Pure & Appl. Chem., Vol. 60, No. 12, pp. 1807–1816, 1988.
Printed in Great Britain.

Sequestering agents specific for high oxidation state cations

Kenneth N. Raymond*, Thomas M. Garrett

*Department of Chemistry, University of California, Berkeley CA 94720 USA

Abstract - The development of sequestering agents specific for high oxidation state cations such as Fe(III), Pu(IV), Ce(IV), V(IV), and V(V) is discussed. The similarities and differences of common bidentate binding subunits are reviewed. The thermodynamic properties of 2,3 dihydroxyterephthalamide ligating groups and hexadentate macrocyclic and macrobicyclic ligands containing these groups are presented. Recent ligand syntheses designed for specific complexation of Fe(III) and Pu(IV) are detailed. Unusual chemistry of high oxidation state metal ions is examined.

INTRODUCTION

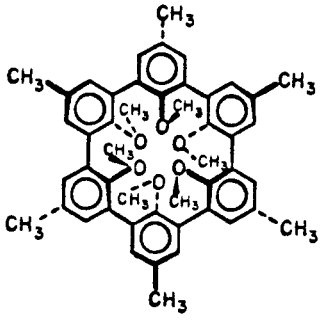
Current interest in the solution chemistry of high oxidation state metal cations is primarily due to the variety of applications afforded by higher oxidation state complexes and the increased awareness of the biological importance of these metal ions. Most prominently, the ferric ion occupies a unique niche in the biochemistry of living organisms, since iron is required by almost all forms of life (ref. 1). And yet, while excess iron is toxic, there is no biological pathway in man for the decorporation of the ferric ion (ref. 2). Thus there is wide interest in both the biochemistry of Fe(III) and in iron decorporation pharmaceuticals for treatment of chronic iron overload (ref. 3). Although plutonium is an abiological element, the charge to ionic-radius ratio of Pu(IV) is similar to Fe(III) and both ions have parallel transport and storage in the body. The resultant well-known biological hazard of plutonium generates considerable interest in decorporation agents for that metal ion (ref. 4).

Compounds that act as sequestering agents for the higher oxidation state cations must strongly and specifically chelate the metal ion. When these ligands are bound to metals that normally prefer lower oxidation states, remarkable changes in solution chemistry often result. Examples are stabilization of unusually high oxidation states such as V(V) (ref. 5) and Ce(IV) (ref. 6) and the production of good reducing agents from metal centers that are traditionally thought of as oxidizing agents (ref. 7). Finally, such ligands provide *in vivo* stability to metal centers needed for radiopharmaceuticals (ref. 8) and magnetic resonance imaging contrast agents (ref. 9).

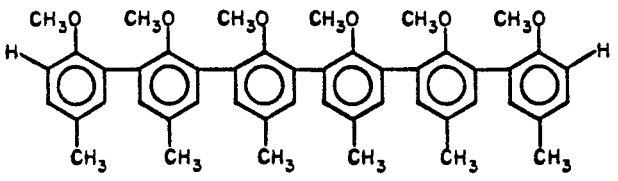
CHOICE OF BINDING SUBUNITS

High oxidation state metal cations present very different problems for the rational design of sequestering agents when compared to cations such as sodium and potassium. For the latter, macrocyclic specific sequestering agents have been largely based on size of the ion and preorganization of the coordination site as the most important part of the ligand

design. An example of the successful use of macrocycles can be found in comparison of the spherand **1** to the podand **2**. These compounds demonstrate a difference of 10^{12} in formation constants for binding to Li^+ (ref. 10).



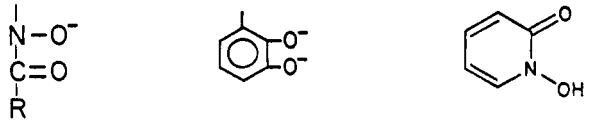
1



2

Fig. 1. Molecular structure of a spherand **1** and a podand **2**.

In contrast, the greater acidity of cations such as iron(III) and the actinide(IV) ions make them hydrolyze extensively even at relatively low pH and so precipitation as the hydroxides is a strongly competing reaction even for relatively strong complexing agents. Strongly basic ligands, such as the catecholate dianion, hydroxypyridinonate, and hydroxamate are produced by plants and bacteria in order to form water-soluble ferric complexes. Such naturally-occurring Fe(III) sequestering agents, used to obtain growth limiting iron, are known as siderophores (ref. 11). The first siderophore to be discovered was mycobactin, which was isolated in 1949 as its aluminium complex (ref. 12). Since that time more that 80 siderophores have been isolated and characterized (ref. 11). These compounds demonstrate a wide range of ligand topologies, molecular weights, and solubilities. All siderophores, however, have at least one binding subunit that is either a)hydroxamate, b)catecholate, or c)hydroxypyridinonate (Fig. 2).



