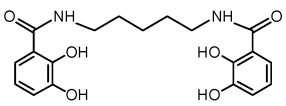
2-LICAM[259]

1



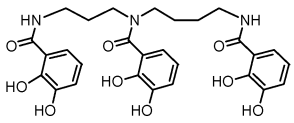
4-LICAM[259]

2



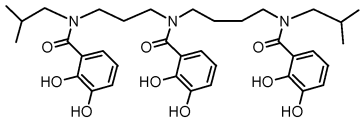
6-LICAM[259]

3



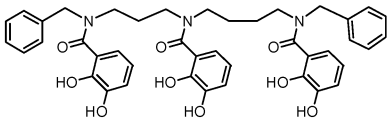
3,4-LICAM[274]

4



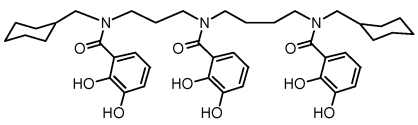
Dip-3,4-LICAM[a]

5



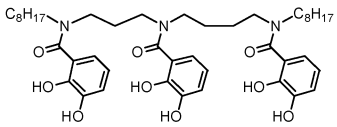
DBn-3,4-LICAM[a]

6



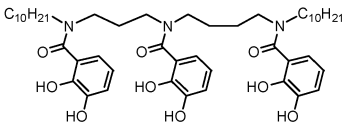
DC-3,4-LICAM[a]

7



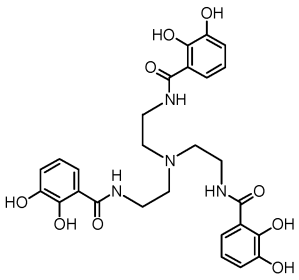
Bis(n-octyl)-3,4-LICAM[a]

8



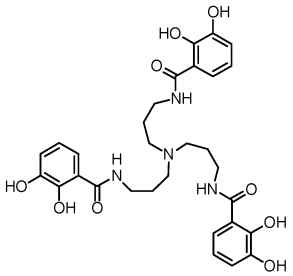
Bis(n-decyl)-3,4-LICAM[a]

9



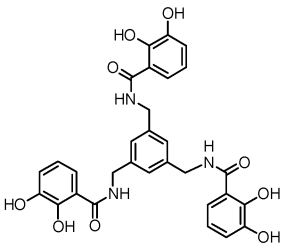
TRENCAM[275]

10



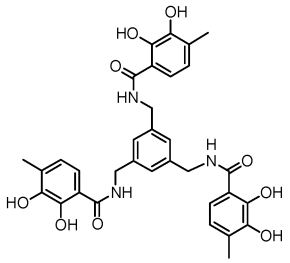
TRPNCAM[b]

11



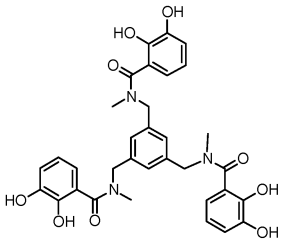
MECAM[274]

12



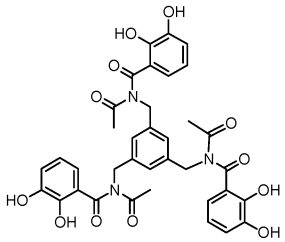
MECAMMe[274]

13



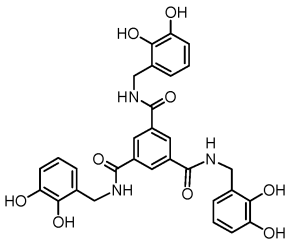
NMeMECAM[249]

14



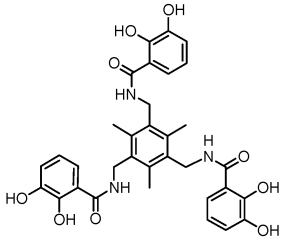
NAcMECAM[249]

15



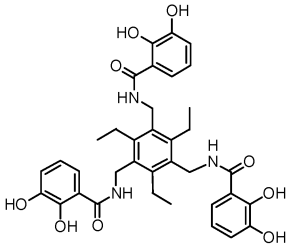
TriMECAM[274]

16



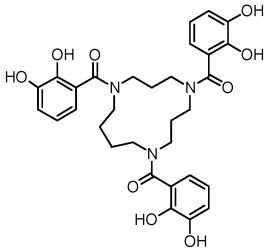
MeMECAM[244]

17



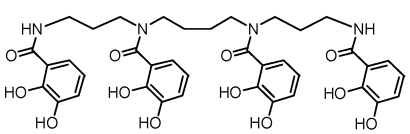
EtMECAM[244]

18



CYCAM[274]

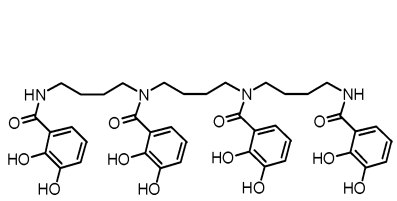
19



3,4,3-LICAM[259]

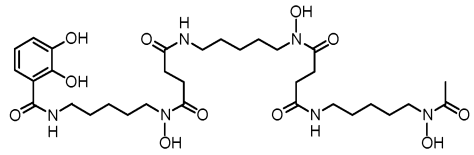
20

Table 4. (Continued)



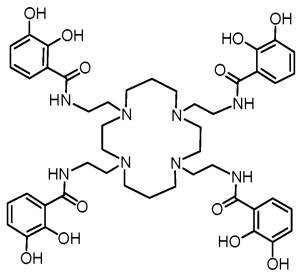
4,4,4-LICAM[259]

21



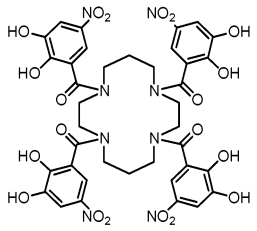
DFO-CAM[227]

22



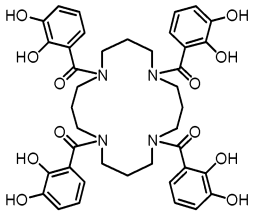
TAEC-CAM[169]

23



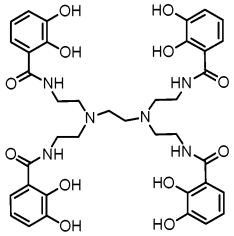
3,2,3,2CYCAM(NO$_2$)[149]

24



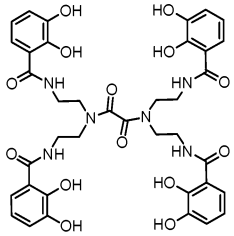
3,3,3,3-CYCAM[149]

25



H(2,2)-CAM[169]

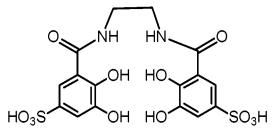
26



OxoH(2,2)-CAM[e]

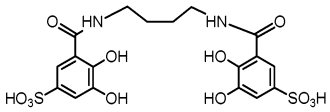
27

CAMS Ligands:



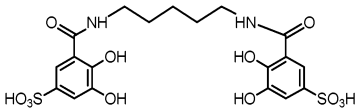
2-LICAM(S)[259]

28



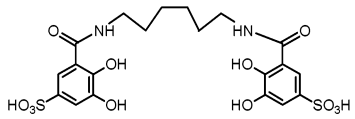
4-LICAM(S)[259]

29



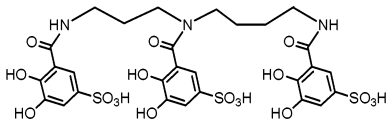
5-LICAM(S)[157]

30



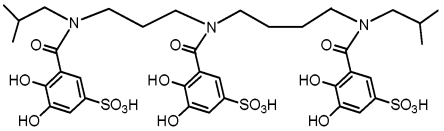
6-LICAM(S)[259]

31



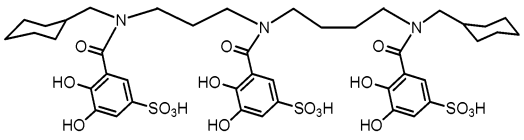
3,4-LICAM(S)[d]

32



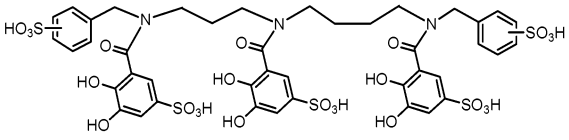
DiP-3,4-LICAM(S)[d]

33



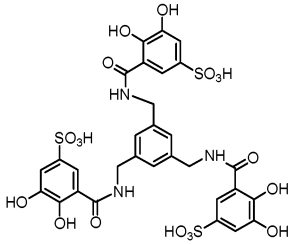
DC-3,4-LICAM(S)[e]

34



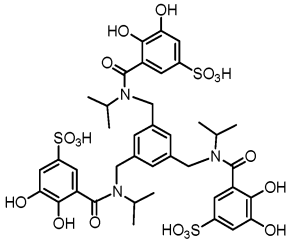
DB-3,4-LICAM(S)[e]

35



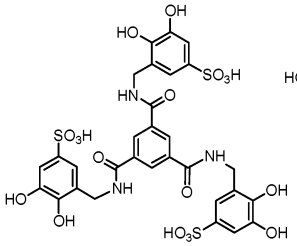
MECAM(S)[274]

36



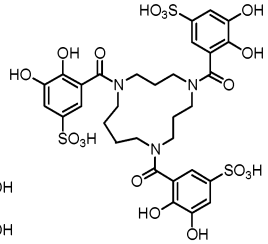
TiPMECAM(S)[e]

37



TriMECAM(S)[274]

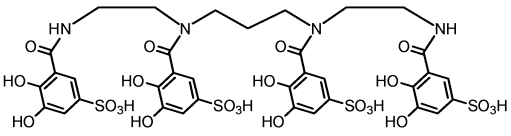
38



CYCAM(S)[d]

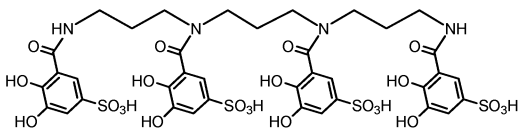
39

Table 4. (Continued)



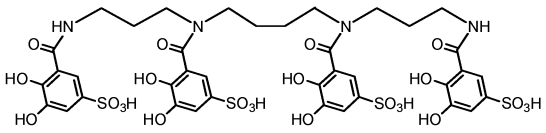
2,3,2-LICAM(S)[149]

40



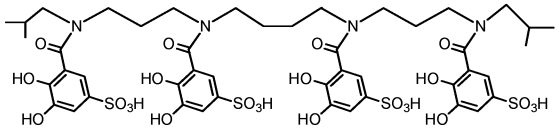
3,3,3-LICAM(S)[149]

41



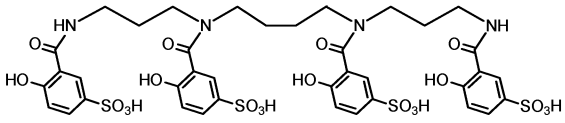
3,4,3-LICAM(S)[259]

42



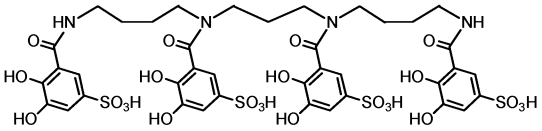
DiP-3,4,3-LICAM(S)[159]

43



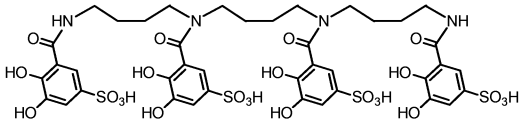
3,4,3-LISAM(S)[159]

44



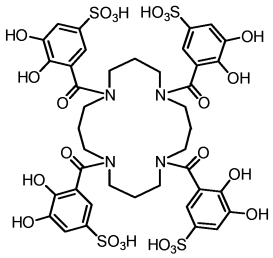
4,4,4-LICAM(S)[149]

45



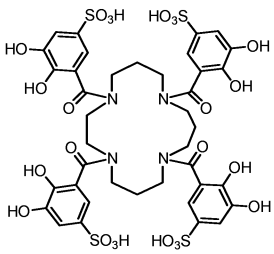
4,4,4-LICAM(S)[259]

46



3,3,3,3-CYCAM(S)[259]

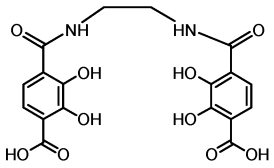
47



2,3,3,3-CYCAM(S)[149]

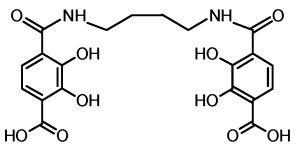
48

CAMC Ligands:



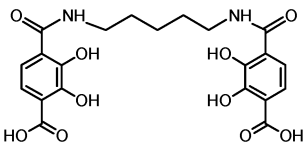
2-LICAM(C)[159]

49



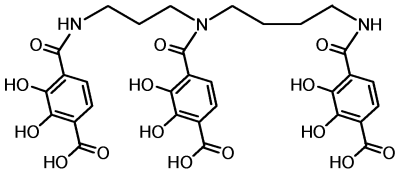
4-LICAM(C)[157]

50



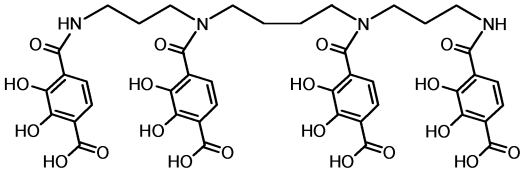
5-LICAM(C)[157]

51



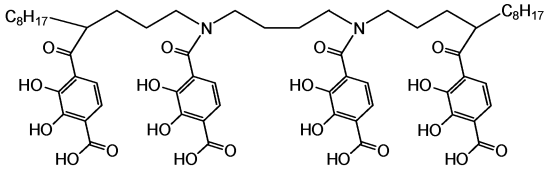
3,4-LICAM(C)[82]

52



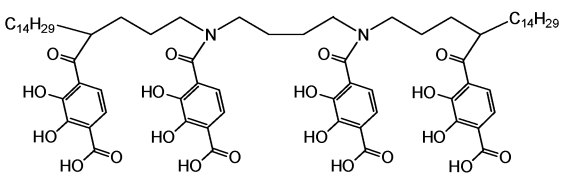
3,4,3-LICAM(C)[82]

53



Bis(n-octyl)-3,4,3-LICAM(C)[159]

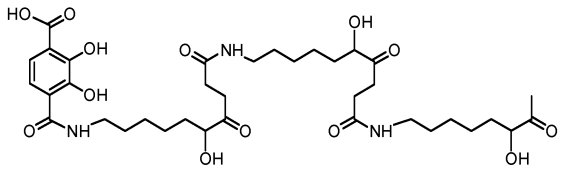
54



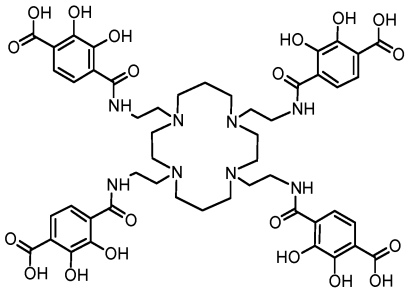
Bis(n-tetradecyl)-3,4,3-LICAM(C)[159]

55

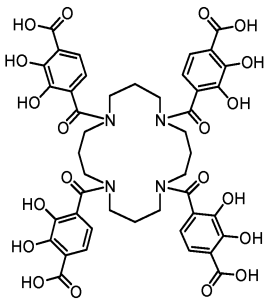
Table 4. (Continued)



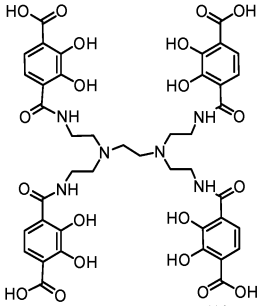
DFO-CAM(C)[227]
56



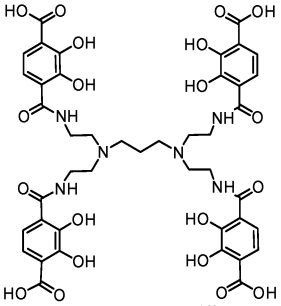
TEAC-CAM(C)[169]
57



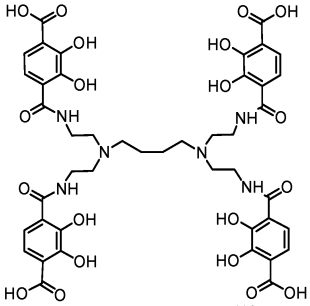
3,3,3,3-CYCAM(C)[159]
58



H(2,2)-CAM(C)[116]
59

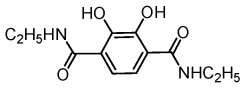


H(3,2)-CAM(C)[169]
60

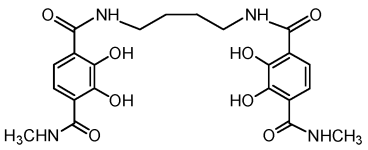


H(4,2)-CAM(C)[116]
61

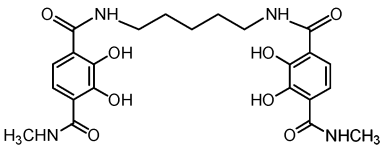
TAM Ligands:



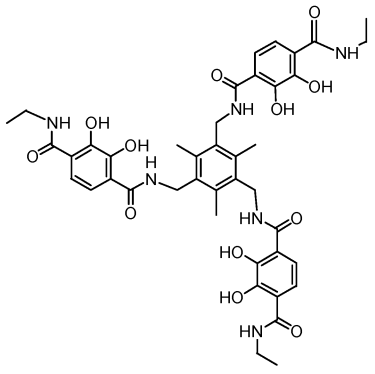
EtTAM[285,286]
62



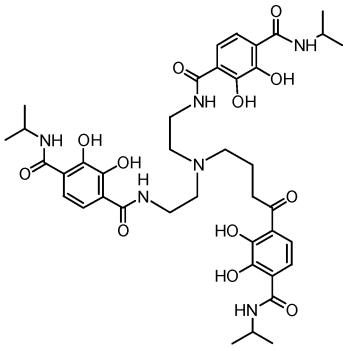
4-LIMeTAM[157]
63



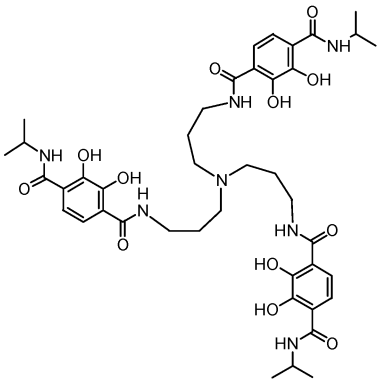
5-LIMeTAM[157]
64



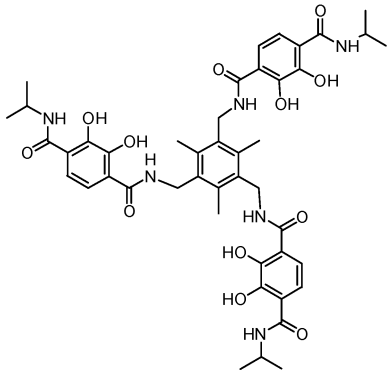
MeME-EtTAM[245]
65



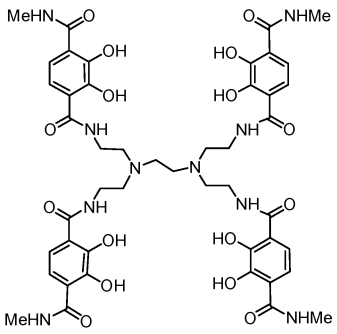
TREN-*i*-PrTAM[169]
66



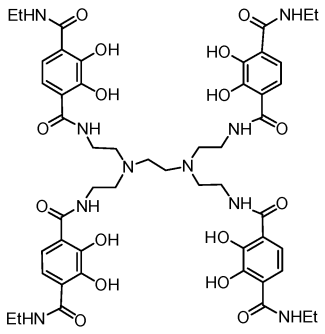
TRPN-*i*-PrTAM[169]
67



MeME-*i*-PrTAM[169]
68

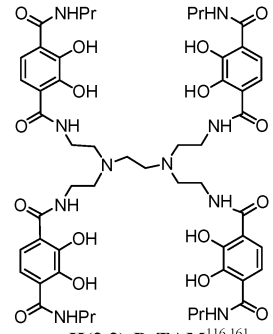


H(2,2)-MeTAM[161]
69



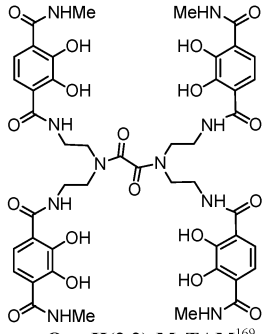
H(2,2)-EtTAM[116,161]
70

Table 4. (Continued)



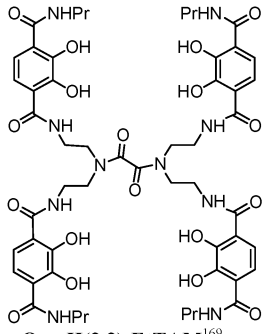
H(2,2)-PrTAM[116,161]

71



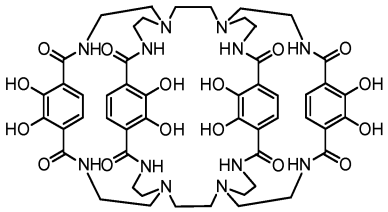
Oxo-H(2,2)-MeTAM[169]

72



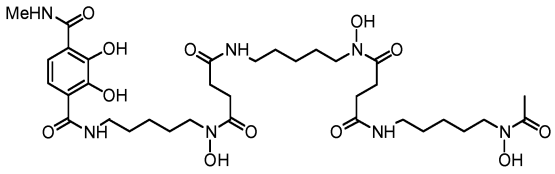
Oxo-H(2,2)-EtTAM[169]

73



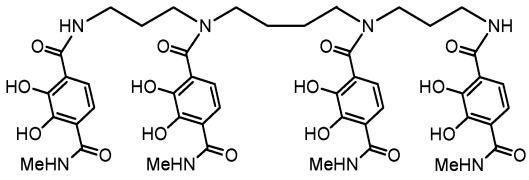
BH(2,2)CAM[258]

74



DFO-MeTAM[298]

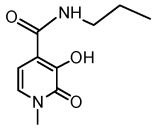
75



3,4,3-LIMeTAM[169]

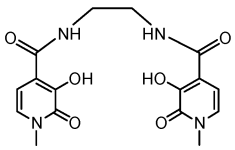
76

Me-3,2-HOPO Ligands:



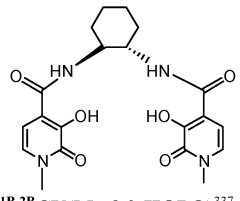
PR(Me-3,2-HOPO)[337]

77



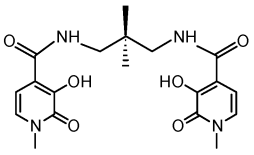
2LI(Me-3,2-HOPO)[337]

78



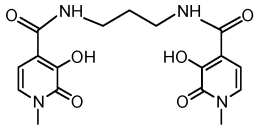
1R,2R CY(Me-3,2-HOPO)[337]

79



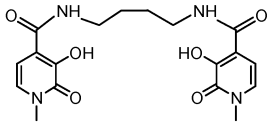
2,2-Dime(Me-3,2-HOPO)[f]

80



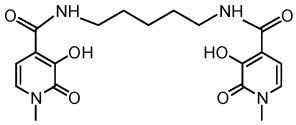
3LI(Me-3,2-HOPO)[337]

81



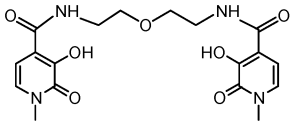
4LI(Me-3,2-HOPO)[337]

82



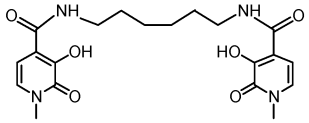
5LI(Me-3,2-HOPO)[337]

83



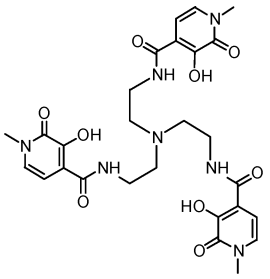
5LIO(Me-3,2-HOPO)[337]

84



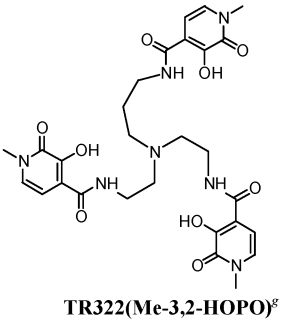
6LI(Me-3,2-HOPO)[337]

85



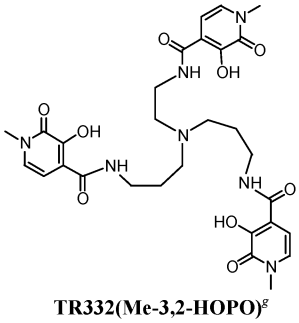
TREN(Me-3,2-HOPO)[367]

86



TR322(Me-3,2-HOPO)[g]

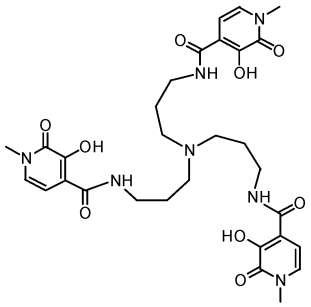
87



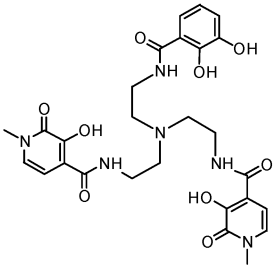
TR332(Me-3,2-HOPO)[g]

88

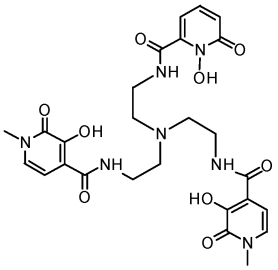
Table 4. (Continued)



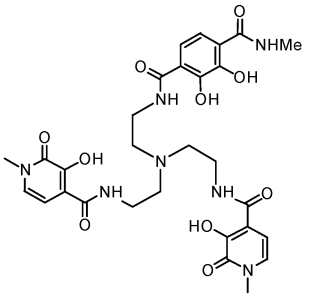
TRPN(Me-3,2-HOPO)[g] **89**



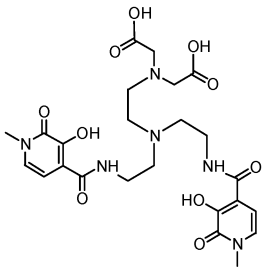
TREN-CAM(Me-3,2-HOPO)[245] **90**



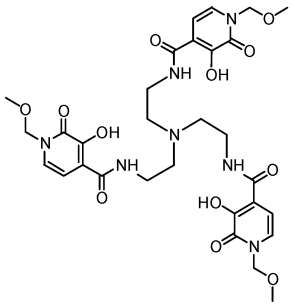
TREN(1,2-Me-3,2-HOPO)[145] **91**



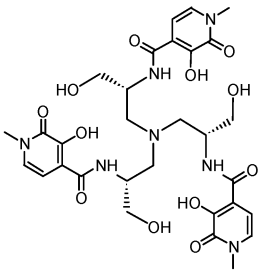
TREN(Me-3,2-HOPO)MeTAM[30] **92**



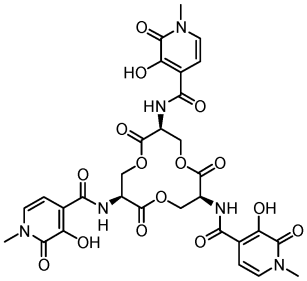
TREN(Me-3,2-HOPO)BAC[299] **93**



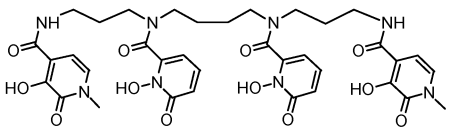
TREN(MOE-3,2-HOPO)[297] **94**



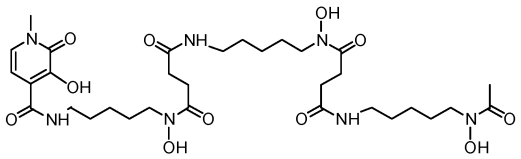
TriSerine-TREN(Me-3,2-HOPO)[368,h] **95**



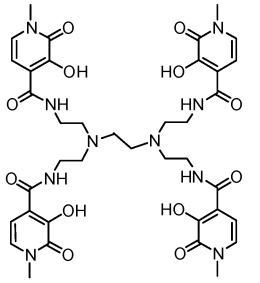
(Me-3,2-HOPO)Bactin[h] **96**



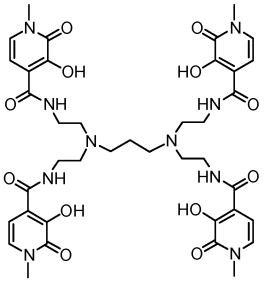
3,4,3-LI(1,2-Me-3,2-HOPO)[170] **97**



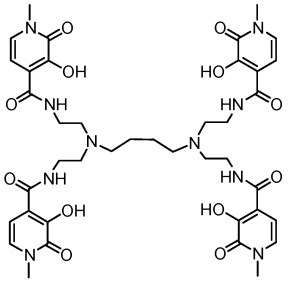
DFO(Me-3,2-HOPO)[160] **98**



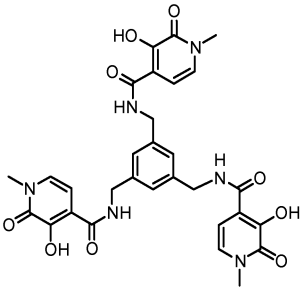
H(2,2)-(Me-3,2-HOPO)[160] **99**



H(3,2)-(Me-3,2-HOPO)[160] **100**

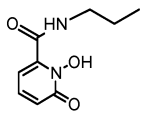


H(4,2)-(Me-3,2-HOPO)[160] **101**

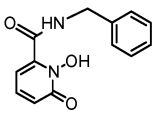


ME-(Me-3,2-HOPO)[160] **102**

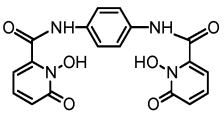
1,2-HOPO Ligands



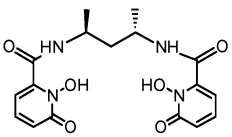
PR(1,2-HOPO)[337] **103**



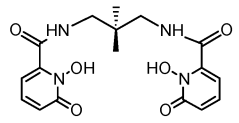
Bn(1,2-HOPO)[167] **104**



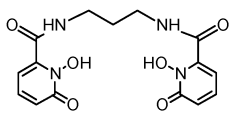
***p*-Ph(1,2-HOPO)**[167] **105**



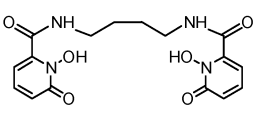
^{1R,3R}3LI(1,2-HOPO)[167] **106**



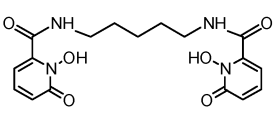
2,2-Dime-3LI(1,2-HOPO)[308] **107**



3LI(1,2-HOPO)[167] **108**

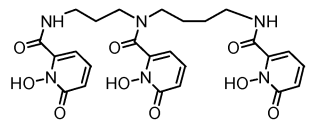


4LI(1,2-HOPO)[150] **109**



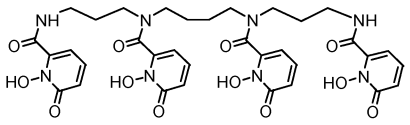
5LI(1,2-HOPO)[150] **110**

Table 4. (Continued)



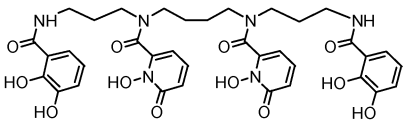
3,4-LI(1,2-HOPO)[167]

111



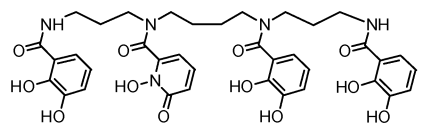
3,4,3-LI(1,2-HOPO)[167]

112



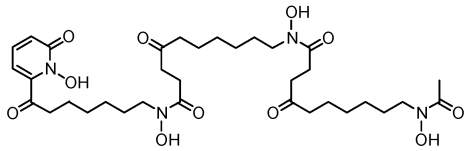
3,4,3-LI(diCAM-di-1,2-HOPO)[166]

113



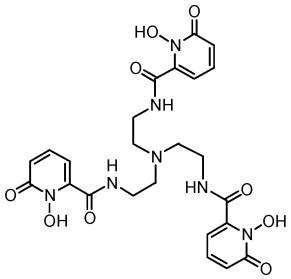
3,4,3-LI(TriCAM-1,2-HOPO)[166]

114



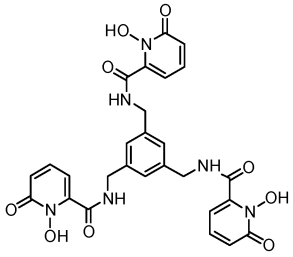
DFO(1,2-HOPO)[167]

115



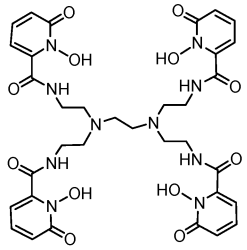
TREN(1,2-HOPO)[150]

116



ME(1,2-HOPO)[167]

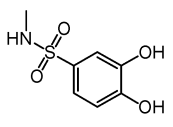
117



H(2,2)-(1,2-HOPO)[150]

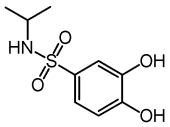
118

SFAM Ligands



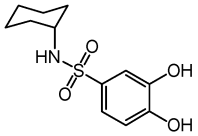
Me(SFAM)[301]

119



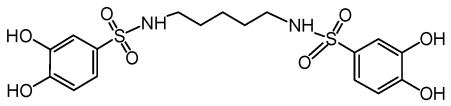
***i*-PR(SFAM)**[301]

120



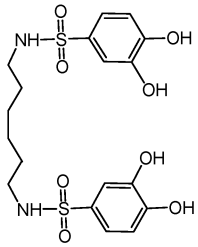
Cyhexyl(SFAM)[301]

121



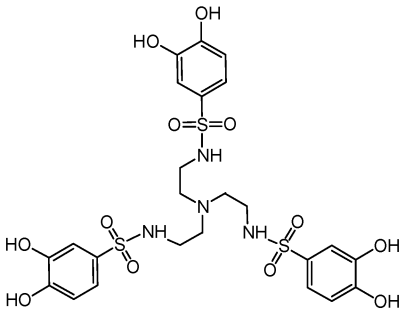
5LI(SFAM)[301]

122



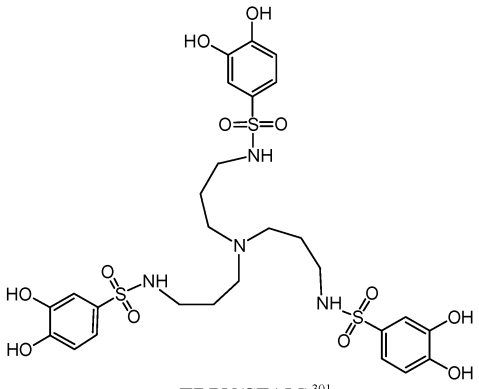
6LI(SFAM)[301]

123



TREN(SFAM)[301]

124



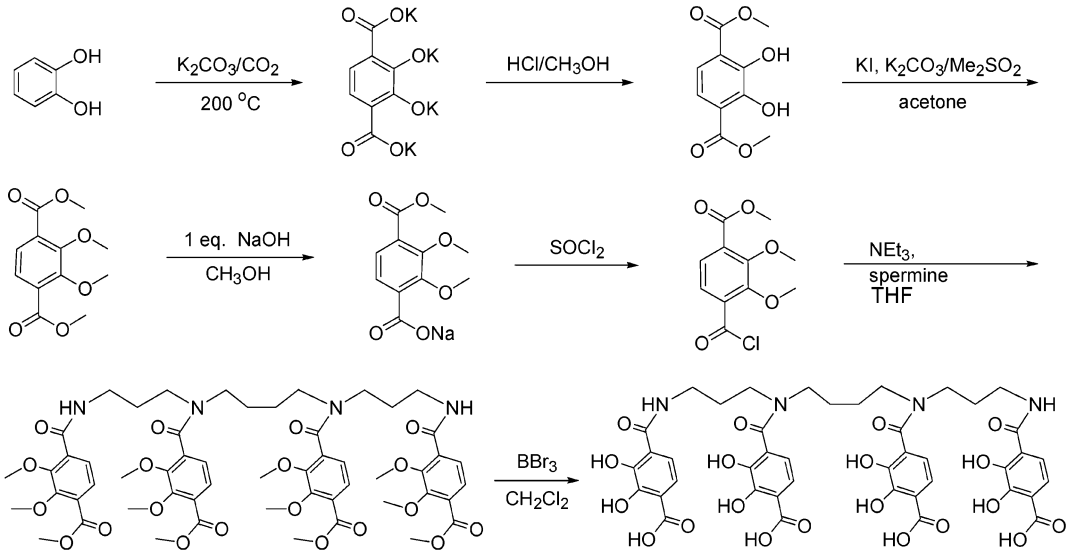
TRPN(SFAM)[301]

125

[a] Weitl, F. L.; Raymond, K. N. *J. Org. Chem.* **1981**, *46*, 5234. [b] Stack, D., unpublished results. [c] Bergeron, R. J.; Kline, S. J.; Navratil, J. D.; Smith, C. M. *Radiochim. Acta* **1984**, *35*, 47. [d] Harris, W. R.; Raymond, K. N.; Weitl, F. L. *J. Am. Chem. Soc.* **1981**, *103*, 2667. [e] Kappel, M. J.; Pecoraro, V. L.; Raymond, K. N. *Inorg. Chem.* **1985**, *24*, 2447. [f] Xu, J.; Parac, T. N.; Raymond, K. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2878. [g] Xu, J.; O'Sullivan, B.; Raymond, K. N. *Inorg. Chem.* **2002**, *41*(25), 6731−6742. [h] Meyer, M.; Telford, J. R.; Cohen, S. M.; White, D. J.; Xu, J.; Raymond, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 10093.

with all of the possible geometries discussed previously. A system of abbreviated nomenclature was devised for the synthetic multi-(catechoylamide) ligands based on CAM as an acronym for catechoyl-

Scheme 1. Synthesis of CAM(C) To Generate 3,4,3-LI-CAM(C)



53

amide groups, TAM as the acronym for the 2,3-terephthalamide groups, and HOPO for the hydroxypyridinone groups. The suffix of CAM(C) or CAM(S) is indicative of carboxylation or sulfonation of the final chelating subunit. The prefix abbreviation LI indicates a linear ligand system, CY indicates a cyclical system, and the other amines used (such as tris(3-aminopropyl)amine[280] or 1,3,5-tris(aminomethyl)benzene)[274] would also be abbreviated (TREN or TRPN, respectively.) The numbers in the prefix (separated by commas, as in 3,4,3-LI(1,2-HOPO) (**112**) for example) indicate the number of methylene groups in the connecting chains.

