competitive. Whatever the reason, however, there is no doubt that the electron-transfer rate constant is slowest for compound B, regardless of the solvent used.

Attempts to determine whether spin conversion occurs before or after electron transfer have, to date, proven unsuccessful. Variable-scan measurements did not reveal the presence of either an EC (*e*lectrochemical–*c*hemical) mechanism or a CE (*c*hemical–*e*lectrochemical) mechanism. Differentiation between these mechanisms might be achieved by measurements of electron-transfer rates for a series of intermediate-spin (spin-equilibrium) complexes that possess differing populations of the high-spin and low-spin states (as was possible for the $[Fe(X\text{-}Sal)_2trien](PF_6)_2$ spin-equilibrium complexes).[10] Unfortunately, complexes of this type are not widely available.

In summary, we have measured electron-transfer rate constants for three similar Fe(II) complexes, differing mainly in these spin states in order to determine the effect of spin state on heterogeneous electron-transfer rates. Contrary to initial expectation, similar rate constants were obtained for the $Fe(II)_{HS}/Fe(III)_{HS}$ and $Fe(II)_{LS}/Fe(III)_{LS}$ complexes, while the rate constant for the oxidation of a spin-equilibrium Fe(II) complex was slower than for either the purely high- or low-spin species, and this appears true independent of the solvent system utilized. Finally, similar to our earlier results for reduction of an Fe(III) spin-equilibrium system, the rates of spin conversion for the present $Fe(II)_{LS} \rightleftarrows Fe(II)_{HS}$ spin-equilibrium process may be slower at the electrode surface than in the bulk of solution. It would seem that this possibility needs to be investigated further, both theoretically and experimentally.

Acknowledgment. We gratefully acknowledge the Robert A. Welch Foundation [Grants E-680 (K.M.K.) and C-627 (L.J.W.)], the National Institutes of Health [Grant GM-25172 (K.M.K.)], and the National Science Foundation [Grant CHE 77-14594 (L.J.W.)] for support of this work.

Registry No. A, 55222-32-7; B, 55190-34-6; C, 55190-36-8.

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Ferric Ion Sequestering Agents. 10. Selectivity of Sulfonated Poly(catechoylamides) for Ferric Ion[1]

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Received January 25, 1982

Complexation equilibria have been evaluated by potentiometric titration of several biologically significant divalent metals as well as Fe(III) with the sulfonated poly(catecholate) ligands 1,6-bis(2,3-dihydroxy-5-sulfobenzoyl)-1,6-diazahexane (4-LICAMS), 1,3,5-tris(((2,3-dihydroxy-5-sulfobenzoyl)amino)methyl)benzene (MECAMS), and 1,5,10,14-tetrakis-(2,3-dihydroxy-5-sulfobenzoyl)-1,5,10,14-tetraazatetradecane (3,4,3-LICAMS). For all ligands studied the titrations demonstrate the following relative stabilities Fe(III) >> Cu(II) > Zn(II) > Ni(II), Co(II) > Mg(II) > Ca(II). These poly(catechoylamide) ligands possess great selectivity for ions of high charge to ionic radius ratios such as Fe(III) and Pu(IV); their selectivity is similar to that shown by desferrioxamine B, the current chelating agent for iron overload, and is greater than that demonstrated by DTPA, the chelating agent most often used for plutonium and other heavy-metal ion decorporation.

Introduction

Chelation therapy as a means of treatment for removal of metals or metalloids from the body has been used since British antiLewisite (2,3-dimercaptopropanol) was discovered to be an effective sequestering agent for arsenic in the early 1940s.[2] Subsequent development of amine polycarboxylates such as ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA), effective in vivo sequestering agents for a variety of metal ions,[3] has spurred the search for the development of other effective chelating agents.

Although the synthetic chelating agents EDTA and DTPA effectively remove toxic metals from the body, they also bind divalent calcium and zinc[4] and must be administered as the calcium or zinc salts to avoid depletion of these elements from the body. Even then, toxicity results when these ligands are administered to test animals over prolonged periods.[5] Laboratory animals die, apparently at least in part as a result of Zn(II) depletion, when a high level of DTPA is maintained in the blood by multiple injections.[6] Thus, there is a need for development of chelating agents that are capable of selectively chelating the toxic metal without removing biologically significant divalent metal ions.