HYDROXAMATE CATECHOLATE 1-HYDROXY-2(1H)-PYRIDINONE

Fig. 2. Binding subunits found in the siderophores.

These binding subunits possess the anionic oxygen donors most preferred by Fe(III), a classic "hard" metal ion. Three such binding subunits can form an octahedral array about the metal to achieve iron's preferred coordination number of six. The ferric complexes have highly negative reduction potentials (≈-1V vs NHE (ref. 13) which demonstrate a great preference for Fe(III) over Fe(II). The complexes are invariably high spin, with an $^6A_1$ electronic ground state. The three binding subunits used in the siderophores, while similar, possess some differences. In general, catecholate > hydroxypyridinonate > hydroxamate > amino carboxylate for stability at high pH and the opposite trend is true for stability at low pH. The standard formation constants only reflect the stability at high pH. The siderophore formation constants are extremely large. Enterobactin, a siderophore secreted by E. coli, is a tri-catecholate siderophore with binding subunits pendant from a macrocyclic tri-ester backbone. It has the highest formation constant known for the ferric ion, $K_f = 10^{52}$ (ref. 14). Catechols, hydroxypydrinones, and hydroxamic acids tend to be extremely specific for Fe(III) and Pu(IV). In contrast, the amino carboxylates are much less specific.

Fe(III)

We have chosen a biomimetic approach in designing sequestering agents for the ferric ion and model our ligands after the siderophores. Enterobactin itself is unsuitable for use in vivo either as the ligand or the iron complex. This is because a) the ligand backbone is easily hydrolyzed and b) the ferric enterobactin complex is used as an iron source by bacteria and it promotes the growth of pathogenic organisms. Early studies therefore centered on the synthesis of enterobactin analog compounds such as MECAM, and CYCAM (containing binding subunit A in Fig. 3). These compounds form highly stable ferric complexes ($K_f \simeq 10^{46}$) but are not highly soluble, precluding their use as iron decorporation pharmaceuticals (ref. 15). To remedy this, anionic electron withdrawing groups were appended to the aromatic rings. As a result of their carboxylate and sulfonate substituents, ligands such as LICAM-C and LICAM-S (binding subunits B and C respectively in Fig. 3) are highly soluble (refs. 16,17). They are also excellent iron removal drugs, demonstrating efficacies up to four times greater than the current drugs being used (ref. 18). The formation constants are also large, but still several orders of magnitude lower than enterobactin's (ref. 19). Clearly, the upper limit on the formation constant for iron complexation has not yet been reached.

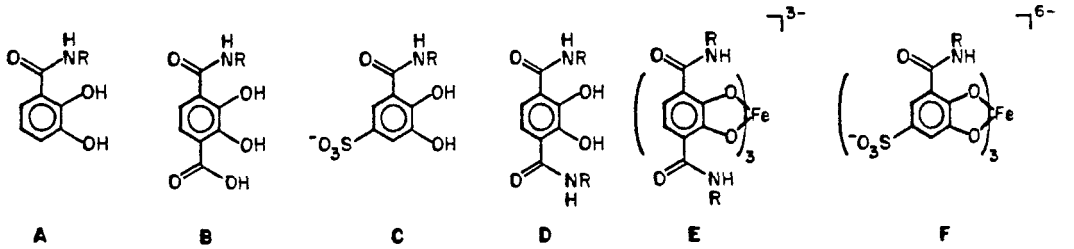


Fig. 3. Catechoylamide binding subunits and their ferric complexes.

Inspired by the work of Lehn (ref. 20) and Sargeson (ref. 21), we (refs. 22,23) and others (refs. 24,25) began investigating macrocyclic and macrobicyclic iron(III) sequestering agents. Compounds of this topology offer several potential advantages. One might expect that the increased entropic advantage would lead to higher formation constants. Also, the increased kinetic chelate effect should slow demetallation and ligand exchange rates. Finally, a more efficient chelating agent should result in a higher efficacy per mole of injected ligand for decorporation studies - as well as a higher LD_{50} for the metal complex used as a MRI contrast agent.

Three ligand topologies were considered, exocyclic, macrocyclic, and macrobicyclic. Because exocyclic systems had been thoroughly investigated in the past, and because they possess no macrocyclic or macrobicyclic effect, attention was focused on the macrocyclic and macrobicyclic ligands. In 1984 Vögtle and coworkers published the first macrocyclic iron sequestering agent, the macrobicycle bicappedMECAM shown in Fig. 4 (ref. 25). This was soon followed by our report of endocyclic tricatecholate macrocycles in 1985 (ref. 22) and endocyclic biscatecholate/biscarboxylate compounds by Martell in 1986 (ref. 24).

These compounds contained a new binding subunit **D** (Fig. 3) based on 2,3-dihydroxyterephthalic acid, rather than the 2,3-dihydroxybenzoic acid subunits **A** and **B**.