The first two tetracatechol chelating agents (**24** and **25**) were synthesized by the reaction of 2,3-dioxomethylene- or 2,3-dimethoxybenzoyl chloride with 1,4,8,11-tetraazacyclotetradecane or 1,5,9,13-tetraazacyclohexadecane, followed by deprotection of the hydroxyl groups with BBr_3 to form an octadentate cyclic ligand.[20] A more acidic analogue was prepared from 2,3-dimethoxy-5-nitrobenzoic acid and 1,4,8,11-tetraazacyclotetradecane (**24**). The sulfonated analogue (**47**) could also be prepared by regiospecific monosulfonation at the 5-position of the 2,3-dihydroxybenzoyl group with 20−30% SO_3 in H_2SO_4 at room temperature. The sulfonation product can then be isolated at pH 4 as either its hydrated tetrasodium or potassium salt.[259] Similar methods were used to prepare derivatives from linear tetraamines (**40**−**46**).[259]

The catechol of the chelate may also be functionalized by the introduction of a carboxylate group in the 4-position.[82] For example, as depicted in the synthesis of 3,4,3-LI-CAM(C) (**53**) in Scheme 1, this is done through an alternative synthesis, beginning with catechol carboxylated according to a procedure modified from that of Cason and Dyke.[281] This carboxylate derivative is then heated to reflux temperature in methanol with HCl to afford the dimethyl ester. Permethylation is achieved with potassium carbonate and dimethyl sulfate in acetone heated to reflux temperature, the product of which, when heated in methanol and treated with 1 equiv of 6 M NaOH, provides the monosodium salt, which can then be converted to the acid chloride with the addition of neat surfuryl chloride. This acid chloride provides the required functionalization for attachment of the chelating subunit to a variety of amine backbones. Demethylation with an excess of BBr_3 yields the final product.[82]

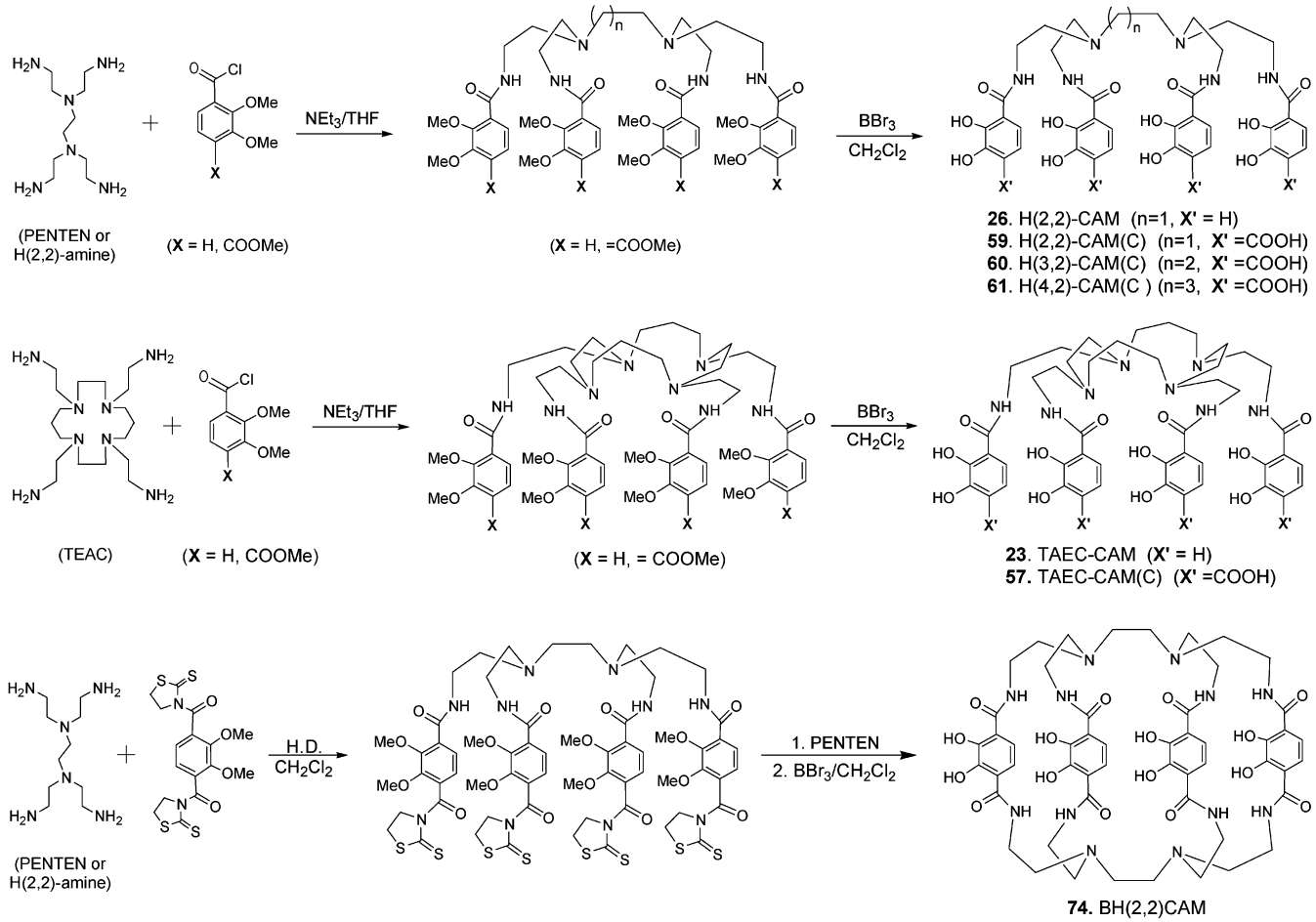
A new structural class of tetracatechoyl ligands was later designed, incorporating "H-shaped" tetraprimary-amine backbones and the ligating subunits in both open and closed or macrotricyclic architectures. The nomenclature system has been extended to include these tetrakis(catechoylamide) ligands, by the use of H(*m*,*n*)-CAM, H(*m*,*n*)-CAM(C), H(*m*,*n*)-TAM, Oxo-H(*m*,*n*)-CAM, or Oxo-H(2,2)-TAM as acronyms for the corresponding ligands. For these, solutions of the appropriate tetraamine, PENTEN (H(2,2)-amine) or *N*,*N*′′-bis(2,3-dimethoxybenzamidoethyl)amine in CH_2Cl_2, were added to 2,3-dimethoxy-1-(2-mercaptothiazolide)benzamide[282] with stirring. The resulting products can be deprotected with BBr_3 (Schemes 2 and 3).[169]

5.3. Terephthalamide (TAM) Ligands

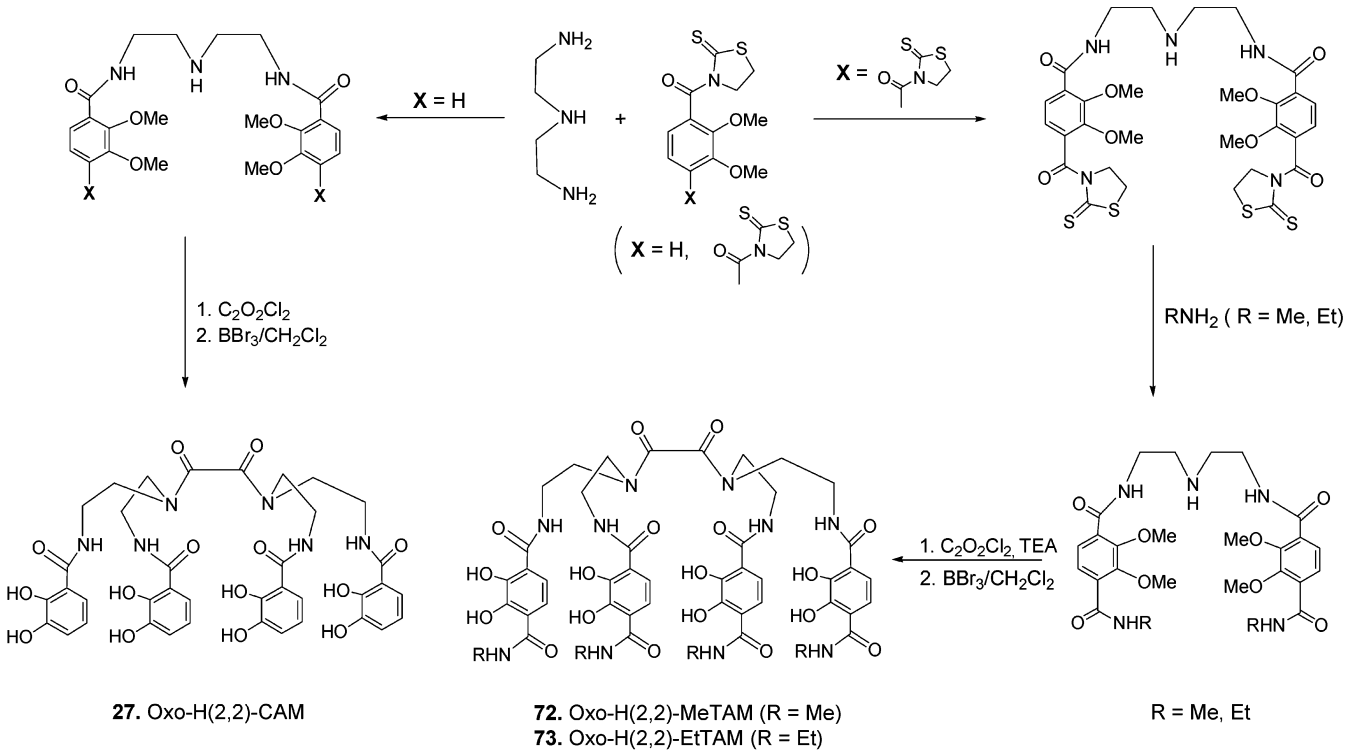
The 2,3-dihydroxyterephthalamide (TAM) ligating group, while similar in structure to the catecholamide groups found naturally occurring in siderophores, is substantially more acidic than the CAM ligating group, is less air sensitive, and displays the greatest affinity for ferric ion of any catecholate derivative.[283,284] These properties are believed to be derived from the strong hydrogen bonding between the amide proton and the ortho hydroxyl group. Recent improvements to the TAM subunit synthesis have been developed that avoid the protection and deprotection of the phenolic hydroxy groups and allow for both symmetric and asymmetric amide linkages, drastically reducing the time and cost of preparation.[285]

The typical TAM synthesis follows six steps: carboxylation of catechol, followed by conversion of the carboxylic acids to methyl esters, methyl or benzyl

Scheme 2. Synthesis of Octadentate Catecholamide Ligands

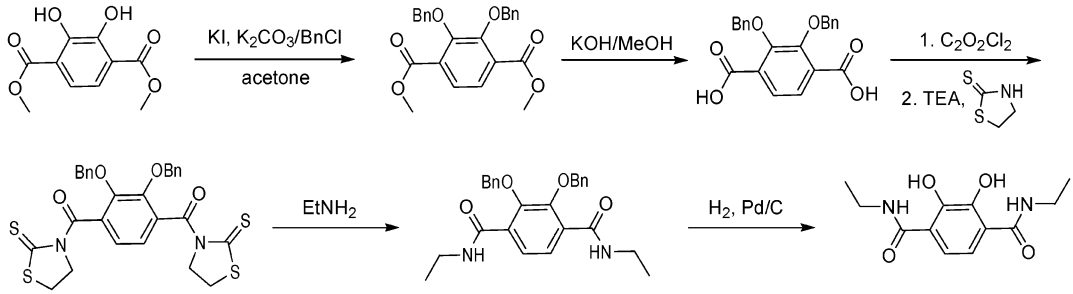


Scheme 3. Synthesis of Octadentate Oxo-catecholamide Ligands

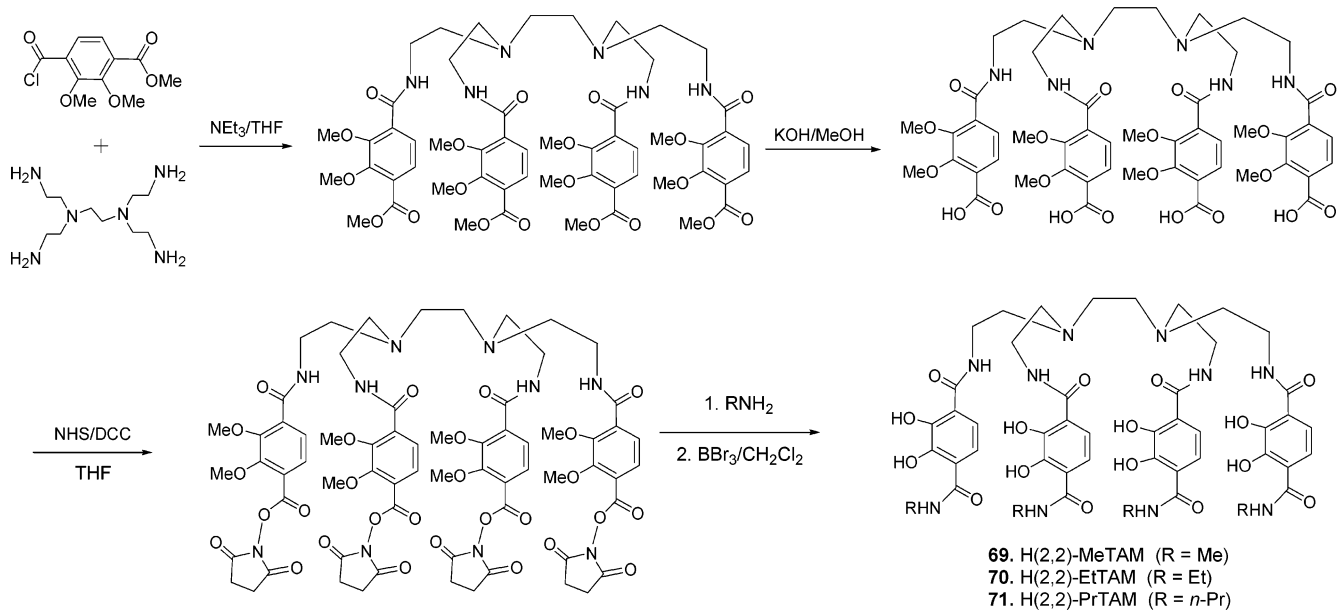


protection of the catecholate oxygens, saponification of the esters to the carboxylic acid, which can then be converted to the acyl chloride or thiazolide for coupling with the desired amine, resulting in the final

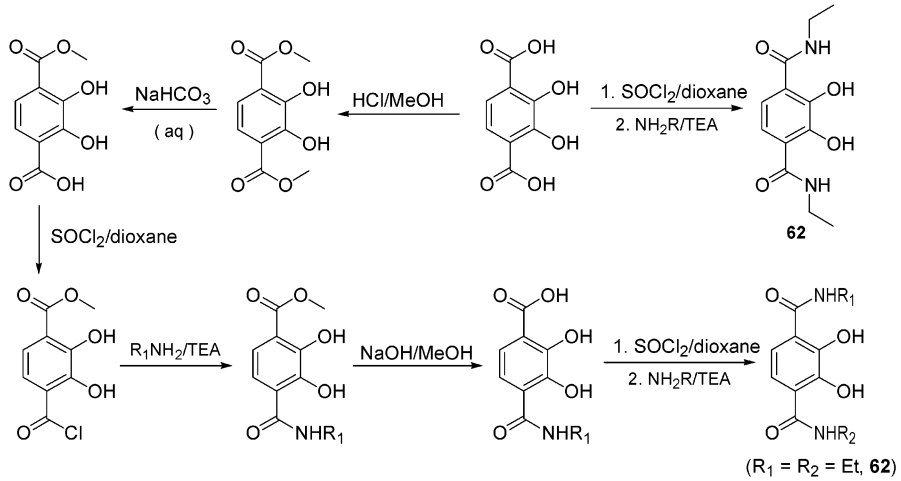
Scheme 4. Synthesis of EtTAM



Scheme 5. Synthesis of Octadentate 2,3-Dihydroxyterephthalamide Ligands



Scheme 6. Synthesis of Asymmetric TAM Ligands under a New Methodology



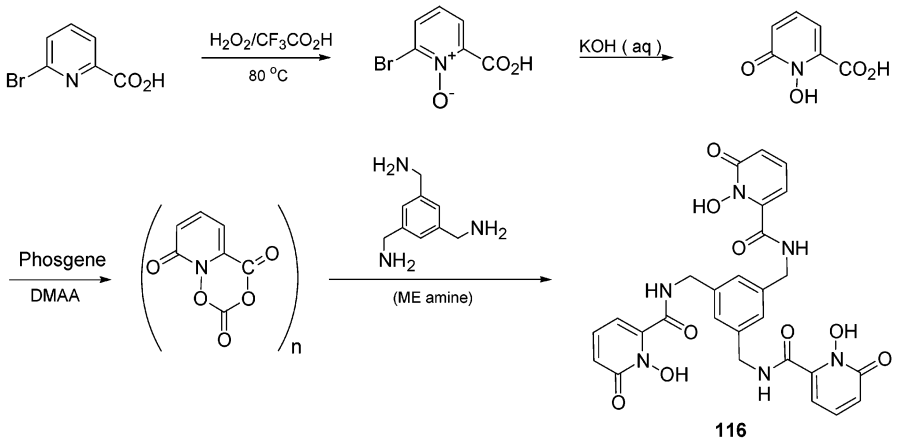
protected TAM ligand to be deprotected (for an example, see Scheme 4). This procedure differs from the synthesis of CAM ligands in that it requires the saponification of both esters.[82,283,286] Like the CAM ligands, TAM ligands can be used to create a wide variety of ligand systems by their attachment to linear or H-shaped amines (for an example, see Scheme 5).

In the improved methodology, the protection of the phenolic oxygens is not required, as the direct activation of the 2,3-dihydroxyterephthalic acid with sulfuryl chloride is followed directly by reaction with an amine. In eliminating these two steps, it is no longer necessary to use the hazardous reagent dimethyl sulfate, the BBr_3 deprotection is eliminated, and the time required is reduced. This protocol can also be applied in an asymmetric synthesis of TAM-functionalized ligands (Scheme 6).[285]

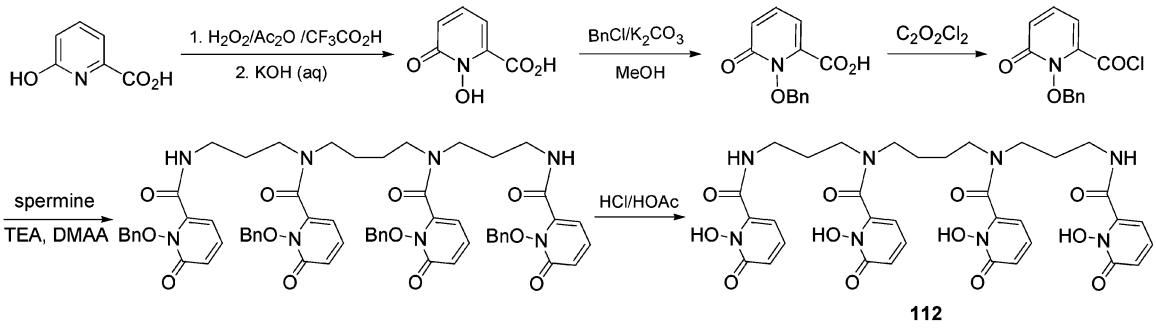
5.4. Hydroxypyridinone (HOPO) Ligands

Pursuant to the efforts to develop more effective sequestering agents for use in the treatment of

Scheme 7. Synthesis of 1,2-HOPO for Me-1,2-HOPO



Scheme 8. Synthesis of 3,4,3-LI(1,2-HOPO)



human iron toxicity, other bidentate functional groups have been developed for use in these siderophore-based ligands.[145] Among these are several hydroxypyridinones in which the hydroxy group is ortho to the ketone functionality. The three unsubstituted chelating hydroxypyridinones are 1-hydroxy-2(1*H*)-pyridinone (1,2-HOPO), 3-hydroxy-2(1*H*)-pyridinone (3,2-HOPO), and 3-hydroxy-4(1*H*)-pyridinone (3,4-HOPO).[287]

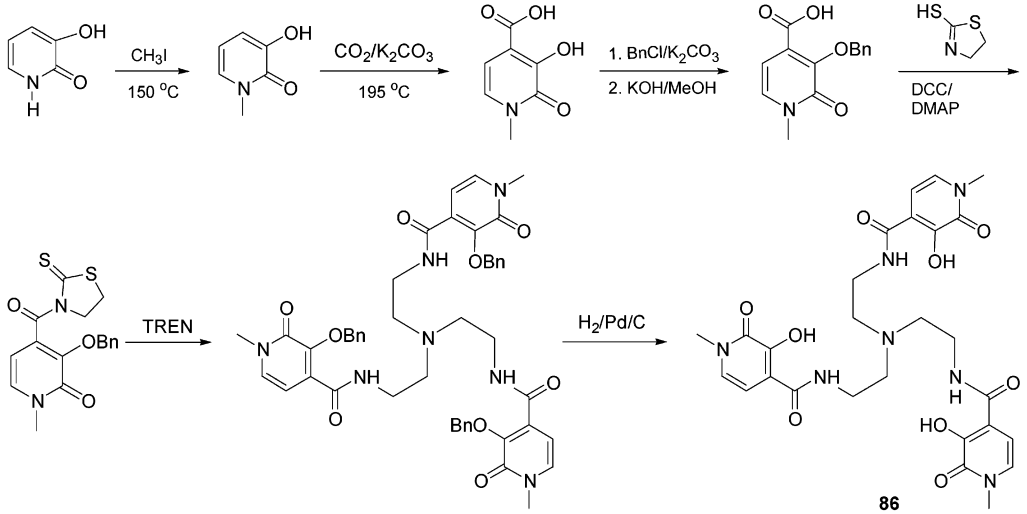
Both 1,2-HOPO and 3,2-HOPO are commercially available, but modified ligands must be prepared to afford the appropriate functionalization for the attachment to amine backbones. For the synthesis of the functionalized 1,2-HOPO, the original procedure begins with 6-bromopyridine-2-carboxylic acid stirred into a solution containing trifluoroacetic acid and hydrogen peroxide. With heating, 2-bromopyridine-6-carboxylic acid 1-oxide is produced, precipitating as a white solid on concentration of the reaction mixture. This product may be used to synthesize 1-hydroxy-2(1*H*)-pyridinone-6-carboxylic acid by treatment with aqueous potassium hydroxide, followed by an acidic workup. Phosgene and DMAA are used to activate the ligand, which, as with the CAM and TAM ligands, may be reacted with a variety of amines under acidic conditions to attach the chelating 1,2-HOPO subunit to the ligand backbone to afford multidentate ligand systems (Scheme 7).[287]

In an independent report by Bailly and Burgada, a new scheme affording a better yield of the pure final product has been prepared using 1-benzyloxy-2(1*H*)-pyridinone-6-carbonyl chloride as the activated species. The use of the benzyl ester as an alternative means for the protection of the HOPO hydroxide group allows for deprotection using HCl rather than the harsher BBr_3.[288] More recently, we have further improved on this synthesis. The benzyl protection of carboxylic acid-functionalized 1,2-HOPO is easily accomplished if potassium carbonate is used as the base in methanol. This acid can be isolated in improved yield, and the addition of oxalyl chloride yields the acyl chloride in 95% yield. This is then ready for attachment to the ligand backbone, followed by deprotection under acidic conditions in HOAc and HCl, which are less harsh than the BBr_3 deprotection. Alternatively, this carboxylic acid may be converted to the 1,2-HOPO-thiazolide in a reaction with 2-mercaptothiazoline in dicyclohexylcarbodiimide and 1,4-(dimethylamino)pyridine or converted to NHS or other activated esters for use in coupling reactions with amines (Scheme 8).[170]

The 3,4-HOPO chelating subunit may be synthesized from commercially available mimosine according to a literature procedure developed by Hart, et al.[289] Although investigated for their iron chelation abilities, these have as yet to be developed or tested as actinide-sequestering agents.[290−293] The pyrimidinone analogue of the HOPO ligand class, the 6-carboxamido-5,4-hydroxypyrimidinones, or HOPY ligand systems, have been investigated as lanthanide coordination complexes, but not as sequestering agents to date.[294]

Another class of chelating agents based on 4-carbamoyl-3-hydroxy-2-pyridinones has been developed more recently: the Me-3,2-HOPO ligands. These feature optional terminal substituents on the nitrogens in the hydroxypyridinone ring. A very important characteristic of these chelating subunits is that, in

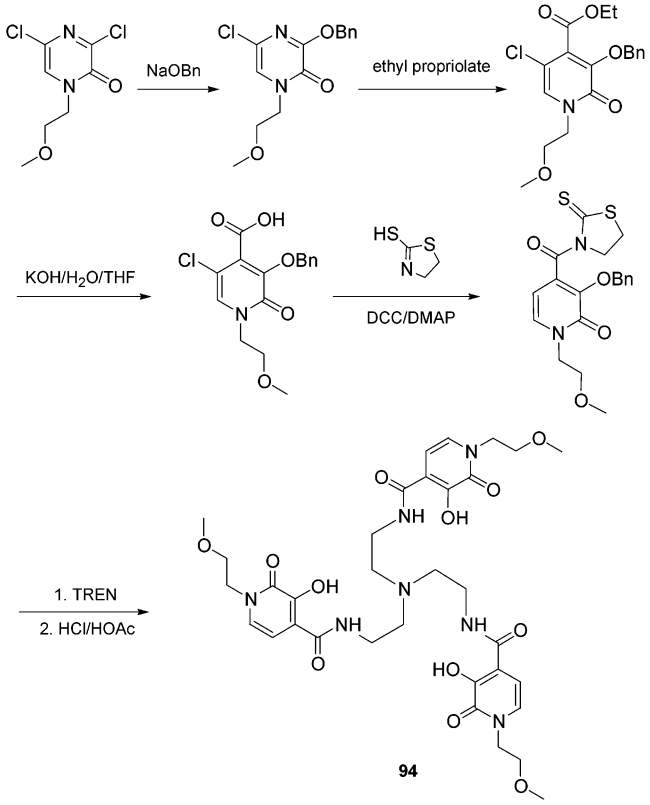
Scheme 9. Synthesis of Me-3,2-HOPO for TREN(Me-3,2-HOPO)



a fashion similar to that of the CAM complexes, these HOPO derivatives form strong hydrogen bonds between the amide proton and the adjacent oxygen of the phenolate in the metal complex, serving to enhance the overall stability of the complex.[160] The general synthetic scheme for ligands with this chelating subunit is shown in Scheme 9. The amidation of 2,5-dimethoxytetrahydrofuran-2-carboxylic acid methyl ester by primary alkylamines, followed by the acid-catalyzed rearrangement, yields the *N*-alkyl-3-hydroxy-2-pyridinones. The rearrangement reaction is promoted by the presence of metal ions, such as Fe^{3+}, Cu^{2+}, or Zn^{2+}, which have high affinities for the bidentate hydroxypyridinone binding group.[295] The 1-methyl-3-hydroxy-2(1*H*)-pyridinone is carboxylated under Kolbe−Schmidt conditions with carbon dioxide and base. The resulting 4-carboxy-3-hydroxy-1-methyl-2(1*H*)-pyridinone is then protected with benzyl chloride to give the phenol ether and ester species, which is then hydrolyzed with base to give the protected carboxylic acid. The acid is converted to the activated species 3-benzyloxy-1-methyl-4-[(2-thioxothiazolidin-1-yl)carbonyl]-2(1*H*)-pyridinone, which on reaction with a suitable backbone ligand amine results in the multidentate product. The protecting groups can then be removed by either acidic means or catalytic hydrogenation.[160]

Alternatively, a newly developed scheme for producing *N*-alkyl-substituted HOPO ligands involves a Diels−Alder addition followed by a retro-Diels−Alder elimination of substituted 5-chloro-3-alkoxy-*N*-alkyl-2(1*H*)-pyrazinones as developed by Hoornaert and co-workers, as in Scheme 10.[296] This provides a high degree of flexibility in the synthesis of the pyrazinone precursor, allowing for alternative substitution of the *N*-alkyl group, which has been used to great advantage in the development of more soluble systems for lanthanide-chelating systems, as in the synthesis of the TREN-MOE−3,2-HOPO (**94**) ligand system, for example.[297] However, this method has not yet been applied to the development of actinide-sequestering systems and is described in detail elsewhere.[276,297]

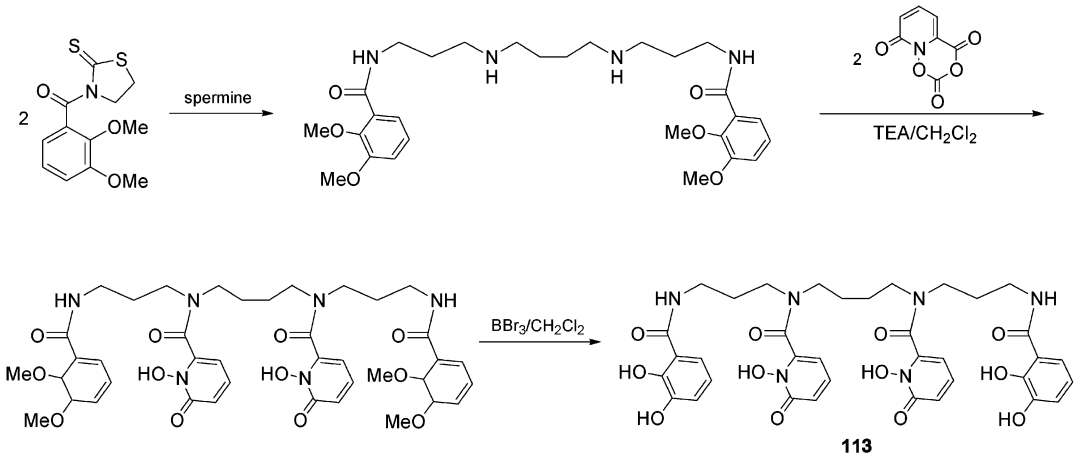
Scheme 10. Synthesis of TREN-MOE(3,2-HOPO)



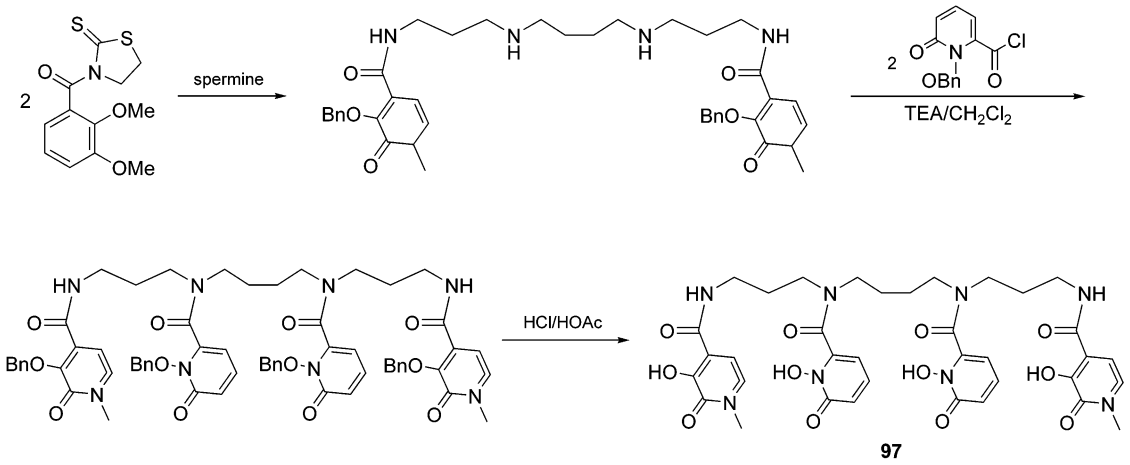
5.5. Mixed Ligands

Synthetic procedures were well established for catecholate ligands, and CAM, TAM, and HOPO binding units were used for the initial evaluations of ligands using amide backbones.[161,258] Mixed ligands with combinations of these and other coordinating units have also been prepared for studies with actinides. The CAM (**22**), CAM(C) (**56**), MeTAM (**75**), Me-3,2-HOPO (**98**), and 1,2-HOPO (**115**) chelating subunits have also been used to functionalize hexadentate DFO to identify if any improvement in chelation properties can be achieved in the combination of these two subgroups.[27,167,298] The free amine of DFO allows for the derivatization of this naturally occurring siderophore with the additional chelating

Scheme 11. Synthesis of 3,4,3-LI(diCAM-di-1,2-HOPO)



Scheme 12. Synthesis of 3,4,3-LI(1,2-Me-3,2-HOPO)



subunit to produce these new ligands with the higher octadentate denticity.[27]

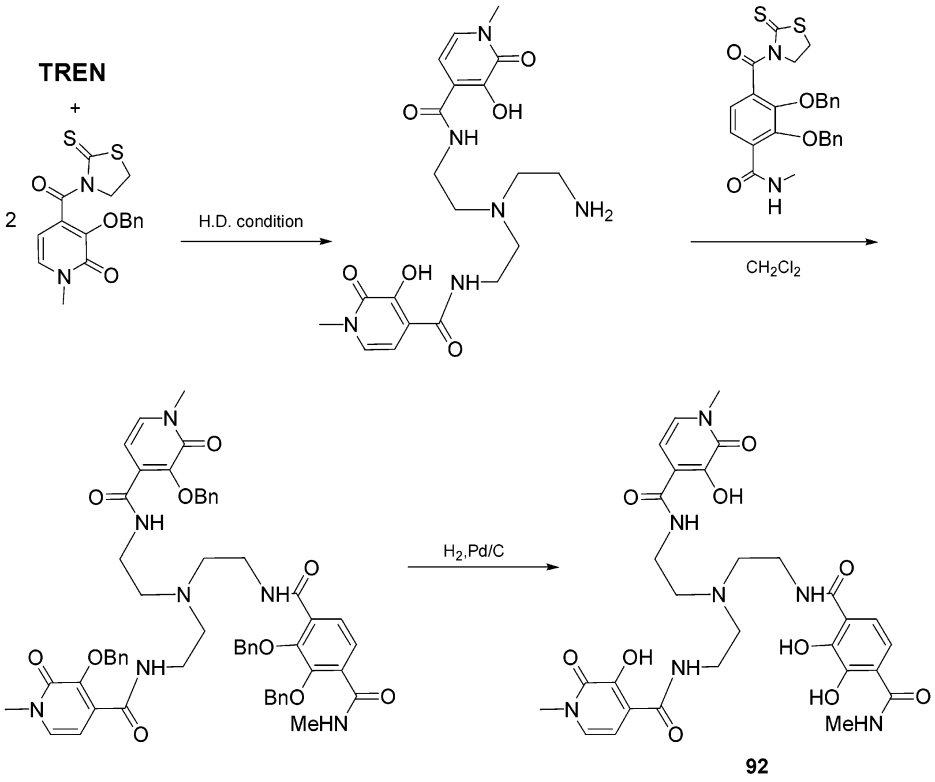
Mixed ligands containing combinations of the TAM, CAM, and HOPO subgroups have also been prepared in turn.[166,170,299] The syntheses of the mixed ligands 3,4,3-LI(tri-CAM-(1,2-HOPO)) (**114**) and 3,4,3-LI-(diCAM-di-1,2-HOPO) (**113**) were exceedingly difficult, and the yields were so small that metal complex structures could not be isolated and stabilities could not be measured.[166] These ligands were produced in low yield from a stepwise synthesis, as in Scheme 11. The 3,4,3-LI(diCAM-di-1,2-HOPO) (**113**) was made by first producing diCAMspermine by the careful addition of spermine to a solution of 2-(2,3-dimethoxybenzoyl)thiazolidine-2-thione, and then combining this with 1-hydroxy-2-pyridone-6-carboxylic acid treated with DMAA and deprotecting with BBr_3 to produce the 3,4,3-LI(diCAM-diHOPO) (**113**) ligand. The tri- variety was also made from diCAMspermine.[166] Recent improvements to the synthesis of 1,2-HOPO ligands, detailed above (Scheme 12), have made the linear mixed ligand systems more readily available. The improved synthesis and protection with the benzyl ester allows for improved yields of mixed spermine backbone ligands.[170]

Using mixed systems based on the TREN backbone with these chelating subunits demonstrated improved ease of synthesis for the development of mixed ligand systems. One example would be in the synthesis of the mixed ligand TREN-3,2-HOPO-MeTAM (**92**), in which a solution containing 2 equiv of 3-benzoxy-4-(2-thioxothiazolidin-1-yl)carbonyl-2-pyridinone was slowly added to TREN in CH_2Cl_2, resulting in the disubstituted bis(Me-3,2-HOPO)-TREN. To this would then be added 1 equiv of 1,4-bis(2-thioxothiazolidin-1-yl)carbonyl-2,3-dimethoxybenzene to add the TAM subunit. Amination of the TAM subunit with methylamine and deprotection would result in the mixed ligand product **92** (Scheme 13).[257,299] An analogous synthetic procedure can be used with the TREN backbone and other chelating units to isolate TREN-CAM(Me-3,2-HOPO) (2 1,2-HOPOs, 1 CAM, **90**)[145,245] and TREN(1,2-Me-3,2-HOPO) (2 1,2-HOPOs, 1 Me-3,2-HOPO, **89**)[145] Bis-(Me-3,2-HOPO)TREN was likewise used in the synthesis of a ligand with two HOPO functionalities and two bis(acetate) functionalities, TREN(Me-3,2-HOPO)BAC (**93**), by reacting it with an excess of benzyl 2-bromoacetate and anhydrous potassium carbonate in THF. Deprotection by reductive hydrogenation using palladium hydroxide on carbon affords the final product.[299] The reactivity of these systems has been studied with lanthanides and iron, but not, as yet, characterized with actinide metals.

5.6. Sulfonamide Ligands

New catechol derivatives have also been prepared as sulfonic acids. On the basis of the ability of the

Scheme 13. Synthesis of TREN(3,2-HOPO)MeTAM



sulfonated catecholates, the CAM(S) ligands, to bind metals, we envisioned that the corresponding sulfonamide catecholates (or SFAM ligands) would prove excellent chelators for high-oxidation-state metals such as the actinides. While bidentate Tiron is soluble only in water, a virtually infinite selection of amines may be coupled to the sulfonic acid to yield SFAM ligands and metal complexes with improved solubility and higher order denticities (tetradentate, hexadentate, or higher).[300] The solution properties and coordination chemistry of this new class of sulfonamide (or SFAM) catecholate-based ligands appended with sulfonamide groups are still being explored.[301] The catecholate SFAM ligands were synthesized in three steps by preparing the sulfonyl chloride of veratrole, coupling this with the desired amine, and finally removing the methyl ethers through a deprotection step with BBr_3 to yield the free ligand. Several bidentate and tetradentate SFAMs (**119**−**125**) were prepared by coupling the SFAM chelating subunit with the desired amine, diamine, or triamine under basic conditions and then removing the methyl ether protecting groups with a standard BBr_3 deprotection.

6. Plutonium-Sequestering Agents

6.1. Plutonium Coordination Chemistry

The chemical nature and α-radiation of plutonium have limited the exploration of its fundamental coordination chemistry. As described previously, actinides form easily hydrolyzed acidic metal ions that form strong complexes with common chelating agents.[2,3,7] These ions preferentially interact with hard acid donor atoms, such as oxygen or carboxylate, alkoxide, and fluoride anions, but demonstrate some covalency in their interactions with softer donor atoms such as chloride, nitrogen, and sulfur.[3] The coordination chemistry of Pu is a complex issue. Although Pu can be found in each of the oxidation states from III to VI in aqueous solution, the Pu(IV) state is preferred. The complexes of Pu(III) and Pu(V) with organic ligands are stable only in a very narrow pH range. Under biological conditions, organic sequestering agents cause disproportionation, resulting in only the Pu(IV) complexes. The biological evidence indicates that most, if not all, exists as Pu(IV) *in vivo*.[43] A better understanding of Pu(IV) coordination chemistry is essential for the design of potent *in vivo* Pu(IV)-sequestering agents.