The in vivo sequestering of ferric ion is of particular interest because of its toxicity if in excess in the body. With the microbial iron sequestering agent enterobactin[7,8] as a model, synthetic catechoylamide ligands have been designed to bind ferric ion.[9] This work has recently been reviewed.[10]

In addition to binding ferric ion, synthetic catechoylamide ligands will bind other metals with high charge to ionic radius ratios such as Pu(IV), the oxidation state most likely to exist under physiological conditions. Pu(IV) and Fe(III) possess notable chemical similarities: (1) they have similar charge to ionic radius ratios (4.2 and 4.6 e/Å, respectively);[11] (2) both have large hydrolysis constants; (3) Pu(IV) is known to follow biological iron-transport pathways.[12] With these similarities

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Table I. Protonation Constants[a] of Sulfonated Catecholate Ligands[b]

ligand	$\log K_3^H$	$\log K_4^H$	$\log K_5^H$	$\log K_6^H$	$\log K_7^H$	$\log K_8^H$	$\log K_{av}^H$
4-LICAMS	6.61 (1)	5.96 (1)					6.3
MECAMS[c]		7.26 (2)	6.44 (2)	5.88 (2)			6.5
3,4,3-LICAMS			8.26 (2)	7.62 (3)	6.69 (2)	6.13 (1)	7.3

[a] $K_N^H = [H_nL]/([H_{n-1}L][H])$. [b] Measurements were made at 25 °C and 0.10 M (KNO_3) ionic strength. [c] See ref 22.

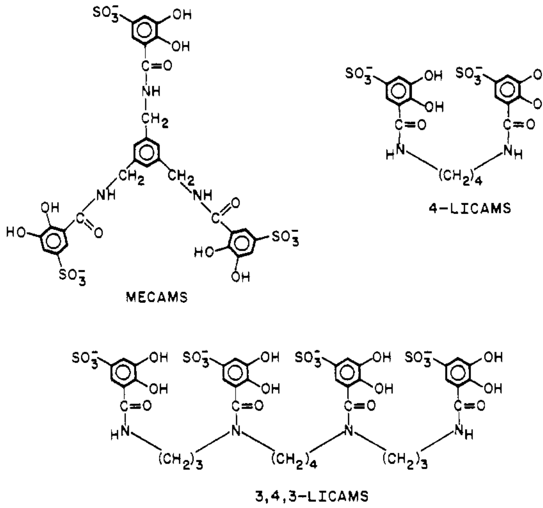

Figure 1. Structural formulas of sulfonated catechoylamide ligands.

in mind, catechoylamide ligands were designed[13] to bind Pu(IV), which is usually eight-coordinate with bidentate ligands. In vivo tests of sulfonated derivatives of tetrakis(catechoylamides) have shown them to be effective in chelating Pu(IV).[14] Several comprehensive reviews of the design concepts for, and syntheses of, these ligands, as well as the results of in vivo testing, recently have been published.[15,16] For catechoylamide ligands to be considered as possible alternatives to chelating agents presently in use, the evaluation of their selectivity for ferric ion or Pu(IV) is important. This paper reports the stabilities determined by potentiometric titrations of Ca(II), Mg(II), Cu(II), Zn(II), Ni(II), and Co(II) with several sulfonated catechoylamide ligands: a bis(catechoylamide), 1,6-bis(2,3-dihydroxy-5-sulfobenzoyl)-1,6-diazahexane (4-LICAMS); a tris(catechoylamide), 1,3,5-tris(2,3-dihydroxy-5-sulfobenzoyl)triaminomethylbenzene (MECAMS); a tetrakis(catechoylamide), 1,5,10,14-tetrakis(2,3-dihydroxy-5-sulfobenzoyl)-1,5,10,14-tetraazatetradecane (3,4,3-LICAMS). Structural formulas for these ligands are shown in Figure 1.

Experimental

Reagents. Stock solutions of $Zn(NO_3)_2$ and $Mg(NO_3)_2$ were standardized by direct titration with disodium ethylenediaminetetraacetate (Na_2EDTA) using Eriochrome Black T as an indicator. Stock solutions of $Ca(NO_3)_2$, $Co(NO_3)_2$, and $Ni(NO_3)_2$ were standardized by back-titration of a measured excess of Na_2EDTA with a standarized solution of $Zn(NO_3)_2$ using Eriochrome Black T as the indicator. The $Cu(NO_3)_2$ solution was standarized with Pyrocatechol Violet by direct titration with Na_2EDTA. Details of the standardization procedures are presented elsewhere.[17] Stock solutions of carbonate-free KOH and $Fe(NO_3)_3$ were prepared and standardized as previously described.[18] Samples of each ligand were prepared as described earlier.[13,19] Molecular weights of the ligands were determined by potentiometric titration with KOH.