Furthermore, although both **C** and **D** are 2,3-dihydroxyterephthalic acid derivatives, **D** does not carry the extra charge that the subunit **C** imparted to ligands like LICAM-C. Studies of the previous bidentate binding subunits had established that putting more electron

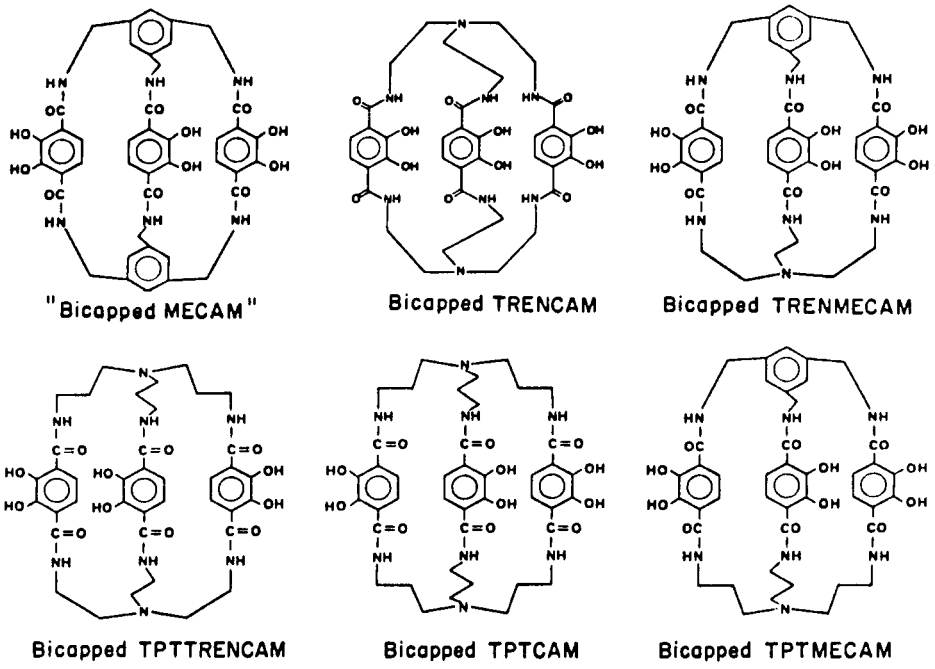
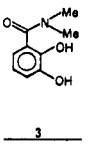
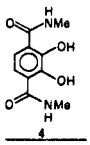
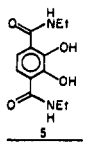
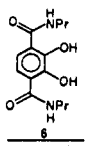
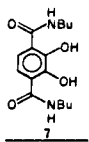


Fig. 4. Macrobicylic iron(III) sequestering agents.

withdrawing groups on the catechol lowers the protonation constants of the catechol protons and thereby increases the pM of the binding subunit at pH 7.4 (ref. 19). For previously studied hexadentate ligands containing three binding subunits it was observed that the increase in ligand acidity was accompanied by a decrease in the formation constant, resulting in no net change in the pM^{13} value.(ref. 19). However, in examining the fully formed ferric complexes of the LICAM-S binding subunit **F** (Fig. 3) and that of the new compounds **E**, the charge on **F** is twice that on **E**. It is expected therefore, that the complex **E** should be more stable than **F**. Indeed, it may be expected that both the lower protonation constants of D and lower charge of **E** should make D and macrocycles incorporating D better ligands than those using A or **C** as the binding subunit, irrespective of any macrocyclic effect.

In order to test these assumptions about the new binding subunit a series of simple 2,3-dihydroxyterephthalamide ligands were made (ref. 26). The results of solution thermodynamic studies of these ligands and their Fe(III) complexes are shown in Table 1.

Table 1

	 3	 4	 5	 6	 7
log K_{110}	17.8	16.4(1)	16.3(1)	(16.0)*	-
log K_{120}	13.9	14.5(1)	14.4(1)	15.2(1)	-
log K_{130}	8.5	10.9(1)	11.5(1)	11.9(1)	-
log β_{130}	40.2	41.8	42.2(1)	43.1(1)	-
pM	15.0	21.1	21.6	22.7	-
log K_{011}	(12.1)*	11.1(1)	11.1(1)	11.0(1)	11.0 (1)
log K_{012}	8.42	6.1(1)	6.0(1)	6.0(1)	-

pM = -log[Fe] at pH 7.4, $[L]_T = 10^{-5}$ *M*, $[Fe]_T = 10^{-6}$ *M*.

*Estimate.