The plutonium cation Pu(IV), which is present in solution at pH ~0, hydrolyzes with increasing pH to form dark-green colloidal plutonium hydroxides, $[Pu(OH)_x]_n$, with molecular weights in the range 1000 to >1 000 000.[51] The redissolution of the plutonium hydroxide can take a very long time, even in strong acid, once extensive polymerization has occurred. This presumably contributes to the long retention times of plutonium *in vivo*. Chelating ligands such as DFOE, DFOB, EDTA, citrate, and Tiron increase this dissolution, albeit slowly.[28] The chemistry of plutonium in biological fluids has been reviewed in detail.[302] The most important soluble plutonium complex formed *in vivo* is that with transferrin.[43,47]

There are a limited number of examples of characterized plutonium complexes and only a handful of these by single-crystal X-ray diffraction.[303] Some of those characterized are phosphino complexes that have demonstrated their utility in the modeling and development of phosphinopyridine ligands as selective extractants.[304−306] Structural data of bis(ammo-

nium)hexanitratoplutonium(IV) have been used to provide further understanding of separation processes using nitric acid solutions currently in use,[307] while structural characterization of plutonium carbonate complexes provides insight into what types of systems might be found in an environmental situation.[303] Most recently, the first quaternary plutonium thiophosphates, a potential intermediate that becomes important should PuS replace more common mixed oxides in nuclear fuel, have been structurally characterized.[308] One complex in particular worth mentioning in this context is that of the desferrioxamine E (DFOE)−Pu(IV) complex, as this is the one siderophore−Pu(IV) complex structurally characterized to date. It is also of interest as the one discrete Pu(IV) molecule characterized via X-ray crystallography to have a nine-coordinate Pu(IV) ion. As one would expect, the Pu(IV) increases the metal−hydroxamate bond lengths, and the larger Pu(IV) ion is not entirely encapsulated by the DFOE as Fe(III) is in that structure.[24] This provides unique insight into the nature of the plutonium complex of this and other siderophore-based Pu-coordinating systems.

6.2. Ce(IV) and Hf(IV) as Models for Pu(IV)

Ce(IV) complexes are good models for the study of Pu(IV) coordination chemistry.[130] The ionic size of Ce(IV) is the same as that of Pu(IV) (0.94 Å) within experimental error.[309] The aqueous coordination chemistry of Ce(IV) parallels that of Pu(IV), giving identical shifts in the M(IV)/M(III) redox potentials.[22]

To establish the shape and dimensions of a cavity into which the tetravalent Pu could best be trapped, a series of isostructural tetrakis(catecholato) complexes have been prepared and characterized. (As representative of these, the molecular structure of the thorium complex, tetrakis(catecholato)thorate(IV), $Na_4[Th(C_6H_4O_2)_4]\cdot 21H_2O$, is depicted in Figure 5. For comparison, the relevant metal−oxygen bond lengths and angles of several tetrakis(catecholato)−M(IV) complexes are given in Table 5.) This effort to better understand the nature of actinide complexes with catechol serves to elucidate the coordination chemistry of plutonium with these complexes. The first of these model Ce complexes reported, the cerium(IV)−tetrakis(catecholato) complex, $Na_4[Ce(O_2C_6H_4)_4]\cdot 21H_2O$, is best considered as a simple catechol complex. Crystallographic characterization established the formation of the Ce(IV)−tetrakis(catecholato) complex rather than a Ce(IV)−tris(catecholato)-(semiquinone) complex, which was also structurally a possibility. The bright red Ce(IV)−tetrakis(catecholato) complex is diamagnetic over a temperature range of 4−300 K. The observed formal potential of the Ce(IV/III)$(cat)_4$ couple, taken with the corresponding Ce(IV)/Ce(III) standard potential, implies that the tetrakis formation constants for Ce(IV) and Ce(III) differ by a factor of 10^{36}. The crystal structure was determined to be dodecahedral in geometry with little to no distortion of the metal−oxygen bonds, which averaged 2.36 Å in length.[310]

For clarification of the structural effect of the 5f electrons, the corresponding complex using the transition metal hafnium, $Na_4[Hf(O_2C_6H_4)_4]\cdot 21H_2O$, the Hf(IV)−tetrakis(catecholato) complex, was also prepared and examined crystallographically (Figure 6). It was found to be colorless, and the smaller ionic radius of hafnium resulted in some distortion of the metal−oxygen bonds. These bond lengths averaged 2.197 Å, as the ionic radius of hafnium is 0.22 Å smaller than that of Ce(IV).[310] This was followed by later studies in which the tetrakis(*N*-methyl-*p*-thiotolylhydroxamato)−Hf(IV) complex, $Hf(CH_3C_6H_4(S)N(O)CH_3)_4\cdot C_2H_5OH$, based on another common chelating subunit found in siderophores, hydroxamate, was prepared and characterized for comparison. The colorless Hf complex was found to be quite stable, with the Hf−S distances averaging 2.68 Å and the Hf−O distances averaging 2.15 Å, more comparable to the metal−oxygen distances found in the tetrakis(catecholato) complex. What is unusual about this second hafnium complex is its geometry, as it displays a bicapped trigonal prismatic coordination polyhedron, a polyhedron not normally observed in catecholato and hydroxymato complexes, and quite different from the dodecahedral geometry preferred by Pu(IV).[311] The first Hf(IV) catecholate complex was later re-examined and determined to contain an error in which one of the water molecules on the pseudo-mirror countercations was misassigned. This new

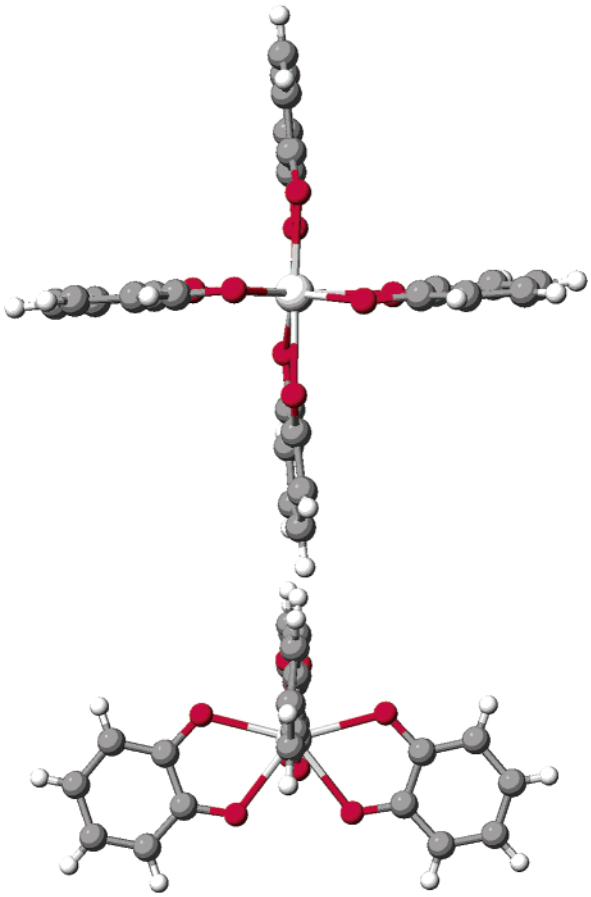


Figure 5. Molecular structure (top and side views) of $Na_4[Th(O_2C_6H_4)_4]\cdot 21H_2O$ as representative of the catecholate crystal structures. The carbon atoms are depicted as gray, the oxygen red, the central thorium atom white, and the peripheral hydrogen atoms smaller and white. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 310.

Table 5. Relevant Bond Lengths and Angles for Five Structurally Characterized Catecholate Complexes, $Na_4[Th(O_2C_6H_4)_4 \cdot 21H_2O$,[310] $Na_4[U(C_6H_4O_2)_4] \cdot 21H_2O$,[310] $Na_5[Gd(C_6H_4O_2)_4] \cdot 19.2H_2O$,[312] $Na_4[Ce(O_2C_6H_4)_4 \cdot 21H_2O$,[336] and $Na_4[Hf(O_2C_6H_4)_4 \cdot 21H_2O$[336] for Comparison[a]

Bond Lengths (Å)					
atoms	Th[310]	U[310]	Gd[312]	Ce[336]	Hf[336]
M−O1	2.418(3)	2.362(4)	2.393(2)	2.357(4)	2.195(1)
M−O2	2.421(3)	2.389(4)	2.422(2)	2.362(4)	2.224(1)
O1−C1	1.349(6)	1.352(6)	1.337(3)	1.350(6)	1.348(2)
O2−C2	1.340(5)	1.346(6)	1.341(3)	1.355(5)	1.339(2)
C1−C2	1.415(6)	1.407(7)	1.420(3)	1.402(7)	1.410(3)
C2−C3	1.401(6)	1.402(6)	1.400(3)	1.394(6)	1.397(3)
C3−C4	1.385(8)	1.385(8)	1.397(4)	1.396(9)	1.394(3)
C4−C5	1.396(11)	1.395(11)	1.376(5)	1.327(10)	1.386(4)
C5−C6	1.421(16)	1.425(15)	1.402(8)	1.527(16)	1.401(7)
C6−C1	1.396(7)	1.401(7)	1.404(3)	1.422(7)	1.393(3)

Bond Angles[b] (deg)					
atoms	Th[310]	U[310]	Gd[312]	Ce[336]	Hf[336]
O1−M−O2	66.8(1)	67.7(1)	68.05(6)	68.3(1)	71.51(5)
O1−M−O2 (90°)[b]	80.7(1)	80.0(1)	79.86(7)	79.2(1)	76.89(6)
O1−M−O2 (180°)[b]	142.3(1)	141.8(1)	141.40(6)	141.9(1)	141.84(5)
O1−M−O1 (90°)[b]	93.64(4)	93.73(4)	93.71(2)	93.90(5)	94.72(2)
O1−M−O1 (180°)[b]	150.8(2)	150.4(2)	150.52(9)	149.8(2)	146.65(8)
O2−M−O2 (90°)[b]	128.6(1)	129.5(1)	129.97(5)	129.8(1)	131.93(5)

[a] Estimated standard deviations in the least significant figure are given in parentheses. [b] The angle between catechols containing the two oxygens is given in parentheses.

solution of the structure has a new average metal−catecholate oxygen bonding distance of 2.2 Å; however, the molecule still has some disorder.[312] These results may indicate that Hf(IV) is not as suitable a model for the actinide systems as the lanthanide Ce(IV) complexes due to some ligand field differences.[312]

The next related Ce complex prepared and characterized for study was the Ce(IV) complex with Tiron, the tetrakis(tironato)cerate(IV), $Na_{12}[Ce(C_6H_2I_2(SO_3)_2)_4] \cdot 9H_2O \cdot 6C_3H_7NO$ (Figure 7). This ligand was chosen because of its similarity to the sulfonated catecholamide ligands that were of interest for actinide sequestering. The preferred coordination polyhedron for free sulfonated catechol ligand with M(IV), analogous to that in tetrakis(catecholato) complexes, had not been established and so justified the characterization of this system. The formation of the purple-brown tetrakis(tironato)cerate(IV) complex was determined to be 10^{33} times that of the Ce(III) complex. The coordination geometry is the expected trigonal-faced dodecahedral arrangement; however, the metal−oxygen distances are not all equivalent, with the cerium offset within a trapezoid, the longer metal−oxygen length averaging 2.363 Å, 0.037 Å longer than the shorter side metal−oxygen bond length, 2.326 Å. While in the catecholato case the complex has four-site symmetry, in this case the individual ligands lack any symmetry.[142]

After studying these basic subunits of the chelating siderophore-based structures, it became clear that it would be most desirable to study the structures of the actual sequestering agents to be used in this application. This research enables one to observe the effects of steric hindrance or ligand field effects that may be occurring with the multidentate ligands. A detailed assessment of the architecture of the simple prototypical complexes formed between actinides and the simple bidentate hydroxypyridinone (or HOPO) ligands is particularly important if the desired synthetic chelating ligands are to be suitably designed for the specific coordination requirements of the actinide ions. Accordingly, several Ce(IV) complexes with various bidentate and tetradentate HOPO ligands were synthesized as models for Pu(IV)-coordinating HOPOs, and their crystal structures have been determined.[130]

The Me-3,2-HOPO ligand, absent additional substitution or bridging amide groups, forms a somewhat distorted trigonal dodecahedron on crystallization as the Ce(IV)−tetrakis(Me-3,2-HOPO) complex.[130] The 1-oxy-2-pyridonate complex with Ce(IV) was previously reported but was not stable enough to be structurally characterized.[313] The Ce(IV) atom in this complex is coplanar with the HOPO oxygens of each pair of oxygens from the Me-3,2-HOPO ligands; however, each HOPO ring plane is tilted slightly toward its attached chelate plane. The average cerium−oxygen bond length for this system is 2.36 Å.[130] This is quite comparable to the metal−oxygen bond lengths of the Ce(IV)−tetrakis(catecholato) complexes described previously[310] (Figure 8).

The structures of Ce[5-LI(Me-3,2-HOPO)]$_2$ (from organic solvent) and Ce[5-LIO(Me-3,2-HOPO)]$_2$ (from water) have also been determined via X-ray crystallography (using ligands **81** and **82**, respectively). In each case, the central Ce(IV) is eight-coordinated by two tetradentate ligands.[130] The coordination polyhedrons of the two complexes are essentially square antiprisms. Solution thermodynamic studies gave overall formation constants (log β_2) for Ce[5-LI(Me-3,2-HOPO)]$_2$ and Ce[5-LIO(Me-3,2-HOPO)]$_2$ of 41.9 and 41.6, respectively. From these constants, extraordinarily high pM values for Ce(IV) are obtained with the two ligands (37.5 and 37.0, respectively). Due to their similarity in charge-to-ionic size ratio, the constants for Pu(IV) are expected to be essentially the same. Thus, it has been demonstrated that small changes in the linear backbone of the ligands and the nature of the chelating subunits greatly affect the structures of the metal complexes. These complexes

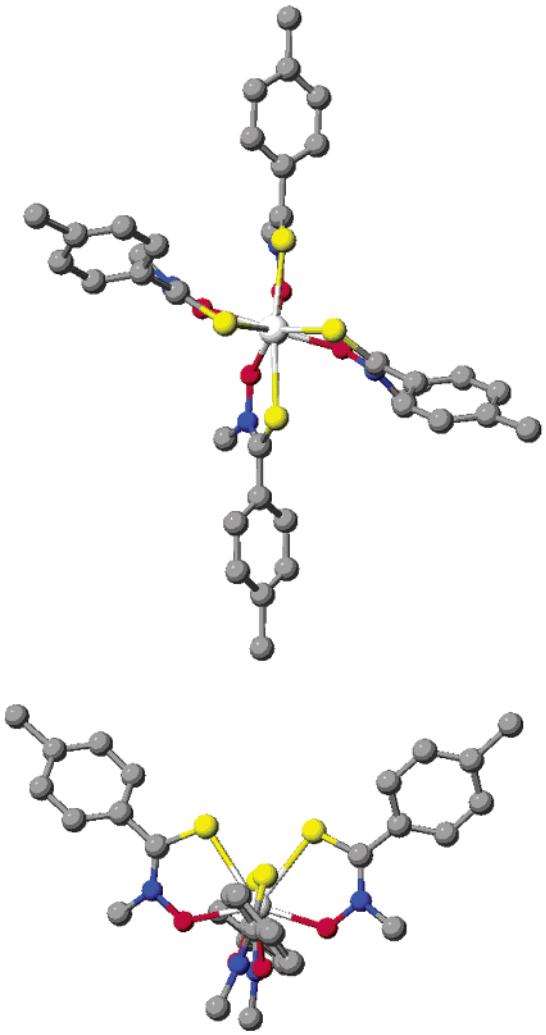


Figure 6. Molecular structure (top and side views) of the tetrakis(*N*-methyl-*ρ*-thiotolylhydroxamato)hafnium(IV) complex, $Hf(CH_3C_6H_4(S)N(O)CH_3)_4 \cdot C_2H_5OH$. The carbon atoms are depicted as gray, the oxygen red, the sulfur yellow, the nitrogen blue, the central hafnium atom white, and the peripheral hydrogen atoms smaller and white. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 311.

are extraordinarily stable, and one would expect plutonium complexes to behave in a similar fashion, given their similar nature[22,130] (Figure 9).

6.3. Catecholamide (CAM)-Based Plutonium-Sequestering Agents

6.3.1. Cyclic Systems

Typically, siderophores employ three bidentate chelating moieties bound to a trimeric backbone. Initial studies using this model as the basis for synthetic sequestering agents followed a similar structure. The first of these siderophore-inspired systems prepared and tested in vivo as a plutonium-sequestering agent, a multidentate catecholate ligand, was a structural and functional octadentate analogue of enterobactin, 3,3,3,3-CYCAM, containing four catechol groups attached through amide linkages to the uniformly spaced nitrogens of a cyclic 16-unit tetrakisaminoalkane (**25**). The four catechols were

Table 6. Relevant Bond Lengths and Angles with the Averages for the Tetrakis(*N*-methyl-*p*-thiotolyl-hydroxamato)hafnium(IV) Complex, $[Hf(CH_3C_6H_4(S)N(O)CH_3)_4 \cdot C_2H_5OH]$[311]

Bond Lengths (Å)					
atoms	ring 1	ring 2	ring 3	ring 4	avg
Hf−S	2.688	2.673	2.699	2.653	2.678
Hf−O	2.175	2.139	2.144	2.141	2.150
C−S	1.709	1.694	1.701	1.695	1.700
N−O	1.365	1.352	1.347	1.357	1.355
C−N	1.284	1.310	1.301	1.317	1.303
C−C(Ph)	1.484	1.485	1.476	1.478	1.481
Bond Angles (deg)					
atoms	ring 1	ring 2	ring 3	ring 4	avg
O−Hf−S	70.11	71.67	70.28	72.35	71.10
S−C−N	118.8	119.7	118.5	119.3	119.1
S−C−C(Ph)	120.2	120.0	119.3	119.6	119.8
N−C−C(Ph)	121.1	120.3	122.2	121.1	121.2
O−N−C(CH_3)	111.1	112.0	111.9	111.3	111.6
O−N−C	120.7	120.4	120.8	120.8	120.7

provided to give eight-coordinate geometry preferred by actinide(IV) ions, as well as to introduce specificity.[20] This first ligand described had the advantages of being less susceptible to hydrolysis than enterobactin while at the same time being less susceptible to air oxidation than the 2,3-dihydoxybenzoyl group (DHB) chelating subunit alone.[20]

Because it prevented Pu hydrolysis at high pH, the log K_{ML} for the eight-coordinate Pu chelate was expected to be on the order of 52.[20] When 3,3,3,3-CYCAM (**25**) was injected into mice 1 h after im injection of Pu(IV) citrate, the sparingly soluble ligand chelated circulating Pu, but instability at low pH caused it to dissociate, depositing nearly all of the chelated Pu in the kidneys.[149] Ligand solubility, binding group acidity, and oxidative stability at physiological pH were improved by adding sulfonate [3,3,3,3-CYCAM(S), **47**] or carboxylate [3,3,3,3-CYCAM(C), **58**] substituents to the catechol rings. This second generation of cyclic ligands, 3,3,3,3-CYCAM-(S) (**47**) and -CAM(C) (**58**), chelated circulating Pu, and the chelates were sufficiently stable to be excreted, but reduction of body Pu was significantly less than was obtained with $CaNa_3$−DTPA, and substantial Pu residues were deposited in the kidneys.[149,159] However, the macrocycle was found to have significantly improved excretion compared with sulfonated monomeric DHB.

A sparingly soluble bicyclic ligand, BH(2,2)-CAM (**74**), with a preformed coordination cavity spatially suitable for Pu encapsulation, was found to be a more effective chelator of Pu *in vivo* than the planar cyclic ligands prepared earlier. This ligand reduced skeleton and soft tissue Pu as much as $CaNa_3$−DTPA, but it reduced liver and body Pu less than $CaNa_3$−DTPA. The Pu chelate of **74** was apparently sufficiently stable at low pH to be excreted in urine without depositing Pu in the kidneys.[161] Other groups have used similar backbones for the purposes of modeling new ligand systems, employing cyclam backbones for the synthesis of cyclam tetrahydroxamate (CYTROX) and cyclam tetraacetonylacetone (CYTAC) chelating agents for the purpose of actinide sequestration. However, it is important to note that

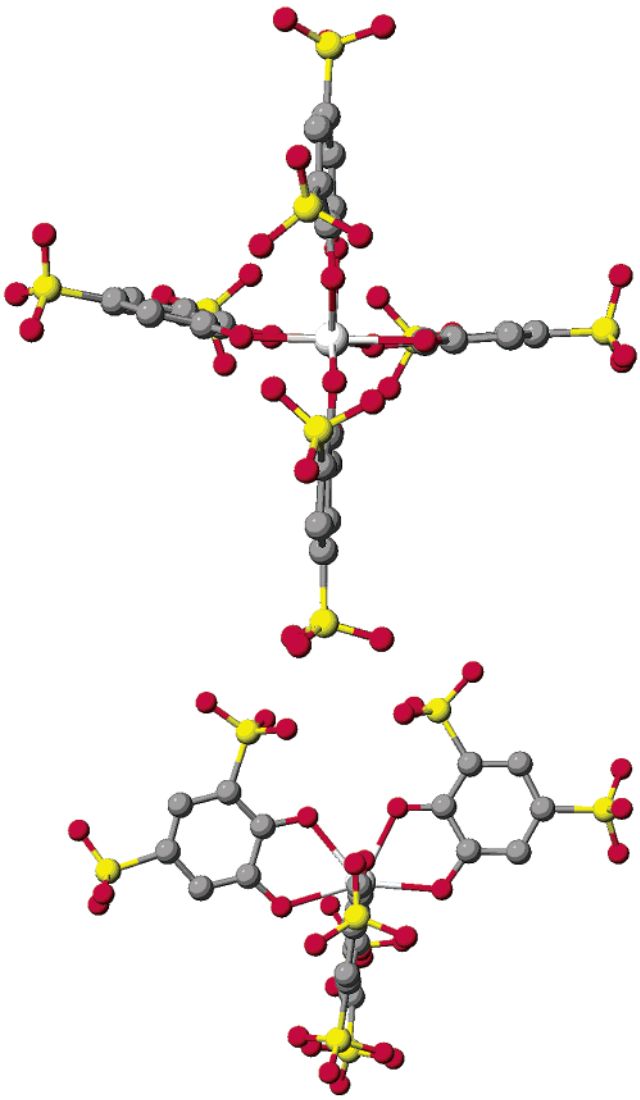


Figure 7. Molecular structure (top and side views) of the cerium(IV) complex with Tiron, the tetrakis(tironato)-cerate(IV), $Na_{12}[Ce(C_6H_2O_2(SO_3)_2)_4]\cdot 9H_2O\cdot 6C_3H_7NO$. The average Ce−O(A) distance of 2.363(9) Å is longer than the average Ce−O(B) distance of 2.326(15) Å, and the average O−Ce−O angle is 67.9(1)°. The carbon atoms are depicted as gray, the oxygen red, the sulfur yellow, and the central cerium atom white. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 142.

these have primarily been investigated via computer-generated models, and neither studies with the Pu(IV) metal nor *in vivo* investigations have been reported as yet.[314]

6.3.2. Multidentate Linear Systems

The rigid planar structure and short intergroup spacing of the cyclic ligands hinder close approach to the Pu of the minimum number of catechol groups (later shown to be three) required for stable chelation at physiological pH.[21,22,164] While both cyclic and acyclic systems present attractive backbones for anchoring ligand moieties, linear systems present greater stereochemical freedom that may lead to more effective chelation.[36,139] This stereochemical freedom enables the system to more closely align in the preferred D_{2d} trigonal-faced dodecahedral geometry, and this consideration proved to be of greater importance than the metal−ion encapsulation geometry of the cyclic complexes.

Commercially available spermine, a tetrakisaminoalkane, provided a favorable backbone that was a compromise between a less-than-ideal intergroup spacing and a ligand solubility greater than that of longer alkane backbones.[82,259] The greater stereochemical freedom afforded by the linear backbone of 3,4,3-LI-CAM (**20**), -CAM(S) (**42**), and -CAM(C) (**53**) increased the stabilities of their Pu chelates at physiological pH. *In vivo*, Pu removal from mice using 3,4,3-LI-CAM (**20**) as a chelating agent was significantly greater than that obtained with its cyclic analogues. The two linear ligands with acidifying ring substituents, 3,4,3-LI-CAM(S) (**42**) and 3,4,3-LI-CAM-(C) (**53**), promoted about as much Pu excretion as $CaNa_3$−DTPA, and reductions of skeletal Pu by hydrophilic 3,4,3-LI-CAM(S) (**42**) and of liver Pu by more lipophilic 3,4,3-LI-CAM(C) (**53**) were significantly greater than the reductions of Pu in those tissues by an equimolar amount of $CaNa_3$−DTPA. A significant fraction of the Pu chelated by 3,4,3-LI-CAM(C) (**53**) was diverted to fecal excretion, suggesting that the ligand was chelating Pu already deposited in liver cells.[149,159,164]

6.4. Biological Evaluation Leads to Improved Ligand Systems

Since 1978, the Raymond and Durbin collaboration has produced and evaluated 55 multidentate ligands attached to a variety of molecular backbones. Many of these were prepared for reasons other than actinide chelation, but all were evaluated for Pu(IV) chelation in mice. The resulting biological data proved invaluable for guiding ligand design and for understanding some of the relationships underlying the overall effectiveness of a ligand for actinide chelation *in vivo* (denticity, binding group acidity, backbone flexibility, and solubility at pH 7). Among that array of ligands, 23 promoted Pu excretion as well as or better than an equimolar amount of $CaNa_3$−DTPA. Biological evaluation of the sequestration capabilities of the ligands using the mouse model has enabled the development of new and improved sequestering agents to continue to evolve.

For example, there was a dramatic increase in the Pu sequestration capabilities *in vivo* with the change from the cyclic CYCAM systems to the multidentate linear LI-CAMs; the mouse model experiments provided key data for evaluation of the efficacy of these ligands and experimental evidence for the supposition that the improved solubility and flexibility of the linear ligands do indeed provide for more effective Pu excretion and prevention of Pu deposition in bone and soft tissue.[149] In a similar fashion, sulfonated derivatives of the LI-CAM ligands were found to have increased water solubility. Greater solubility in combination with enhanced phenolic acidity (and hence metal complexing strength at neutral pH) improved oxidative stability and served to improve their chelation abilities. The linear LI-CAM(S) ligand, 3,4,3-LI-CAM(S) (**42**), was found to be an efficient sequestering agent, with 65% removal of injected Pu, as

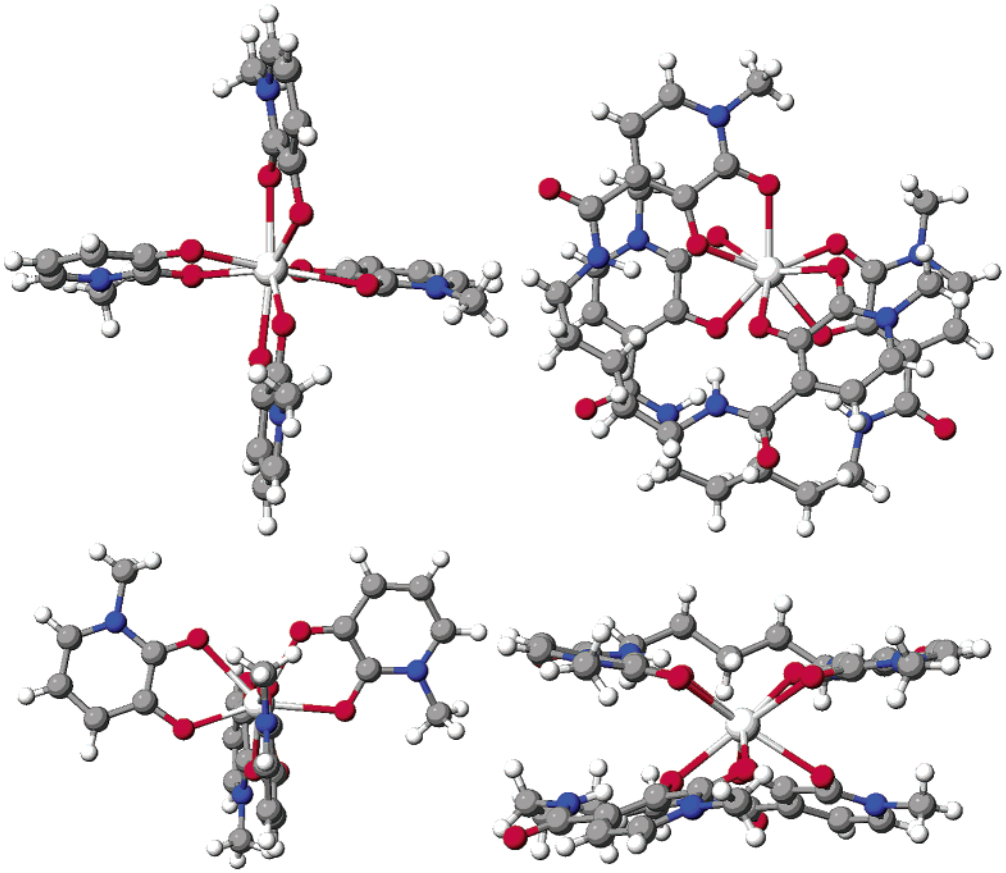


Figure 8. Molecular structures (top and side views) of the Ce(IV) complexes Ce(IV)tetrakis(Me-3,2-HOPO) and Ce(5-LI-(Me-3,2-HOPO))$_2$. The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, the central cerium atoms white, and the peripheral hydrogen atoms smaller and white. These figures were generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 130.

compared to 63% for DTPA.[149] Following this rationale again, 4-carboxylate derivatives of the LI-CAM ligands, LI-CAM(C), were prepared. The tetrameric 3,4,3-LI-CAM(C) (**53**) removed 63% of Pu, comparable to 3,4,3-LI-CAM(S) (**42**),[159,165] with reduced toxicity.[155,159,184]

Concurrent with the initial success with 3,4,3-LI-CAM(C) (**53**), other ligands containing CAM groups were prepared for chemical investigations and chelation of Fe(III).[249,273] These were then also tested with Pu(IV) for sequestering capabilities. A salicyl analogue of 3,4,3-LI-CAM(S) (**42**), 3,4,3-LISAM(S) (**44**), did not alter Pu distribution in mice or promote Pu excretion, demonstrating that both of the ortho phenolic groups of catechol are required for metal chelation at physiological pH. Tetra- and hexadentate CAM ligands with linear [2-LI (**1**) or 3,4-LI (**4**)] or mesitylene [ME (**12**)] backbones formed less stable Pu chelates *in vivo* than octadentate ligands containing the same functional groups. These ligands promoted less Pu excretion and left larger Pu residues in the kidneys. When isopropyl groups were added to the terminal secondary amine nitrogens of Dip-3,4,3-LI-CAM(S) (**43**) to protect them against enzymatic attack, ligand effectiveness was reduced. Likewise, octane chains, added to the terminal nitrogens of 3,4,3-LI-CAM(C) (**54**) to increase lipophilicity, slightly reduced *in vivo* Pu chelation and diverted excreted chelated Pu to feces, while the addition of decane chains (**55**) greatly reduced *in vivo* Pu chelation and severely hampered Pu excretion.[159]

Removal of Pu from the transferrin complex (Pu−Tf) by 3,4,3-LI-CAM(C) (**53**) or 3,4,3-LI-CAM(S) (**42**) *in vitro* is the same for Pu−Tf prepared from Pu nitrate or Pu−tri-*N*-butyl phosphate (Pu−TBP) or obtained from the serum of rats injected with Pu−TBP. In each case, Pu chelation by 3,4,3-LI-CAM(C) (**53**) or 3,4,3-LI-CAM(S) (**42**) is 100−500 times more efficient than that of $CaNa_3$−DTPA.[175,201,202] The catecholate ligands are 10−100 times more effective than $CaNa_3$−DTPA in doses less than 30 μmol kg^{-1} for reducing body and skeleton Pu and, depending on the species, also liver Pu. Unlike $CaNa_3$−DTPA, prompt oral administration of a catecholate ligand reduced body and tissue Pu significantly compared with Pu-injected controls.[165,172]

Dogs were injected with ^{237}Pu and ^{239}Pu, and 30 min later they were given an iv injection (30 μmol kg^{-1}) of a catecholate ligand, $CaNa_3$−DTPA, or 3,4,3-LI-CAM(S) (**42**) and $CaNa_3$−DTPA combined; the immediate chelation of circulating Pu was shown by the rapid clearance of plasma Pu in the catecholate-treated dogs. After 7 days, body Pu of the catecholate-treated dogs was close to one-half of that obtained with $CaNa_3$−DTPA. Greater reduction of skeletal Pu by 3,4,3-LI-CAM(S) (**42**) and of liver Pu by 3,4,3-LI-CAM(C) (**53**), compared with $CaNa_3$−DTPA, confirmed the findings in mice. Removal of Pu by 3,4,3-LI-CAM(S) (**42**) was not enhanced by combining it with $CaNa_3$−DTPA. Renal toxicity at effective dose,

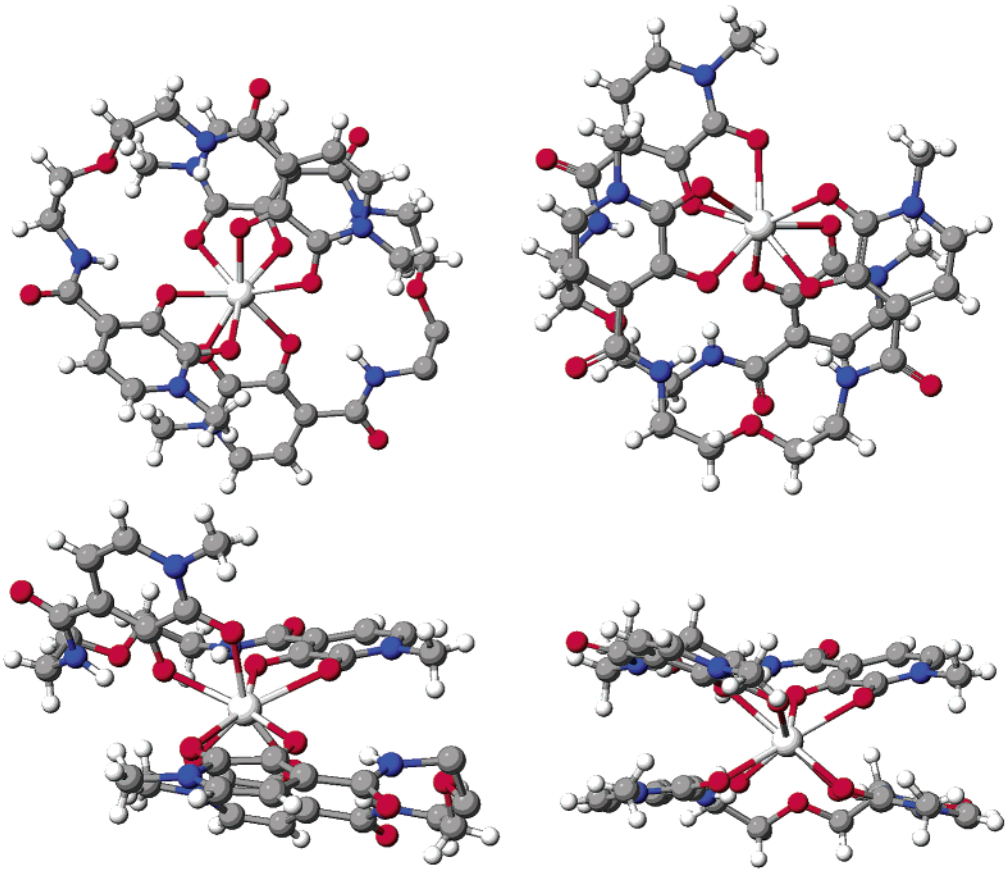


Figure 9. Molecular structures of (top and side views) of the Ce(IV) complexes Ce(IV)[bis(5-LIO-Me-3,2-HOPO)]$_2$·2CH$_3$OH and Ce(IV)[bis(5-LIO-Me-3,2-HOPO)]$_2$·4H$_2$O. The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, the central cerium atoms white, and the peripheral hydrogen atoms smaller and white. These figures were generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 130.

observed in dogs treated with 3,4,3-LI-CAM(S) (**42**) at standard dose,[184,200] caused this ligand to be abandoned except as an investigational tool.

