Novel Tetrahydroxamate Chelators for Actinide Complexation: Synthesis and Binding Studies

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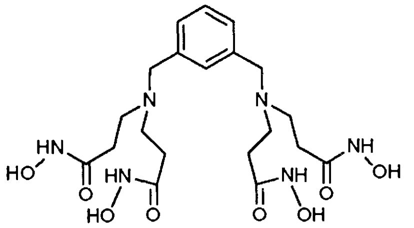
The chelators **1** and **2**, members of a new class of tetrahydroxamate chelators, are readily synthesized and are shown by potentiometric studies to have high affinities for thorium(IV), iron(III) and neodymium(III).

The design and synthesis of chelators for the specific binding of actinide ions is both of pharmacological and environmental interest. Since the advent of the Manhattan Project in the early 1940s, radioactive actinides have been discharged in various forms into the world environment.[1] These discharges have occurred as a result of weapons production, medical research and other sources including nuclear power plant by-products. Selective removal of radioactive and highly toxic actinide ions such as plutonium(IV) and americium(III) from process waste streams and soils, which often contain high concentrations of iron or aluminium presents a formidable challenge.

Hydroxamates and catecholates are known for their ability to complex strongly highly charged metal ions such as plutonium(IV) and iron(III). Therefore, many chelators containing these functionalities have been synthesized and their actinide sequestration properties have been examined.[2] It is generally accepted that octadentate ligands possess the appropriate denticity necessary for selective actinide complexation. The larger size of the actinide ion and its flexible coordination geometry relative to transition metals provides an avenue for their differentiation.

As part of a research programme for the development of cost-effective organic chelators for practical remediation of actinides, we have recently identified a new class of tetrahydroxamates (see Fig. 1) that show potential for environmental applications. Two such chelators, **1** and **2**, were chosen based on the following considerations. (*i*) The arrangement of the four hydroxamate groups provides the potential for octadentate coordination to an actinide ion. (*ii*) The diamine bridge can be readily varied to optimize actinide selectivity. (*iii*) These chelators are easily prepared from readily available starting materials and can be modified for incorporation into polymeric supports. (*iv*) The presence of the amines helps to provide water solubility for the ligand and its complexes.

Treatment of *m*-xylylenediamine with an excess of ethyl



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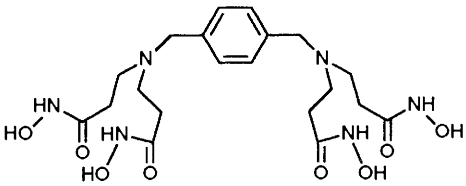

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Fig. 1 New tetrahydroxamate chelators

acrylate gave the corresponding addition product, the tetraethyl ester, in good yields. Reaction of the tetraester with an excess of hydroxylamine in basic solution at room temperature proceeds cleanly to give the desired tetrahydroxamate, **1**, in 64% yield, as its potassium salt.[3]† The *para* analogue, **2**, was prepared in a similar manner.

The ligands were evaluated potentiometrically‡ to determine their protonation and metal binding constants.[4,5] The titration data are illustrated in Fig. 2. The protonation and metal complex formation constants for compounds **1** and **2** were determined by least-squares analysis of the titration data[5] and are listed in Tables 1 and 2, respectively.

The first four protonation constants (K_1 to K_4) have been assigned to the hydroxamic acids and the remaining protonation constants (K_5 and K_6) have been assigned to the amines based on proton NMR studies as a function of pH. The values found for the hydroxamates are consistent with those observed for similar polyhydroxamic acid chelators.[4] The nearly identical protonation constants for these two chelators indicates that the position of attachment of the ligand groups about the benzene ring does not significantly affect their relative basicity.

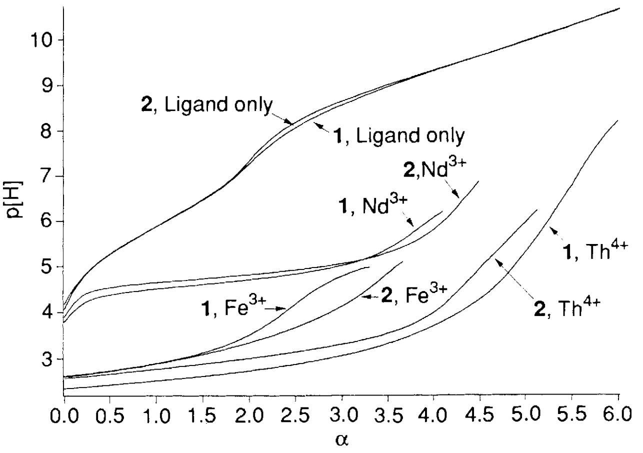

Fig. 2 Potentiometric equilibrium curves for **1** and **2**, in terms of $-\log[H^+]$ as a function of added base (α = mol KOH/mol ligand) for ligand alone, and for 1 : 1 molar ratios of ligand to metal ion. All constants measured at 25.0 ± 0.1 °C in 0.10 mol dm^{-3} KNO_3.

Table 1 Protonation constants of chelators **1** and **2** at 25 °C and μ = 0.10 mol dm^{-3}

Quotient K^a	logK^b for **1**	log$K$ for **2**
$[HL]/[H][L]$	10.18	10.22
$[H_2L]/[HL][H]$	9.64	9.60
$[H_3L]/[H_2L][H]$	8.99	9.05
$[H_4L]/[H_3L][H]$	8.17	8.31
$[H_5L]/[H_4][H]$	6.38	6.40
$[H_6L]/[H_5L][H]$	5.36	5.35

^{a} Charges have been omitted for simplicity. ^{b} Standard deviations for all reported log$K$ values are ±0.01 log units as indicated by the program BETA.