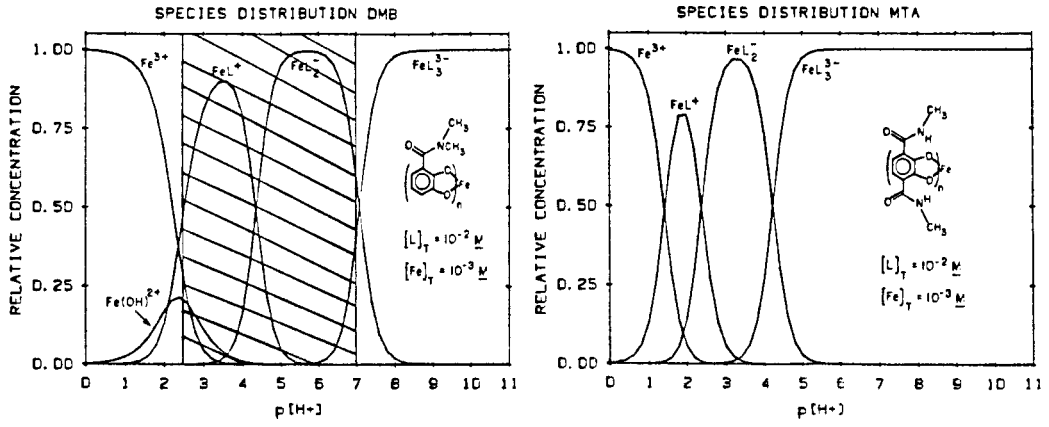


Fig. 5. Species distribution of the ferric complexes of DMB and MTA.

As can be clearly seen in Fig. 5 these bidentate ligands demonstrate a much greater efficacy as chelating agents at pH 7.4 than do the dihydroxybenzamides.

Under comparable conditions ($[L]_T = 10^{-2}$ M, $[M]_T = 10^{-3}$ M), MTA (ref. 13), the least powerful of the three ligands studied, remains as the FeL_3^{3-} complex until below pH 5 while, in contrast, the FeL_3^{3-} complex of DMB[13], **6**, begins to dissociate below pH 8. In fact, DMB is effectively demetallated below pH 7 due to precipitation of $Fe(OH)_3$, while the pH must be lowered below 1.5 to achieve greater than 50% demetallation of MTA. These results are a direct consequence of the lower ligand protonation constants coupled with an increase in β_{130} (ref. 13) for the terephthalamide ligands. Within the catechoylamides, as protonation constants decrease the concentration of the HL^- and L^{2-} species necessary for metal binding at pH 7.4 increase, making for a more effective sequestering agent at the lower pH. Normally, the decrease in protonation constant is accompanied by a decrease in metal ligand binding constant. This effect is seen here in the lower K_{110}'s for the terephthalamides versus DMB and, as discussed above, results from the lower protonation constants of the 2,3-dihydroxyterephthalamides and the fact that the two acid-base reactions

$$L + H^+ = LH^- \quad \text{and} \quad L + M^+ = ML^- \tag{1}$$

tend to have a linear free energy relationship. However, ligand and complex charges and solvation energies are known to contribute important secondary effects. Charge effects may explain why, although the K_{110} values are decreased relative to DMB, the K_{120} and K_{130} values are higher for the terephthalamide ligands. As the charge builds up on a complex with each subsequent ligation the sequential stepwise formation constants tend to decrease. However, in the terephthalamide series the increased π network can to some degree delocalize this charge more than can the benzamides, resulting in a smaller decrease in each sequential stepwise formation constant in the terephthalamide ligands. Thus, the equilibrium constant for the reaction

$$ML_2^- + L^{2-} = ML_3^{3-} \tag{2}$$

is greater for L = **4**, **5**, **6**, than for L = DMB (**3**). This novel result of increased ligand acidity coupled with an increased formation constant is reflected in the higher pM values of the terephthalamides. The pM is a direct thermodynamic measurement of a ligand's ability to bind the metal ion at a given pH. The pM values for the terephthalamides are the highest yet known for any bidentate ligand, up to eight orders of magnitude higher than DMB.

Macrocyclic polycatechol ligands with endocyclic 2,3-dihydroxyterephthalamide binding subunits have been synthesized in up to 24% yield using high dilution techniques (ref. 22). An example of this class of compounds, the ethane trimer (named after the three ethylene bridges that unite the three 2,3-dihydroxyterephthalamides) forms a ferric complex for which the pM is only slightly higher than that obtained for TRENCAM (27.8), a tripodal ligand incorporating three 2,3-dihydroxybenzamide binding subunits on a tris(2-aminoethyl)amine (TREN) backbone.

We have also made macrobicyclic iron sequestering agents (refs. 23,27). The ligand properties were varied by incorporation of TREN, mesitylene triamine, and TPT backbones. Table 2 lists the reduction potentials for the macrobicyclic series as compared to previously studied compounds.

Several important trends can be noted. First, the reduction potentials are all highly negative. Thus the selectivity for Fe(III)/Fe(II) has been retained in the macrobicylic series. Second, ratios of K_f vary overall by three orders of magnitude between the compounds shown and vary by 1.4 orders of magnitude within the macrobicyclic series. This could be seen as an expected correlation of cavity size and rigidity. Note that all tripodal ligands have formation constant ratios greater than the bicapped compounds. This may be due to a greater increase in K_f^{II} brought on by the macrobicyclic topology. Notice however that the large changes aren't between tripods and macrobicycles but rather between TRENCAM and enterobactin and between bicappedTRENCAM and bicappedTPTCAM.