Protracted therapies with 3,4,3-LI-CAM(C) (**53**) and $ZnNa_3$−DTPA were also compared in dogs. Starting 14 days after injection of ^{237}Pu and ^{239}Pu, $ZnNa_3$−DTPA (30 μmol kg^{-1} d^{-1}) was injected daily for 320 days, or 30 μmol kg^{-1} of 3,4,3-LI-CAM(C) (**53**) was injected daily for the first 14 days and 3 μmol kg^{-1} each day thereafter. By 152 days, at which point the ^{237}Pu had decayed, Pu in non-liver tissue (mainly bone) had been reduced more by 3,4,3-LI-CAM(C) (**53**) (50% of control) than by $ZnNa_3$−DTPA (70% of control). Retention of Pu in the liver was not changed by 3,4,3-LI-CAM(C) (**53**), while $ZnNa_3$−DTPA effectively reduced Pu. Mild plasma hypoferremia was noted during the daily injections of the larger 3,4,3-LI-CAM(C) (**53**) dose, but plasma iron returned to within normal limits when the dose was reduced. Blood chemistry was within normal limits for all treated dogs during the year of observation.[185]

In a collaborative research program with the EULEP group, 3,4,3-LI-CAM(C) (**53**) was synthesized in several batches in their laboratories and designated EU-LI-CAM(C) (**53**).[175,183,315] The chelation of injected Pu citrate, inhaled Pu nitrate, and inhaled Pu−TBP was studied in several mouse and rat strains, Chinese and Syrian hamsters, and baboons. EU-LI-CAM(C) (**53**) was administered once (3−30 μmol kg^{-1} injected, 100 μmol kg^{-1} orally) or as many as five times in 4 days starting 30−60 min after iv injection of ^{238}Pu, and animals were killed at 1−28 days. The results of these studies generally agreed with the original evaluations in mice.[159] In the same protocols, treatment with EU-LI-CAM(C) (**53**) was as effective as or somewhat more effective than $CaNa_3$−DTPA for reduction of Pu in the body and tissues. Compared with Pu-injected control rats, substantial and significant reductions of Pu in bone and liver were obtained by prompt oral treatment (100 μmol kg^{-1}) with EU-LI-CAM(C) (**53**).[172] Delay between nuclide injection and chelation treatment progressively reduced effectiveness for promoting Pu excretion. Substantial residues of Pu were deposited in the renal cortex of all species given EU-LI-CAM(C) (**53**). These renal Pu deposits, which were the greatest in Chinese hamsters and the least in mice, were cleared with a half-time of about 20 days.[172−175,183,188]

Starting 30 min after rats inhaled an aerosol of ^{238}Pu nitrate, EU-LI-CAM(C) (**53**) or $CaNa_3$−DTPA was injected once or five times in 4 days. Clearance of the Pu from lung and tissues by EU-LI-CAM(C) (**53**) was generally less than was obtained with $CaNa_3$−DTPA; kidneys of rats given EU-LI-CAM(C) (**53**) contained Pu residues about as large as those observed in studies of injected Pu.[174,175] Baboons inhaled Pu−TBP and were repeatedly injected with 3 or 30 μmol kg^{-1} of EU-LI-CAM(C) (**53**) or 30 or 100

Table 7. Relevant Bond Lengths and Angles for the Cerium(IV) Complexes of Me-3,2-HOPO: Cerium(IV) Tetrakis(Me-3,2-HOPO), Ce[5-LI(Me-3,2-HOPO)]$_2$, Ce[5-LIO(Me-3,2-HOPO)]$_2$·2MeOH, and Ce[5-LIO(Me-3,2-HOPO)]$_2$·4H$_2$O[a]

Ce^{IV}(Me-3,2-HOPO)$_4$ Bond Lengths (Å)				Ce^{IV}[5-LI(Me-3,2-HOPO)]$_2$ Bond Lengths (Å)			
Ce1−O1	2.470(6)	Ce1−O5	2.386(5)	Ce1−O1	2.378(3)	Ce1−O2	2.303(3)
Ce1−O2	2.253(5)	Ce1−O6	2.288(6)	Ce1−O6	2.408(3)	Ce1−O5	2.301(3)
Ce1−O3	2.401(5)	Ce1−O7	2.462(6)	Ce1−O7	2.426(3)	Ce1−O8	2.291(3)
Ce1−O4	2.310(6)	Ce1−O8	2.306(6)	Ce1−O12	2.397(3)	Ce1−O11	2.333(3)
Bond Angles (deg)				Bond Angles (deg)			
O1−Ce1−O2	65.9(2)	O1−Ce1−O4	74.6(2)	O1−Ce1−O2	67.6(1)	O1−Ce1−O5	120.8(1)
O1−Ce1−O8	73.0(2)	O5−Ce1−O8	77.6(2)	O5−Ce1−O6	67.3(1)	O2−Ce1−O6	109.0(1)
O3−Ce1−O4	66.5(2)	O1−Ce1−O5	85.0(2)	O7−Ce1−O8	67.2(1)	O7−Ce1−O11	117.3(1)
O2−Ce1−O7	157.3(2)	O4−Ce1−O8	81.2(2)	O11−Ce1−O12	67.0(1)	O8−Ce1−O12	117.5(1)
O5−Ce1−O6	67.5(2)	O2−Ce1−O3	81.7(2)	O1−Ce1−O7	73.4(1)	O2−Ce1−O7	73.5(1)
O3−Ce1−O6	72.3(2)	O3−Ce1−O7	80.9(2)	O1−Ce1−O12	76.8(1)	O2−Ce1−O8	83.5(1)
O7−Ce1−O8	65.8(2)	O2−Ce1−O6	80.5(2)	O5−Ce1−O8	80.0(1)	O6−Ce1−O11	74.8(1)
O4−Ce1−O5	154.1(2)	O6−Ce1−O7	80.4(2)	O5−Ce1−O11	78.6(1)	O6−Ce1−O12	75.5(1)
Ce(IV)[5-LIO(Me-3,2-HOPO)]$_2$·2CH$_3$OH Bond Lengths (Å)				Ce(IV)[5-LIO(Me-3,2-HOPO)]$_2$·4H$_2$O Bond Lengths (Å)			
Ce1−O1	2.395(3)	Ce1−O2	2.290(3)	Ce1−O1	2.414(2)	Ce1−O2	2.313(1)
Ce1−O7	2.387(3)	Ce1−O6	2.308(3)	Ce1−O7	2.431(2)	Ce1−O6	2.277(1)
Ce1−O8	2.424(3)	Ce1−O9	2.305(3)	Ce1−O8	2.387(2)	Ce1−O9	2.292(1)
Ce1−O14	2.422(3)	Ce1−O13	2.282(3)	Ce1−O14	2.405(2)	Ce1−O13	2.291(1)
Bond Angles (deg)				Bond Angles (deg)			
O1−Ce1−O2	67.21(10)	O1−Ce1−O7	80.29(10)	O1−Ce1−O2	66.96(7)	O1−Ce1−O7	88.45(6)
O6−Ce1−O7	67.33(9)	O2−Ce1−O6	78.22(10)	O6−Ce1−O7	67.22(6)	O2−Ce1−O6	74.15(6)
O8−Ce1−O9	66.48(10)	O8−Ce1−O14	88.6(1)	O8−Ce1−O9	67.74(6)	O8−Ce1−O14	83.97(6)
O13−Ce1−O14	66.91(10)	O9−Ce1−O13	78.1(1)	O13−Ce1−O14	67.33(6)	O9−Ce1−O13	73.44(6)
O1−Ce1−O14	79.8(1)	O1−Ce1−O6	97.8(1)	O1−Ce1−O14	74.61(6)	O1−Ce1−O6	117.71(6)
O2−Ce1−O8	97.8(1)	O2−Ce1−O7	128.3(1)	O2−Ce1−O8	143.16(6)	O2−Ce1−O7	115.98(6)
O6−Ce1−O9	71.14(10)	O8−Ce1−O13	126.1(1)	O6−Ce1−O9	83.46(6)	O8−Ce1−O13	119.53(6)
O7−Ce1−O13	73.58(10)	O9−Ce1−O14	111.5(1)	O7−Ce1−O13	135.17(6)	O9−Ce1−O14	109.53(6)

[a] Estimated standard deviations in the least significant figure are given in parentheses.[130]

μmol kg^{-1} of CaNa$_3$−DTPA (10 ligand injections in 28 days starting at 30 min). Lung Pu was not influenced by either treatment. Treatment with 30 μmol kg^{-1} of EU-LI-CAM(C) (**53**) reduced liver and bone Pu to 20% and 80% of the respective levels achieved with CaNa$_3$−DTPA, but 3 μmol kg^{-1} was less effective than 30 μmol kg^{-1} of CaNa$_3$−DTPA. The kidneys of the baboons given EU-LI-CAM(C) (**53**) contained significant Pu residues.[188,197,316]

There was no evidence of toxicity in liver or kidneys of rats given repeated injections (30 μmol kg^{-1}) of EU-LI-CAM(C) (**53**), in agreement with earlier findings in mice[159] and dogs;[185] however, a toxic response was observed in the kidneys of baboons given ten 30 μmol kg^{-1} injections of EU-LI-CAM(C) (**53**). Blood chemistry indicated renal insufficiency, and there was vacuolization of proximal renal tubule cells. A reduction in the EU-LI-CAM(C) (**53**) dose, its combination with CaNa$_3$−DTPA, or the addition of a bicarbonate infusion reduced the number and size of the vacuoles, and the adverse renal reaction was slowly reversible.[188,197] Several possible causes for this unusual renal toxic response, which appeared to be specifically related to the species and/or the EU-LI-CAM(C) (**53**) preparation, have been suggested.[164]

Experiments were undertaken to identify the cause of the renal actinide deposits in the animals given EU-LI-CAM(C) (**53**) as opposed to the behavior of the original preparation in mice. It was found that the Pu(IV)−EU-LI-CAM(C) (Pu(IV)−**53**) chelate, injected into rats and mice, was not completely eliminated. The ligand behavior was species specific, and, on average, 28% and 17% respectively of the injected Pu was retained at 24 h, and the kidneys contained respectively 16% and 4.8%. Rats intratracheally intubated with the Pu(IV)−EU-LI-CAM(C) (Pu(IV)−**53**) chelate excreted only 46% of the intubated Pu in 7 days, and 19% of the intubated Pu was retained in the lungs.[188] Neither EU-LI-CAM(C) (**53**)[315] nor the original 3,4,3-LI-CAM(C) (**53**)[159,164] had been completely deprotected in the final synthetic step, and as a consequence, some or all of the 4-carboxyl groups were still esterified, thereby increasing ligand lipophilicity. EU-LI-CAM(C) (**53**) was fractionated, and 3,4,3-LI-CAM(C) (**53**) was resynthesized. The results of new Pu removal studies using purer, more soluble preparations differed little from the results obtained with the more lipophilic forms.[164,173,175] Ligand insolubility had suppressed chelate formation, but the major cause of Pu deposition in the kidneys, and perhaps its inability to solubilize a lung deposit, was instability of Pu(IV)−3,4,3-LI-CAM(C) (Pu(IV)−**53**) at the lower end of the range of physiological pH. As later confirmed *in vitro* by removal of Pu from Pu−Tf in horse serum, 3,4,3-LI-CAM(C) (**53**) does not stably chelate Pu(IV) at pH < 6, while the reaction is complete at pH 7.4.[175]

The biological data suggested that even the most soluble and acidic tetrakiscatecholate ligand, 3,4,3-LI-CAM(S) (**42**), structurally and functionally analo-

gous to 3,4,3-LI-CAM(C) (**53**), was a functionally hexadentate ligand.[159,167] That suspicion was verified chemically. Over the pH range 7.6−12, Pu(IV) deprotonates only six of the eight available phenolic groups, and Pu(IV)−3,4,3-LI-CAM(C) (Pu(IV)−**53**) is a functional triscatecholate. As the pH declines below 7.6, Pu binding by 3,4,3-LI-CAM(C) (**53**) is progressively less stable, more protonated species dominate, and the Pu chelate formed at higher pH dissociates, releasing Pu. Thus, while the linear multidentate CAM systems were advantageous in that they did not compete for divalent metals as much as DTPA, at pH 7.4, 3,4,3-LI-CAM(C) (**53**) is functionally hexadentate and at pH 6.5 it is mainly tetradentate,[22,164,317] making it unsuitable for use as a therapeutic agent for Pu, except perhaps as part of a ligand mixture.[172]

Because further increasing the acidity of the LI-CAM ligands via the introduction of strongly electron-withdrawing nitro groups into the aromatic rings had been found to result in ligands that were acutely active poisons,[149] new directions in developing sequestering agents were needed.

6.5. Terephthalamide (TAM)-Based Ligands

New ligand backbones had been prepared to improve octadentate actinide binding by attaching metal-binding units to H(*n*,*m*)-(PENTEN) backbones, which are partially preorganized for binding.[258] Synthetic procedures were well established for catecholate ligands, and CAM(C) and terephthalamide (TAM) binding units were used for biological evaluation of these backbones.[161] In addition, the oral effectiveness of 3,4,3-LI-CAM(C) (**53**) was an incentive to try to improve catecholate binding units before abandoning them altogether. Ligands incorporating TAM binding groups (4-LI-MeTAM (**63**), for example) were prepared, placing a somewhat more acidic amide with good H-bonding properties, instead of a carboxyl group, at the 4-position on the CAM ring;[284] the Fe(III) complexes with TAM units at pH 7.4 are more stable than those formed with any other investigated group.[286]

Several of these ligands were evaluated for *in vivo* Pu chelation in mice.[161] Pu chelation *in vivo* was nearly the same for the octadentate ligands with 3,4,3-LI and H(2,2) backbones containing the same metal-binding unit. Given orally or injected, reductions of Pu in all tissues and body were somewhat greater than, or the same as, those obtained with oral or injected 3,4,3-LI-CAM(C) (**53**). The Pu chelate of 3,4,3-LI-MeTAM (**76**) was excreted without depositing a Pu residue in the kidneys, but the instability of Pu(IV)−H(2,2)-MeTAM (Pu(IV)−**69**) at low pH (kidney Pu 115% of control) resembled that of 3,4,3-LI-CAM(C) (Pu(IV)−**53**) (kidney Pu 125% of control). Ligands containing larger TAM units are sparingly soluble at pH ≤ 8; they were less effective for *in vivo* Pu chelation than their more soluble analogues, and their chelates were less efficiently excreted and less stable at the pH of the kidneys.[161] Although reductions of liver and body Pu by H(2,2)-MeTAM (**69**) were significantly greater than those obtained with $CaNa_3$−DTPA, the Pu chelate was no more stable than that with 3,4,3-LI-CAM(C) (**53**) at pH < 7.4. The octadentate MeTAM ligands are lipophilic and not very soluble at pH < 8, and in solution are readily air oxidized; they have not been investigated further.[161]

6.6. Hydroxypyridinone (HOPO)-Based Plutonium-Sequestering Agents

The first generation of actinide-sequestering agents based on siderophores contained synthetic catecholate derivatives or derivatives of DFOM, and the most efficacious of these ligands were only marginally more effective, and in some cases less effective, than $CaNa_3$−DTPA.[149,159,161] Bidentate functional groups more acidic than catechol or hydroxamic acid were needed to achieve full-octavalent coordination with actinide(IV) ions in dilute aqueous solution at physiological pH. Investigations shifted to studies focusing on ligands using a different chelating subunit, the less common cyclic hydroxypyridinonate (HOPO) metal-binding unit found in a few siderophores and plant products.[287,318,319] Several octadentate and tetradentate HOPO ligands have been designed and synthesized in the pursuit of systems that will best fit the coordination requirements of Pu(IV) especially meeting the key point of forming 1:1 or 1:2 complexes.[150,160,167]

The three HOPO isomers are structural and electronic analogues of both hydroxamic acid and catechol.[287] Like hydroxamic acids, the hydroxypyridinones are monoprotic acids that bind to metal ions by two oxygen atoms. There is substantial delocalization in the bonding of the metal−hydroxypyridinonate complexes. These factors make the hydroxypyridinones good chelators for hard metal ions such as lanthanides and actinides. The cyclic HOPO groups are more acidic than aliphatic hydroxamic acids.[287] The 1,2-HOPO group is ionized at pH > 5; ligands containing that functional group were expected to be soluble and fast-acting at pH 7, and their metal complexes were expected to be stable over the entire range of physiological pH, 5−8. In fact, since they selectively display a high affinity for ferric and other metal ions of charge/radius ratio comparable to that of Pu(IV) within the physiological pH range, the HOPOs are uniquely suitable for the design of actinide-sequestering agents. In addition, the formation constants of Fe(III)−HOPO complexes are 4−9 orders of magnitude greater than those formed with biologically essential divalent cations, another essential quality.[320]

The first requirement for the development of multidentate actinide-sequestering agents based on hydroxypyridinones was the derivatization of the bidentate prototype hydroxypyridinone units to provide a point of attachment such that these units could be appended to suitable molecular scaffolds. There are two different ways to modify the bidentate hydroxypyridinones. The first is replacement of the hydrogen atom attached to the ring nitrogen to make a point of linkage (Figure 10). This approach has been used in the synthesis of some multidentate 3,2- and 3,4-HOPO ligands; however, the geometry of such derivatized ligands is not appropriate for making discrete metal complexes. The fact that such ligands

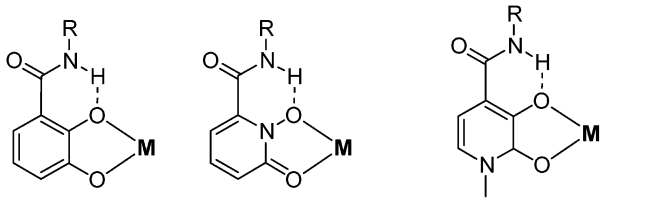


Figure 10. Metal coordination complexes of CAM, 1,2-HOPO, and Me-3,2-HOPO.

form oligomeric metal complexes at physiological pH indicates that they are not good multidentate sequestering agents for metal ions.

To synthesize useful multidentate 1,2- and 3,2-HOPO ligands, the ring carbon atom ortho to the ligating phenolic groups was functionalized by addition of a carboxyl group, and an amide linkage was then made to a suitable amine backbone.[160,167,321] The resultant ligands have favorable coordination geometries and are more strongly acidic, and therefore have increased solubility and complexation ability. A very important feature of (Me-3,2-HOPO)-4-ylamide and 1,2-HOPO-6-ylamide ligands (abbreviated as Me-3,2-HOPO and 1,2-HOPO ligands below) is that, as observed in the catecholamide complexes, strong hydrogen bonds between the amide proton and adjacent oxygen donor enhance the stability of their metal complexes.[160] X-ray crystal structures of metal complexes of these ligands, discussed elsewhere in this work as analogues of the Pu(IV) system, exhibit this hydrogen bonding.[130,322]

Alternatively, a hydroxy group may be introduced on the 5-position of 3,4-HOPO, and this can be used to form an attachment to a molecular scaffold via an ether linkage. The advantage of this approach is not only that it provides multidentate ligands with proper coordination geometry, but also that the metal complexes formed are further stabilized by hydrogen bonding between the amide hydrogen and the phenolic oxygen donor, as in the case of metal complexes with catecholamides. Furthermore, the introduction of carboxyl, as an electron-withdrawing group, stabilizes the HOPO ring system against reduction or oxidation.

Tetradentate 3-LI(1,2-HOPO) (**108**), the first HOPO ligand synthesized, was as effective for *in vivo* Pu chelation in mice as hexadentate 3,4,3-LI-CAM(S) (**42**) and left no Pu residue in the kidneys.[167,317] Three additional linear ligands containing 1,2-HOPO were prepared: two hexadentate ligands and the octadentate ligand, 3,4,3-LI(1,2-HOPO) (**112**). Reductions of Pu in the skeleton and all soft tissues including kidneys of mice by those octadentate 1,2-HOPO ligands and by the Fe(III) and Zn(II) complexes of 3,4,3-LI(1,2-HOPO) (**112**) were markedly and significantly superior to those obtained with an equimolar amount of $CaNa_3$−DTPA. The great stability of Pu(IV)−3,4,3-LI(1,2-HOPO) (Pu(IV)−**112**) and the great selectivity of 3,4,3-LI(1,2-HOPO) (**112**) for Pu(IV), relative to Fe(III), were shown by the efficient displacement of Fe(III) by Pu(IV). Stability of the Pu(IV) chelate at low pH was shown by the absence of Pu residues in the kidneys. Enhanced Pu excretion was dependent on the denticity of the 1,2-HOPO ligands; injected ip promptly in mice, octadentate 3,4,3-LI(1,2-HOPO) (**112**) promoted excretion of 73% of the injected Pu, while hexadentate 3,4-LI(1,2-HOPO) (**112**) promoted 58%, implying that all four HOPO groups of 3,4,3-LI(1,2-HOPO) (**112**) participate in binding Pu(IV). Injected ip at 24 h or given orally, 3,4,3-LI(1,2-HOPO) (**112**) was markedly and significantly more effective than $CaNa_3$−DTPA. Reduction of body Pu to 50% of control was achieved with a dose of 3,4,3-LI(1,2-HOPO) (**112**) (ligands injected ip at 1 h), 1/100 of the required dose of $CaNa_3$−DTPA.[165]

The improvement in *in vivo* results with the HOPO ligands as compared to the CAM(S) ligands closely parallels their relative binding properties. Plutonium removal by the CAM(S) ligands increased across the series mono < bis < tris = tetrakis.[159] Since the Pu(IV) ion is expected to be eight-coordinate, the absence of improvement from tris to tetrakis was suprising; however, thermodynamic solution studies demonstrated that, at neutral pH, only three of the catechol groups will deprotonate and bind to Pu(IV), rendering the tetrakis ligand functionally hexadentate.[22] The greater acidity of the HOPO ligands allows the ligands with these chelating subunits to form eight-coordinate complexes that are stable at physiological pH, which in turn should lead to increased selectivity for Pu(IV).[287,321] As illustrated in Figure 11, the efficacy of the HOPO ligands greatly increases across the series mono < bis < tris < tetra, with the largest change between the mono- and bis-substituted ligands.[167]

The 3,4,3-LI(1,2-HOPO) (**112**) ligand was chosen for extended study by the EULEP group. Pu(IV) sequestration was investigated in growing and adult rats by the same nuclide exposure and chelation therapy protocols used previously to evaluate 3,4,3-LI-CAM(C) (**53**).[118,176−178,180−182,191−196,199] 3,4,3-LI(1,2-HOPO) (**112**) was markedly superior to $CaNa_3$−DTPA for reduction of Pu in tissues (including kidneys and lungs) in all of the combinations of nuclide exposure (e.g., iv injection, inhalation) and treatment protocols (single or repeated ip, im, or s.cut. injection, oral administration, or infusion). The oral efficacy of 3,4,3-LI(1,2-HOPO) (**112**) was confirmed.[118,182] Combined therapy with 3,4,3-LI(1,2-HOPO) (**112**) and $CaNa_3$−DTPA was not more effective than treatment with the HOPO ligand alone.[118,176] 3,4,3-LI(1,2-HOPO) (**112**) was more effective than $CaNa_3$−DTPA for reducing inhaled Pu in lung and tissues when the ligand (30 μmol kg^{-1}) was injected promptly after inhalation of the ^{239}Pu−TBP complex.[195,196]

The ability of 3,4,3-LI(1,2-HOPO) (**112**) to mobilize and divert to excretion ^{238}Pu, ^{239}Pu, or ^{238}Pu−TBP infiltrated by im or s.cut. injection in rats to simulate contaminated wounds was also investigated.[177−180] The 3,4,3-LI(1,2-HOPO) (**112**) ligand was effective to very effective for reducing Pu introduced as nitrate, both at the wound site and in tissues for either mode of exposure and all treatment protocols, whether by prompt or delayed local injection of 3 or 30 μmol kg^{-1},

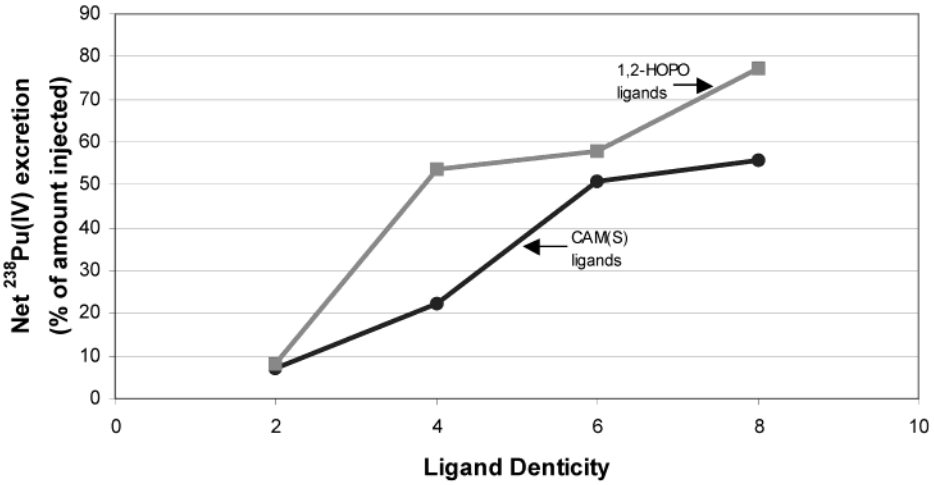


Figure 11. Net excretion in 24 h of ^{238}Pu (total excretion − control excretion) promoted in mice injected ip with 30 μmol kg^{-1} of a ligand after an iv injection of ^{238}Pu(IV) citrate by structurally analogous CAM(S) [LI-CAM(S) = Tiron, 2-LI-CAM(S) (**28**), 3,4-LI-CAM(S) (**32**), 3,4,3-LI-CAM(S) (**42**)] and 1,2-HOPO ligands [1,2-HOPO = 1,2-HOPO-6-CO_2H, 3-LI-(1,2-HOPO) (**108**), 3,4-LI(1,2-HOPO) (**111**), 3,4,3-LI(1,2-HOPO) (**112**)].[167]

with or without follow-up repeated ip injections, infusion, or oral administration by gavage or in drinking water. In experiments comparing both ligands, 3,4,3-LI(1,2-HOPO) (**112**) was as effective as or markedly more effective than $CaNa_3$−DTPA for reducing Pu at the wound site and in tissues. While the 3,4,3-LI(1,2-HOPO) (**112**) was more efficacious than $CaNa_3$−DTPA for mobilizing an equal amount of ^{239}Pu radioactivity (300 times larger mass of Pu than ^{238}Pu) from a wound site and from tissues, both ligands were somewhat less effective at that smaller ligand:metal molar ratio.[177,178,180] Rats with im or s.cut. wounds infiltrated with the ^{238}Pu−TBP complex were treated with 3,4,3-LI(1,2-HOPO) (**112**) or $CaNa_3$−DTPA (30 μmol kg^{-1}) promptly by one local infiltration or iv injection, and 3,4,3-LI(1,2-HOPO) (**112**) was significantly more effective for mobilizing Pu from the wound site and for reducing Pu in tissues for both exposure modes and both treatment protocols. Unfortunately, the efficacies of both ligands for mobilization from the wound site of Pu, introduced as ^{238}Pu−TBP, were less than those for mobilization of Pu introduced as Pu nitrate.[194]

The original synthesis of 3,4,3-LI(1,2-HOPO) (**112**), while a highly effective ligand for Pu(IV), was difficult, the yields were low, and there were concerns about the inadequacy of the initial assessments of its acute toxicity.[167,176,199] Improvements leading to a simpler, more reliable, higher yielding synthetic procedure for 3,4,3-LI(1,2-HOPO) (**112**)[170,288] have enabled the production of sufficient product to allow for re-evaluation in the same acute toxicity protocols used in mice to investigate several ligands containing CAM(S) and Me-3,2-HOPO groups.[121,150,170] However, at the time, concerns raised by those considerations led to the preparation of a new set of 13 ligands containing the slightly less acidic hydroxypyridinone isomer, 3,2-HOPO.[160] A structural analogue of catechol, 3,2-HOPO was expected to form slightly more stable metal complexes at physiological pH than 1,2-HOPO, a structural analogue of hydroxamic acid. The N-substituted functional group, 1-Me-3,2-HOPO, was used to enhance complex stability, and the 4-position of Me-3,2-HOPO was derivatized with a carboxyl group to provide a point of attachment, through amide linkages, that placed the amide carbonyl ortho to the phenol at the 3-position—a structural relationship necessary for stable metal binding. New backbones were also introduced to determine the effect of ligand geometry on chelation. These new backbones included the following:

Tetradentate. Three linear diaminoalkanes, butylene to hexalene (**82**, **83**, **85**), to investigate Pu(IV) binding as a function of the spacing between functional groups, and more soluble five-unit diaminodiethyl ether (**84**).

Hexadentate. N-Centered tris(2-aminoethyl)amine (TREN, **86**), which provides five-unit spacing.

Octadentate. Three versions of H-shaped PENTEN, with ethylene to butylene central bridges to form ligands that provide five-unit spacing and partial preorganization for metal binding (**99**−**101**).

All 12 Me-3,2-HOPO ligands significantly reduced Pu in all tissues of mice, compared with controls. Seven Me-3,2-HOPO ligands reduced liver and body Pu significantly more than $CaNa_3$−DTPA. Five Me-3,2-HOPO ligands, given orally within minutes after the Pu injection, reduced body Pu to less than 50% of control. In contrast to ligands containing CAM(S) or 1,2-HOPO functional groups, *in vivo* Pu chelation in mice by the Me-3,2-HOPO ligands (30 μmol kg^{-1}) did not depend on denticity; rather, reductions of body Pu were nearly the same for the three most effective tetra-, hexa-, and octadentate Me-3,2-HOPO ligands, indicating that the stabilities of their Pu(IV) chelates all exceed those of Pu−Tf.[159,160,167,323] An intergroup spacing of four or five carbons, more closely mimicking the structure of EB and DFOM, appears to be optimal for Pu(IV) binding, as reductions of body Pu were significantly less for linear ligands with three- or six-carbon spacing than for linear ligands with four- or five-unit spacing. Expanding the coordination cavity of the PENTEN-based Me-3,2-HOPO ligands (i.e., **99**−**101**) by lengthening the central bridge from two- to three- or four-

carbons decreased solubility and effectiveness for *in vivo* Pu chelation.[160]

Hexadentate TREN(Me-3,2-HOPO) (**86**) was the first of the Me-3,2-HOPO ligands to be synthesized, because of synthetic ease and its potential usefulness for iron chelation.[146] Initial evaluations of *in vivo* actinide chelation in mice showed it to be nearly as effective as 3,4,3-LI(1,2-HOPO) (**112**) for reducing Pu(IV) in the soft tissues and body (30 μmol kg^{-1} injected ip at 1 h or orally at 3 min) but not as effective as 3,4,3-LI(1,2-HOPO) (**112**) when ligand injection was delayed 24 h.[156,160] The acute and subchronic toxicities of TREN(Me-3,2-HOPO) (**86**) were found to be low.[121]

Low-toxicity hexadentate TREN(Me-3,2-HOPO) (**86**) and tetradentate 5-LI(Me-3,2-HOPO) (**81**)[121] were subsequently investigated for their ability to chelate ^{238}Pu nitrate inhaled or infiltrated in wounds. The Me-3,2-HOPO ligands were about as effective for reduction of the inhaled actinides in the lungs and tissues as $CaNa_3$−DTPA, but less effective than octadentate 3,4,3-LI(1,2-HOPO) (**112**). They were more effective for reducing actinides from wound sites and tissues than $CaNa_3$−DTPA, but again, not as effective as 3,4,3-LI(1,2-HOPO).[179,180]

In mice, 5-LI- (**83**) or 5-LIO(Me-3,2-HOPO) (**84**) [30 μmol kg^{-1} dose injected ip 1 h after iv injection of ^{238}Pu(IV)] removed 82−84% of the injected Pu(IV) from mice, a much better result than that obtained with an equimolar amount of $CaNa_3$−DTPA, 67%. It is notable that, unlike the catecholamide ligands, the tetradentate Me-3,2-HOPO ligands injected at the standard dose promote as much Pu(IV) excretion as the octadentate ligands 3,4,3-LI(1,2-HOPO) (**112**) (86%) or H(2,2)-(Me-3,2-HOPO) (**99**) (81%). Apparently, the ligand concentration established in the tissues at the standard injected dose are large enough to allow the tetradentate ligands to complex Pu(IV) in competition with biological ligands; however, octadentate ligands have a 1:1 stoichiometry when binding Pu(IV), and when these latter ligands are given at a lower dose or orally, their potency for reducing Pu(IV) in animal tissues exceeds that of tetradentate or hexadentate HOPO ligands. For example, for the octadentate ligand 3,4,3-LI(1,2-HOPO) (**112**), the same degree of efficacy is observed at injected doses from 0.3 to 30 μmol kg^{-1},and it is orally active. All of the tetradentate ligands need larger doses (at least 10 times) and are not as orally active.

Five Me-3,2-HOPO ligands reported in the literature are not reviewed in detail here. These include three tetradentate linear ligands, 3-LI- (**81**), 4-LI- (**82**), and 6-LI(Me-3,2-HOPO) (**85**), determined to be toxic,[121] ME-(Me-3,2-HOPO) (**102**), which has poor solubility, and 5-LI(Me-3,2-HOPO) (**83**), which has Pu removal properties nearly the same as those of 5-LIO(Me-3,2-HOPO) (**84**).[160]

Four pairs of ligands are now available with the same backbones but different HOPO binding groups.[150] This is excellent for direct comparison of the abilities of the chelating subunits. For the tetradentate pairs, 4-LI(Me-3,2-HOPO) (**82**) and 4-LI(1,2-HOPO) (**109**), and 5-LI(Me-3,2-HOPO) (**83**) and 5-LI(1,2-HOPO (**110**), and the hexadentate pair, TREN(Me-3,2-HOPO) (**86**) and TREN(1,2-HOPO) (**116**), effectiveness for Pu removal is somewhat greater for the Me-3,2-HOPO ligands. Reductions of Pu in mouse tissues by the pair of octadentate ligands, H(2,2)-(Me-3,2-HOPO) (**99**) and -(1,2-HOPO) (**118**), are nearly the same. Reductions of Pu in the tissues, particularly the skeleton, by 4-LI(1,2-HOPO) (**109**) and TREN-(1,2-HOPO) (**116**) are not great enough to be considered remarkable. Removal of Pu by 5-LI(1,2-HOPO) (**110**) was so poor, with 48% of Pu retained, that a second synthetic batch was prepared, which verified the original disappointing result.[130,150,168]

6.7. Mixed Ligands

The first mixed ligand prepared was a decadentate dihydroxamic acid derivative of DTPA, diisopropyl-H_3-DTPA-DX.[324] Good solubility properties and an iron chelate more stable than Fe(III)−DTPA prompted its evaluation for *in vivo* Pu chelation.[117,118,165] DTPA-DX is unselective for chelation of divalent metal ions, as is DTPA, and the Zn chelate was substituted in animal studies. While reduction of skeletal Pu was less, the reduction of liver Pu was significantly greater than that by $CaNa_3$−DTPA, so that the overall amounts of Pu removed from the body were the same for both ligands.[117,165] Participation of both hydroxamate groups in the coordination of Pu was demonstrated by a major shift of chelated Pu to fecal excretion. Modest improvement of oral effectiveness was presumed to be due to somewhat greater effectiveness of DTPA-DX at low doses.[165]

Single or repeated injections of ZnNa−DTPA-DX in adult rats after inhalation or injection of Pu were less effective than those of $CaNa_3$−DTPA for removing the Pu.[117] In rapidly growing rats, a single injection or oral administration of ZnNa−DTPA-DX following injection of Pu was less effective than $CaNa_3$−DTPA.[118] Infusions of the two ligands with implanted osmotic pumps were equally effective.[118] From these studies, it was concluded that the DTPA-DX derivative offered no significant advantages as an actinide removal agent in comparison with DTPA.

New ligands were prepared to improve the kinetics of DFOM.[227] Synthetic procedures were well established for catecholate ligands, and CAM(C) and terephthalamide binding units were used for the initial evaluations of this new class of DFO-based octadentate ligands.[161] The MeTAM binding group was prepared, placing a somewhat more acidic amide with good H-bonding properties, instead of a carboxyl group, at the 4-position on the CAM ring.[284] The Fe(III) complexes with TAM units at pH 7.4 are more stable than those formed with any other CAM or HOPO binding group.[286] These new ligands were evaluated for *in vivo* Pu chelation in mice. For both DFO-CAM(C) (**56**) and DFO-MeTAM (**75**), reductions of Pu in all tissues were the same as or somewhat greater than those obtained with 3,4,3-LI-CAM(C) (**53**); reductions of liver and body Pu by DFO-MeTAM (**75**) were significantly greater than those obtained with $CaNa_3$−DTPA, and their Pu chelates were excreted without depositing Pu residues in the kidneys. Although reductions of liver and body Pu by

DFO-MeTAM (**75**) were significantly greater than those obtained with $CaNa_3$−DTPA and the Pu chelate is more stable than that with 3,4,3-LI-CAM(C) (**51**) at pH < 7.4, the octadentate DFO-MeTAM(**75**) ligand is lipophilic and not very soluble at pH < 8, and the solutions are readily air oxidized.[286]

Octadentate DFO(1,2-HOPO) (**115**) was one of the first HOPO ligands prepared.[167] When injected promptly, DFO(1,2-HOPO) (**113**) was as effective as 3,4,3-LI(1,2-HOPO) (**112**) for reducing body and tissue Pu of mice and rats, implying that all three hydroxamate groups, as well as the 1,2-HOPO group, participate in Pu binding.[165,167] However, the effectiveness of DFO(1,2-HOPO) (**113**) for *in vivo* Pu chelation was about the same as that of 3,4,3-LI-CAM(C) (**53**) when it was administered orally at 3 min or injected 24 h after Pu; the dose of DFO(1,2-HOPO) (**115**) injected 1 h after Pu, required to reduce body Pu to 50% of control, was about 1/10 of the $CaNa_3$−DTPA dose.

In additional investigations by the EULEP group, DFO(1,2-HOPO) (**115**) was evaluated in growing and adult rats, and it was found to be substantially more effective than $CaNa_3$−DTPA for reducing Pu in all tissues, when injected (30 μmol kg^{-1}, ip) promptly once or as many as five times in 3 days after iv injection of ^{238}Pu. DFO(1,2-HOPO) (**115**) was a markedly more effective ligand for Pu than $CaNa_3$−DTPA, when given orally immediately (100 μmol kg^{-1}) or infused (3 μmol kg^{-1} d^{-1}) with an osmotic pump implanted 3 min after injection of ^{233}Pu. Injected or infused, combinations of DFO(1,2-HOPO) (**115**) plus $CaNa_3$−DTPA or $ZnNa_3$−DTPA were significantly more effective for Pu removal than either ligand alone, and they achieved marked reductions in tissue and body Pu. After inhalation of a ^{233}Pu nitrate aerosol, DFO(1,2-HOPO) (**115**) was significantly less effective than $CaNa_3$−DTPA for reducing Pu in the lungs and tissues, whether injected ip promptly (30 μmol kg^{-1}, once or as many as five times in 3 days).[117,118] Although the added 1,2-HOPO unit converted relatively ineffective hexadentate DFOM to a potent octadentate ligand for circulating Pu, the weak acidity of the hydroxamic acid groups apparently prevents both DFOM and DFO(1,2-HOPO) (**115**) from competing effectively for Pu in the more acidic environment of the lungs.[287]

Octadentate DFO(Me-3,2-HOPO) (**98**) was prepared. Reductions of body and tissue Pu in mice injected with DFO(Me-3,2-HOPO) (**98**) were substantially and significantly poorer than those obtained with DFO(1,2-HOPO) (**115**), DFO-CAM(C) (**56**), or DFO-MeTAM (**75**), but better than those obtained with native DFOM.[160,161,165] Large Pu residues were present in the kidneys and bulk soft tissues (specific tissue not identified) of mice injected with DFO(Me-3,2-HOPO) (**98**), but not in those of mice injected with DFOM. Replication of the injection study verified those unusual results. Given orally, both DFO(1,2-HOPO) and DFO(Me-3,2-HOPO) (**98** and **115**) ligands promoted about the same amount of Pu excretion as 3,4,3-LI-CAM(C) (**53**) and significantly more than DFO-MeTAM (**75**) or DFOM.[160,161,165] The internal distributions of the retained Pu were different in the mice given the two HOPO ligands orally; compared with controls, DFO(1,2-HOPO) (**115**) reduced bone but not liver Pu, while DFO(Me-3,2-HOPO) (**98**) significantly reduced both liver and bone Pu and left large and significant amounts of Pu in the kidneys and soft tissues. The poor efficacy of DFO(Me-3,2-HOPO) (**98**) for *in vivo* chelation of Pu is likely to be due to its low solubility and the instability of its Pu complex in the physiological pH range.[160]

Two mixed octadentate ligands, 3,4,3-LI(diCAM-di-1,2-HOPO) (**113**) and 3,4,3-LI(tri-CAM-1,2-HOPO) (**114**), were prepared to test the following possibility: if the four functional groups act independently, mixed ligands containing the effective 1,2-HOPO group can be obtained in which toxicity is suppressed without compromising metal-binding efficiency.[166] Synthesis of the mixed ligands was exceedingly difficult, and yields were so small that metal complex structures and stabilities could not be measured. The effectiveness of the mixed ligands for Pu removal from mice was midway between those of 3,4,3-LI-CAM(C) (**53**) and 3,4,3-LI(1,2-HOPO) (**112**), and most closely resembled those of structurally or functionally hexadentate ligands.[159,166,167] The biological data suggested that the 1,2-HOPO groups were probably binding preferentially, and that at least one CAM group did not participate in binding. Synthetic difficulty and mediocre efficacy for Pu removal have limited interest in further pursuit of mixed ligands containing CAM groups.[166]

Six of the Me-3,2-HOPO ligands are as effective for promoting excretion of iv-injected Pu as an equimolar amount of 3,4,3-LI(1,2-HOPO) (**112**) when promptly injected in mice (30 μmol kg^{-1} ip at 1 h after the Pu injection).[160] On the basis of studies of Th(IV) complexes, K_{ML} for the Pu^{IV}(Me-3,2-HOPO)$_4$ complex is estimated to be 41, compared with $K_{ML} = 39$ for Pu^{IV}-(1,2-HOPO)$_4$.[323] However, linear octadentate spermine-based 3,4,3-LI(1,2-HOPO) (**112**) is superior to octadentate-branched H(2,2)-(Me-3,2-HOPO) (**99**) for reduction of Pu in the body and tissues of mice.[150] Those results suggested that the more flexible spermine backbone and the greater hydrophilicity of 3,4,3-LI(1,2-HOPO) (**112**) confer advantages for full eight-coordination of Pu(IV) and greater accessibility to Pu in tissue deposits *in vivo*, although the 1,2-HOPO functional groups are thermodynamically less potent than Me-3,2-HOPO units. It was reasoned that introduction of Me-3,2-HOPO into a spermine-based octadentate ligand would result in ligands with enhanced affinity for Pu(IV). Because the central part of such a ligand would be analogous to 4-LI(Me-3,2-HOPO) (**80**), which is severely toxic in mice,[150] and a ligand containing four Me-3,2-HOPO groups was likely to be quite lipophilic and sparingly soluble at physiological pH, the tetrameric ligand, 3,4,3-LI(Me-3,2-HOPO), was not prepared. A mixed ligand, 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), was synthesized as a reasonable compromise. In this ligand, two 1,2-HOPO units occupy the central secondary amines of the spermine scaffold in a structure analogous to the much less toxic 4-LI(1,2-HOPO) (**109**),[150] and two Me-3,2-HOPO groups are attached to the terminal primary amines.[170]

When injected promptly in mice (30 μmol kg^{-1} ip at 1 h after iv injection of Pu), the mixed ligand reduces skeleton, soft tissue, and kidney Pu as much as 3,4,3-LI(1,2-HOPO) (**112**), but it is significantly less effective for reducing liver Pu; however, the mixed ligand is significantly more effective than 3,4,3-LI(1,2-HOPO) (**112**) for Pu decorporation when injected at very low dose ($\leq$0.1 μmol kg^{-1}). Given orally to normally fed as well as to fasted mice at 3 min after a Pu injection, the two octadentate ligands are equally and highly effective for reducing Pu in the whole body and all tissues. Introduction of two Me-3,2-HOPO groups into the spermine backbone along with two 1,2-HOPO units slightly increased the stability of the resultant Pu(IV) complex at pH 7.4, the lipophilicity of the ligand, and its potential oral activity, while somewhat reducing acute toxicity at high dose.[170]

6.8. Orally Effective HOPO Ligands

The current FDA-approved drugs for chelation of internally deposited actinides, $CaNa_3$−DTPA and $ZnNa_3$−DTPA, are not orally effective at the usual clinical dose of 30 μmol kg^{-1} and are administered by injection. It would be most advantageous to have actinide-sequestering agents of greater oral efficacy, because of the ease of distribution and the importance of administering treatment soon after exposure to divert as much as possible of Pu intake to excretion prior to bone deposition. For example, industrial physicians could keep materials accessible in the event of an emergency in the work areas. Currently, our understanding of oral effectiveness is limited, and it is difficult to predict whether a ligand has high oral bioavailability or not. Factors known to influence oral effectiveness of a ligand are its absorption from the gastrointestinal tract, which is, in turn, influenced by lipophilicity, ionic state, molecular weight, and molecular shape of a ligand, and the stabilities of its actinide chelates.[94,150,160,166,325] This raised questions that could only be answered with new studies designed with oral activity in mind.