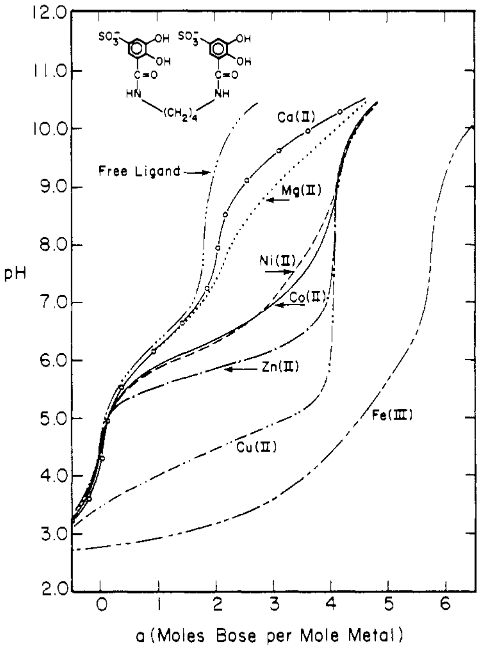

Figure 2. Potentiometric equilibrium curves of 4-LICAMS free ligand, 1:1 4-LICAMS to divalent metal, and 3:2 4-LICAMS to ferric ion. $[M^{2+}] \approx 1.1 \times 10^{-3}$ M; $[Fe^{3+}] = 6.6 \times 10^{-4}$ M; $\mu = 0.10$ M (KNO_3); $T = 25$ °C.

Potentiometric Measurements. The apparatus and detailed procedures used for potentiometric measurements have been described previously.[18] All measurements were made at 25 ± 0.05 °C and 0.10 M (KNO_3) ionic strength. The pH meter was calibrated with a standard solution of HNO_3 and a buffered acetic acid solution. Standardization of the meter was then completed by titrations of acetic acid to read $-\log [H^+]$ where $[H^+]$ is the hydrogen ion concentration, not activity. Equilibrium constants were calculated by a weighted nonlinear least-squares refinement in which the log β's were varied to minimize the sum of the squared differences between the observed and calculated pH at each point in the titration curve.[20]

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(20) From an initial set of guesses for the log β's, values for pH, pL, and pM were calculated for each data point by varying these parameters to minimize the differences between calculated and analytical concentrations of total hydrogen, total ligand, and total metal. The weighted residual for each data point is $r_i = (1/\sigma_i)(pH_{obsd} - pH_{calcd})_i$. The derivatives $D_{ij} = \partial r_i/\partial \log \beta_j$ were computed numerically, and the shifts in β values, computed to minimize the sum of the residuals, were applied from the vector–matrix equation

$$\Delta \log \beta = (\mathbf{D}^T\mathbf{D})^{-1}\mathbf{D}^T\mathbf{r}$$

The weighting factor, $1/\sigma_i$, was based on the estimated uncertainty in the pH reading at each point in the titration curve. This uncertainty has two components: the precision of the pH meter itself and the precision of titrant delivery (volume V_T). Thus the weight was calculated as

$$\sigma_i^2 = \sigma_{meter}^2 + (\partial pH/\partial V_T)_i^2 \sigma_{V_T}^2$$

where $\sigma_{meter} = 0.003$ pH unit, $\sigma_{V_T} = 0.002$ mL, and $\partial pH/\partial V_T$ is the slope of the titration curve at each point in the titration. This weighting scheme emphasizes the more accurate data from buffer regions and minimizes the relatively inaccurate pH readings from the steep inflections.