An unusual electrochemical result that was found concerns the dependence of reduction potential on the pH. At relatively low pH reduction of the $Fe^{II}L$ species occurs simultaneously with a protonation reaction which involves a molecular rearrangement that is slow on the electrochemical time scale. Since this does not happen for enterobactin but does happen for all compounds with tertiary amines (both tripods and macrobicycles) we conclude that this is due to inversion of the tertiary amine. Park has observed similar inversion equilibria in macrobicyclic bridgehead amines (ref. 28).

The solution thermodynamic behavior of the bicappedTRENCAM macrobicycle has also been investigated. Spectrophotometric studies on the FeL complex showed isosbestic behavior corresponding to a two proton protonation, with a formation constant of 10.65 (i.e. at pH 5.33). This behavior is quite similar to ferric enterobactin which also has its first protonation near pH 5 (ref. 19). Unlike the tripods, however, protonation does not occur stepwise. The stepwise protonation of ferric enterobactin and its analogs has been proven to occur through a salicylate mode of bonding (ref. 29). This appears not to be the case for Fe(bicappedTRENCAM), which is more geometrically constrained and which rather undergoes protonation of the tertiary amines.

The protonation behavior of the metal free bicappedTRENCAM ligand was also studied using NMR spectra of the compound at high pH by UV visible spectrophotometry at lower pH. This gave the equilibria described in Table 3.

These results are surprising for several reasons. The primary one is that the average protonation constant = 6.8, which is extremely low for catechols. The average value predicted by Et_3N (10.75) and 2,3-dihydroxyethylterephthalamide (11 and 7) is 9.1. Catechol deprotonation has not been seen below pH 6.5, (ref. 11) but this compound has five catechol

Table 2 Electrochemical Results

Ligand	E^{o}(Fe(III)L / Fe(II)L)	log K_f^{III}/K_f^{II}	No. H^+ transferred	pK_a
MECAM	-1.07*	31.2	2.2	9.5
TRENCAM	-1.04	30.6	0.69	11.2
Enterobactin	-0.99	29.8	1.00	10.4
TPTCAM	-0.98	29.7	0.52	11.0
BicappedTRENCAM	-0.97	29.5	0.36	11.0
BicappedTPTCAM	-0.92	28.6	0.62	10.3
BicappedTPTTRENCAM	-0.90	28.3	0.59	9.4
BicappedTRENMECAM	-0.90	28.3	0.00	-
BicappedTPTMECAM	-0.89	28.1	0.46	11.0

*vs NHE

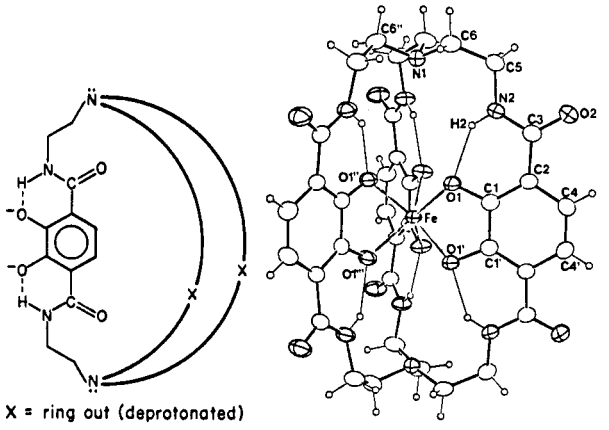


Fig. 6. Proposed L^{6-} form of bicappedTRENCAM and ORTEP of Fe(bicappedTRENCAM).

Table 3 Speciation in BicappedTRENCAM

Number of H^+	Species	logK	pH at midpoint	Assignment(basis)
2	LH_2	27.2(1)	13.6	catecholate(^{1}H NMR, Ar shift)
1	LH_3	8.3(1)	8.3	amine(^{1}H NMR, α-CH_2 shift)
2	LH_5	8.73(1)	4.37	catecholate(λ_{max})
3	LH_8	9.75(1)	3.25	catecholate(λ_{max})

protonations that occur below pH 4.5. Another interesting result is the number of polyprotic steps. Most tris-catecholyamides have single proton steps. That bicappedTRENCAM has three equilibria with two or more protonations demonstrates an unusual degree of cooperativity and implies the presence of important conformational changes with protonation state. Molecular modelling studies are underway to characterize these conformations.