In the first tests of the oral effectiveness of the siderophore-based ligands, several octadentate ligands were administered by gastric intubation to fasted mice and rats. The ligands 3,4,3-LI(1,2-HOPO) (**112**), 3,4,3-LI-CAM(S) (**44**), 3,4,3-LI-CAM(C) (**53**), and DFO(1,2-HOPO) (**115**) all reduced total body and tissue Pu significantly compared with animals similarly treated with $CaNa_3$−DTPA and with their controls.[118,150,165,172,182] The former two ligands reduced total body Pu by the same amount as if they had been administered by ip injection.[118,165,182] These findings eventually led to improvement of the synthesis and new toxicity measurements, which confirmed the acute toxicity of 3,4,3-LI(1,2-HOPO) (**112**) at high doses.[150,167] The search for alternatives stimulated the generation of a new set of ligands containing Me-3,2-HOPO groups[150,160] and ultimately the mixed ligand, 3,4,3-LI(1,2-Me-3,2-HOPO) (**98**).[170]

Orally administered (30 μmol kg^{-1} by gavage at 3 min after iv injection of Pu), octadentate ligands containing CAM(C), CAM(S), or TAM groups and nearly all of the tetra-, hexa-, and octadentate ligands containing 1,2-HOPO and/or Me-3,2-HOPO groups substantially and significantly reduce body and tissue Pu compared with controls and promote significantly more Pu excretion than an equimolar amount of $CaNa_3$−DTPA.[150,156,160,161,165] Gastrointestinal absorption of the multidentate CAM and HOPO ligands, which appears to be independent of ligand denticity or structure, is in the range of 2−5% of the intubated amount in mice and rats. Absorptions of that order were measured for several ^{14}C-labeled HOPO ligands in rats and mice[94,147,326] and were also estimated by comparing the oral and ip-injected ligand doses needed to elicit equal amounts of net Pu excretion from rats and mice.[118,150,160,165−167,170,172,182] It was suggested that, if the absorbed fractions of those ligands were small, then their marked oral effectiveness compared with that of $CaNa_3$−DTPA was probably the result of the greater stabilities of their Pu(IV) complexes. Results from several lines of investigation support that suggestion.[118]

Eight structurally matched 1,2-HOPO and Me-3,2-HOPO ligands [4-LI-, 5-LI-, TREN-, and H(2,2)-(1,2-HOPO) (**109**, **110**, **116**, **118**) and 4-LI-, 5-LI-, TREN-, and H(2,2)-(Me-3,2-HOPO) (**82**, **83**, **86**, **99**)] were injected promptly in Pu-injected mice (30 μmol kg^{-1} ip at 1 h), and all but one HOPO ligand (5-LI(1,2-HOPO), **110**) promoted about the same amount of Pu excretion, an amount substantially and significantly greater than that achieved with an equimolar amount of $CaNa_3$−DTPA. At that injected dose, Pu removal by these ligands appeared to be independent of ligand denticity, contrary to the expected relative stabilities of their Pu(IV) complexes, that is, octadentate > hexadentate > tetradentate.[150,160,323] However, dose−effectiveness (D−E) studies with the set of eight HOPO ligands (variable doses ip injected at 1 h) showed that, at low dose ($\leq$1 μmol kg^{-1}), reduction of body and tissue Pu is clearly dependent on ligand denticity. At low doses, the octadentate HOPO ligands are more effective for Pu removal than the hexadentate or tetradentate ligands containing the same HOPO group, but even the HOPO ligands of lesser denticity are more effective for *in vivo* Pu chelation than $CaNa_3$−DTPA. On average, the injected ligand doses required to promote 45% net Pu excretion from mice in 24 h were 0.2, 3, and 10 μmol kg^{-1}, respectively, for the octadentate HOPO ligands, the hexadentate and tetradentate HOPO ligands, and $CaNa_3$−DTPA.[150]

When these same ligands were administered orally (30 μmol kg^{-1} by gavage to fasted mice at 3 min after an iv Pu injection), reductions of body and tissue Pu achieved with the octadentate ligands were significantly superior to those obtained with the HOPO ligands of lesser denticity.[150] If the absorbed fraction of an octadentate HOPO ligand or $CaNa_3$−DTPA is about 5% of the gavaged amount, an oral dose of 30 μmol kg^{-1}, 3 min after an iv Pu injection, is equivalent to about 1.5 μmol kg^{-1} injected, a dose of an octadentate HOPO ligand that is expected to promote net excretion of 70% of newly injected Pu, while the same oral dose of $CaNa_3$−DTPA is expected to promote only 12% additional Pu excretion.

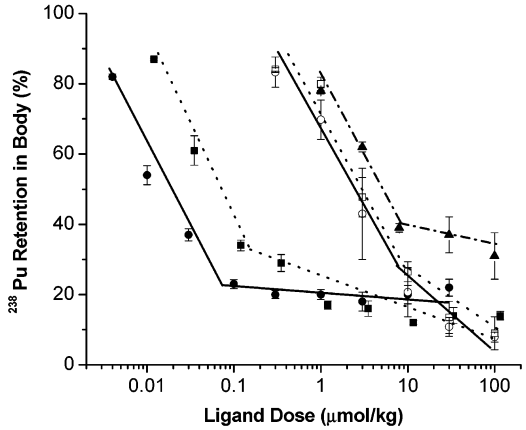


Figure 12. Dosage-dependent removal of ^{238}Pu from mice with −●−, 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), ip; ···■···, 3,4,3-LI(1,2-HOPO) (**112**), ip; −○−, 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), oral; ···□···, 3,4,3-LI(1,2-HOPO) (**112**), oral; and -·-▲-·-, $CaNa_3$−DTPA, ip. Reprinted with permission from ref 170. Copyright 2002 American Chemical Society.

The linear octadentate HOPO ligands, 3,4,3-LI(1,2-HOPO) (**112**) and 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), are the most orally active ligands for Pu(IV) yet prepared. One oral dose of either ligand as small as 5 μmol kg^{-1} (gavaged at 3 min after an iv Pu injection in fasted mice) reduced body and tissue Pu more than a 30 μmol kg^{-1} oral dose of $CaNa_3$−DTPA, and 100 μmol kg^{-1} of the HOPO ligands orally diverted 90% of the iv-injected Pu to excretion in 24 h, a result not achieved with the same amount of $CaNa_3$−DTPA injected ip at 1 h.[170] In Figure 12, the efficacies for the total body reduction of Pu of 3,4,3-LI(1,2-HOPO) (**112**) and 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), injected ip or administered orally, over the dose range 0.003−100 μmol kg^{-1}, in comparison with injected $CaNa_3$−DTPA, are represented graphically. The ligand D−E is described by pairs of intersecting straight lines relating Pu retention to the logarithm of the ligand dose (μmol kg^{-1}).[150] Suitability for clinical application was further shown by the equal effectiveness of these two ligands in normally fed as well as fasted mice,[170] and even when the oral administration of these ligands was delayed for as long as 24 h after the Pu injection, significant amounts of Pu were excreted compared with controls.[147] These two octadentate HOPO ligands were repeatedly administered orally (daily for 5 days per week for 3 weeks) to fed mice starting at 4 h after an iv Pu injection. Overall, the best result was obtained with a daily oral dose of 100 μmol kg^{-1} of 3,4,3-LI(1,2-HOPO) (**112**), which reduced Pu in all tissues significantly compared with controls and reduced Pu in the skeleton and whole body significantly compared with the results obtained with mice similarly treated with 100 μmol kg^{-1} of the mixed HOPO ligand or 300 μmol kg^{-1} of $CaNa_3$−DTPA.[147]

The octadentate HOPO ligands have an additional advantage as oral Pu(IV) chelators: they are selective for Pu(IV). The stabilities of their Pu(IV) complexes greatly exceed those of their analogous Fe(III) complexes, while the stabilities of the 1:1 Fe(III) and Pu(IV) complexes with the hexadentate and tetradentate HOPO ligands are nearly the same.[130,287,323] The selectivity of the octadentate HOPO ligands for Pu(IV) was demonstrated *in vivo* by administering the ferric complexes of the HOPO ligands to mice by prompt injection or orally. In each of those protocols, treatments with the ferric complexes reduced body and tissue Pu by nearly the same amounts as the same doses of the free ligands, indicating little interference by circulating or dietary iron with Pu(IV) chelation.[150]

6.9. Ligand Toxicity

The potential clinical usefulness of new ligands for the actinides rests mainly on two criteria: the ligands must be more efficacious for *in vivo* actinide chelation than $CaNa_3$−DTPA and must be of acceptably low toxicity at effective dose. Therefore, it is impractical to expend effort on investigation of ligands which, even though effective, are toxic at effective dose. Acute toxicities in mice were investigated for 13 octadentate siderophore-based ligands and two ferric complexes with potential as chelators for Pu, seven hexadentate ligands with potential as chelators for trivalent actinides, lanthanides, and iron, and 14 tetradentate ligands and one ferric complex of chemical interest or with potential as chelators for U(VI). Summaries of the results for 27 of those ligands and the two ferric complexes of octadentate ligands have been reported.[121,149,150,157,159,161,167,170]

The acutely toxic siderophore-based ligands cause primarily a toxic (i.e., chemical) nephrosis, which results in damage and/or death of proximal renal tubule cells, water retention in and swelling of the kidneys, and an elevated level of non-protein nitrogen (mainly urea) in the blood (BUN). Most of the observations of renal toxicity were made several days after the first ligand administration, at which time the degree of kidney damage could only be judged by the progress of the repair and replacement processes, that is, by the presence and amount of renal cortical tissue that contained atypical flat replacement tubule cells or had become fibrotic.

In addition to variable amounts of kidney damage, hepatic cell damage was noted in mice given five of the seven ligands composed of CAM(S) groups.[121,149,326] Severe local inflammation was noted in mice injected s.cut. with ≥100 μmol kg^{-1} of 4-LI- (**63**) or 5-LI-MeTAM (**64**) or ≥500 μmol kg^{-1} of s.cut. or im-injected 3,4,3-LI(1,2-HOPO) (**112**).[150,187]

The acute toxicity classifications are defined as follows:

Absent to Mild Toxicity. No deaths; no changes in organ weights or BUN; minimal or no transient changes in microscopic tissue structures.

Moderate Toxicity. Evidence of kidney and/or liver damage at 11 days; enlarged kidneys and/or liver; elevated BUN and/or abnormal microscopic kidney and/or liver structure, returns to nearly normal function and structure at 21 days.

Severe Toxicity. Acute deaths; grossly enlarged kidneys and elevated BUN; among 21-day survivors, some unrepaired tissue damage, a still elevated BUN, and replacement of some unrepaired kidney and/or liver tissue with nonfunctional fibrous tissue.

Table 8. Classification for Acute Toxicity of Multidentate Siderophore-Based Ligands[a,b]

	metal-binding group				
backbone	CAM(C)	1,2-HOPO	Me-3,2-HOPO	MeTAM	CAM(S)
		Tetradentate			
3-LI		mod	tox	tox	tox
4-LI	low	low	tox	tox	low
5-LI	low	low	low		
5-LIO			low		
6-LI			tox[c]		
		Hexadentate			
3,4-LI	low[c]	mod			tox
ME		tox			tox[c]
TREN		low	low		
		Octadentate			
3,4,3-LI	low	mod	mod[d]		mod
DIP-3,4,3-LI					mod[c]
4,4,4-LI					tox
DFO		low		low	
H(2,2)		tox	tox	low[c]	
H(3,2)			tox[c]		
H(4,3)			tox[c]		
		Ferric Complexes			
Fe(III)-4-LI			mod[c]		
Fe(III)-3,4,3-LI		low			

[a] tox, severly toxic; mod, moderately toxic; low, toxicity absent to mild. [b] References 149, 150, 155, 159, 161, 167, and 170. [c] Unpublished results. [d] Mixed ligand 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**).

Table 8 summarizes the assignments to toxicity classes (toxic, moderate, low) of the ligands and ferric complexes evaluated for acute toxicity in mice. Unpublished results of toxicity testing have been used to classify the toxicities of the following ligands for inclusion here: severe [ME-CAM(S) (**36**) and 6-LI-(**85**), H(3,2)- (**100**), and H(4,2)-(Me-3,2-HOPO) (**101**)]; moderate [bis(isopropyl)-3,4,3-LI-CAM(S) (**43**) and Fe(III)−4-LI(Me-3,2-HOPO) (Fe(III)−(**82**)]; and absent to mild [DFO-MeTAM (**75**), 3,4-LI-CAM(C) (**52**)].[326] Other investigators have reported observations relevant to the acceptably low toxicity of 3,4,3-LI(1,2-HOPO) (**112**)[176,199,327] at effective dose and the unsuitability of 3,4,3-LI-CAM(C) (**51**) for *in vivo* Pu chelation.[160,172−174,176,177,183,188,197,198,200,316] Both the structures of the ligand backbones and the properties of the metal-binding groups appear to contribute to ligand toxicity. The backbones most often associated with toxic ligands are ME (mesitylene), 3-LI, 4-LI, 6-LI, and H(2,2). The backbones most often associated with moderate to low toxicity ligands are 5-LI, 5-LIO, TREN, DFO, 3,4-LI, and 3,4,3-LI.

The ligands that were investigated for acute toxicity contained five different metal-binding groups: CAM(S), CAM(C), 1,2-HOPO, MeTAM, or Me-3,2-HOPO. The contributions of the metal-binding groups to ligand toxicity can be assessed by comparing the toxicities of the ligands with the same backbone but containing a different binding group. The matrix of ligands that were studied for toxicity (Table 8) includes five backbone structures that were used as scaffolds for at least three ligands with different binding groups: 4-LI, 5-LI, or 5-LIO, 3,4-LI, 3,4,3-LI, and H(2,2). Inspection of the toxicity classifications of the ligands with these backbones suggests that, based on its binding group, the likelihood that it will be toxic increases in the order CAM(C) < 1,2-HOPO < MeTAM = Me-3,2-HOPO < CAM(S).

Administration of severely toxic 4-LI(Me-3,2-HOPO) (**82**) or H(2,2)-(Me-3,2-HOPO) (**99**) or moderately toxic 3,4,3-LI(1,2-HOPO) (**112**) as ferric complexes nearly eliminated their toxicities, while the efficacies of the ferric complexes of the octadentate ligands for *in vivo* Pu chelation were almost the same as those of the free ligands. The findings suggest that the renal toxicities of these, and probably other similar ligands containing powerful iron-binding groups, involve removal of, or interference with, essential iron in or on the surfaces of renal tubule cells. The toxicities of the tetradentate ligands with the 4-LI backbone (four of five severely toxic) and those with the 5-LI or 5-LIO backbone (five of six, toxicity absent to mild) are markedly different. However, the only difference between those ligands is the one unit (methyl or ether oxygen) of intergroup chain length, indicating that ligands with backbones incorporating the 4-LI spacing are structurally suited for specific binding in or on the renal tubule cells that results in the blockage of normal functions.[121,147,150]

That possibility was addressed by pharmacokinetic investigations with six ^{14}C-labeled multidentate ligands containing Me-3,2-HOPO and/or 1,2-HOPO and also $CaNa_3$−[^{14}C]DTPA. Renal uptake and retention were assessed by calculating the AUC_k for the kidneys, where AUC_k is the area under the curve relating the percent of iv-injected ^{14}C in the kidneys to time after injection from 1 min to 24 h. Renal toxicity was positively and highly correlated with AUC_k. For the two toxic ligands, 4-LI(Me-3,2-HOPO) (**82**) and H(2,2)-(Me-3,2-HOPO) (**99**), AUC_k was (1−3) × 10^4 %-min; for the two moderately toxic ligands, 3,4,3-LI(1,2-HOPO) (**112**) and 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), AUC_k was about 4.2 × 10^3 %-min; and for the two low-toxicity ligands, 5-LIO(Me-3,2-HOPO) (**84**) and TREN(Me-3,2-HOPO) (**86**), as well as $CaNa_3$−DTPA, AUC_k was (0.56−1.4) × 10^3 %-min.[147] A

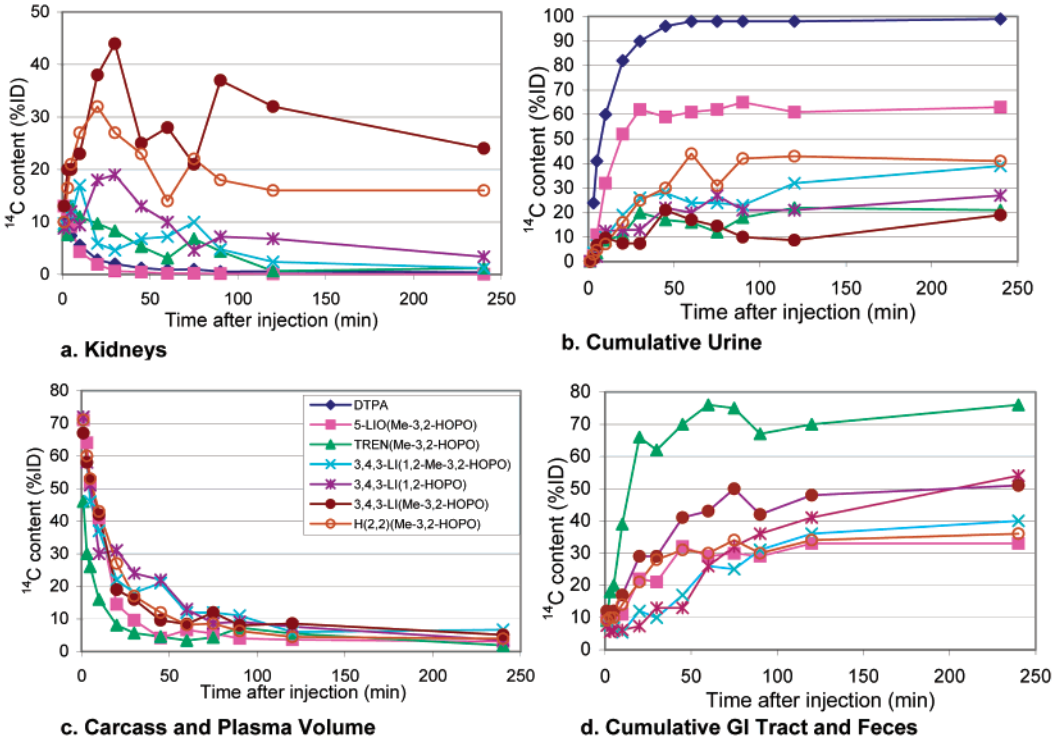


Figure 13. Uptake and retention over 240 min of iv-injected ^{14}C-labeled HOPO ligands and $CaNa_3$−DTPA (30 μmol kg^{-1} total ligand) in (a) kidneys, (b) cumulative urine, (c) carcass and plasma volume, and (d) cumulative GI tract and feces. DTPA is omitted from (c) and (d) because 99% of the ligand is excreted in urine after 240 min. All of the symbols are the same as shown in Figure 13c.[147,326]

comparison of the uptake and retention of ^{14}C-labeled samples of these HOPO-based ligands is shown in Figure 13.

All five of the metal-binding groups investigated form stable tris-Fe(III) complexes at physiological pH,[286,287,328] but the relative toxicities of the ligands that contain these groups are not correlated with the stabilities of their Fe(III) complexes. The relative toxicities of four of the five binding groups (hydrophilic CAM(S) is the exception) correlate with their lipophilicity, with CAM(C) being the least and Me-3,2-HOPO the most lipophilic.

Taken all together, the pattern of the relative toxicities of the siderophore-based ligands suggests that, while all five metal-binding groups are capable of binding essential iron in the kidneys, only those with backbone structures particularly suited to presenting the binding groups to the specific kidney structure(s) would cause sufficient Fe(III) immobilization to elicit a toxic response. The contribution of ligand lipophilicity to renal toxicity is unclear, but poor solubility in the tubular urine as it is acidified and becomes more concentrated[329] could amplify renal toxicity by causing nonspecific binding.

6.10. Comparison of Efficacy for Pu Sequestration

During a period of about 25 years, this biomimetic model for actinide-sequestering agents based on siderophores has led to the preparation of several promising, highly selective agents for *in vivo* chelation of Pu(IV)-containing hydroxypyridinonate (1,2-HOPO or Me-3,2-HOPO) metal-binding units and to the determination of trends in their behavior.[150] Tests of their efficacies in combination with the results of toxicity testing have provided several leads toward new treatments for Pu contamination.

After iv injections of Pu, the efficacy of chelation treatment is determined in large part by the effective ligand dose that can reach blood and extracellular fluids and the availability of the actinides for chelation, which, in turn, is a function of the amount of time elapsed since the introduction of the actinides into the body.[150,182] Thus, the ligand concentration established in the tissues must be large enough to allow ligands to complex Pu(IV) in competition with biological ligands. The octadentate ligands have a 1:1 stoichiometry when binding Pu(IV), and when these are given at a low dose or orally, their potency for reducing Pu(IV) in animal tissues exceeds that of tetradentate or hexadentate HOPO ligands. For example, in mice, the same high degree of efficacy of the octadentate ligand 3,4,3-LI(1,2-HOPO) (**112**) is observed at injected doses from 0.3 to 30 μmol kg^{-1}, and it is orally effective. To achieve the same amount of body Pu reduction, larger doses of the tetradentate ligands are required (at least 10 times more), and they are not as orally active.

In vitro, denticity was the major factor underlying the abilities of the HOPO ligands to remove Pu bound to artificial bone mineral: Pu removal was in the order octadentate > hexadentate > tetradentate.[171] In the investigations simulating wound contamination, actinide chelation by the HOPO ligands was also influenced mainly by ligand denticity, and effectiveness was in the order octadentate > hexadentate > tetradentate.[179] In the inhalation case, reduction of lung and tissue actinide by HOPO ligands was also

influenced by ligand solubility and the greater acidity of the 1,2-HOPO unit, which forms more stable metal chelates at lower pH than the Me-3,2-HOPO unit.[179,287]

For effective elimination in accident-based model situations, ligand affinity for an actinide must be great enough to solubilize hydroxides formed under the nearly neutral conditions at the wound site or the slightly acidic conditions in the lung. Reduction of tissue deposits or diversion of actinide slowly transported from a reservoir requires a ligand that is effective at low concentration. Ligand dose−effectiveness is directly related to denticity, and the octadentate HOPO ligands are much more effective at low concentration than those of lesser denticity. These same ligand dose−effectiveness relationships also underlie the greater oral effectiveness of the octadentate compared with the tetra- and hexadentate HOPO ligands.[150]

Four of the HOPO ligands, 5-LIO(Me-3,2-HOPO) (**84**), TREN(Me-3,2-HOPO) (**86**), 3,4,3-LI(1,2-HOPO) (**112**), and 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), stand out as the most promising therapeutic Pu chelators. These ligands demonstrate remarkable chelating ability, forming highly stable Pu complexes in combination with low toxicity at effective low dose. The most efficient and/or facile of the effective ligands appear to be octadentate 3,4,3-LI(1,2-HOPO) (**112**)[147,150,165,179,327] and tetradentate 5-LIO(Me-3,2-HOPO) (**84**). The 5-LIO(Me-3,2-HOPO) (**84**) and TREN(Me-3,2-HOPO) (**86**) possess the advantage of lower toxicity, and they can be administered frequently at 3 times the standard dose (100 μmol kg^{-1}) without causing unacceptable tissue damage.[121] In addition, the TREN(Me-3,2-HOPO) (**86**) has been found to be an effective *in vivo* chelator of Fe(III) and Am(III), and the latter will be discussed in detail later.

The dose−effectiveness of H(2,2)-(Me-3,2-HOPO) (**99**) for removal of Pu from the skeleton is nearly the same as that of 3,4,3-LI(1,2-HOPO) (**112**), and both are more effective at low dose than octadentate H(2,2)-(1,2-HOPO) (**118**).[150] All three octadentate HOPO ligands are 5−8 times more effective at doses 1 μmol kg^{-1} less than the two lower-denticity Me-3,2-HOPO ligands. Injected, H(2,2)-(Me-3,2-HOPO) (**99**) is toxic at high dose,[121] but orally (30 μmol kg^{-1} per day for 12 days), it was effective for Pu removal from mice and was tolerated without causing damage in the intestinal tract, liver, or kidneys.[326] The most recent development in the area of chelating agents for selective Pu removal is the octadentate, mixed HOPO ligand 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), which demonstrates excellent removal of Pu(IV) at physiological pH, with results comparable to those of octadentate 3,4,3-LI(1,2-HOPO) (**112**) or H(2,2)-(Me-3,2-HOPO) (**99**) at injected doses of 0.01−0.3 μmol kg^{-1} and when those the ligands are given orally. The effectiveness of this mixed ligand is remarkable when given orally at 30 μmol kg^{-1}: reduction of body Pu(IV) equals that obtained by injection of 10−30 μmol kg^{-1} of 3,4,3-LI(1,2-HOPO) (**112**). The oral efficacy of **97** (one feeding of 100 μmol kg^{-1} at 3 min) significantly exceeds that of any injected ligand prepared to date.[170]

6.11. Ligands for Plutonium Removal from Bone

The lack of treatments for the removal of actinides once they have been deposited on the anatomical surfaces of bone remains an unresolved problem in decorporation therapy. Such deposition leaves the contaminated individual at high risk of developing radiation-induced cancer, for which no efficient dose and risk reduction treatments are currently available. DTPA, whether in Ca or Zn chelate form, can intercept actinides released slowly from bone surfaces during normal structural remodeling, but it is not effective for extraction of actinides from bone mineral.[111,171] Ten multidentate siderophore-based ligands that were evaluated in *in vivo* studies in mice [3,4,3-LI-CAM(S) (**42**), 3,4,3-LI-CAM(C) (**53**), 5-LIO(Me-3,2-HOPO) (**84**), TREN(Me-3,2-HOPO) (**86**), H(2,2)-(Me-3,2-HOPO) (**99**), 4-LI(1,2-HOPO) (**109**), 3,4,3-LI(1,2-HOPO) (**112**), DFO(1,2-HOPO) (**115**), TREN(1,2-HOPO) (**116**), and H(2,2)-(1,2-HOPO) (**118**)] were subsequently studied in an *in vitro* system in which Pu or Am was allowed to bind to a bone mineral surrogate, calcium hydroxyapatite (HAP).[171] The ability of each ligand to solubilize the bound actinide was expressed as functions of ligand concentration and contact time. Because the mechanisms by which the actinides are bound to the bone mineral crystals are yet to be elucidated, it was not possible to predict which ligands would prove most useful for removal from bone. Several of the ligands investigated were found to be effective, markedly more effective compared with $ZnNa_3$−DTPA, which demonstrated no dissolution of Pu and only 1.4% removal of Am at a concentration of 100 μM (24−48 h contact).[171]

The most effective agents (100 μM, 24−48 h contact) for Pu extraction were, in order of decreasing efficacy, 3,4,3-LI-CAM(S) (**42**) > 3,4,3-LI-CAM(C) (**53**) > 3,4,3-LI(1,2-HOPO) (**112**) > H(2,2)-(Me-3,2-HOPO) (**99**) > DFO(1,2-HOPO) (**115**). The denticity of the test ligands would appear to be the most important factor underlying effective Pu removal in this *in vitro* model system, in agreement with the results obtained *in vivo*.[154,160,167] The five most effective ligands for solubilizing Pu bound to bone mineral are octadentate. The specific properties of a ligand's functional groups would also be important in its effectiveness for removing Pu from bone mineral. By analogy to their Fe(III) complexes, the affinities at pH 7.2 of the functional groups of these octadentate ligands for "hard" metal ions is expected to be in the order CAM(S) > CAM(C) > Me-3,2-HOPO ≥ hydroxamate > 1,2-HOPO.[164,286,287,328] In this model, it would appear that the effectiveness of these five octadentate ligands for removing Pu from bone mineral at pH 7.2 (100 μM, 24−48 h contact) is positively correlated with the estimates of log K_{ML} for their 1:1 Pu(IV) complexes.[22,27,130,164,323] Ligand hydrophilicity and reaction kinetics, properties largely determined by the functional groups, also contribute to overall effectiveness. The two least soluble ligands, 3,4,3-LI-CAM(C) (**53**) and H(2,2)-(Me-3,2-HOPO) (**99**), removed the least Pu from the bone mineral in 1 h and also were the least effective for reducing skeletal Pu in mice.[150,165] Removal of Pu from the bone mineral appeared to be biphasic, and in 1 h four of the five effective

octadentate ligands solubilized 32−56% of their 24−48 h maximum amounts removed, while the initial rate of Pu removal by 3,4,3-LI-CAM(C) (**53**) was much slower. Plutonium removal from bone mineral in 1 h *in vitro* is inversely correlated with skeletal Pu retention at 24 h in mice treated with these ligands; that is, the faster-acting ligands left smaller Pu residues in the skeletons of the treated mice.[150,165] The *in vitro* study provided additional evidence that the binding of Pu to bone mineral is more stable than that of Am, and the results with Am will be discussed in greater detail later, but this *in vitro* model successfully demonstrates that several of the test ligands are substantially more effective for removal of Pu from bone mineral than $ZnNa_3$−DTPA.

7. Thorium-Sequestering Agents

7.1. Thorium Coordination Chemistry—Similarities to Pu(IV)

Considerably less work has been directed toward the development of sequestering agents for actinide cations other than plutonium. Although thorium is the most abundant natural actinide element (found in the mineral monazite with the lanthanides) and much more common than uranium (8.1 ppm in the earth's crust versus 2.4 ppm for uranium),[123] the decorporation of thorium (^{228}Th) has not been as great a concern as plutonium due to its lower specific alpha radioactivity and limited use. Thorium can capture slow neutrons to form ^{233}Th, which forms fissionable ^{233}U through two β-decays, and thorium has in some rare instances been used experimentally as nuclear fuel.[330,331] Thorium is most commonly used in lantern mantles,[124] and its applications are on a much smaller scale than those of uranium or plutonium;[4] thus, it is much less likely to be encountered in a hazardous situation. Because of its relatively low specific radioactivity, Th(IV) is often used as a surrogate for Pu(IV) in nuclear waste separation studies. Given that isotopes of thorium are formed as daughter products of the most important isotopes of uranium, and that thorium is a potential contaminant in the reprocessing of nuclear fuels and a contributor to radioactive wastes, as well as a toxic metal and potential hindrance to plutonium decorporation, thorium decorporation is worthy of continued research.

At pH 7.4 (near physiological pH), thorium salts hydrolyze to form colloidal particles of $Th(OH)_4$. The only stable oxidation state for thorium in aqueous solutions is Th(IV). The similar ionic radii, coordination number, and preferred oxidation state of Th(IV) make it a good analogue for the more radioactive and hazardous Pu(IV).[124,125] Thorium is a toxic heavy metal; either Th(IV) ion or its hydroxide colloids readily react *in vivo* with proteins, amino acids, and nucleic acids to form stable complexes in the tissues,[193,279] primarily in the bone, liver, bone marrow, spleen, and kidneys.[44,193,279,327,332,333]

Like Pu(IV), Th(IV) is transported in the bloodstream bound to transferrin.[334,335] Studies of the interactions of transferrin with Th have demonstrated that, at pH 7, Tf coordinates two Th(IV) metal ions in nonequivalent sites.[48] The stability of Th(IV) complexes with DFO and derivatives of DFO has been used to estimate the stability of Pu(IV) complexes with DFO-CAM(C) and DFO(1,2-HOPO) by assuming a linear free energy relationship between the Th(IV) and Pu(IV) complexes and relating these to the stability constants found for Pu(IV)−DFO.[27]

It is generally thought that, while the lanthanides exhibit almost exclusively electrostatic interactions, there is some evidence of covalency in the interactions of actinide systems.[124] This makes an actinide analogue attractive even when lanthanide models have already been obtained. The complexes formed by actinide(IV) ions and the catecholate dianion, in which the steric restraints of a macrochelate are absent, have served as structural archetypes for designing optimum actinide(IV) macrochelates.[310]

7.2. Structural Characterization as Model for the Pu(IV) System

The tetrakis(catecholato)thorate(IV) complex, $Na_4[Th(C_6H_4O_2)_4]\cdot 21H_2O$, has been prepared. The crystals, which were found to be isomorphous with those of the Ce(IV) complex, formed readily from aqueous solution and were found to be very close in geometry to the idealized trigonal-faced dodecahedron polyhedra. Chelating ligands for applications with actinides need to allow appended catecholates to dispose themselves about the metal ion in such a dodecahedral geometry. Like the tetrakis(tironato)cerate(IV) complex discussed above, the metal−oxygen distances are not all equivalent. The metal is slightly offset within a trapezoid, the longer metal−oxygen length averaging 2.417 Å and the shorter side metal−oxygen bond length, 2.421 Å. This slight difference in comparison to the Ce(IV) complex is believed to be due to a ligand field effect in the Ce(IV) complex and other like complexes.[310] (Refer to Figure 5 for an illustration of this molecular structure.)

To better characterize hydroxamic acids used in quantitative analysis and solvent extraction of actinides, two tetrakis(*N*-alkylalkanehydroxamato)thorium(IV) complexes were prepared and characterized, Th[*i*-PrN(O)C(O)-*t*-Bu]$_4$ and Th[*i*-PrN(O)C(O)neopentyl]$_4$. Both of these complexes were found to be remarkably lipophilic and volatile due to their hydrocarbon substituents. It is these substituents that are believed to cause their dramatically different coordination properties due to the different steric constraints imposed. The *tert*-butyl-substituted hydroxamate is forced into a distorted cubic geometry with S_4 crystallographic symmetry, while the additional methylene group in the neopentyl derivative relaxes steric requirements such that the less constrained complex demonstrates the more typical trigonal-faced dodecahedral arrangement. Such an arrangement leads to the prediction that the framework neopentyl derivative should form a very stable complex for an improved Pu-chelating agent.[80]

The third chelating subunit found in siderophores, hydroxypyridinone, also forms stable complexes with Th(IV) (Figure 15). It was anticipated that the

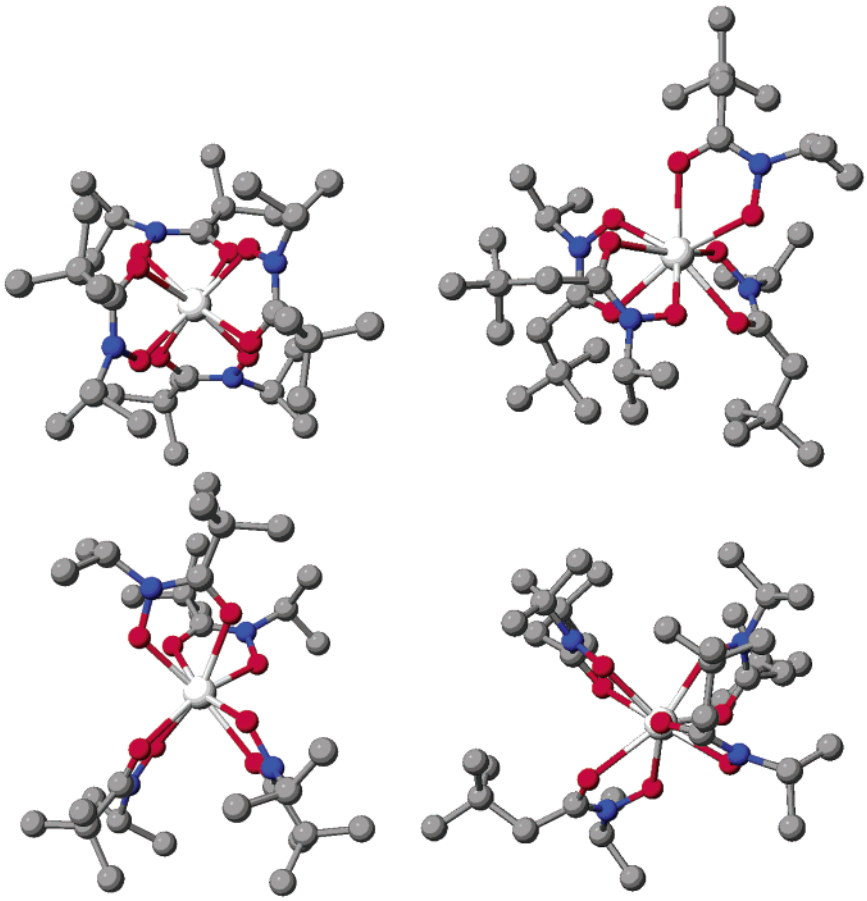


Figure 14. Molecular structures (top and side views) of Th[*i*-PrN(O)C(O)-*t*-Bu]$_4$ and Th[*i*-PrN(O)C(O)neopentyl]$_4$. The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, and the central thorium atoms white. The hydrogen atoms have been omitted for clarity. These figures were generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 80.