Table II. Equilibrium Constants[a] of Divalent Metals with Sulfonated Catecholate Ligands[b]

	Cu(II)	Zn(II)	Ni(II)	Co(II)	Mg(II)	Ca(II)	Fe(III)
			MECAMS				
$\log \beta_{111}$	35.88 (5)	30.2 (1)	26.5 (2)	26.3 (2)	22.3 (2)		
$\log \beta_{112}$	42.21 (5)	37.01 (6)	34.17 (8)	33.9 (1)	27.9 (1)		
$\log \beta_{110}$							41[c]
			3,4,3-LICAMS				
$\log \beta_{114}$	60.8 (2)	54.75 (7)	53.42 (8)	53.24 (6)	50.5 (3)	48.89 (8)	
$\log \beta_{113}$	52.7 (2)	46.9 (5)	45.4 (3)	45.2 (3)	42.5 (4)	39.86 (6)	
$\log \beta_{112}$	46.0 (2)	39.9 (2)	37.9 (2)	37.7 (2)	34.3 (3)	30.12 (4)	
$\log \beta_{210}$	43.8 (2)	31.8 (1)	28.2 (2)	27.9 (2)	19.9 (2)	16.2 (2)	
$\log \beta_{111}$							43[d]
			4-LICAMS				
$\log \beta_{110}$	21.2 (2)	15.63 (5)	14.0 (2)	13.6 (1)			27.4 (1)
$\log \beta_{121}$							51.1 (5)
$\log \beta_{122}$							58.3 (5)
$\log \beta_{230}$							76 (1)

[a] $\beta_{mlh} = [M_mL_lH_h]/([M]^m[L]^l[H]^h)$. [b] Measurements were made at 25 °C and 0.10 M (KNO_3) ionic strength. [c] See ref 22. [d] See ref 10.

Results and Discussion

4-LICAMS Titrations. The potentiometric titration curve of the free dicatechol ligand, 4-LICAMS, is shown in Figure 2. (The abscissa of the graph in this titration is mol of base/mol of *ligand.*) The curve shows a break at 2 equiv. This is indicative of the deprotonation of the two phenolic oxygens that are ortho to the carbonyl. The increased acidity of the ortho phenolic hydrogens over the meta phenolic hydrogens is due to the combined resonance and inductive effects of the carbonyl and sulfonate groups.[21] The average ligand-protonation constants for the two monoprotonated catechoylamide arms have been estimated[22] to be $K \approx 10^{11.5}$. These estimated protonation constants are based on literature values reported for similar, but simple, sulfonated benzamide ligands; such estimates have been shown to be good approximations.[4,23] The ligand protonation constants for the ortho phenol moieties of 4-LICAMS are listed in Table I.

The titration curves of one to one 4-LICAMS to divalent metal are shown in Figure 2. The Cu(II), Zn(II), Co(II), and Ni(II) curves show breaks at 4 equiv due to formation of a bis(catecholato)metal complex. From simple stoichiometric considerations, it is impossible to determine whether the complexes formed are monomeric or dimeric. Analysis of the buffer regions using the model-dependent computer program[20] yielded refinements for monomeric and dimeric complexes. However, the stability constants obtained by assuming dimeric complexes present had errors 10–20 times greater than those of the stability constants obtained by assuming formation of monomeric complexes. In addition, titrations were performed by varying the metal concentration while the ligand concentration was kept constant. No shift of the buffer region to lower pH was observed at higher metal concentrations—as is expected if dimeric complexes were formed. Bis(catecholate) complexes of Cu(II), Co(II), Ni(II), and Zn(II) for simple monocatechol ligands are known.[24] Even at higher 4-LICAMS to metal ratios there was no evidence of the formation of tris(catecholate) complexes.

By the depression of the titration curves, the relative stabilities of the 4-LICAMS divalent metal complexes are Cu(II) > Zn(II) > Co(II), Ni(II) > Mg(II) > Ca(II). These relative stabilities are reflected in the refined log β values listed in Table II. It is noteworthy that both Ca(II) and Mg(II) show very little affinity for the ligand and that their titration curves resemble only slight depressions of the free-ligand titration curve.

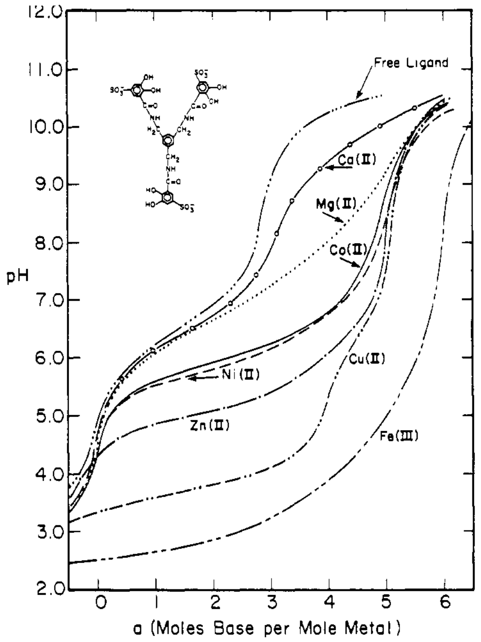

Figure 3. Potentiometric equilibrium curves of MECAMS free ligand and 1:1 MECAMS to metal. $[M^{2+}] \approx 1.1 \times 10^{-3}$ M; $[Fe^{3+}] \approx 1.3 \times 10^{-3}$ M; $\mu = 0.10$ M (KNO_3); $T = 25$ °C.