Because the Fe(bicappedTRENCAM) complex precipitates out of solution prior to metal decorporation, the formation constant was determined by competition with CDTA. The equilibrium

$$FeL + L' = FeL' + L \qquad (3)$$

where L = bicappedTRENCAM and L' = CDTA was reached for five different pH's. Equilibrium took > 35 hours to be reached. This is 4-5 times greater than previous experiments with enterobactin or MECAM and reflects the increased kinetic chelate effect of the macrobicylic ligand topology. The value of log K_f (Fe(bicappedTRENCAM)) was determined to be 43(1). This value is surprisingly low compared to prediction and to Vögtle's published result of 10^{59} for "bicappedMECAM" (Table 5) (ref. 30). It is less than that calculated for TRENCAM suggesting (1) an absence of a macrobicyclic effect, (2) an absence of ligand preformation for iron binding and (3) that enthalpy may be a much more important factor in iron complexation than reorganization entropy. The X-ray structural determination of Fe(bicappedTRENCAM) represents the first for any ferric(tris-catechoylamide) complex and demonstrates the first trigonal prismatic coordination seen for the ferric ion. Comparison between the proposed L^{6-} form of bicappedTRENCAM and the X-ray structure shows no evidence of ligand preformation (Fig. 6).

The pM value is calculated to be 30.7. The high pM reflects this ligand's dramatically lower pK's coupled with only a 0.6 log unit decrease in formation constant from TRENCAM. This result of an excellent pM value parallels the results found for the 2,3-dihydroxyterephthalamide binding subunit and again suggests the importance of enthalpy as the dominant factor in the free energy of iron binding.

Pu(IV)

Since tris-catecholate hexadentate ligands are quite effective Fe(III) sequestering agents and because the charge to radius ratio of Pu(IV), 4.17(e/Å) (ref. 31), is similar to that of Fe(III), 4.65, the catecholate ligand should function as an excellent chelating agent for Pu(IV) as well. Crystals of the tetrakis (catcholato)cerate(IV) complex and related actinide (IV) complexes were prepared. They are all nearly perfect trigonal-faced dodecahedral structures (ref. 32). Encouraged by this, synthetic poly(catchoylamide)ligands containing four catechols connected by alkyl chains were made. The most effective tetracatecholate ligands promoted prompt excretion of as much as 70% of a ^{238}Pu(IV) tracer administered 1 hour earlier to mice, and 88% of ^{238,239}Pu(IV) administered 30 minutes earlier to dogs (ref. 33). However, at physiological pH (about 7.4), the relatively weak acidity of the catechol hydroxyl groups and the eight-proton stoichiometry of the complexation reaction prevent the tetracatechoyl ligands from forming octadentate Pu(IV) or Ce(IV) complexes, forming instead a tris catecholato complex (ref. 34).

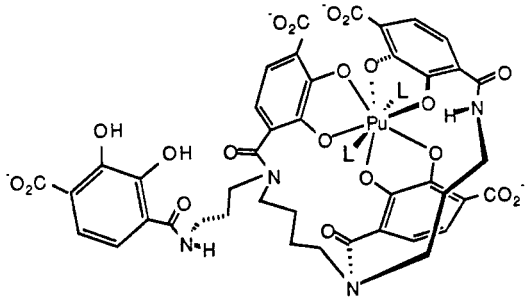
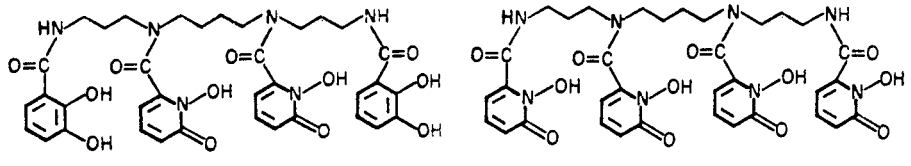


Fig. 7. Tris catecholato complex of Pu(IV) formed by LICAM-C at pH 7.4.

Therefore a new series of sequestering agents have been designed with metal-binding groups similar to, but more acidic than, catechol so as to coordinate fully with actinide(IV) ions in dilute solution at pH 7.4. One such compound, 3,4,3-LIHOPO (ref. 35), when given as the ferric complex promoted more Pu excretion than any other ligand previously studied, eliminating 86% of the injected Pu in a 24 hour period (in mice) (ref. 36).



DICATECHOL-DIHOPO 3,4,3-LIHOPO

Fig. 8. The Pu(IV) specific sequestering agents 3,4,3-LIHOPO and dicatechol-diHOPO.

Mixed compounds such as the dicatecatechol-diHOPO have also been synthesized (ref. 37). These compounds should combine the high formation constants of the catecholates with the low pH stability of the hydroxypyridinones. Thermodynamic and animal testing studies are in progress.

UNUSUAL HIGH OXIDATION STATE CHEMISTRY

Ligands containing catecholate, hydroxypyridinonate, and hydroxamate functionalities stabilize complexes with unusually high oxidation states. For example, hydroxamic acids form highly colored complexes with V(V) or V(IV) and have been used extensively as analytical reagents for the detection of this metal (ref. 5). Compounds of this type have recently been structurally characterized (ref. 38). Oxochlorobis(benzohydroxamato) vanadium(V) is found to have a distorted octahedral geometry, with the chloro and the oxo cis to each other. This complex shows a strong trans influence, the bond trans to the oxo group being significantly lengthened. A similar, but dimeric, oxoisopropoxobis-(hydroxamato)complex has also been characterized (ref. 38).