Table 9. Relevant Bond Lengths and Angles for the Thorium(IV) Complex, Th[*i*-PrN(O)C(O)-*t*-Bu]$_4$[a]

Bond Lengths (Å)			
Th−O1	2.357(3)	C1−C2	1.547(5)
Th−O2	2.492(3)	C2−C3	1.528(7)
O1−O2	2.512(3)	C2−C4	1.543(6)
O1−N	1.376(4)	C2−C5	1.538(6)
O2−C1	1.261(5)	C6−C7	1.512(7)
N−C1	1.316(5)	C6−C8	1.520(8)
Bond Angles (deg)			
O1−Th−O2	62.32.(9)	C1−C2−C4	110.1(3)
Th−O1−N	121.4(2)	C1−C2−C5	111.9(4)
Th−O2−C1	120.3(2)	C3−C2−C4	108.2(4)
O1−N−C1	116.3(3)	C3−C2−C5	107.5(4)
C1−N−C6	113.0(3)	C4−C2−C5	111.2(4)
O2−C1−N	130.4(3)	N−C6−C7	109.5(4)
O2−C1−C2	117.6(3)	N−C6−C8	110.5(4)
N−C1−C2	119.0(3)	C7−C6−C8	112.7(5)
C1−C2−C3	107.8(4)		

[a] Estimated standard deviations in the least significant figure are given in parentheses.[80]

complexation of Th(IV) would resemble the Ce(IV) catecholate system[336] and that hydroxypyridinonates such as 1,2-HOPO and 3,2-HOPO ligands would show high affinities toward actinide(IV) ions. The crystal structure of tetrakis(1-oxy-2-pyridonato)aquothorium(IV) dihydrate, $(C_5H_4NO_2)_4(H_2O)Th\cdot 2H_2O$, has been determined through X-ray diffraction techniques.[322] While the Ce(IV) complexes are eight-coordinate, the X-ray crystal structure of Th(PR-1,2-HOPO)$_4\cdot 0.5H_2O$ (Th(IV)−**103**) shows that thorium is nine-coordinate, and the complex forms an infinite chain coordination polymeric structure.[130,322] This nine-coordinate complex resembles a D_{3h} tricapped trigonal prism, with four bidentate oxypyridinone ligands coordinating the Th(IV) metal ion. The difference between this structure and the similar nine-coordinate tetrakis(tropolonato)(*N*,*N*-dimethylformamide)thorium(IV) complex, which is a monocapped Archimedean antiprism of C_{4v} symmetry, is due to the asymmetric charge distribution of the oxypyridinone ligand. The average metal−oxygen bond distance of the thorium to the ligand oxygens is 2.44 Å, with an average O−O bite distance of the oxypyridonate of 2.58 Å. It is also important to note that, in the free ligand, the amide nitrogen atom forms a strong hydrogen bond with the adjacent phenolic oxygen atom (average $N_{amide}-O_{phenolic} = 2.00$ Å), while the phenolic proton also forms a hydrogen bond with the adjacent oxo oxygen atom (average $N_{amide}-O_{phenolic} = 2.28$ Å). This hydrogen bond scheme enforces a coplanar arrangement of the HOPO ring and the amide moiety; the same ligand geometry has been observed in all crystal structures of the Me-3,2-HOPO−metal complexes to date.[130,169,337] Unlike catecholamides or 2,3-dihydroxyterephthalamides, no 180° rotation of the amide group accompanies metal complexation,[284] so for the Me-3,2-HOPO ligands the

Table 10. Relevant Bond Lengths and Angles for the Thorium(IV) Complex, Th[*i*-PrN(O)C(O)Neopentyl]$_4$[a]

Bond Lengths (Å)

atoms	1	2	3	4	avg
Th−O1	2.387(4)	2.334(4)	2.358(4)	2.355(4)	2.359(11)
Th−O2	2.410(4)	2.468(4)	2.498(4)	2.479(4)	2.464(19)
O1−O2	2.507(5)	2.514(6)	2.530(6)	2.530(6)	1.520(6)
O1−N	1.376(6)	1.352(6)	1.373(6)	1.377(6)	1.370(6)
O2−C1	1.267(6)	1.281(9)	1.245(7)	1.252(7)	1.261(8)
N−C1	1.313(7)	1.311(9)	1.305(8)	1.303(8)	1.308(3)
C1−C2	1.505(10)	1.524(10)	1.529(9)	1.512(9)	1.518(6)
C2−C3	1.548(8)	1.495(12)	1.524(11)	1.536(10)	1.526(12)
C3−C4	1.518(10)	1.500(10)	1.509(12)	1.551(13)	
C3−C5	1.536(10)	1.531(12)	1.524(11)	1.498(13)	1.525(8)
C3−C6	1.506(10)	1.593(14)	1.540(15)	1.499(11)	
N-C7	1.468(7)	1.469(8)	1.482(8)	1.476(8)	1.474(4)
C7−C8	1.521(10)	1.463(11)	1.492(8)	1.496(12)	
C7−C9	1.492(9)	1.528(10)	1.496(11)	1.506(13)	1.499(7)

Bond Angles (deg)

atoms	1	2	3	4	avg
O1−Th−O2	63.0(1)	63.1(2)	62.7(2)	63.1(2)	63.0(1)
Th−O1−N	118.6(3)	122.7(3)	118.7(3)	121.4(3)	120.4(1)
Th−O2−C1	121.0(3)	119.2(3)	117.5(3)	119.9(3)	119.4(8)
O1−N−C1	115.8(4)	115.7(5)	116.8(5)	116.2(5)	116.1(3)
O1−N−C7	114.4(4)	113.1(5)	111.8(5)	112.3(5)	112.9(6)
C1−N−C7	129.8(5)	131.1(6)	131.3(6)	131.5(6)	130.9(4)
O2−C1−C2	119.0(5)	119.3(7)	120.1(7)	118.5(6)	119.2(4)
02-C1−N	117.9(5)	118.6(6)	118.9(6)	119.4(6)	118.7(3)
N−C1−C2	123.0(5)	122.0(7)	120.9(6)	122.1(6)	122.0(5)
C1−C2−C3	114.3(4)	114.6(7)	115.6(6)	115.8(6)	115.1(4)
C2−C3−C4	111.2(6)	113.0(8)	109.4(8)	109.3(7)	
C2−C3−C5	111.7(6)	112.8(8)	108.5(9)	110.5(7)	110.1(6)
C2−C3−C6	107.3(6)	107.1(7)	112.7(9)	107.5(7)	
C4−C3−C5	108.0(7)	108.7(7)	108.5(9)	109.3(8)	
C4−C3−C6	110.2(7)	107.5(9)	110.8(11)	108.3(8)	108.8(4)
C5−C3−C6	108.4(7)	107.3(8)	106.8(12)	112.0(8)	
N−C7−C8	109.4(5)	111.5(6)	109.5(6)	109.5(7)	
N−C7−C9	110.5(5)	108.9(6)	109.4(6)	109.8(7)	109.8(3)
C8−C7−C9	112.8(6)	111.6(7)	112.9(9)	113.0(8)	112.6(4)

[a] Estimated standard deviations in the least significant figure are given in parentheses.[80]

uncomplexed and complexed ligands share the same conformation.

Most recently, structures have been reported for terephthalamide complexes with thorium. These are based on the reaction of 2,3-dihydroxyterephthalamide (e.g., **62**) with thorium in various proportions in order to form the monomeric complex $[(C_6H_5CH_2)_3NCH_3]_4$·$[Th(C_{12}H_{12}O_4N_2)_4]$ (or $[Th(EtTAM)_4]^{4-}$) and two different dimer complexes, $[Th(C_{12}H_{12}O_4N_2)_3(CH_3OH)]_2$·$4N(CH_3)_4$] and $[Th(C_{12}H_{12}O_4N_2)_3(CH_3OH)]_2$·$4N(CH_3)_4$·$6CH_3OH$·$3H_2O$] (called $[Th(EtTAM)_3]_2^{4-}$). The monomer was synthesized as the tetra-tribenzylmethylammonium salt using a stoichiometric amount of tribenzylmethylammonium hydroxide, resulting in an octacoordinate complex featuring coordination geometry most closely resembling the bicapped trigonal prismatic (C_{2v}) polyhedron. The average Th−O distance is 2.42 Å. The previously discussed 3,2-HOPO−Th(IV) complex was found to be nine-coordinate, and this difference in the coordination sphere of the thorium is most likely due to the stronger Lewis basicity of the ETAM (**62**) ligand, which serves to decrease the effective charge on the thorium.[338]

The isomorphous dimer complexes were prepared in a ratio of 3:1, ligand-to-metal [ETAM (**60**):Th(IV)], producing two structures with different solvent coordination. As before, with the earlier described catecholate and hydroxamate ligands, the coordination number is nine. Around each metal ion, two TAM ligands coordinate in the expected fashion, that is, similarly to the catecholates, while the third also binds the first metal ion with its catecholate oxygens and bridges to the second thorium ion. The Th−O metal-coordinating terephthalamide distances are of a wide range, from 2.33 to 2.64 Å, but they average 2.44 Å, very close to what is seen in the monomer. In all of the related structures discussed previously, the amide is oriented such that it forms a hydrogen bond with the deprotonated coordinating catecholate oxygen, but not in this case. This observation raises some questions regarding the nature of these complexes and their activity in solutions in which there may be a large excess of ligand. It would be most interesting to see if related bimetallic complexes could be characterized.[339]

These measurements in the solid state with the chelating subunits can be used to predict or model what sorts of ligand backbones would prove optimal for the design of the multidentate ligands that we have been pursuing in order to optimize selectivity. By demonstrating what sorts of bite angles and distances form stable complexes, we can determine what sorts of systems will make the formation of our specific desired metal complex favorable.

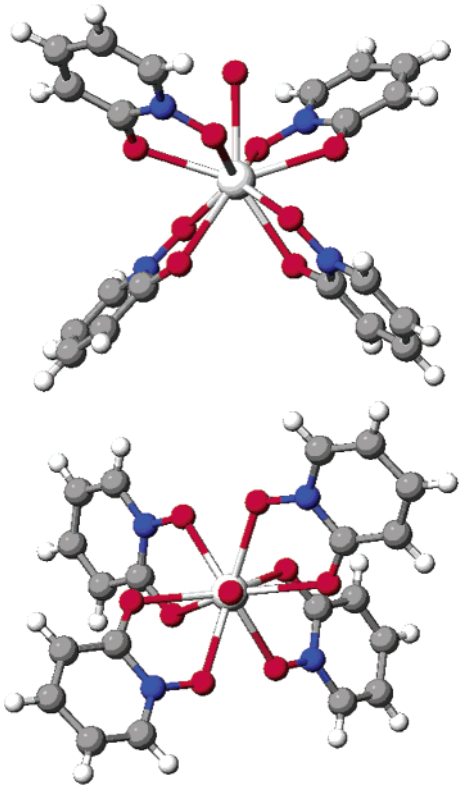


Figure 15. Molecular structure (top and side views) of tetrakis(1-oxy-2-pyridonato)aquothorium(IV)·$2H_2O$. The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, the central thorium atom white, and the peripheral hydrogen atoms smaller and white. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 322.

Table 11. Relevant Bond Lengths and Angles for Tetrakis(1-oxy-2-pyridonato)aquothorium(IV)·$2H_2O$[a]

Bond Lengths (Å)			
Th1−O1A	2.507(5)	N1A−C2A	1.382(11)
Th1−O1B	2.433(11)	N1A−C6A	1.410(9)
Th1−O1C	2.606(8)	N2A−C7A	1.345(11)
Th1−O1D	2.553(17)	N2A−C8A	1.414(13)
Th1−O2A	2.448(5)	C2A−C3A	1.408(12)
Th1−O2B	2.261(8)	C3A−C4A	1.409(10)
Th1−O2C	2.373(6)	C4A−C5A	1.412(9)
Th1−O2D	2.541(11)	C4A−C7A	1.468(11)
Th1−O3AA	2.381(6)	C5A−C6A	1.354(10)
O1A−C2A	1.312(8)	C7A−O3AB	1.359(15)
O2A−C3A	1.281(9)		

Bond Angles (deg)			
O2A−Th1−O1A	63.93(16)	O2B−Th1−O3AA	92.7(7)
O2B−Th1−O1B	68.0(3)	O2B−Th1−O2C	94.9(6)
O2C−Th1−O1C	59.2(6)	O2C−Th1−O1D	83.2(6)
O2D−Th1−O1D	61.9(5)	O3AA−Th1−O1D	70.9(6)
O3AA−Th1−O1A	78.17(19)	O2C−Th1−O3AA	147.3(2)
O3AA−Th1−O2D	63.0(7)	O2B−Th1−O1D	140.3(4)
O3AA−Th1−O1B	76.5(6)	O1A−Th1−O1C	108.1(5)
O1B−Th1−O1D	73.0(2)	O2A−Th1−O2D	97.7(5)
O2C−Th1−O1B	77.0(5)	O1B−Th1−O1A	132.8(6)
O2A-Th1−O1C	69.2(4)	O1B−Th1−O2A	134.7(5)
O2D−Th1−O1C	63.2(3)	O1B−Th1−O1C	119.1(4)
O1A−Th1−O2D	72.6(6)	O1B−Th1−O2D	126.5(4)

[a] Estimated standard deviations in the least significant figure are given in parentheses.[322]

7.3. Decorporation of Thorium

DTPA is the recommended treatment for chelation of ingested or inhaled thorium; however, treatment with DTPA is only partially effective for thorium decorporation when treatment is delayed by 30 min or more. Hence, thorium decorporation remains an unresolved issue.[8,10,87,193] The siderophore analogue 3,4,3-LI(1,2-HOPO) (**112**), which produced excellent results in the decorporation of plutonium, has also been studied for its ability to remove ^{228}Th in simulated wound contamination studies with rats.[193] In these studies, a ^{228}Th nitrate solution was administered by s.cut. or im injection (3 kBq kg^{-1}). Treatments included direct injection of 30 μmol kg^{-1} of the 3,4,3-LI(1,2-HOPO) (**112**) or DTPA into the wound site at 30 min, 6 h, or 24 h, accompanied in some cases by three or four daily ip ligand injections. Under these comparable conditions, the 3,4,3-LI(1,2-HOPO) (**112**) was considerably more effective than DTPA for removal of Th both from wound sites and from other body tissues. Thorium nitrate, $^{228+232}$Th (4 ng) or $^{228+232}$Th (4 μg), was administered to rats by inhalation.[327] Five daily ip injections of 3,4,3-LI(1,2-HOPO) (**112**) or $CaNa_3$−DTPA (30 μmol kg^{-1})

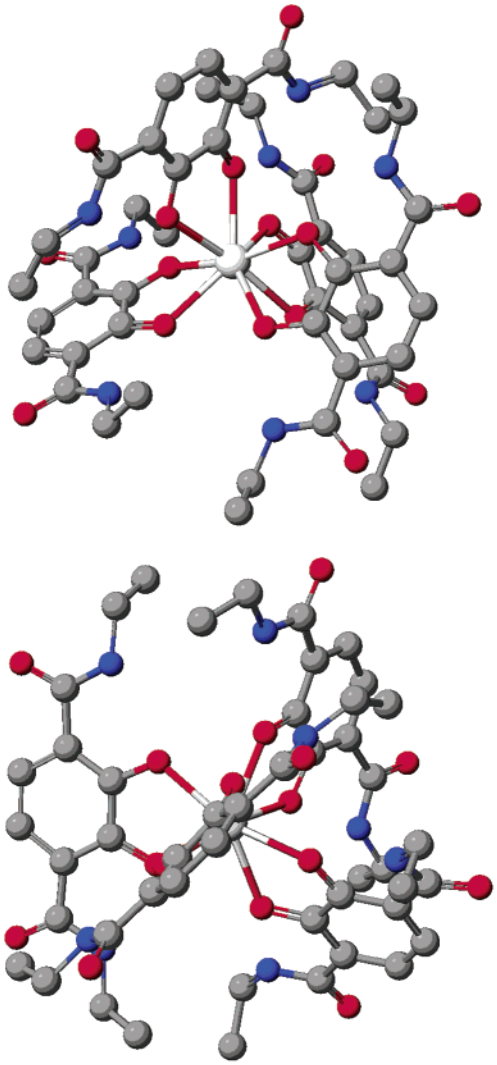


Figure 16. Molecular structure (top and side views) for the Th(IV) complex Th[ETAM]$_4$ ([$(C_6H_5CH_2)_3NCH_3]_4$·[Th$(C_{12}H_{12}O_4N_2)_4$]). The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, and the central thorium atoms white. The hydrogen atoms have been omitted for clarity. This figure was generated from unpublished data, refs 338 and 339.

Table 12. Relevant Metal−Oxygen Bond Lengths and Angles for the Th(IV) Complex Th[ETAM]$_4$ ([$(C_6H_5CH_2)_3NCH_3$]$_4$·[$Th(C_{12}H_{12}O_4N_2)_4$]) and the Dimeric Th(IV) Complex [$Th(C_{12}H_{12}O_4N_2)_2(CH_3OH)$]$_2$·$4N(CH_3)_4$·$3CH_3OH$[a]

			[$(C_6H_5CH_2)_3NCH_3$]$_4$·[$Th(C_{12}H_{12}O_4N_2)_4$]				
			Bond Lengths (Å)				
Th1−O1	2.410(5)	Th1−O5	2.490(5)	Th1−O8	2.414(5)	Th1−O13	2.445(5)
Th1−O2	2.413(5)	Th1−O6	2.395(5)	Th1−O10	2.428(5)	Th1−O14	2.381(5)
			Bond Angles (deg)				
O1−Th1−O2	64.8(2)	O2−Th1−O5	91.8(2)	O5−Th1−O9	92.9(2)	Th1−O5−C13	117.2(4)
O1−Th1−O5	74.5(2)	O2−Th1−O6	94.5(2)	O5−Th1−O10	97.1(2)	Th1−O6−C14	119.5(4)
O1−Th1−O6	132.9(2)	O2−Th1−O9	162.8(2)	O5−Th1−O13	168.3(2)	Th1−O9−C25	117.9(4)
O1−Th1−O9	132.4(2)	O2−Th1−O10	130.7(2)	O10−Th1−O14	132.3(2)	Th1−O10−C26	116.9(5)
O1−Th1−O10	71.2(2)	O2−Th1−O13	93.9(2)	O13−Th1−O14	64.8(2)	Th1−O13−C37	120.3(4)
O1−Th1−O13	98.8(2)	O2−Th1−O14	71.8(2)	Th1−O1−C1	120.8(5)	Th1−O14−C38	123.2(5)
O1−Th1−O14	132.3(2)	O5−Th1−O6	63.9(2)	Th1−O2−C6	120.8(5)		
			[$Th(C_{12}H_{12}O_4N_2)_2(CH_3OH)$]$_2$·$4N(CH_3)_4$·$3CH_3OH$				
			Bond Lengths (Å)				
Th−O1	2.33(1)	Th−O4	2.38(1)	Th−O5	2.48(1)	Th−O7	2.64(1)
Th−O2	2.41(1)	Th−O5	2.51(1)	Th−O6	2.37(1)	Th−O14	2.42(1)
Th−O3	2.42(1)						
			Bond Angles (deg)				
O1−Th−O2	65.0(5)	O2−Th−O6	115.5(5)	O4−Th−O7	138.3(4)	O7−Th−O14	74.9(4)
O1−Th−O3	137.4(5)	O2−Th−O7	133.1(4)	O4−Th−O14	146.4(4)	Th−O1−C1	122(1)
O1−Th−O4	104.8(5)	O2−Th−O14	69.7(5)	O5−Th−O5	67.8(5)	Th−O2−C2	117(1)
O1−Th−O5	129.2(4)	O3−Th−O4	65.6(5)	O5−Th−O6	63.7(4)	Th−O3−C14	117(1)
O1−Th−O5	134.6(4)	O3−Th−O5	90.1(4)	O5−Th−O7	72.7(3)	Th−O4−C15	119(1)
O1−Th−O6	68.1(4)	O3−Th−O5	69.4(4)	O5−Th−O14	132.0(4)	Th−O5−Th	112.2(5)
O1−Th−O7	76.5(5)	O3−Th−O6	135.3(4)	O5−Th−O6	123.5(4)	Th−O5−C26	118(1)
O1−Th−O14	73.9(5)	O3−Th−O7	139.4(5)	O5−Th−O7	70.1(4)	Th−O5−C26	129(1)
O2−Th−O3	72.4(5)	O3−Th−O14	92.2(5)	O5−Th−O14	68.4(4)	Th−O6−C27	123(1)
O2−Th−O4	79.3(5)	O4−Th−O5	75.5(4)	O6−Th−O7	69.3(4)	Th−O7−C38	124(1)
O2−Th−O5	153.7(4)	O4−Th−O5	120.6(4)	O6−Th−O14	132.4(4)	Th−O14−C32	138(1)
O2−Th−O5	120.8(5)	O4−Th−O6	72.8(5)				

[a] Estimated standard deviations in the least significant figure are given in parentheses.[338,339]

were given, starting at 30 min. Net excretion of the smaller Th mass promoted by the HOPO ligand or $CaNa_3$−DTPA was 58 and 16% of the injected amount, respectively, and of the larger Th mass, 24 and 7% of the injected amount, respectively. Treatment with 3,4,3-LI(1,2-HOPO) (**112**) was about 3.5 times more effective than that with $CaNa_3$−DTPA for decorporating both levels of inhaled Th. It can be concluded from those observations that 3,4,3-LI(1,2-HOPO) (**112**) is worth continued study as a potential ligand for thorium decorporation, especially in contamination accident situations involving unknown mixtures of actinides.[193,327]

8. Americium-Sequestering Agents

8.1. Americium Coordination Chemistry

Americium, a common byproduct of fission reactions as a daughter product of plutonium, is present in large amounts in high-level wastes. It is used as an ion source in smoke detectors,[5,340] as a photon source in oil well logging instruments,[341] and in combination with beryllium as a neutron source in instruments for measuring soil moisture.[342] Because many actinide isotopes are byproducts of fission, the ability to isolate them from the matrix of fission products and uranium remains of great concern in nuclear fuel fabrication, processing, and disposal. While the development of solvent extraction processes overcame many of these limitations, current methods rely on extraction of the Pu and its subsequent reduction to the trivalent state, leaving the uranium in the extractant phase for subsequent recovery and recycle.[125,126] The goal of this process is the limitation of the volumes of high-level actinide waste generated in fission that must then be maintained in long-term storage or geological repositories; however,[5,126,127] this process is not 100% effective in isolating uranium and plutonium and does not allow purification of the other actinides produced during fission, namely, americium, curium, and neptunium.[5,126,340] Accordingly, efficient separation processes continue to be sought, and this is the context in which most current research on the chemical behavior of Am takes place in the pursuit of ligands for waste remediation and environmental protection applications.[126,138,343−350]

Because of its high specific alpha activity, only a few americium complexes have been structurally characterized, and most of these are basic binary complexes or metal salts.[351−355] The closest of these to the catecholate and terephthalamide complexes with which we are interested is an aquotris(salicylato)americium(III).[356] The high specific radioactivity of ^{241}Am is such that radiolysis of aqueous solutions causes many ligands to decompose. The potential for accidents during investigations of the nature of the metal, or when working with fuel waste materials themselves, makes Am decorporation a valid concern. One can imagine many industrial situations in which both Am and Pu would be present in an accident leading to inhalation, ingestion, or contaminated

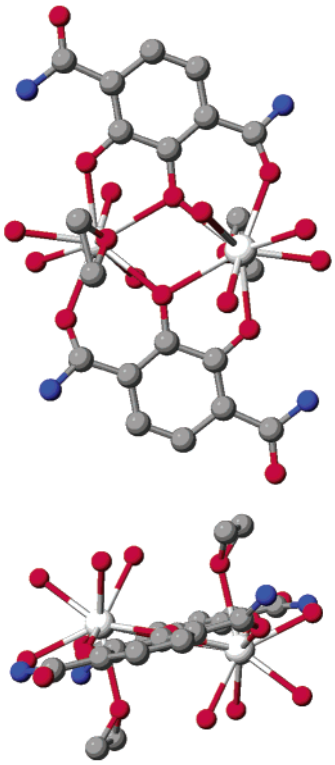


Figure 17. Molecular structure (top and side views) for the dimeric Th(IV) complex, $[Th(C_{12}H_{12}O_4N_2)_2(CH_3OH)]_2 \cdot 4N(CH_3)_4 \cdot 3CH_3OH$. The ethyl groups on the terephthalamide ligands and two of the ETAM ligands have been omitted to better view the geometry of the metal coordination centers. The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, the central thorium atoms white, and the peripheral hydrogen atoms smaller and white. This figure was generated from unpublished data, refs 338 and 339.

Table 13. Relevant Bond Lengths and Angles for the Gd(III) Complex of Catechol, $Na_5[Gd(C_6H_4O_2)_4] \cdot 19.2H_2O$[a]

Bond Lengths (Å)			
M−O1	2.393(2)	C2−C3	1.400(3)
M−O2	2.422(2)	C3−C4	1.397(4)
O1−C1	1.337(3)	C4−C5	1.376(5)
O2−C2	1.341(3)	C5−C6	1.402(8)
C1−C2	1.420(3)	C6−C1	1.404(3)

Bond Angles (deg)			
O1−M−O2	68.05(6)	O1−M−O1 (90°)	93.71(2)
O1−M−O2 (90°)	79.86(7)	O1−M−O1 (180°)	150.52(9)
O1−M−O2 (180°)	141.40(6)	O2−M−O2 (90°)	129.97(5)
		O2−M−O2 (180°)	73.45(8)

[a] Estimated standard deviations in the least significant figure are given in parentheses.[312]

wounds.[87] While $CaNa_3$−DTPA greatly increases the excretion of Am, the greatest benefit occurs if treatment is provided immediately upon exposure.[50] Treatments that can increase the decorporation of Am(III) from bone would be of particular value. This is of distinct concern, given the reasons described above for the need for chelation therapy (see section 2.3) if one considers that ^{241}Am has approximately 60 times the specific alpha activity of ^{239}Pu.[357]

In a fashion similar to plutonium, americium generally forms eight-coordinate complexes with ligands having hard donor atoms, but it is more like the lanthanides than plutonium in its chemistry, and under physiological conditions Am is only found as Am(III).[51,128] As discussed previously, the early actinides exist in a variety of oxidation states; however, toward the heavier end of the actinide series, shielding of the 5f electrons becomes more regular, and hence americium behaves more like the lanthanides, in a predominately +3 oxidation state.[123,128,330] It is also significant to note the size similarity between trivalent lanthanides in the same column as their trivalent actinide counterparts.[137]

While very similar in their properties, the actinides and lanthanides do differ slightly in their binding to ligands. These differences were first observed by Diamond, et al., who found that trivalent actinide cations interact somewhat more strongly with chloride ions than lanthanides do, thus enabling a cation-exchange resin-based separation of moderate efficiency.[358] This relativistic effect was attributed to f-electron covalency present in the actinide−chloride complex that is essentially absent in the lanthanides. While this rationale remains subject to debate, subsequent research has demonstrated a similar effect in both ion exchange and solvent extraction separations based on thiocyanate anion;[359] all of the presently used techniques for effecting Ac(III)/Ln(III) group separations are based on the stronger interactions of actinide cations with soft donor atoms like Cl, S, or N.[127,138,141] The current literature shows that such methods for liquid−liquid extractions are being developed based on a variety of ligand systems including *N*,*N*′-dialkyamides,[348] malonimides,[340] and oligopyrroles,[360] as well as derivatives of terpyridine[361,362] and bis(1-phenyl-3-methyl-4-acylpyrazol-5-one),[363] in addition to various resins impregnated with organic extractants [e.g.,octyl(phenyl)-*N*,*N*-diisobutylcarbamoyl-methylphosphine oxide (CMPO) or bis(2,4,4-trimethylpentyl)dithiophosphinic acid (Cyanex 301)].[357,364] Despite these subtle differences, trivalent lanthanides are good models for trivalent actinides, and lanthanides are often used for the structural characterization of actinide−lanthanide separation ligands, due to their availability in quantity and relative ease of use.[362]

8.2. Lanthanides(III) as Models for Am(III): Eu(III) and Lu(III)

Since charge-to-ionic radius ratio plays such an important role in determining the stability and coordinating capabilities of synthetic catecholate chelating agents, studies of the lanthanide(III) catecholates may be extended to estimating the stability of the corresponding actinide(III) systems, particularly since the shift in redox potentials of lanthanide(IV)/(III) and actinide(IV)/(III) catecholates have been found to be comparable.[317,365] A variety of siderophore-like chelating ligands have been studied with europium (Eu(III)) and lutetium (Lu(III)) by potentiometric and spectrophotometric means in order to predict the behavior of Am(III)-based systems. These lanthanides were of particular interest because lutetium, the smallest of the lanthanides, should form the strongest complexes with catecholates, while Eu-

(III), with an eight-coordinate ionic radii of 1.066 Å, is similar in size to Am(III), with an eight-coordinate ionic radii of 1.090 Å.[137,317] (As mentioned in section 2.1, in their trivalent state, actinides exhibit ionic radii similar to those of the trivalent lanthanides in the same column of the periodic table or one column to the left; Eu(III) is directly above Am(III) in the periodic table.)[137] The ligands used for these studies were Tiron, N-cat, catechol, 5-sulfo-2,3-dihydroxy-*N*,*N*-dimethylbenzamide (DMBS), and the tetracatecholate 3,4,3-LI-CAM(S). The stoichiometries of the complexes formed with Eu(III) were identical to those with Lu(III); however, the stabilities of the Lu(III) complexes were always found to be greater than those of the Eu(III) complexes, presumably due to the smaller size of Lu(III).[317]

It was also determined that these lanthanide(III) complexes (and hence the actinide(III) complexes) are not as stable as the corresponding metal ion(IV) complexes. For the higher 3:1 and 4:1 complexes, the metal ion/catecholate stepwise formation constants are small and so cannot be accurately measured by the techniques commonly used.[317] This was determined through the comparison of the results of these lanthanide(III) systems with those of previously studied Ce(IV) complexes (see section 6.2).[310] These systems were not characterized structurally, and the solid-state nature of ligands like this is important to understand if the goal is to design actinide-specific chelating agents. To this end, other lanthanides were also used to gather data about these ligands and their coordination chemistry.

8.3. Gd(III) Complexes as Models for Am(III)

As discussed above, americium generally forms eight-coordinate complexes with ligands having hard donor atoms, but it only exists as Am(III) under physiological conditions. One row above and one to the left of Am(III) in the periodic table, Gd(III) has an eight-coordinate ionic radius of 1.053Å, and the size and coordination properties of Am(III) and Gd(III) are nearly the same, making Gd(III) a useful model to probe the coordination chemistry of Am(III).[137] For these purposes, several gadolinium(III)−catecholate complexes have been prepared, and the tris- and tetrakis(catecholate) systems have been characterized in the solid state via X-ray crystallography. Although they have not been structurally characterized, the identification of 1:1 and 1:2 metal-to-catecholate systems serves to support data that only the 1:1 complex is of consequence at neutral pH. The tris and tetrakis systems were prepared at pH's of 11.8 and 12.8, respectively.[312]

The gadolinium(III) tetrakis(catecholate) complex, $Na_5[Gd(C_6H_4O_2)_4]\cdot 19.2H_2O$, was found to be isomorphous with the previously described Th, Ce, and Hf structures consisting of an eight-coordinate dodecahedral geometry.[310−312] The change in charge of the metal ion is accounted for by the additional sodium counterion. The dimeric tris(catecholate) complex, $Na_6[Gd(C_6H_4O_2)_3]_2\cdot 20H_2O$, features each metal ion coordinated by two bridging catecholates, forming a very unusual seven-coordinate geometry in which the gadolinium and can be viewed as either a bicapped trigonal bipyramid or a distorted capped octahedron. The metal−catecholate oxygen average bond distance is 2.360 Å. Solely on the basis of their ionic radii, one would expect the Th(IV) and Gd(III) complexes to be very similar, and indeed, they are.[312] In each complex, the metal is slightly offset within a trapezoid. The longer metal−oxygen length averaged 2.417 Å for the Th(IV) complex and 2.422 Å for the Gd(III), while the shorter side metal−oxygen bond length was found to be 2.421 Å for the Th(IV) complex and 2.393 Å for the Gd(III)[310,312] (Figure 18).In related studies, the hexadentate hydroxypyridonate ligand, TREN(Me-3,2-HOPO) (**86**), was characterized with Gd(III) (Figure 19). While first considered as an Fe(III)-sequestering agent,[146] this ligand in particular was chosen for study with Gd(III) because its hexadentate chelating ability made it attractive for potential applications as a specific Am(III)-sequestering agent. The X-ray crystallographic structure of Gd(III)−TREN(Me-3,2-HOPO) (Gd(III)−**86**) shows a 1:1 eight-coordinate complex with the six oxygen donors of TREN(Me-3,2-HOPO) (**86**) and two oxygen atoms of coordinated waters. This complex is stable, $\log \beta_1 = 19.3$, pGd = 19, and that stability is expected to be the same for the Am(III) complex. Unlike the free dodecahedral Gd(III) tetrakis(catecholate) complex, the more constraining ligand makes this complex a slightly distorted bicapped trigonal prism. Due to the stability of this ligand, and the two coordinated water molecules, this potential Am(III)-sequestering agent became very attractive in terms of the water proton relaxivity. The competition between strong complexation and free water coordination sites available for exchange is a significant challenge inherent in the rational design of magnetic resonance imaging (MRI) contrast agents.[366] More ion-discriminating than other currently available contrast reagents, this tris-bidentate chelating agent is unique among potential imaging agents, offering the advantages of high chelate stability,[367] low toxicity,[121] and increased relaxivity,[368] and thus could represent a entirely new class of "second generation" MRI contrast agents.[297,367] Other more water-soluble TREN(Me-3,2-HOPO) (**86**) ligands and mixed ligands containing two HOPO chelating groups and a different third chelating subunit [e.g., salicylamide (SAM), 2-hydroxyisophthalamide (IAM), or 2,3-dihydroxyterephthalamide (TAM)] have been investigated for their Gd(III)-coordinating and relaxivity properties.[297,299]

8.4. Multidentate Amino Acetic Acids for Am(III) Chelation Therapy

Americium in the blood is bound weakly to either albumin or transferrin. The americium−Tf complex is not as stable as that of plutonium.[47,51,59] In bone, Am, like Pu and many other metal ions, is associated with the bone mineral and bone sialoprotein.[111,369] The mode of uptake of americium into liver cells is probably similar to that of plutonium; however, there are significant differences in their soluble fractions.[46,152] While DTPA can more easily remove Am than Pu from bone deposits *in vivo*,[42,88,101] *in vitro* studies with bone mineral showed that Am extraction was time dependent, indicating that *in vivo* multiple

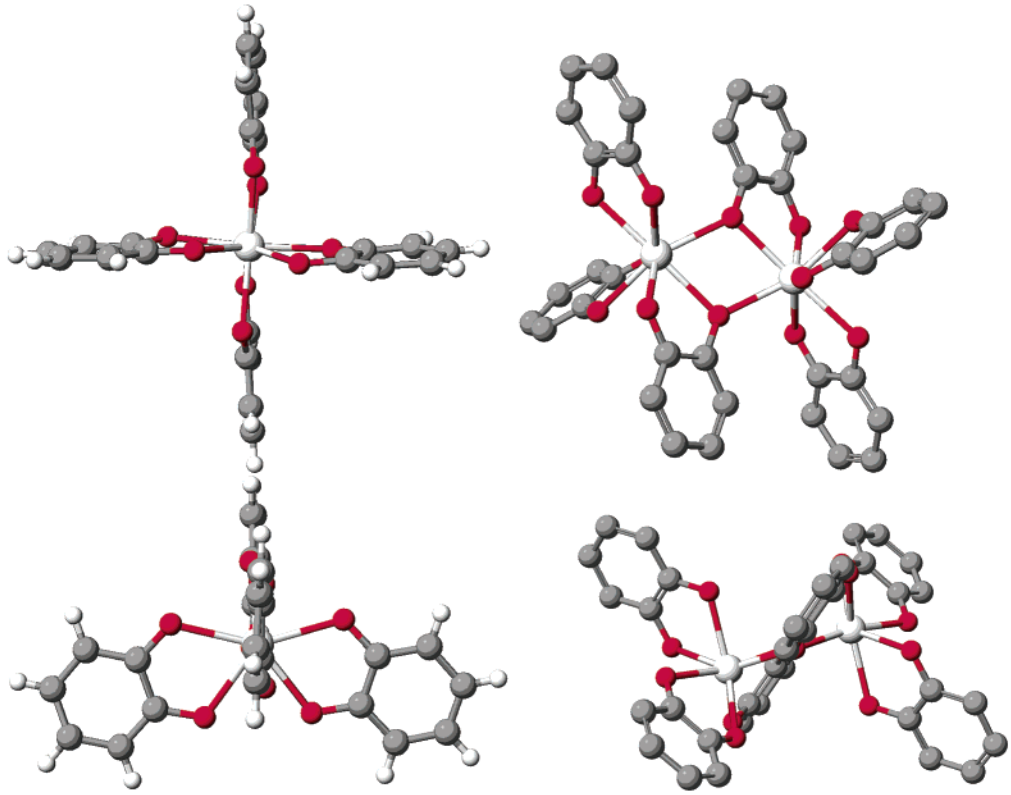


Figure 18. Molecular structure (top and side views) for the Gd(III) complex of catechol, $Na_5[Gd(C_6H_4O_2)_4]\cdot 19.2H_2O$, and the dimer, $Na_6[Gd(C_6H_4O_2)_3]_2\cdot 20H_2O$. The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, the central gadolinium atoms white, and the peripheral hydrogen atoms in the catecholate complex smaller and white. The hydrogen atoms of the dimeric complex have been omitted for clarity. These figures were generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 312.