The ferric ion titration with 4-LICAMS (Figure 2) is performed with a three to two ligand to metal ratio due to the six-coordinate nature of Fe(III). Ratios less than this lead to hydrolysis of the metal and subsequent "drifts" in the pH readings. This problem is not encountered with the divalent metals due to their smaller hydrolysis constants.[4] The break at $a = 6$ indicates that six phenolic oxygens bind to each ferric ion. Such a structure is probably dimeric in character and may be analogous to the coordination of ferric ion by rhodotorulic acid, a dihydroxamate ligand in which metal complexation also occurs in a three to two ligand to metal ratio.[25] The refined value of log β_{230} for the dimeric Fe(III) complex is 76 (1), where β_{mlh} is the formation constant written in terms of free metal, ligand, and hydrogen concentrations. The

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subscript *mlh* denotes the number of metal, ligand, and hydrogen ions incorporated in the complex.[26]

MECAMS Titrations. The titration of the free tricatechol MECAMS ligand is shown in Figure 3. The ligand protonation constants have been reported previously[22] and are listed in Table I. The break at $a = 3$ (mol of base/mol of *ligand*) denotes deprotonation of the three more acidic phenol groups ortho to the carbonyl on each of the catechol moieties.

One to one titrations of MECAMS with divalent zinc, cobalt, nickel, and magnesium (Figure 3) show no other features than a break at $a = 5$. This indicates the formation of a bis(catecholate) complex followed by deprotonation of the remaining OH group ortho to the carbonyl. A distinct inflection at $a = 4$ following the formation of the bis(catecholate) complex is present only in the titration of Cu(II) with MECAMS, in which case metal complex formation is strong enough not to overlap with the equilibrium of ligand deprotonation. By monitoring the C–O stretch of the carbonyl, which is adjacent to the catechol, as a function of increasing pH in the Cu(II)–MECAMS complexes, one can assign the peak that develops at $\nu = 1611$ cm^{-1} to that of a free catechol arm—similar to the stretch observed at $\nu = 1613$ cm^{-1} for deprotonated MECAMS.[27]

The refined log β values are listed in Table II. The relative stabilities of these complexes are the same as those noted with 4-LICAMS. The Ca(II) complexation is very weak, that metal again showing little affinity for the catecholate moieties.

The Fe^{III}[MECAMS] titration curve (Figure 3) indicates formation of a tris(catecholate) complex with concomitant release of six protons ($a = 6$). Spectrophotometric titration results as well as competitions performed with EDTA are reported elsewhere.[22] The strong one to one MECAMS to ferric ion complex which is formed with *no* free catecholate arms can be compared to the one to one MECAMS to divalent metal complexes which have one free catecholate arm and weaker complexation. It is clear that ferric ion forms a stronger complex and better utilizes the coordinating capability of the ligand.

3,4,3-LICAMS Titrations. The titration curve of the free tetra(catechol) ligand 3,4,3-LICAMS (a is mol of base/mol of *ligand*) is shown in Figure 4. This curve shows an inflection at $a = 4$. Analogous to the case of 4-LICAMS and MECAMS deprotonation curves, this represents the dissociation of the four phenolic hydrogens ortho to the carbonyl. The ligand protonation constants are given in Table I.