Unusual chemistry often results from the thermodynamic stabilization of higher oxidation states produced by these ligands. In reaction of vanadyl salts with catechol, both the (bis-catecholato)oxovanadium(IV) and the tris-(catecholato)vanadium(IV) can be isolated and have been characterized by X-ray crystallography (ref. 39). A similar V(III) tris-catecholato complex of TRENCAM has recently been studied by crystallographic methods (ref. 40). This compound is predicted to have a highly positive shift in the oxidation potential and thermodynamic studies are in progress. Such behavior is, in fact, typical of these ligands. For example the Ce(IV)/Ce(III) potential shifts -2 Volts upon formation of the tetrakis(catecholato) complex (ref. 34).

Since the higher oxidation states have highly negative reduction potentials, the lower oxidation states are highly reducing. Shilov has noted that V(II) in basic solutions with catechol carries out a reduction of dinitrogen (ref. 7). Thus, low-valent vanadium has been transformed into an extraordinary reducing agent. Development of efficient small molecule reducing agents represents yet another potential application for sequestering agents specific for high oxidation state cations.

Acknowledgements

We thank our co-workers named in the references and acknowledge their contributions to this paper.

REFERENCES

1. J.B. Neilands, Structure and Bonding 11, 145 (1970).
2. W.H. Crosby, "Iron Absorption" In Best and Taylor's "Physiological Basis of Medical Practice", 10th ed., J.R. Brobeck, Ed., Williams and Wilkins, Baltimore (1979).
3. A.E. Martell, W.F. Anderson and D.G. Badman, Eds., Development of Iron Chelators for Clinical Use, Elsevier-North Holland, New York (1981). W.F. Anderson, M.C. Hiller, Eds., Development of Iron Chelators for Clinical Use, Dept. of HEW, Publication No. (NIH) 77-994, (1975).
4. K.N. Raymond, "Specific Sequestering Agents for Iron and the Actinides" Environmental Inorganic Chemistry, pp. 331-347, K.J. Irgolic and A.E. Martell, Eds., Proceedings, U.S.-Italy International Workshop on Environmental Inorganic Chemistry, San Miniato, Italy, June 5-10, 1983, VCH Publishers, Deerfield Beach, Florida, (1985).
5. Y.K. Agrawal and G.D. Mehd, Internat.J.Environ.Anal.Chem. 10, 183-188 (1981). Y,K. Agrawal, Bull.Soc.Chim.Belg. 89, 261-265 (1980). R.R. Nanewar and U. Tandon, Talanta 25, 352-354 (1978). D.C. Bhura and S.G. Tandon, Anal.Chim.Acta 53, 379-386 (1971). S.G. Tandon and S.C. Bhattacharya, J.Ind.Chem.Soc. 47, 583-589 (1970). R.M. Cassidy and D.E. Ryan, Can.J.Chem. 46, 327-330 (1968). D.E. Ryan, Analyst 85, 569-574 (1960). G.D. Lutwick and D.E. Ryan, Can.J.Chem. 32, 949 (1954).
6. M.J. Kappel, Ph.D. Dissertation, University of California, Berkeley (1983).
7. A.E. Shilov J.Mol.Catalysis 41, 221-234 (1987).
8. Inorganic Chemistry in Biology and Medicine, Chapters 5, 6 & 7, A.E. Martell, Ed., ACS Symposium Series 140, American Chemical Society, Washington, D.C. (1980).