Table 14. Relevant Bond Lengths and Angles for the Dimeric Gd(III) Complex of Catechol, $Na_6[Gd(C_6H_4O_2)_3]_2\cdot 20H_2O$[a]

Bond Lengths (Å)							
Gd−Gd	3.840(1)	Gd−O22	2.346(2)	O12−C12	1.350(3)	O32−C32	1.346(3)
Gd−O11	2.372(2)	Gd−O31	2.361(2)	O21−C21	1.346(3)	C11−C12	1.416(3)
Gd−O11	2.333(2)	Gd−O32	2.372(2)	O22−C22	1.342(3)	C21−C22	1.413(4)
Gd−O12	2.348(2)	O11−C11	1.348(3)	O31−C31	1.351(3)	C31−C32	1.413(3)
Gd−O21	2.362(2)						

Bond Angles (deg)							
Gd−O11−C11	133.58(15)	O31−C31−C32	117.87(21)	O11−Gd−O12	69.26(5)	O11−Gd−O31	82.75(6)
Gd−O11−C11	112.10(14)	O32−C32−C31	117.98(21)	O21−Gd−O22	69.76(6)	O11−Gd−O32	109.22(6)
Gd−O12−C12	112.52(13)	O11−C11−C16	122.76(22)	O31−Gd−O32	68.86(6)	O12−Gd−O21	140.12(6)
Gd−O21−C21	114.50(14)	O12−C12−C13	122.86(23)	O11−Gd−O21	90.82(6)	O12−Gd−O22	76.20(6)
Gd−O22−C22	115.14(15)	O21−C21−C22	122.95(23)	O11−Gd−O22	90.96(6)	O12−Gd−O31	78.98(6)
Gd−O31−C31	115.48(14)	O22−C22−C23	122.13(23)	O11−Gd−O31	119.50(6)	O12−Gd−O32	117.04(6)
Gd−O32−C32	115.30(14)	O31−C31−C36	122.70(23)	O11−Gd−O32	171.15(6)	O21−Gd−O31	139.63(6)
O11−C11−C12	117.62(20)	O32−C32−C33	123.26(23)	O11−Gd−O12	118.73(6)	O21−Gd−O32	80.42(6)
O12−C12−C11	118.37(20	O11−Gd−O11	70.64(6)	O11−Gd−O21	83.39(6)	O22−Gd−O31	129.80(6)
O21−C21−C22	118.38(21)	Gd−O11−Gd	109.36(6)	O11−Gd−O22	147.37(6)	O22−Gd−O32	84.88(6)
O22−C22−C21	118.48(22)						

[a] Estimated standard deviations in the least significant figure are given in parentheses.[312]

administrations would be required to maintain a high enough concentration over a long enough time to reduce bone deposits.[171] Knowledge of the human metabolism of americium is limited; most of what is known arose from the 10-year treatment of one victim of an industrial accident in 1976.[205] Key among the findings of the study of this individual after his accident are the decreased toxicity and increased efficacy of $ZnNa_3$−DTPA in comparison to $CaNa_3$−DTPA; however, although most of the ^{241}Am was cleared from the liver after 400 days of treatment, the clearance of Am from bone was not affected by DTPA, except perhaps during the first week of treatment. Prompt treatment with DTPA (within 30 min of the accident) also appears to have been crucial for diverting Am entering through the contaminated skin to excretion, effectively preventing Am deposition in bone.[205]

Partially lipophilic polyaminopolycarboxylic acids have been identified as potential decorporation agents for deposited Am(III). These compounds take advantage of the basic chelating properties of the polyaminopolycarboxylic acids, such as DTPA and EDTA, while improving the pharmacological properties by

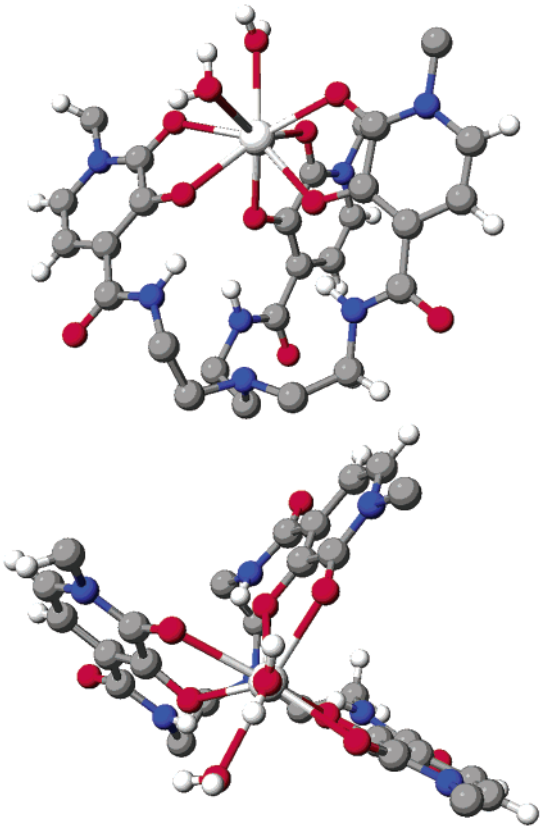


Figure 19. Molecular structure (top and side views) for the Gd(III) complex Gd(III)−TREN(Me-3,2-HOPO). The carbon atoms are depicted as gray, the oxygen red, the nitrogen blue, the central gadolinium atom white, and the peripheral hydrogen atoms smaller and white. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 367.

Table 15. Relevant Bond Lengths (in Å) for the Gd(III)−TREN(Me-3,2-HOPO) Complex[a]

Gd−O1	2.346(4)	Gd−O7	2.338(4)	N2−O1	2.652(7)
Gd−O2	2.430(5)	Gd−O8	2.409(5)	N3−O4	2.654(7)
Gd−O4	2.390(4)	Gd−O10	2.446(5)	N4−O7	2.729(7)
Gd−O5	2.386(5)	Gd−O11	2.436(4)		

[a] Estimated standard deviations in the least significant figure are given in parentheses.[367]

means of an increase in lipophilicity. This quality allows for greater penetration through cell barriers and eased passage through the intestinal barrier. Such compounds could potentially increase oral bioavailability over what is found for the catecholamide-based ligands that are strongly hydrophillic. Two such chelating agents, C_{12}- and C_{22}-triethylenetetraminepentaacetic acid (C_nTT, n = 12, 22), have been tested for bioavailability and chelation properties.[104]

In studies by Bruenger, et al., gel permeation chromatography of the ligand mixed with a solution of the actinide was used to demonstrate chelation of Am, and *in vitro* studies were used to demonstrate plutonium extraction from liver cytosol. The increased alkyl chain length in the C_{22}TT compound serves to increase intestinal absorption and to direct the agent primarily to the liver, one of the key target organs of Am(III). Preliminary studies *in vivo* demonstrated that these ligands were indeed effective when administered orally. No acute toxicity was observed, but further detailed toxicity measurements are required. Compared to untreated controls, the C_{12}TT and C_{22}TT were found to reduce whole body Am in rats to 29% and 44%, respectively. Most impressive were the extraction results from the liver, with a 71% and 89% reduction for the two ligands. It is believed that this is due to the formation of micelles that are more readily incorporated in the liver. These studies were not compared directly to results with EDTA or DTPA, but they present unique possibilities in the area of oral bioavailability. Further studies with other competing actinides will also be necessary to determine their real-world viability.[104]

8.5. Multidentate CAM Ligands for Am(III) Chelation Therapy

The first testing of siderophore-based ligands for Am(III) decorporation was done as part of cooperative studies initiated in dogs to determine the efficacies of 3,4,3-LI-CAM(C) (**53**) and 3,4,3-LI-CAM(S) (**42**) in a large animal. These were combined with investigations of Pu decorporation, and the dogs were given a mixture of $^{237+239}$Pu and ^{241}Am citrate. Both CAM ligands were found to coordinate Am weakly *in vivo*, but both CAM ligands were able to compete with biological ligands for Am and promote some excretion [close to 30% for 3,4,3-LI-CAM(C) (**53**) and 35% for 3,4,3-LI-CAM(S) (**42**), compared to almost 75% for $CaNa_3$−DTPA]. In mice treated with these ligands (killed at 24 h), Am retention was reduced to 76% of control by 3,4,3-LI-CAM(C) (**53**) and to 66% of control by 3,4,3-LI-CAM(S) (**42**). In dogs sacrificed after 7 days, Am retention in the body was about 78% of control for both 3,4,3-LI-CAM(S) (**42**) and 3,4,3-LI-CAM(C) (**51**), compared with 22% of control for $CaNa_3$−DTPA. The 3,4,3-LI-CAM(S) (**42**) was renally toxic in dogs, and studies with that ligand were discontinued.[184]

The EULEP group investigated *in vivo* chelation of Am(III) by 3,4,3-LI-CAM(C) (**53**) in mice, rats, and hamsters.[173,175,176] The ^{241}Am was given by iv injection as the citrate or by inhalation as the nitrate, and EU-LI-CAM(C) was injected ip (30 μmol kg^{-1}) once or as many as five times in 4 days, starting 30−60 min after the ^{241}Am exposure. Reductions of tissue and body Am and clearance of inhaled Am from the lungs were significantly less than those obtained with an equimolar amount of $CaNa_3$−DTPA. Substantial Am residues were deposited in the kidneys of all three test species.

Subsequent chemical investigations explained the failure of the CAM ligands, 3,4,3-LI-CAM(C) (**53**) and 3,4,3-LI-CAM(S) (**42**), to stably chelate Am(III) *in vivo*. Their complexes with Am(III) and trivalent lanthanides are weak. At pH 7, only three of the eight available phenolic oxygens can be deprotonated to participate in binding those ions,[22,317] and the participation of the 4-carboxyl substituents further weakens Am(III) binding.[239] These results indicated that the use of functionalities more acidic than catechol would be required for effective *in vivo* Am chelation.[22]

8.6. Multidentate HOPO Ligands for Am(III) Chelation Therapy

After the disappointing results with the CAM ligand trials, new research was begun exploring 1,2-HOPO-based ligands as chelating agents for Am. These studies were performed in conjunction with continuing studies of Pu-sequestering agents; i.e., the actinides were administered as mixtures in a model based on potential accident scenarios. The more acidic HOPO substituents were expected to chelate Am more stably. Initial evidence in rodents indicated that a 1,2-HOPO derivative of DFO, DFO(1,2-HOPO) (**115**), was much more effective than $CaNa_3$−DTPA for removing iv-injected Pu,[167] but it did not significantly enhance excretion of Am(III).[117,118]

The next studies that included Am decorporation compared the efficacies of 3,4,3-LI(1,2-HOPO) with those of $CaNa_3$−DTPA and $ZnNa_3$−DTPA. The actinides were administered to rats by iv injection as the citrates or the nitrates, or by inhalation, or in a simulated contaminated wound as the nitrate.[118,176,178,180] In the inhalation studies, $CaNa_3$−DTPA was found to be more effective initially than 3,4,3-LI(1,2-HOPO) (**112**), but after five ligand injections they were equally effective. In the iv-injected rats, the Am content of the body of those given one or more injections of 3,4,3-LI(1,2-HOPO) (**112**) was reduced as much as or more than in those given the same treatment with DTPA. Oral administration of 3,4,3-LI(1,2-HOPO) (**112**) was markedly more effective than an equimolar amount of $CaNa_3$−DTPA.[118]

In contaminated wound simulations, rats were given s.cut. or im injections of ^{238}Pu and ^{241}Am. The most effective treatment scenario was a local injection followed by five daily ip injections of 30 μmol kg^{-1} each of 3,4,3-LI(1,2-HOPO) (**112**), which reduced whole body Am at 7 days to 7 and 1.2% of control, respectively, after either s.cut. or im contaminated wounding. Those amounts of Am retained in the body were 1/4 and 1/20 respectively, of the Am retention in rats given equimolar amounts of $CaNa_3$−DTPA in the same exposure−treatment regimens.[178,180] The efficacies of tetradentate 5-LI(Me-3,2-HOPO) (**83**) and 5-LIO(Me-3,2-HOPO) (**84**), hexadentate TREN-(Me-3,2-HOPO) (**86**), and octadentate 3,4,3-LI(1,2-HOPO) (**112**) for *in vivo* chelation of Am have been compared with that of $CaNa_3$−DTPA in several exposure−treatment regimens. Two of the HOPO-based ligands, TREN(Me-3,2-HOPO) (**86**) and 5-LI-(Me-3,2-HOPO) (**83**), were incorporated into the study specifically because of their ease of synthesis and low acute toxicity, issues in the cost and use of the 3,4,3-LI(1,2-HOPO) (**112**) ligand.[156,179]

Americium nitrate was administered to rats by inhalation or by s.cut. or im injection in contaminated wounds. After Am inhalation, five daily ip injections (30 μmol kg^{-1} starting at 30 min) of TREN(Me-3,2-HOPO) (**86**) or 5-LI(Me-3,2-HOPO) (**83**) reduced whole body Am at 7 days significantly compared with controls, but the amounts of Am retained were 35 and 87% greater than in rats similarly treated with $CaNa_3$−DTPA. When Am nitrate was implanted in contaminated wounds, one local injection was given at 30 min of 3 μmol kg^{-1} of 5-LI(Me-3,2-HOPO) (**83**) or 30 μmol kg^{-1} of TREN(Me-3,2-HOPO) (**86**) or $CaNa_3$−DTPA, or the local injection was followed by four daily ip injections of 30 μmol kg^{-1} of each ligand, and the HOPO ligands reduced whole body Am retention at 7 days to 30−60% of the amount of Am retained in the rats treated with $CaNa_3$−DTPA.[179] Mice were injected iv with Am citrate, and 30 μmol kg^{-1} of TREN(Me-3,2-HOPO) (**86**) or 3,4,3-LI(1,2-HOPO) (**112**), or 100 μmol kg^{-1} of 5-LIO(Me-3,2-HOPO) (**84**), was injected ip at 3 min. Americium retention in the body at 24 h was reduced, on average, to 30% of the amount of Am retained in mice given 30 μmol kg^{-1} (the standard dose) of $CaNa_3$−DTPA in the same treatment regimen. When those same ligand doses were given orally at 3 min after the introduction of Am, reductions of Am retained in the body at 24 h were the same as [5-LIO(Me-3,2-HOPO) (**84**)] or significantly greater than [TREN(Me-3,2-HOPO) (**86**) and 3,4,3-LI(1,2-HOPO) (**112**)] those obtained with 30 μmol kg^{-1} of injected $CaNa_3$−DTPA.[156,326] The low toxicity and promising results obtained with 5-LIO(Me-3,2-HOPO) (**84**) and TREN-(Me-3,2-HOPO) (**86**) make them exceedingly interesting for continued work.[179]

TREN(Me-3,2-HOPO) (**86**) was investigated in mice for decorporation of Np(V) and U(VI) as well as that of Pu(IV) and Am(III). The specifics of the results of its affinities for uranium and neptunium will be discussed later. For Am(III), TREN(Me-3,2-HOPO) (**86**) was found to significantly reduce the retained Am(III) in kidney, liver, skeleton, total body, and residual soft tissues in amounts that surpassed those obtained with $CaNa_3$−DTPA.[156] This indicates the potential use of the ligand as an Am(III)-specific chelator or as part of a combination of ligands for improved overall decorporation.

Many of the studies described above were done using combinations of actinides, not solely for the purpose of observing Am(III) chelation alone. The reasoning was that the likelihood of ingestion or inhalation of Am would be in an accident at a nuclear facility, in which case multiple actinides would be present.

8.7. Ligands for Americium Removal from Bone

Again, 10 ligands that were evaluated in *in vivo* studies in mice were subsequently studied in an *in vitro* system in which Pu or Am was allowed to bind to a bone mineral surrogate, calcium hydroxyapatite (HAP).[171] The most effective agents for removing Am bound to bone mineral were, in decreasing order of efficacy, H(2,2)-(Me-3,2-HOPO) (**99**) > 3,4,3-LI(1,2-HOPO) (**111**) > TREN(Me-3,2-HOPO) (**86**) = TREN-(1,2-HOPO) (**116**) > 3,4,3-LI-CAM(C) (**53**) = 5-LIO-(Me-3,2-HOPO) (**84**). Those seven test ligands noted above and $ZnNa_3$−DTPA removed potentially useful amounts of Am previously bound to bone mineral, ranging from 1.5% by $ZnNa_3$−DTPA to 21% by H(2,2)-(Me-3,2-HOPO) (**99**). The *in vitro* study provided additional evidence that the binding of Pu to bone mineral is more stable than that of Am.

The efficacies of the ligands containing only HOPO groups for removing Am from bone mineral were generally in the order octadentate > hexadentate >

tetradentate. Octadentate linear 3,4,3-LI(1,2-HOPO) (**112**) was more effective than its branched H-shaped counterpart, H(2,2)-(1,2-HOPO) (**118**). The octadentate ligands more than satisfy the requirement for hexadentate coordination, and provided that three of their bidentate functional groups can bind Am without steric hindrance, the extra binding unit appears to enhance the stabilities of their Am complexes. The tripodal hexadentate backbone of the ligands with a TREN backbone is nearly ideal for full six-coordination of Gd(III),[367] and presumably that is also the case for Am(III). It seems likely that the tetradentate HOPO ligands can form incomplete 1:1 Am complexes.

In general, the Me-3,2-HOPO ligands removed more mineral-bound Am than their structural 1,2-HOPO analogues, in agreement with the relative stabilities of their tris-Fe(III) complexes,[287] except that by 24−48 h the amounts of Am removed by TREN(Me-3,2-HOPO) (**86**) and TREN(1,2-HOPO) (**116**) were the same. Apparently, the favorable spatial orientation around Am(III) afforded by the TREN backbone allowed the less potent 1,2-HOPO functional group to slowly remove appreciable mineral-bound Am. Tetradentate 5-LIO(Me-3,2-HOPO) (**84**) removed almost 6% of mineral-bound Am in 24−48 h, suggesting that log K_{ML} of its 1:1 Am(III) complex is greater, while that of the less effective tetradentate 4-LI(1,2-HOPO) (**109**) is less than 22.9, the formation constant of Am(III)−DTPA.[370] Three of the tested ligands contain functional groups that are unsuitable for Am(III) complexation at pH 7.2: the catecholates [CAM(C) and CAM(S)] and hydroxamate [as in DFO-(1,2-HOPO) (**112**)]. The efficacies of the octadentate ligands containing those functional groups were poor for reducing Am retention in the skeletons of dogs or rodents.[117,172,184,224] Unlike the HOPO functional groups, which are ionized and ready for metal binding at physiological pH, the hydroxyl groups of catechol and hydroxamate must first be deprotonated,[167,371] and Am(III) apparently cannot deprotonate a sufficient number of catecholate or hydroxamate groups to form stable complexes in that pH range.[22,317]

The *in vitro* model showed that several of the test ligands are substantially more effective for removal of Pu and/or Am from bone mineral than $ZnNa_3$−DTPA. The important structural features that determine whether a ligand will be effective for removing an actinide from bone mineral are appropriate denticity, good aqueous solubility at physiological pH, and functional groups that form stable complexes at reasonably fast rates in the physiological pH range. Among the eight most effective ligands for Pu and or Am removal from bone mineral, three have serious toxicity-related problems at effective dose *in vivo*: 3,4,3-LI-CAM(S) (**42**),[184] 3,4,3-LI-CAM(C) (**53**),[164,172] and H(2,2)-(Me-3,2-HOPO) (**95**).[150] The five ligands of low to moderate toxicity at effective dose *in vivo* included DFO(1,2-HOPO) (**115**) (effective only for Pu),[167] TREN(Me-3,2-HOPO) (**86**), TREN(1,2-HOPO) (**114**) and 5-LIO(Me-3,2-HOPO) (**84**) (effective only for Am),[121,150] and 3,4,3-LI(1,2-HOPO) (**112**), which stands out as the only ligand with acceptably low toxicity at effective dose that removed both Pu and Am from bone mineral.[150,176,199]

9. Uranyl Ion-Sequestering Agents

9.1. Uranium and Uranyl Coordination Chemistry

Unlike the later actinides, the coordination chemistry of uranium predates the Atomic Age, and much more is known about its fundamental chemistry.[7,123] There are several recent reviews in the actinide literature covering specific areas of uranium chemistry (organoactinide,[372,373] solution and extraction behavior,[125,138] carbonate,[7] and macrocycles,[374,375]), but there has not been a comprehensive review of uranium coordination chemistry in more than 20 years. Uranium is the second most common naturally occurring actinide (after thorium), is more often encountered, and is found in more applications than thorium. Uranium is most commonly used as nuclear fuel in fission reactors for civilian energy generation purposes, but it has many other uses: as a pigment in glass and ceramics, as fissile weapons material (in the form of enriched uranium, ^{235}U), as armor plating, and in armor piercing projectiles (in the form of depleted uranium, ^{238}U, 99.3% of naturally occurring uranium).[4,124]

Like plutonium, uranium exhibits diverse redox chemistry, possessing four principal oxidation states: III, IV, V, and VI. The penta- and hexavalent oxidation states exist as linear dioxocations in most solutions and in many solids.[3] The most common oxidation states of uranium are U(IV) and U(VI), and these are the most likely to be encountered under environmental conditions.[7] The majority of U complexes reported in the literature are those of U(IV).[376] Almost all of the uranium complexes that have been structurally characterized are neutral. Examples of charged species (III, IV, and V) complexes are quite unusual.[377,378]

Early on, hexavalent uranyl ion (UO_2^{2+}, U(VI)) was found to be the most stable species in aqueous solutions and *in vivo*.[73] U(IV) complexes tend to be very hygroscopic, eventually being oxidized to U(VI), making U(IV) a poor model for Pu(IV) in aqueous solutions.[124] The uranyl ion, a hard Lewis acid, has a high affinity for hard donor groups.[123] For example, uranium is highly oxophilic, and far fewer examples of complexes containing U−S bonds than those featuring U−O bonds have been reported.[379] Equatorial pentacoordination generally results from five- and six-membered chelate rings with bidentate ligands, as in the case of $[UO_2(acac)_2(H_2O)]$,[380] or with a monodentate ligand, as in $[UO_2(DMSO)_5]^{2+}$.[381] A recent resurgence of interest in the coordination chemistry of the 5f elements, much of it focused on uranium, has been inspired by a need not only to ameliorate environmental contamination but also to expand structural diversity, develop new synthetic methods, develop new separations techniques, and determine reactivity and catalytic properties.[7,373]

The origins of organoactinide chemistry stem from investigations to develop volatile compounds to be used as agents for uranium isotope separation early

in the Manhattan Project and continued with the synthesis of complex numerous cyclopentadienide (Cp) compounds in the early 1950s.[372] Following the synthesis of the first actinide−Cp complex in 1956,[382] the Cp complexes of a large number of the actinides have been investigated, including several of the transplutonium elements.[2,383] This early work and subsequent developments have been reviewed,[372,384,385] and more complete reviews of the structural aspects of the bonding and structural characterization can be found elsewhere.[371,383] Much of this work focuses on the structural trends between organoactinides and organolanthanides and questions surrounding the modes of bonding. A dominant question concerning organometallic compounds of the f metals is the degree to which "covalency" is important in the bonding.[371]

Streitwieser's observation that the highest occupied molecular orbitals of the octagonal dianion, obtained by adding two electrons to cyclooctatetraene (COT), have appropriate symmetry to engage in bonding with the uranium 5f orbitals led to the prediction and subsequent synthesis of uranocene, a remarkable success for orbital symmetry theory.[386,387] This was the first example of an f transition metal containing the COT dianion, and it was the suggestion of increased f orbital participation in bonding that served as the impetus for further research.[383] This system was later structurally characterized by X-ray crystallography, confirming the symmetrical π-complex sandwich structure, as predicted.[388]

The reaction of UCl_4 with an excess of $Na_2[(3)\text{-}1,2\text{-}C_2B_9H_{11}]$ yields the anion $U[(3)\text{-}1,2\text{-}C_2B_9H_{11}]_2Cl_2^{2-}$, the first f metal carborane complex.[389] The U(dicarbollide)$_2Cl_2^{2-}$ ion has a formal coordination number of 8, with a geometry not unlike that of Zr(Cp) $_2Cl_2$. While the dicarbollide ligand coordinates through a pentagonal face and is functionally isoelectronic with the Cp anion, it is substantially larger and carries a 2− charge. This is explained by the steric considerations, and also explains why this metallocarborane can be formed whereas a true UCp_2Cl_2 has not been isolated.[371,390]

While uranium in the +3 oxidation state is kinetically stable, it will eventually reduce water.[391] Because of this, like the metallocarborane, the vast majority of the organoactinide complexes are prepared using U(IV), but recently U(III) complexes have become more common.[400,421] A new, readily prepared starting material, $UI_3(THF)_4$, has made U(III) complexes more accessible,[392] and this has been used to form several new compounds stabilized by the use of sterically demanding alkyl, amide, and phenolate ligands, in addition to the classical cyclopentadienyls often used in organometallic chemistry.[391] Sterically demanding ligands such as these are frequently required to generate low-coordination-number complexes of uranium and have been exploited in the preparation of a trigonal monopyramidal triamidoamine trivalent uranium compound which forms an extraordinary complex with dinitrogen.[376] The combination of a high reducing power and high susceptibility to incoming Lewis acids makes these new U(III) systems highly reactive coordination and organometallic compounds.[391] The nonaqueous chemistry of U(III) is still not completely defined, and there are still far fewer examples of characterized U(III) compounds than U(IV) or U(VI) compounds.[373,392]

In aqueous solution, the pentavalent UO_2^+ ion, U(V), quickly disproportionates into the U(IV) and U(VI) oxidation states to give U^{4+} and UO_2^{2+}.[124] Examples of complexes of U(V) are subsequently often air and/or water sensitive and uncommon,[373] but a number of these have been characterized.[377,393] The first organouranium (V) complexes were prepared in 1984 by Brennan and Andersen, by oxidation of the trivalent metallocene with either Me_3SiN_3 or PhN_3 to prepare $(C_5H_4Me)_3U{=}NR$, where R is $SiMe_3$ or Ph, respectively.[373] More recently, an unusual hexakis-amidouranium(V) anion was prepared using U(III) as the starting material and employing anthracene elimination as the means for oxidation to prepare a U(V) hexakis-amido complex.[377] The paramagnetism, structural flexibility, and redox behavior make uranium attractive as the basis of molecular precursors of novel conducting and magnetic materials. To this end, homoleptic uranium dithiolene complexes have been prepared, and one of these recently described, [Na(18-crown-6)-(THF)]-[U(η^8-C8H8)(5,6-dihydro-1,4-dithiin-2,3-dithiolate] (where the crown ether is a cocrystallization agent), is the first U(V) complex featuring a direct metal−sulfur bond.[393]

Complexes featuring multiple bonds between uranium and other elements are uncommon. Of those that have been reported, most are uranium imido (U=N−R) complexes.[391] The multiply bonded oxo (M=O) group is isoelectronic with imido ligands (M=N−R), and this similarity has been exploited often.[394] In 1992, Arney and Burns reported the first syntheses of uranium imido complexes,[395,396] later improving on the synthesis in 1998.[397] These researchers also found the actinide in these complexes to be capable of C−H bond activation.[398] Direct reduction of azides resulted in the uranium bis-imido complexes.[397] These have now been prepared with U(IV) and U(VI),[399] and this work has inspired the recent synthesis of the first actinide ketimido complex, $(C_5Me_5)_2U(-N{=}CPh_2)_2$,[399] as well as the first actinide hydrazonato complex, $[(C_5Me_5)_2U(\eta^2\text{-}(N,N')\text{-}CH_3{-}NN{=}CPh_2)(OTf)]$.[400]

There are fewer examples of imido ligands bound directly to U(VI); presumably the failure of traditional organometallic methods has been the result of the highly electropositive nature of uranium.[394] The reaction of uranyl(VI) ion (UO_2^{2+}) (as K(18-crown-6)$_2[UO_2Cl_4]$) with the triamidoamine ligand $Li_3[N(CH_2{-}CH_2NSiBu^tMe_2)_3]$ results in an unusual mixed-valent (V/VI) dimeric complex in which the coordination geometry at each uranium center is that of a capped trigonal bipyramid, each coordinated to one of the oxo groups and one of the triamidoamine ligands through the capping amine and two of the three pendant amido ligands, while the third of the pendant amido ligands forms a bridging imido ligand with the second metal center.[401] In another recent preparation, triamidoamine complexes of trivalent

uranium have been used to prepare new imido and hydrazido complexes and a bridging oxo dimer.[391]

The field of organoactinide chemistry appears of late to have been driven by the development of new uranium-based catalysts. Uranium organoactinide complexes (e.g., of the structure $Cp^*_2UR_2$) have been found to be effective catalysts for alkene hydrogenation and C−H bond activation and, when supported by dehydroxylated alumina, olefin hydrogenation and polymerization.[373,398] The first example of intramolecular C−H activation of a pentamethylcyclopentadienyl methyl group in an actinide complex was observed in the thermolysis product of bis(Cp*)U(=NAd)$_2$ (Ad = 1-adamantyl). The resulting activation product is a reduced U(IV) metallocene bis(amide) complex, with one methylene formed by the nitrogen of one amide group coordinating the methyl group.[398]

Uranium(IV) and uranyl (U(VI)) salts have been found to be both efficient and reusable catalysts for the acylation of aromatic compounds. When protected from water, the catalytic reaction is highly specific, and both the mono- or bisacylation products are obtained in high yield, free of uranium. The strongest Lewis acids, the uranyl salts, produce the best yields, and these also possess the advantage of aqueous solubility, key for an increased ease of extraction from the organic products.[402] Taking advantage of the Lewis acidic properties of the uranium, uranium triiodide has been found to be an efficient catalyst for Diels−Alder reactions requiring only short reaction times and 1 mol % amounts of catalyst.[403]

Stepping away from catalytic applications, waste remediation has also been of import in driving research in uranium chemistry. Crucial to the development of new methods of waste treatment and long-term strategies for safe nuclear waste storage are studies of the coordination chemistry and speciation of uranium in aqueous solutions. These studies will aid in defining the modes of migration and transport in natural waters, of import as any actinides released into the environment will eventually come into contact with water.[7,404] As discussed earlier (see section 6.1), plutonium is readily immobilized in sediments in natural waters[9,23] but has been found to migrate in carbonate rich soils.[7,23] Carbonate and hydroxide strongly complex uranyl and will also affect the mobility of this ion in natural groundwaters. It is widely held that carbonate complexes of actinides play a role in their migration from a contamination site, making carbonate chemistry crucial to understanding the geochemical behavior of uranium.[7]

Many macrocyclic systems have been studied as uranyl (U(VI))-coordinating ligands for potential use in applications such as waste remediation and/or water purification. Tabushi first introduced polyketone-based systems as uranyl cation-complexing agents.[405,406] Others have sought to design or modify calixarene systems expressly for the complexation or extraction of uranyl (UO_2^{2+}) cations.[407] To this end, the uranyl (UO_2^{2+}) complexes of calix[6]arenes,[408] calix[7]arenes,[409] and double-pocket calix[12]arenes[408] have been reported, and calix[4]arene systems substituted with CMPO or HOPO have been designed expressly for the selective coordination of uranyl (UO_2^{2+}).[410−413] In addition, crown ethers have been studied extensively as uranyl coordination ligands, and it has been established crystallographically in the solid state that crown ethers form complexes with either U(IV) or U(VI) cations in a variety of solvent systems, although some of these complexes do not feature an in-cavity mode of interaction.[414−420] Uranyl (UO_2^{2+}) Schiff base complexes produced both by templating with the metal ion and independently of the metal have been explored.[421−424] Another widely known example of this templating scheme for the formation of uranyl complexes is the superphthalocyanine uranyl (UO_2^{2+}) complex of Marks and Day.[425,426] Perhaps inspired by this, expanded porphyrin (UO_2^{2+}) complexes have been designed as uranyl coordination ligands.[359,360,374,375,421,424,427,428]

To better understand the nature of the siderophore-based complexes of uranium and their potential use in the development of extraction and sequestering agents, the tetrakis(catecholato)uranate(IV) complex, $Na_4[U(C_6H_4O_2)_4]\cdot 21H_2O$, has been prepared in strongly alkaline solution and structurally characterized. This crystal formed readily from aqueous solution as isomorphous crystals that were very close in geometry to the idealized trigonal-faced dodecahedron polyhedra. Chelating ligands for applications with actinides should allow appended catecholates to dispose themselves about the metal in the preferred dodecahedral geometry. Precession photographs revealed that the unit cells of the tetrakis(catecholato)thorate(IV) and tetrakis(catecholato)uranate(IV) are nearly identical. Also, like the tetrakis(catecholato)thorate(IV) and the tetrakis(catecholato)cerate(IV) complexes discussed earlier (see sections 7.2 and 6.2), the metal−oxygen distances in the tetrakis(catecholato)uranate(IV) complex are not all equivalent. The difference is even more striking than that of the thorate complex, differing by 0.027 Å. The metal is slightly offset within a trapezoid, the longer metal−oxygen length averaging 2.362 Å, and the shorter side metal−oxygen bond length, 2.389 Å. This greater difference in comparison to the thorium(IV) complex is undeniably due to the $5f^5$ electronic configuration of the uranium. The difference in the average M−O distances between the two catecholate actinide complexes, 0.044 Å, is close to that of their slightly different ionic radii.[310] (For comparison to the other related catecholate complexes characterized, refer to Figure 5 and Table 5.) To date, the development of catalysts and pursuit of new solutions to issues of waste remediation resulting from energy and weapons production have been the major driving forces in the research of uranium chemistry.[429]

9.2. Uranium in Biological Systems

The rationale for actinide chelation therapy is that reduction of tissue burdens and cumulative radiation doses significantly diminishes radiation-induced tissue damage and carcinogenesis. In the case of uranium and neptunium, chelation therapy also reduces chemical damage in kidneys and liver.[121,122] Recent studies done in Germany, using a small group of

normal healthy volunteers who do not work with or around uranium, have determined that, while adolescents appear to have very little naturally occurring uranium (measured as ^{238}U) and thorium (measured as ^{232}Th) present in their excretions, older subjects had increased concentrations of uranium and thorium in their excretions, and these increased significantly with age. These findings support the view that uranium is a common trace element in the environment, and that some uranium intake and accumulation is natural.[430,431] Comprehensive investigations of the pharmacology and toxicology of uranium compounds were conducted during World War II by the Manhattan Project.[73,432] The hexavalent uranyl ion (UO_2^{2+}, U(VI)) was found to be the most stable form in aqueous solutions and *in vivo*, and most research on absorption, transport, deposition in tissues (most importantly in kidney and bone), and excretion focused on uranyl compounds.[121,433,434]

Uranium(VI) (UO_2^{2+}, uranyl) is nephrotoxic.[73,432] Depending on isotopic composition and dose, U(VI) is also chemically toxic and carcinogenic in bone, the major long-term storage organ for soluble uranium.[435] Depleted uranyl nitrate has been found to transform cultured human osteoblastic cells to the tumorgenic phenotype,[436] while the isotopes of uranium with high specific alpha activity, ^{232}U and ^{233}U, induce bone tumors in mice.[437] The GI tract is not an important excretory pathway for U(VI),[73,432−434] but a small fraction of plasma U(VI) is expected to be passively secreted with the digestive juices in a manner similar to that of serum calcium.[438] Absorption of U(VI) from the GI tract is small, and the endogeneously secreted fraction is excreted in feces.[438]

In humans, unlike the prolonged retention of nearly all of an intake of Pu(IV), the major fraction of a uranium intake is excreted. Approximately two-thirds of an iv injection of a soluble uranium salt is eliminated from the plasma and excreted by the kidneys within 24 h. Some 20% of the total uranium absorbed into the circulation deposits in the bone, and about 12% is deposited into the kidneys. The renal excretion pathway explains the tendency of U(VI) to collect in the kidneys.[44,433,434] The predominant biological endpoint of chemical uranium poisoning, renal injury, has been described, and the dose−response relationships between acute and chronic intakes of uranium compounds and renal damage and lethality, defined in animals, have provided the foundations for the standards of workplace protection currently in place.[433,434]

Although sought for many years, there was no ligand that stably bound U(VI) *in vivo*, promoted its excretion, and efficiently prevented or reduced deposition in the kidneys. Prompt injection of $CaNa_2$−EDTA at a ligand:uranium molar ratio greater than 160 or $CaNa_3$−DTPA at a molar ratio greater than 10 reduced mortality after a lethal injection of UO_2^{2+} in rats or mice. $CaNa_3$−DTPA, at a molar ratio greater than 60, was found to increase urinary uranium excretion.[439−442] Dounce and Lan tested catechol in an *in vitro* protein system at pH 4.5−5, and only very weak U(VI) complexation was observed.[443] It is now recognized that the pH of that system was too low to have obtained stable metal coordination with such a weakly acidic ligand.[239] The more acidic Tiron forms a stable U(VI) complex within the physiological pH range, and when injected promptly, it reduced mortality in uranium-poisoned rabbits,[234] but a molar ratio greater than 200 was required to reduce U(VI) deposition in the kidneys.[235,236,441,442] Chronic chemical renal injury caused by natural uranium and irradiation of bone and lungs from deposited isotopically enriched uranium have largely been avoided in routine operations in the uranium industries by the confinement of sources, strict adherence to air concentration limits, respiratory protection, and regular monitoring of uranium in workers' urine.[444]

9.3. Depleted Uranium

In addition to the ever-increasing amounts of uranium handled worldwide as the use of nuclear power continues to expand,[4,5,445] the use of depleted uranium (DU) has added another dimension to potential introduction of uranium into the human body in the form of finely divided shrapnel.[446−448] A large fraction of the DU leaving enrichment facilities in the United States is converted for use as military ordinance and armor and as ballast in airplane construction. A number of military personnel were accidentally wounded by DU shrapnel during the Gulf War, and the slowly dissolving, finely divided DU fragments are continuous sources of systemic uranyl ion (UO_2^{2+}, uranyl). Persons wounded during the Gulf conflict and in Kosovo with DU shrapnel present a unique medical problem. The fragments of the DU ordinance, many too small to remove surgically, are chemically reactive and locally irritating, and as they slowly dissolve, they are potentially exposing the wounded individuals to chronic kidney poisoning and an unacceptable amount of uranium accumulation in the skeleton.[446−448]

Depleted uranium has been used in heavy armor for tanks as well as in kinetic energy ammunition. The great density of uranium confers DU munitions with better armor-piercing capabilities. On impact, the uranium fragments into many tiny particles that can then ignite. These fragments, whether caused by the impact and subsequent explosion, by damage to armor on vehicles, or by vehicles and munitions damaged by fire, can form a particulate dust that can be inhaled or contaminate wounds.[449,450]

The role of DU in the development of illnesses in veterans of the Persian Gulf conflict has recently been discounted, as the soldiers most directly in contact with dust, namely those in or near explosions of DU ordinance or armored vehicles or others who treated or rescued the wounded, do not exhibit any increase in the symptoms expected in those with more direct exposure.[449,450] Depleted uranium has 40% less specific activity than naturally occurring uranium, but as a heavy metal, it is still chemically toxic.[450] Thus, it follows that the kidney should be the first organ directly affected by poisoning with uranium, and yet these soldiers were not found to have suffered any impairment of renal function.[449] Studies seeking to establish a connection between

uranium exposure and bone cancers are inconclusive.[449] The potential for kidney damage or increased bone cancer is still being followed in these patients, and chelating ligands could be useful in reducing the potential effects of uranium in wounds.

9.4. Uranyl Complexes with Multidentate CAM Ligands

The modestly successful reduction of acute U(VI) toxicity and reduction of body U(VI) with Tiron[205,234,236] and the favorable stability constant of U(VI)−catechol (log $K_{ML} = 15.9$) suggested that multidentate ligands containing CAM or structurally analogous HOPO units would be effective for *in vivo* chelation of U(VI).[121] Several ligands containing two, three, or four bidentate catecholate or hydroxypyridonate metal-binding groups, developed for *in vivo* chelation of other actinides, were found on evaluation in mice to be effective for *in vivo* chelation of U(VI).[157] Several new CAM-based ligands were prepared to identify the most promising backbones and binding groups for U(VI).[121]

Ligands containing CAM(S) [2-LI-CAM(S) (**28**), 4-LI-CAM(S) (**29**), 5-LI-CAM(S) (**30**), 3,4-LI-CAM(S) (**32**), and 3,4,3-LI-CAM(S) (**42**)] or CAM(C) [4-LI-CAM(C) (**50**), 5-LI-CAM(C) (**51**), and 3,4,3-LI-CAM-(C) (**53**)] and $CaNa_3$−DTPA were evaluated for *in vivo* chelation of U(VI) in mice ($^{232+235}UO_2Cl_2$ or $^{233}UO_2Cl_2$ injected iv; ligands injected ip, 30 μmol kg^{-1} at 3 min; ligand:U molar ratio 75 or 92).[121,157] Unlike $CaNa_3$−DTPA, all of the CAM-based ligands reduced whole body and kidney uranium significantly compared with untreated U(VI) injected controls.[121,156] The CAM(S) ligands and 3,4,3-LI-CAM(C) (**53**) also significantly reduced skeleton U(VI) compared with controls. Increasing the ligand:U molar ratio of 5-LI-CAM(S) (**30**) improved its efficacy for reducing U(VI) in the kidneys and skeleton.[121] Unfortunately, 2-LI-CAM(S) (**28**), 4-LI-CAM(S) (**29**), and 3,4-LI-CAM(S) (**32**) were found to be severely toxic, and 3,4,3-LI-CAM(S) (**41**) moderately toxic, producing kidney damage.[121,157]

Small changes in the structures of the CAM chelating agents greatly reduced toxicity, as 5-LI-CAM(S) (**30**), 4-LI-CAM(C) (**50**), 5-LI-CAM(C) (**51**), and 3,4,3-LI-CAM(C) (**53**) were of a low to mild toxicity and promising for continued development.[121,157] In studies of dose−effectiveness with the most effective of these ligands, 5-LI-CAM(S) (**30**) and 5-LI-CAM(C) (**51**), it was determined that 5-LI-CAM(C) (**51**) was not significantly effective for reducing skeleton U(VI).[157] Injected promptly, 5-LI-CAM(S) (**30**) efficiently chelates circulating U(VI) and is able to divert to excretion a significant fraction of the U(VI) already deposited in bone. Sufficient 5-LI-CAM(S) (**30**) was orally bioavailable to reduce kidney U(VI).[157]

9.5. Uranyl Complexes with Multidentate TAM Ligands

Two methylterephthalamide-based chelating ligands (MeTAM) were prepared and investigated for U(VI) chelation.[157] Ligands containing MeTAM binding groups, 4-LI-MeTAM (**63**) and 5-LI-MeTAM (**64**), were synthesized not only to assess binding group efficacy but also to probe the suspected specific renal toxicity of the 4-LI-MeTAM (**63**) structure. The MeTAM ligands reduced both kidney and skeleton U significantly compared with 24-h controls. Both 4-LI-MeTAM (**63**) and 5-LI-MeTAM (**64**) were found to be severely toxic in mice, causing damage to the kidneys, liver, and/or spleen. While unacceptable for this application, this chelating subunit may still be of interest in terms of waste remediation.[157]

9.6. Uranyl Complexes with Multidentate HOPO Ligands

A rational design of uranyl-sequestering agents based on 3-hydroxy-2(1*H*)-pyridinone (3,2-HOPO) ligands resulted in the first effective agent for mammalian uranyl decorporation.[121,156,157] In an initial study, hexadentate TREN(Me-3,2-HOPO) (**86**) reduced kidney U(VI) to less than 50% of control.[156] Although significant reductions in body and kidney U concentrations were achieved with TREN(Me-3,2-HOPO) (**86**), skeletal deposits of U were apparently inaccessible to this ligand, but more than one-half of U still circulating in plasma or loosely bound in soft tissue was eliminated in excess of control excretion.[156] This promising result at the outset encouraged exploration of several multidentate HOPO ligands with a wide range of molecular backbones.