For our metal binding studies we chose thorium(IV) as a surrogate for plutonium(IV) and neodymium(III) for americium(III). A qualitative comparison of the curves in Fig. 2 illustrates that these chelators have a larger affinity for the metal ions that have higher charge to radius ratios. The substantial depression of the titration curves observed for both chelators with thorium, neodymium and iron is an indication that these metals are strongly complexed even at low pH. The lower pH observed for the thorium complex of **1** indicates that significantly more acid is released upon complexation for this system.

This difference is reflected in the equilibrium constants with selected metal ions listed in Table 2. Comparison of the M + $LH_3 \rightleftharpoons MLH_3$ equilibria for each of the metal ions indicates that **1** is more selective for thorium(IV) than iron(III) while **2** shows no selectivity. The selectivity and stronger affinity observed for **1** for thorium(IV) over iron(III) may be due to either enthalpic or entropic factors. Even though neodymium has a substantially smaller charge to radius ratio relative to thorium(IV) and iron(III), it is strongly complexed by both chelators. The similarities of the binding constants indicates no structural bias of either ligand toward neodymium (Table 2). The binding constants of **1** and **2** with the metal ions of interest are comparable to other hydroxamic acid chelators such as desferrioxamine-B.[6,7] We are in the process of using spectroscopic methods and molecular modelling calculations to determine the basis for the observed selectivity.

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† The ^1H NMR and ^{13}C NMR and IR spectra of all intermediates, **1** and **2** are in agreement with assigned structures. Satisfactory C, H, N analyses were obtained for the intermediates and **1** [$C_{20}H_{29}N_6O_8K_3 \cdot 2H_2O$] and **2** [$C_{20}H_{30}N_6O_8K_2 \cdot 2H_2O$]. Further characterization was achieved by conversion of **1** and **2** into their corresponding dihydrochlorides. Mass spectra (FAB-3-nitrobenzyl alcohol matrix) for **1** and **2** showed a molecular ion at *m/z* 485.3 [M + H]$^+$. Mass spectral determinations were made at the Midwest Centre for Mass Spectrometry with partial support by the National Science Foundation, Biology Division (Grant No. DIR 9017262).

‡ The potentiometric equilibrium measurements of **1** and **2** were conducted in a water-jacketed vessel at 25.0 ± 0.1 °C under an ultra-pure argon atmosphere. The titrant was dispensed using a Metrohm 665 Dosimat or a Radiometer ABU93 (combined burette–pH meter) automatic burette utilizing either a 5 ml or 1 ml piston. The pH measurements for the titrations where the 665 Dosimat was used were obtained with an EA 940 pH meter by Orion Research utilizing a combination X-EL pH electrode (cat. no. 476262, plastic bodied) by Corning. A pK_W of 13.78 (0.10 mol dm^{-3}, at 25 °C) was used in all calculations (ref. 4). The electrode was calibrated in a 0.1 mol dm^{-3} KNO_3 ionic strength medium to read $-\log$ [H] directly. The 665 Dosimat and EA 940 were remotely controlled from a personal computer with automated titration software developed in this laboratory. The concentration of the chelators were typically 0.002–0.005 mol dm^{-3} in 15–20 ml of the supporting electrolyte solution. For the metal titrations a stoichiometric amount (1 equiv.) of metal stock solution was added to the ligand–electrolyte solution at an approximate pH of 2.5. The non-linear least-squares refinements of the titration curves were performed on an Apple Quadra 700 computer using the program BETA (ref. 5). Precipitation was observed at pH values above 6–7 for Nd^{III}, above 5 for Fe^{III} and above 6–7 for Th^{IV}, and data above these values were not used in the least-squares analyses nor are shown in Fig. 2.

Table 2 Formation constants for ligands **1** and **2** at 25.0 °C, 0.10 mol dm^{-3} (KNO_3)

	$\log Q^a$					
	Th^{4+}		Fe^{3+}		Nd^{3+}	
Quotient, *Q*	**1**	**2**	**1**	**2**	**1**	**2**
$[ML]/[M][L]$	31.88(6)					
$[MLH]/[M][L][H]$	39.65(5)	36.85(6)			25.54(1)	26.28(1)
$[MLH_2]/[M][L][H]^2$	43.16(4)	42.13(6)		40.50(7)	32.40(1)	32.78(1)
$[MLH_3]/[M][L][H]^3$	45.92(6)	45.18(5)	43.41(2)	45.21(7)	37.04(3)	37.03(1)
$[MLH_4]/[M][L][H]^4$		48.28(7)	47.43(2)	48.70(7)		
$[M_2L_2H_3]/[M]^2[L]^2[H]^3$			74.16(2)			61.6(1)
$[M_2L_2H_5]/[M]^2[L]^2[H]^5$					73.47(1)	
$[MLH_3]/[M][LH_3]$	17.11	16.31	14.60	16.34	8.23	8.16

[a] All constants determined by the program BETA. Numbers in parentheses are the standard deviations computed from calculated pH values relative to those observed experimentally.

Studies are in progress to understand in greater detail the complexation behaviour of these chelators. In particular the structural aspects of these coordination complexes should provide more insight into the basis for the observed selectivity. The synthesis of analogous compounds with acyclic diamine backbones has been completed, and evaluation of their metal binding properties is underway. In conclusion, the relatively simple structure of this class of chelators and their high binding constants for thorium(IV) illustrate their potential for further development towards actinide remediation applications.

The Waste Mangement Education and Research Consortium and the Department of Energy are thanked for their financial support. Wendy Caswell and Doris Ford provided technical assistance, and Dr Birnbaum of NMSU and Dr Brainard of LANL are thanked for helpful discussions.

Received, 6th May 1992; Com. 2/02342C

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