9. Medical Magnetic Resonance Imaging and Spectroscopy: A Primer, Chapter III, T.F. Budinger and A.R. Margulis, Eds., Society of Magnetic Resonance in Medicine, Berkeley (1986). R.B. Lauffer Chem.Rev. 87, 901-927 (1987).
10. D.J. Cram, Angew.Chem.,Int.Ed.Engl. 25, 1039-1057 (1986).
11. K.N. Raymond, G. Müller and B.F. Matzanke, Topics in Current Chemistry 123, 51 (1984).
12. J. Francis, J. Madinaveitia, H.M. Maeturk and G.A. Snow, Nature 163, 365 (1949).
13. Definitions for the equilibrium constants used in the text include: (a)stepwise constant K_{rst} (i) for t = 0: $K_{rst} = [M_rL_s]/[M_rL_{s-1}][L]$ representing $M_rL_{s-1} + L = M_rL_s$, (ii) for r = 0: $K_{rst} = [L_sH_t]/[L_sH_{t-1}][H]$ representing $L_sH_{t-1} + H = L_sH_t$; (b)cumulative constant $\beta_{rst} = [M_rL_sH_t]/[M]^r[L]^s[H]^t$. Abbreviations and symbols used in the text include: DMB, 2,3 dihydroxy-N,N-dimethylbenzamide; MTA, 2,3 dihydroxymethylterephthalamide; ETA, 2,3 dihydroxyethylterephthalamide; PTA, 2,3 dihydroxypropylterephthalamide; BTA, 2,3 dihydroxybutylterephthalamide; DTA, 2,3 dihydroxydecylterephthalamide; pM = -log[Fe] at pH 7.4 and 1 μM $[Fe]_T$, 10 μM $[L]_T$; CDTA, trans-1,2-cyclohexylenedinitrilotetraacetic acid.
14. W.R. Harris, C.J. Carrano, S.R. Cooper, S.R. Sofen, A.E. Avdeef, J.V. McArdle and K.N. Raymond, J.Am.Chem.Soc. 101, 6097-6104 (1979).
15. W.R. Harris and K.N. Raymond, J.Am.Chem.Soc. 101, 6534-6541 (1979).
16. F.L. Weitl and K.N. Raymond, J.Am.Chem.Soc. 102, 2289-2293 (1980).
17. F.L. Weitl, K.N. Raymond and P.W. Durbin, J.Med.Chem. 24, 203 (1981).
18. H. Rosenkrantz and J.J. Metterville "In Vivo Mouse Bioassay of Potential Iron Chelators", Report No. MRI-CA 03-85-01B to the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, Bethesda (1985).
19. W.R. Harris, K.N. Raymond and F.L. Weitl, J.Am.Chem.Soc. 103, 2667 (1981).
20. J.-M. Lehn, Science 227, 849-856 (1985).
21. I.I. Creaser, R.J. Geue, J. Harrowfield, A.J. Hertl, A.M. Sargeson, M.R. Snow and J. Springborg, J.Am.Chem.Soc. 104, 6016-6025 (1982). R.J. Geue, T.W. Hambly, J.M. Harrowfield, A.M. Sargeson and M.R. Snow, J.Am.Chem.Soc. 107, 899-901 (1985).
22. S.J. Rodgers, C.Y. Ng and K.N. Raymond, J.Am.Chem.Soc. 107, 4094-4095 (1985).
23. T.J. McMurry, S.J. Rodgers and K.N. Raymond, J.Am.Chem.Soc. 109, 3451 (1987).
24. Y. Sun, A.E. Martell and R.J. Motekaitis, Inorg.Chem. 25, 4780 (1986).
25. K. Wolfgang and F. Vögtle, Angew.Chem.,Int.Ed.Engl. 23, 714 (1984).
26. T.M. Garrett, P.W. Miller and K.N. Raymond, submitted to Inorg.Chem..
27. T.J. McMurry, M.W. Hosseini, T.M. Garrett, F.E. Hahn, Z.E. Reyes and K.N. Raymond, J.Am.Chem.Soc. 109, 7196-7198 (1987).
28. H.E. Simmons and C.H. Park, J.Am.Chem.Soc. 90, 2428-2429 (1968). C.H. Park and H.E. Simmons, J.Am.Chem.Soc. 90, 2429-2430 (1968).
29. M.E. Cass, T.M. Garrett and K.N.Raymond, submitted to J.Am.Chem.Soc..
30. P. Stutte, W. Kiggen and F. Vögtle, Tetrahedron 43, 2065-2074 (1987).
31. R.D. Shannon, Acta Cryst. 32(A), 751-767 (1976).
32. S.R. Sofen, K. Abu-Dari, D.P. Freyberg and K.N. Raymond, J.Am.Chem.Soc. 100, 7882-7887 (1978).
33. P.W. Durbin, E.S. Jones, K.N. Raymond and F.L. Weitl, Rad.Res. 81, 170-187 (1980). P.W. Durbin, N. Jeung, E.S. Jones, F.L. Weitl, and K.N. Raymond, Rad.Res. 99, 85-105 (1984). R.D. Lloyd, F.W. Bruenger, C.W. Mays, D.R. Atherton, C.W. Jones, G.N. Taylor, W. Stevens, P.W. Durbin, N. Jeung, S.E. Jones, M.J. Kappel, K.N. Raymond and F.L. Weitl, Rad.Res. 99, 106-128 (1984).
34. M.J. Kappel, H. Nitsche and K.N. Raymond, Inorg.Chem. 24, 605-611 (1985).
35. D.L. White, P.W. Durbin, N. Jeung and K.N. Raymond, J.Med.Chem. 31, 11-18 (1988).
36. P.W. Durbin, personal communication.
37. L.C. Uhlir and K.N. Raymond, unpublished results.
38. D.C. Fisher, S.J. Barclay, C.A. Balfe and K.N. Raymond, manuscript in preparation.
39. A.R. Bulls and K.N. Raymond, to be submitted for publication.
40. S.R. Cooper, Y.B. Koh and K.N. Raymond, J.Am.Chem.Soc. 104, 5092-5102 (1982).