Ligands (tetra- to octadentate) containing Me-3,2-HOPO or 1,2-HOPO groups and $CaNa_3$−DTPA were screened for *in vivo* chelation of U(VI) in mice in the same treatment regimens used to investigate the CAM and MeTAM ligands. Resynthesized 3,4,3-LI-(1,2-HOPO) (**112**) was included among the series of new ligands evaluated for *in vivo* chelation of U(VI), because it had recently been reported to reduce body U(VI) in rats.[192] Like the CAM-based ligands, all of the Me-3,2-HOPO-based ligands [tetradentate, 3-LI-(Me-3,2-HOPO) (**81**), 4-LI(Me-3,2-HOPO) (**82**), 5-LI-(Me-3,2-HOPO) (**83**), and 5-LIO(Me-3,2-HOPO) (**84**); hexadentate, TREN(Me-3,2-HOPO) (**86**); and octadentate, H(2,2)-(Me-3,2-HOPO) (**99**) and 3,4,3-LI(1,2-HOPO) (**112**), but not TREN(Me-3,2-HOPO)-BAC (**93**)] were found to reduce whole body and kidney uranium significantly compared with controls, while $CaNa_3$−DTPA was not effective.[121,156,157] The cyclic hydroxamic acid analogues, 4-LI- (**109**) and 5-LI(1,2-HOPO) (**110**), proved to be ineffective for reducing whole body and/or kidney U(VI).[157] Three effective ligands for reducing kidney and/or bone U(VI), 4-LI-(Me-3,2-HOPO) (**82**), 3-LI(Me-3,2-HOPO) (**91**), and H(2,2)-(Me-3,2-HOPO) (**99**), were later determined to be severely toxic and were not investigated further.[121]

On the basis of low toxicity and high efficacy, 5-LI-CAM(S) (**30**), 5-LI-CAM(C) (**51**), 5-LIO(Me-3,2-HOPO) (**84**), TREN(Me-3,2-HOPO) (**86**), and 3,4,3-LI-(1,2-HOPO) (**112**), were chosen for dose efficacy studies. Injected at a molar ratio ≥300, all of these ligands reduced kidney U(VI) to less than 5% of control values; however, renal toxicity compromised the efficacy of 3,4,3-LI(1,2-HOPO) (**112**) at high dose.[121,157] In studies of its biokinetics in mice (Figure 12), 5-LIO(Me-3,2-HOPO) (**84**) was eliminated within

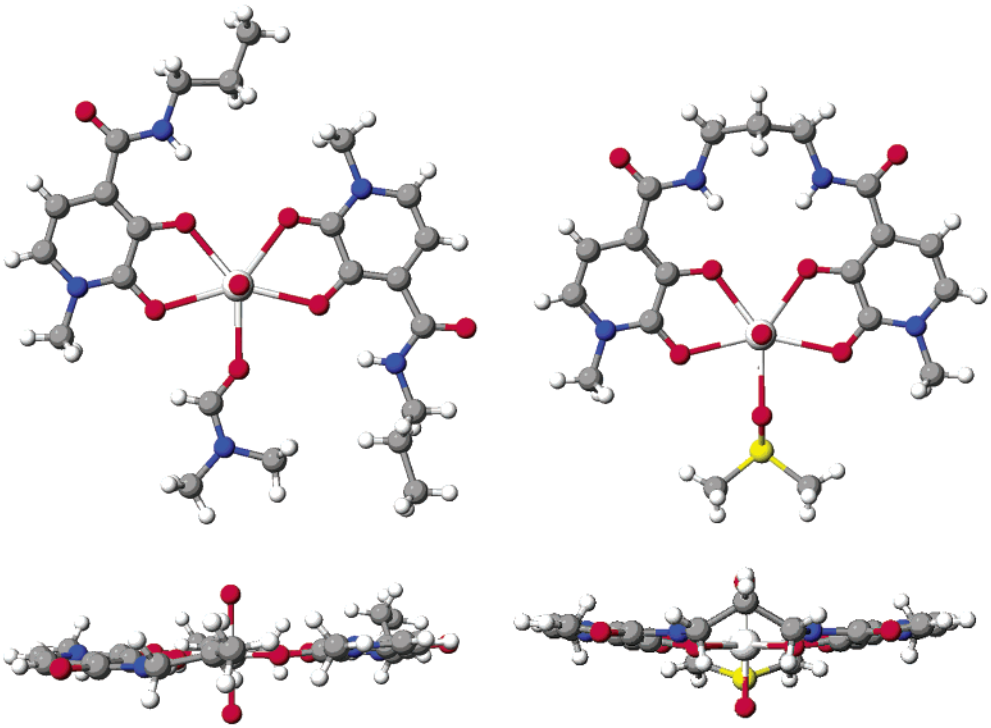


Figure 20. Molecular structure (top and side views) for the U(VI) (UO_2^{2+}) complexes of the bidentate PR(ME-3,2-HOPO) and 3-LI(Me-3,2-HOPO). The carbon atoms are depicted as gray, the oxygen red, the sulfur yellow, the nitrogen blue, the central uranium atoms white, and the peripheral hydrogen atoms smaller and white. These figures were generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 337.

2 h via the kidneys and liver, further reducing concern about the toxicity of other similar ligands.[121,147] Among the low-toxicity ligands, 5-LIO(Me-3,2-HOPO) (**84**) was the most effective for the reduction of U(VI) in the kidneys, and 5-LI-CAM(S) (**30**) was most effective for reducing U(VI) in the skeleton. These studies underscore the importance of the design involving a tetradentate ligand with a linear five-unit backbone for high-efficacy chelation of U(VI) *in vivo*.[157]

To better understand the relationship between the structure and *in vivo* U(VI) chelation efficacy of these ligands, a series of tetradentate Me-3,2-HOPO ligands was characterized via X-ray crystallography.[337] The tetradentate ligands chosen for study were composed of two hydroxypyridonate groups connected by a diamine linker via amide coupling. The crystal structures were determined for four tetradentate ligands: 3-LI(Me-3,2-HOPO) (**81**), 4-LI(Me-3,2-HOPO) (**82**), 5-LI(Me-3,2-HOPO) (**83**), and the bidentate PR-Me-3,2-HOPO(**77**). These were compared and correlated with the chemical and biological properties of the HOPO systems. Crystals were grown using either DMSO or DMF as solvent and can be regarded as replacing water in these systems. Each demonstrates a stable 1:1 ligand system (Figures 20, 21 and Table 16).[337]

The complexes of U(VI) with bidentate anions are relatively stable, and the U(VI) complexes formed *in vivo* with the bidentate HOPO group are equatorial, as expected.[156] The structures demonstrate that UO_2^{2+} is fully bound by those ligands in a nearly planar ring perpendicular to the plane occupied by the oxo oxygen atoms.[337] All of the tetradentate Me-3,2-HOPO ligand uranyl complex structures are similar, comprised of one uranyl, one tetradentate 3,2-HOPO ligand, and one coordinated solvent molecule. In each case, the metal ion is coordinated by seven oxygen atoms in a slightly distorted pentagonal bipyramidal geometry. The 3,2-HOPO rings, their attached oxygen atoms, and the atoms of the amides are coplanar. Some differences are noteworthy. While the HOPO bite angle is constant, the change in the length of the linker has a great influence on the equatorial plane configuration. The dihedral angles between two pyridinone ring planes in these complexes differ as the length of the linear backbone changes, giving these molecules a ruffled shape.[337] As this length increases, the angle between the uranium and the two phenolic oxygen donors also becomes greater, indicating strain caused by the linker. That four carbon atoms may be considered optimal length is consistent with the high efficacy of the 4-LI(Me-3,2-HOPO) (**82**) for *in vivo* U(VI) chelation.[337]

9.7. Ligand Cocktails for Multiple Actinides

Among the 20 ligands evaluated to date (including $CaNa_3$−DTPA), efficacy for reducing U(VI) in both kidneys and skeleton is in the order, based on denticity, tetradentate > hexadentate > octadentate, and based on binding group, MeTAM > CAM(S) = CAM(C) > Me-3,2-HOPO > 1,2-HOPO. Note that for both denticity and binding group, the order of effectiveness for U(VI) is almost the reverse of effectiveness for *in vivo* chelation of Pu(IV).[157] Three highly promising ligands for U(VI) have emerged from this work: 5-LI-CAM(S) (**30**) and -CAM(C) (**51**), and 5-LIO(Me-3,2-HOPO) (**84**).

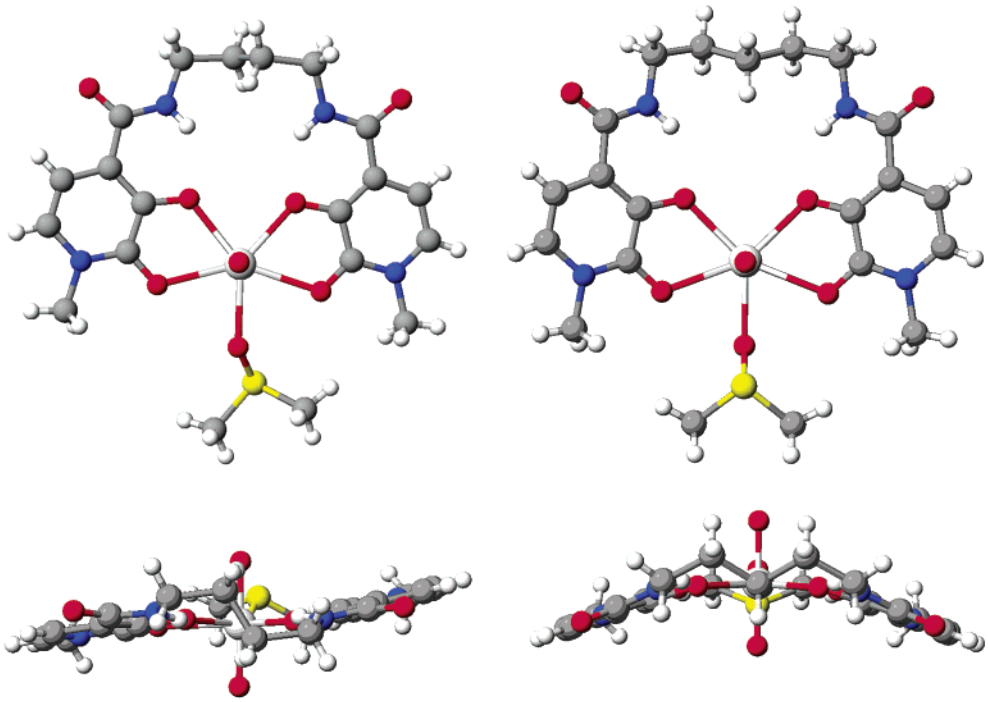
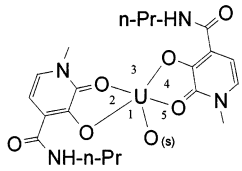
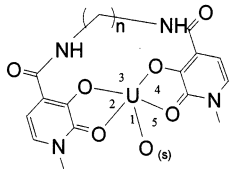


Figure 21. Molecular structure (top and side views) for the U(VI) (UO_2^{2+}) complexes of 4-LI(Me-3,2-HOPO) and 5-LI(Me-3,2-HOPO). The carbon atoms are depicted as gray, the oxygen red, the sulfur yellow, the nitrogen blue, the central uranium atoms white, and the peripheral hydrogen atoms smaller and white. These figures were generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 337.

Table 16. Relevant Bond Lengths and Angles for the U(VI) (UO_2^{2+}) Complexes of PR(Me-3,2-HOPO) (DMF), 3-LI(Me-3,2-HOPO) (DMSO), 4-LI(Me-3,2-HOPO) (DMSO), and 5-LI(Me-3,2-HOPO) (DMSO)[a]



UO_2(PR-ME-3,2-HOPO)$_2$·DMF



UO_2(nLI-Me-3,2-HOPO)·DMSO

Bond Lengths (Å)[b]

UO_2(PR-ME-3,2-HOPO)$_2$·DMF		UO_2(3-LI-Me-3,2-HOPO)·DMSO		UO_2(4-LI-Me-3,2-HOPO)·DMSO		UO_2(5-LI-Me-3,2-HOPO)·DMSO	
U−O1	1.787(5)	U−O1	1.783(4)	U−O1	1.779(5)	U−O1	1.775(4)
U−O2	1.779(6)	U−O2	1.783(4)	U−O2	1.760(4)	U−O2	1.776(4)
U−O3	2.457(5)	U−O3	2.410(3)	U−O3	2.434(4)	U−O3	2.442(3)
U−O4	2.329(5)	U−O4	2.350(3)	U−O4	2.355(4)	U−O4	2.379(3)
U−O5	2.407(5)	U−O(S)	2.357(4)	U−O5	2.421(4)	U−O(S)	2.349(4)
U−O6	2.374(5)			U−O6	2.360(4)		
U−O(S)	2.371(5)			U−O(S)	2.369(5)		

Bond Angles (deg)

	UO_2(PR-ME-3,2-HOPO)$_2$·DMF	UO_2(3-LI-Me-3,2-HOPO)·DMSO (n = 3)	UO_2(4-LI-Me-3,2-HOPO)·DMSO (n = 4)	UO_2(5-LI-Me-3,2-HOPO)·DMSO (n = 5)
angle 1	74.2(2)	76.94(7)	72.7(2)	69.87(7)
angle 2	66.4(2)	66.88(9)	66.6(2)	65.96(7)
angle 3	76.8(2)	72.33(13)	79.8(2)	90.26(14)
angle 4	66.7(2)	66.88(9)	66.2(2)	65.96(9)
angle 5	76.1(2)	76.94(7)	75.0(2)	69.87(7)

[a] Estimated standard deviations in the least significant figure are given in parentheses. Uranyl oxo atoms were omitted for clarity. O1 and O2 are the abbreviations of HOPO oxo donors Oxo1 and Oxo2, respectively. P1 and P2 are the abbreviations of HOPO phenol oxygen donors, respectively. S labels the oxygen from the coordinating solvent molecule.[337] [b] Oxygens 1 and 2 are the uranyl oxo oxygens. Oxygen S is from the solvent molecule. Symmetry in the 3-LI and 5-LI structures results in there being only two metal−oxygen distances for the ligand.

Considering their effectiveness, low toxicity, low cost, and synthetic ease, the most efficient agents for U(VI) appear to be tetradentate ligands with the 5-LI backbone.[157] All of the ligands tested for U(VI)

chelation properties also chelate Pu(IV) *in vivo*. The HOPO ligands also chelate Am(III) and U(IV) *in vivo*. The efficacy of these ligands is in large part determined by the kind and number of metal-binding units.[149,150,156,159,160,164,167,176,179] This makes them potentially extremely useful in contaminations with mixtures of unknown actinides, especially considering the poor chelation ability of DTPA for U(VI).

The most promising approach to chelation therapy for U(VI) appears to be a combination of ligands with somewhat different abilities to gain access to U(VI) in kidney and bone. One such combination of effective low-toxicity ligands takes advantage of the greater ability of 5-LIO(Me-3,2-HOPO) (**84**) to react with U(VI) in the kidneys and the greater ability of 5-LICAM(S) (**30**) to chelate U(VI) already deposited in bone. Combined, the two ligands can achieve greater overall reductions of U(VI) in both kidneys and skeleton than equimolar amounts of either alone.[157] In light of the fact that, for both denticity and binding group, the order of effectiveness for U(VI) is almost the reverse of effectiveness for *in vivo* chelation of Pu(IV),[157] further studies will be required to see if the addition of other ligands to this "cocktail" will enable further increases in efficacy or will enable the production of highly effective treatments for multiple actinides.

10. Neptunium-Sequestering Agents

10.1. Neptunium Coordination Chemistry

Concerns about the potential hazards associated with neptunium have become a significant environmental issue due to the problems inherent in its long-term storage.[1,126,451] The only isotope of industrial or environmental concern is ^{237}Np, which is present in gram amounts in irradiated nuclear reactor fuel and is used in production of ^{238}Pu.[452] Both Np(V) and U(VI) are linear dioxo cations, O═M═O, that bind bidentate anions equatorially in the plane perpendicular to the oxo oxygens. The lower charge on the neptunyl ion leads to weaker and less stable complexes with bidentate anions than those formed by U(VI); however, Np(IV) complexes are as stable as those of Pu(IV).[2] In a dilute solution at pH 4−9.5, neptunium chemistry is dominated by local redox conditions. Under the mildly acidic conditions in aerated surface waters, the dominant species is Np(VI) as NpO_2^{2+}, which is weakly complexed by carbonate, sulfate, and phosphate, while Np(IV) is expected under reducing conditions in anaerobic neutral to alkaline waters such as deep groundwater, soils, or sea floor sediments, or in the presence of stabilizing ligands.[453] In contrast to the other actinides, neptunium is most stable in its pentavalent oxidation state, Np(V), in the form of NpO_2^+ under ambient conditions. This cation is then quite water-soluble and easily transportable under environmental conditions.[454]

The major potential environmental hazard of ^{237}Np is transport from high-level nuclear waste repositories into potable or agriculturally useful waters, thereby enabling its concentration in the food chain.[455] These fears have already been realized, as water discharged from the nuclear fuel plant at Sellafield, UK, has been determined to be the source of ^{237}Np detected in local soil and in grazing sheep.[456] The inherent mobility of neptunium provides a significant challenge in terms of effecting the long-term containment of neptunyl-containing waste, which must be treated with the utmost care because of the potential that this radioactive, toxic metal cation could enter into groundwater or surface waters as the result of seepage or spillage. Currently, there are no means available for extracting neptunium should it be introduced into groundwater; normal geological barriers have been determined to be ineffective.[7] Effective complexing agents could be used to mitigate the environmental threat by capturing the metal, isolating it, and rendering it insoluble in water.[128] Likewise, sequestering agents would be required should drinking water supplies become contaminated.

Like plutonium, the hazards of the alpha activity of neptunium as well as its scarcity have limited the development of its coordination chemistry, and only a handful of complexes have been structurally characterized. One seminal contribution to the field came from the group of Clark, et al., which demonstrated that crown ethers may be used to effect the complexation of neptunyl cations. The 18-crown-6 Np(VI) complex was the first transuranium crown ether inclusion complex to be characterized structurally.[457] More recently, an expanded porphyrin neptunyl complex has been reported. The so-called "isoamethyrin" [hexaphyrin(1.0.1.0.0.0)] forms the stable neptunyl (Np(V), NpO_2^+) complex when treated with an acidic solution containing neptunium(VI) in the presence of a base. This system represents the first crystallographically characterized neptunium complex stabilized by an all-aza donor set and is remarkable for its potential applications due to the fact that the ligand itself is highly pigmented and undergoes a startling color change from yellow as the freebase to rose on metal complexation.[458]

10.2. Neptunium under Physiological Conditions

Unraveling the *in vivo* behavior of neptunium is difficult, because the oxidation state of Np varies so greatly with the solution conditions. The existence of neptunium in several stable oxidation states in the environment and in living systems as Np(IV), Np(V), or Np(VI) complicates the prediction of its health hazards. The potential consequences of human exposure to neptunium have been reviewed.[151,452,459,460]

Chemically, ^{237}Np is as toxic as U(VI), and radiologically, it is about as toxic as ^{239}Pu.[44,452,461] As a chemical poison, ^{237}Np causes microscopic damage and functional impairment of hepatic cells and renal tubular epithelium, similar to the toxic effects of U(VI). These effects were observed in rats and sheep at doses greater than or equal to 1.5 mg/kg.[460] Depending on redox conditions *in vivo*, ^{237}Np exists as weakly complexing Np(V) or as Np(IV), which forms complexes as stable as those of Pu(IV).[2]

Redox conditions *in vivo* range from oxidizing in lungs and arterial blood to reducing in the GI tract lumen. Hence, depending on local concentrations of stabilizing biological ligands, both reduction of Np-

(V) and oxidation of Np(IV) can be expected.[59,452] Rapid plasma clearance and urinary excretion of Np(V) resemble those of U(VI). Deposition and early retention in skeleton and liver resemble those of Pu(IV).[122,461] The dominant neptunium species circulating and excreted in urine is Np(V), while that in bone and liver deposits is presumed to be Np(IV).[122] Neptunium urinary excretion behavior, in a fashion similar to UO_2^{2+} and the alkaline earths, could be explained if a large fraction remained unbound in plasma as NpO_2^+.[461] Initially, Np(V) is the dominant species in the circulation and the species filtered by the kidneys.[461]

In a fashion similar to the distribution of Am(III) and Pu(IV), the primary target tissue of Np is the skeleton, which accumulates, on average, 45% of absorbed Np. Initially, Np is deposited nearly uniformly on all anatomical bone surfaces, resembling Am(III) and U(VI) rather than Pu(IV), but retention is as prolonged as that of Pu(IV). Deposition of Np in liver is variable and much less than that of Am(III) or Pu(IV), on average 7% of total absorbed Np. Similarly to U(VI), a large fraction of absorbed Np (50% on average) is excreted in urine in the first 24 h, and urine continues to be the dominant excretion pathway.[122,151,156,452,459−461]

$CaNa_3$−DTPA was the first agent investigated specifically for *in vivo* chelation of Np. While it was found to increase excretion, thereby reducing damage to liver and kidneys, the modest reduction of bone deposits and the apparent independence of ligand effectiveness and dose were considered discouraging.[86,233,461] A new search for ligands that chelate neptunium *in vivo* and reduce its retention in soft tissue, to prevent or eliminate chemical toxicity, and in bone, to eliminate or reduce carcinogenesis, has begun in response to the recent trepidation concerning the possibilities for Np exposure. A major problem surrounding *in vivo* chelation of neptunium is reduction of circulating Np(V) to Np(IV), which can be stably chelated and excreted. Thus, the efficient decorporation of neptunium requires multidentate ligands that form exceptionally stable An(IV) complexes and facilitate reduction of Np(V).[122]

10.3. Neptunium Decorporation Using Multidentate CAM Ligands

The merit of this hypothesis, that efficient decorporation of neptunium requires multidentate ligands that form exceptionally stable An(IV) complexes and may facilitate the reduction of Np(V) to Np(IV), was explored through initial studies of *in vivo* neptunium chelation with 3,4,3-LI-CAM(C) (**53**) and 3,4,3-LI-CAM(S) (**42**).[122,156,190] The two octadentate CAM ligands and $CaNa_3$−DTPA were given ip (molar ratio 22) to mice 5 min after an iv injection of Np(V), and retention and excretion were determined at 24 h.[122] 3,4,3-LI-CAM(C) (**53**) significantly reduced ^{237}Np in skeleton and all soft tissues compared with controls. Although the sulfonated analogue, 3,4,3-LI-CAM(S) (**42**), reduced Np in the body to about 80% of controls, it did not meet the criteria for efficacy for circulating Np in these initial studies, because it did not increase the excretion of Np to an amount at least 10% greater than spontaneous excretion.[122]

It was also found that treatment with 3,4,3-LI-CAM(C) (**53**) resulted in elevated kidney Np, amounting to 2.7 times control.[122] This behavior is believed to be due to the instability at pH < 7 of the Np(IV)−3,4,3-LI-CAM(C) (Np(IV)−**53**) chelate, causing partial dissociation of the complex and deposition of Np in the kidneys.[122] This effect resembles that for Pu(IV) in rats and mice given this ligand and makes 3,4,3-LI-CAM(C) (**53**) of little use in this application.[164,172,190]

10.4. Neptunium Decorporation Using Multidentate HOPO Ligands

In vivo Np chelation was investigated with eight multidentate HOPO ligands: 5-LI(Me-3,2-HOPO) (**83**), TREN(Me-3,2-HOPO) (**86**), H(2,2)-(Me-3,2-HOPO) (**99**), 5-LI(1,2-HOPO) (**110**), 3,4,3-LI(1,2-HOPO) (**112**), DFO(1,2-HOPO) (**115**), TREN(1,2-HOPO) (**116**), H(2,2)-(1,2-HOPO) (**118**), and $CaNa_3$−DTPA.[156,190] Ligands were given ip (molar ratio 22) to mice 5 min after an iv injection of Np(V), and tissue retention and excretion were determined at 24 h.[122] Compared with controls, all of the HOPO ligands significantly reduced Np in the body, liver, and soft tissue. Whole body Np was reduced to 47% of controls by 5-LI(Me-3,2-HOPO) (**83**) (most effective) and to 73% of controls by TREN(1,2-HOPO) (**116**) (least effective). Most of the HOPO ligands reduced Np in kidneys significantly.[122] Skeletal Np was reduced significantly to about 76% of controls by the two tetradentate HOPO ligands [5-LI(Me-3,2-HOPO) (**83**) and 5-LI(1,2-HOPO) (**110**)] and to about 68% by three of the four octadentate HOPO ligands [H(2,2)-(Me-3,2-HOPO) (**99**), 3,4,3-LI(1,2-HOPO) (**112**), and H(2,2)-(1,2-HOPO) (**118**)]. The five most effective HOPO ligands reduced Np in skeleton, liver, kidneys, and other soft tissue, on average, to 72, 25, 34, and 22% of controls, respectively, while $CaNa_3$−DTPA was ineffective.[122] At the same injected dose, the 1,2-HOPO ligands were somewhat less effective for reducing body and tissue Np than their structural Me-3,2-HOPO analogues. Although significant reductions of body Np were achieved with TREN(Me-3,2-HOPO) (**86**) and TREN(1,2-HOPO) (**116**), skeletal deposits of Np were apparently inaccessible to these ligands.[122,156]

5-LI(Me-3,2-HOPO) (**81**), injected ip at 5 min, significantly reduced Np in the skeleton and all soft tissues by about the same amounts at molar ratios of 22 or 73. The same ligand doses given orally at 5 min significantly reduced Np in liver, soft tissue, and whole body. TREN(Me-3,2-HOPO) (**86**) or TREN(1,2-HOPO) (**116**), injected ip at 5 min (molar ratio 22), significantly reduced Np in liver, soft tissues, and whole body. Increasing the injected dose of the Me-3,2-HOPO ligand to a molar ratio of 73 also achieved reductions of Np in the skeleton that were significant compared both with the controls and with mice given the same ligand at the smaller molar ratio of 22. Given orally at a molar ratio of 22, TREN(1,2-HOPO) (**116**), but not TREN(Me-3,2-HOPO) (**86**), significantly reduced Np in soft tissues and whole body. Significant dose-dependent reductions of soft tissue and whole body Np were obtained with TREN(Me-3,2-HOPO) (**86**) given orally at molar ratios ≥73.

Both H(2,2) (Me-3,2-HOPO) (**99**) and H(2,2)-(1,2-HOPO) (**118**) injected ip at 5 min (molar ratio 22) significantly reduced Np in the skeleton and all soft tissues. Reductions of body and skeleton Np obtained with the Me-3,2-HOPO ligand were significantly better than when that ligand had been injected at the low molar ratio of 5.6. Given orally at 5 min, the Me-3,2-HOPO ligand significantly, and in a dose-dependent fashion, reduced Np in the soft tissues and whole body at molar ratios ≥137, and significantly reduced skeleton Np at the highest test dose (molar ratio 274). 3,4,3-LI(1,2-HOPO) (**112**), injected ip at 5 min (molar ratio 22), significantly reduced Np in the skeleton, liver, kidneys, and whole body, but at that dose was not orally effective. The two tetradentate and one octadentate HOPO ligands evaluated [5-LI-(Me-3,2-HOPO) (**84**) and H(2,2)-(Me-3,2-HOPO) (**99**), and 3,4,3-LI(1,2-HOPO) (**112**)] show promise as therapeutic agents for Np, because of their combined efficacies when given by injection or orally and acceptably low toxicity at effective dose.[122]

Further experiments with 3,4,3-LI(1,2-HOPO) (**112**) were undertaken to examine its efficacy for *in vivo* Np chelation in the case of wound contamination. 3,4,3-LI(1,2-HOPO) (**112**) was used at ligand:Np molar ratios ranging from 4.3 to 285. At the lowest dose, 3,4,3-LI(1,2-HOPO) (**112**) significantly decreased the Np content in the femur, kidneys, wound site, and whole body to 81%, 34%, 20%, and 74%, respectively, of controls. Efficacy for bone decorporation increased linearly with dose to a molar ratio of 143 and then reached a plateau. In contrast, the efficacy for soft tissue decorporation did not increase with dose. Efficacy decreased when time between Np administration and treatment increased. If injected 30 min after Np administration, 3,4,3-LI(1,2-HOPO) (**112**) had no significant effect on the Np levels in individual organs, resulting in only a slight decrease in Np retention in the whole body.[191] This reduced efficacy is similar to that seen in previous observations after iv administration of 3,4,3-LI(1,2-HOPO) (**112**) and Np.[189] The reduction of Np retention in the skeleton, which is the largest part of the body content (80% at 1 day after iv injection), ranged from 20 to 90%, depending on ligand dose and treatment timing. These results demonstrate the ability of the ligand to form an adequately stable complex with Np that can be excreted.[191] The poor results in the time-delayed experiments could be explained by the fast translocation of Np to the target tissues after deposition in a wound. The 3,4,3-LI(1,2-HOPO) (**112**) is able to complex Np within the wound site before translocation to blood, but the Np deposited in the tissues becomes progressively less accessible. The import of these results is that prompt local administration of 3,4,3-LI(1,2-HOPO) (**112**) could be useful in the treatment of a wound contamination with Np.[191]

To date, 10 multidentate CAM and HOPO ligands [3,4,3-LI-CAM(S) (**42**), 3,4,3-LI-CAM(C) (**53**), 5-LI-(Me-3,2-HOPO) (**83**), TREN(Me-3,2-HOPO) (**86**), H(2,2)-(Me-3,2-HOPO) (**99**), 5-LI(1,2-HOPO) (**110**), 3,4,3-LI(1,2-HOPO) (**112**), DFO(1,2-HOPO) (**115**), TREN(1,2-HOPO) (**116**), and H(2,2)-(1,2-HOPO) (**118**)], representative of effective binding units and suitable molecular backbones for chelating Pu(IV), were compared with $CaNa_3$−DTPA for *in vivo* chelation of ^{237}Np in mice (injected ip as NpO_2Cl at 5 min at a ligand:metal molar ratio of 22).[122] All 10 ligands chelated Np (as shown by greatly augmented fecal excretion) and reduced body Np significantly compared with controls, while reduction of body Np with $CaNa_3$−DTPA was not significant. Most of the excess Np excretion was derived from liver and soft tissues, but the five most effective ligands (also most effective for *in vivo* chelation of Pu(IV)) achieved significant reductions of Np in the skeleton. One of those effective ligands, 3,4,3-LI(1,2-HOPO) (**112**), was also shown to chelate ^{237}Np and ^{239}Np in rats.[189] Increasing the ligand:Np molar ratio to a level approaching that of a realistic accident increased Np excretion and achieved greater reductions of skeletal Np and significant reductions of body Np when given orally.[122] The oxidation state of the chelated Np, the structures of the Np chelates with those four ligands, and the modes of binding to Np are under investigation. This work serves as evidence of the potential of these ligands as new agents to supplement and/or replace $CaNa_3$−DTPA as treatment for nuclear accident victims. Because they are more effective for a range of actinides, less time would be required to determine the proper course of treatment in an emergency.

11. Conclusions

The research presented here is the result of many years of collaborative effort in inorganic chemistry, synthetic organic chemistry, and actinide biology. This collaboration has advanced areas of nutritional science, clinical medicine, and radiation protection. Each of these areas will benefit from further studies in this field and the development of new and improved ligands for the treatment of actinide poisoning, whether from accidents or weapons use. Due to our particular research interests, this review was limited to the most common actinides and those deemed most likely to be present in nuclear fuel and wastes, namely plutonium, thorium, americium, uranium, and neptunium.

Much of our particular interest in plutonium is due to its unusual chemical properties *in vivo* and its similarity to Fe(III). Other actinides might also become environmental or worker safety issues, for example, californium, curium, or berkelium, especially if plutonium-based fission reactors become practical or if recycling of nuclear fuel were to become more common.[86] Such practices would increase the amounts of transplutonium actinides, which could then become decorporation problems. Thus, other researchers have investigated decorporation of curium[462−465] and californium[466−468] mainly using DTPA, but this is not discussed in detail here.[86] In an uncertain world, the need for sequestering agents that are also known to be effective for these other transamericium actinides is not beyond the realm of possibility.

Three HOPO-based ligands, tetradentate 5-LIO-(Me-3,2-HOPO) (**84**), hexadentate TREN(Me-3,2-HOPO) (**85**), and octadentate 3,4,3-LI(1,2-HOPO)

(**112**), stand out as the most competent and robust actinide decorporation agents. Among the many ligands evaluated for promoting the excretion of actinides from mice, these are the most effective for reducing the body content of Pu(IV) and Am(III), significantly more effective than $CaNa_3$−DTPA, and for reducing the body content of Np(V)−Np(IV) and U(VI), for which $CaNa_3$−DTPA is not effective. They are orally effective decorporation agents for all four of those actinides, and their toxicities are acceptably low at effective dose. The mixed ligand, 3,4,3-LI(1,2-Me-3,2-HOPO) (**97**), which is highly effective for decorporation of Pu and Am, remains to be evaluated for removal of other actinides, and only 3,4,3-LI(1,2-HOPO) (**112**) has been investigated for *in vivo* chelation of Th.

New studies are needed to address the potential problem of a contamination accident involving an actinide mixture containing substantial amounts of the low-specific-activity isotopes of U and/or Th. These actinides are likely to bind competitively to a therapeutic ligand, reducing its circulating concentration and its ability to chelate the radiologically more hazardous Pu and Am isotopes.

Internal contamination with a mixture of actinides could present special problems in accident situations in which there is limited time to identify the contaminants before initiating treatment. While all three of the HOPO ligands noted above effectively chelate all of the tested actinides *in vivo*, each is especially suitable for chelation of a specific actinide: 3,4,3-LI-(1,2-HOPO) (**112**) for Pu(IV) and Th(IV), TREN(Me-3,2-HOPO) (**86**) for Am(III), 5-LIO(Me-3,2-HOPO) (**84**) for Np, and 5-LIO(Me-3,2-HOPO) (**84**) combined with 5-LI-CAM(S) (**30**) for U(VI). Thus, there is a need for the development of cocktails of several of these agents with their special affinities for specific actinides deposited in specific tissues of the body for the treatment of persons exposed to multiple actinides.

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13. Abbreviations

An = abbreviation for the actinide series of elements
AUC_k = relating the percent of iv-injected ^{14}C in the kidneys to time after injection
BAC = bisacetic acid
BUN = blood urea nitrogen
C_nTT = C_n-triethylenetetraminepentaacetic acid
$C_{12}TT$ = dodecyl-triethylenetetraminepentaacetic acid
$C_{22}TT$ = docosyl-triethylenetetraminepentaacetic acid
CAM = catecholamide
CAM(S) = 5-sulfo-2,3-dihydroxybenzamide
COT = cyclooctatetraene
Cp = cyclopentadienyl
Cp* = pentamethylcyclopentadienyl
CMPO = octyl(phenyl)-*N*,*N*-diisobutylcarbamoyl methylphosphine oxide
CY = cyclic backbone
Cyanex 301 = bis(2,4,4-trimethylpentyl)dithiophosphinic acid
CYTAC = cyclam tetraacetonylacetone
CYTROX = cyclam tetrahydroxamate
D−E = dose−effectiveness
DFO = desferrioxamine
DFOB = desferrioxamine B
DFOE = desferrioxamine E
DFOM = mesylate of desferrioxamine B or "Desferal"
DHB = 2,3-dihydroxybenzoyl group
DMAA = dimethyl acetamide
DMBS = 5-sulfo-2,3-dihydroxy-*N*,*N*-dimethylbenzamide
DTPA = diethylenetriaminepentaacetic acid
DTPA-DX = a decadentate dihydroxamic acid derivative of DTPA
DU = depleted uranium
EB = enterobactin
EDTA = ethylenediaminetetraacetic acid [usually as $CaNa_2$-EDTA, $Ca(O_2CCH_2)_2N(CH_2)_2N(CH_2CO_2)_2Na_2$]
ETAM = *N*,*N*-dimethyl-2,3-dihydroxyterephthalamide
EULEP = European Late Effects Project Group
EU-LI-CAM = LI-CAM ligand made by the European Late Effects Project Group using their alternative procedure
GAO = General Accounting Office, United States government
HAP = calcium hydroxyapatite
HOPO = hydroxypyridinone
1,2-HOPO = 1-hydroxy-2-pyridinone
3,2-HOPO = 3-hydroxy-2-pyridinone
IAM = 2-hydroxyisophthalamide
ICRP = International Commission on Radiological Protection
im = intramuscular
ip = intraperitoneal
iv = intravenous
ME = mesitylene-bridged backbone
MECAM = catecholamides with mesitylene bridge
MECAM(S) = sulfonated catecholamides with mesitylene bridge
MOX = mixed oxides; a refractory solid solution of UO_2 and PuO_2 and the ingrown daughter product $^{241}Am^{187}$
LI = linear backbone
LIO = linear backbone with ether bridge
LI-CAM = linear catecholamides
LI-CAM(S) = sulfonated linear catecholamides
LI-CAM(C) = linear catecholamide with a carboxyl substituent
LI-HOPO = linear hydroxypyridinone
MRI = magnetic resonance imaging
N-cat = 4-nitrocatechol
PACA = polyaminocarboxylic acid
PENTEN = *N*1-(2-aminoethyl)-*N*1-(2-[bis(2-aminoethyl)-amino]ethyl)ethane-1,2-diamine
SAM = salicylamide
s.cut. = subcutaneous
TAM = 2,3-dihydroxyterephthalamide
TBP = tri-*N*-butyl phosphate
Tf = transferrin
TEA = triethylamine
THF = tetrahydrofuran
Tiron = 2,3-dihydroxy-1,5-benzenedisulfonate

TREN = tris(2-aminoethyl)amine backbone
USAEC = United States Atomic Energy Commission

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