The one to one ligand to metal titration curves for 3,4,3-LICAMS with Mg(II), Ni(II), Co(II), and Zn(II) (Figure 4) only show a break at $a = 6$, while the Cu(II) curve also shows an inflection at $a = 4$ as well as $a = 6$. The buffer region from $a = 0$ to $a = 4$ of the Cu(II) curve is attributed to the formation of a bis(catecholate) complex. This is followed by the deprotonation of the phenols ortho to the carbonyl on the two remaining catechoylamide arms ($a = 4$ to $a = 6$). The stronger complexation of Cu(II) by the catecholate moieties allows the break at $a = 4$ to be seen and is the basis for proposing bis(catecholate) formation. Once again, no break at $a = 4$ occurs for the other divalent metals studied due to the overlapping equilibria of metal complexation and ligand deprotonation. Thus, as in the case of MECAMS, all the divalent metals studied except Ca(II) show formation of bis(catecholate) complexes. It is interesting to note that the titration curves of all the divalent metals except Mg(II) and Ca(II) with 3,4,3-LICAMS intersect at $a = 5.5$. At this point the pH is equal to the pK_a of the ortho OH that is remaining on one of the free catecholate arms, analogous to the Bjerrum half-integral $\bar{h}$ plots. The value of 8.2 for the pK_a from the intersection point agrees favorably with the value of log K_5^H = 8.26 in Table I, representative of the least acidic of the four titrable ortho phenols. The log β values (β_{114}, β_{113}, β_{112}) refined from these titrations are given in Table II. The relative stabilities of the metals with 3,4,3-LICAMS are the same as those noted with 4-LICAMS and MECAMS.

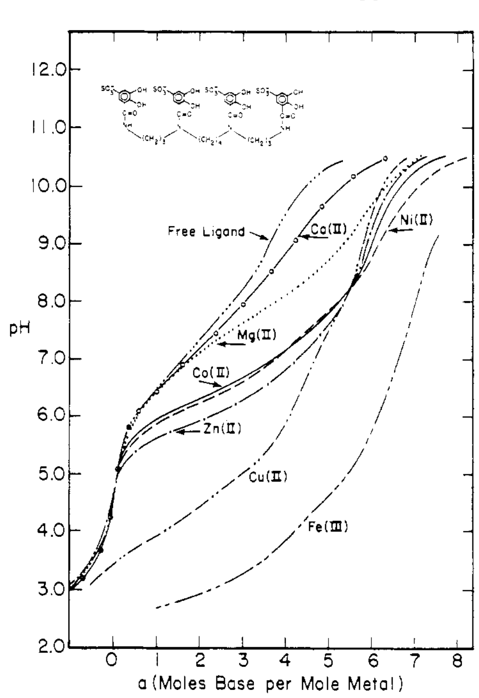

Figure 4. Potentiometric equilibrium curves of 3,4,3-LICAMS free ligand and 1:1 3,4,3-LICAMS to metal. [M^{2+}] = [Fe^{3+}] ≈ 1.1 × 10^{-3} M; μ = 0.10 M (KNO$_3$); T = 25 °C.

The ferric ion titration with 3,4,3-LICAMS breaks at $a = 7$. This is in keeping with the formation of a tris(catecholate) complex followed by deprotonation of the one remaining phenol, which is ortho to the carbonyl. The fact that only *one* catecholate arm is free in the fully formed ferric ion–3,4,3-LICAMS complex demonstrates that ferric ion more effectively employs the ligand denticity of 3,4,3-LICAMS than do the divalent metals. Ferric ion also forms a stronger complex with 3,4,3-LICAMS.

Because of the expanded (octadentate), coordinating capabilities of 3,4,3-LICAMS, titrations were also performed at two to one divalent metal to ligand ratios. These titration curves are shown in Figure 5. (For the free-ligand curve, which is retained for the sake of comparison, the abscissa should read mol of base/0.5 mol of ligand). Note that divalent zinc, copper, cobalt, and nickel show definite breaks at $a = 4$, forming a dimer. The Ca(II) and Mg(II) curves indicate very weak complexation even at these higher metal concentrations. The relative stabilities are the same as in the previous complexes; this is reflected in the log β values given in Table II (β_{210}).

Attempts were made to titrate Mn(II) with MECAMS and 3,4,3-LICAMS. All the titrations were characterized by large "drifts" in the pH readings. This can probably by attributed to the oxidation of Mn(II) to Mn(III) by any residual oxygen in the titration vessel (whose design does not allow for the truly rigorous exclusion of O$_2$) combined with the ability of the catechol ligand to stabilize the higher oxidation state.[28]

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(26) For example, the stability constant of the complex formation given by the reaction

$$Cu^{2+} + MECAMS^{9-} + 2H^+ = [Cu(H_2MECAMS)]^{5-}$$

is β_{112}, where

$$\beta_{112} = [Cu(H_2MECAMS)^{5-}]/([Cu^{2+}][MECAMS^{9-}][H^+]^2)$$

(27) Pecoraro, V. L.; Harris, W. R.; Wong, G.; Carrano, C.; Raymond, K. N., submitted for publication.

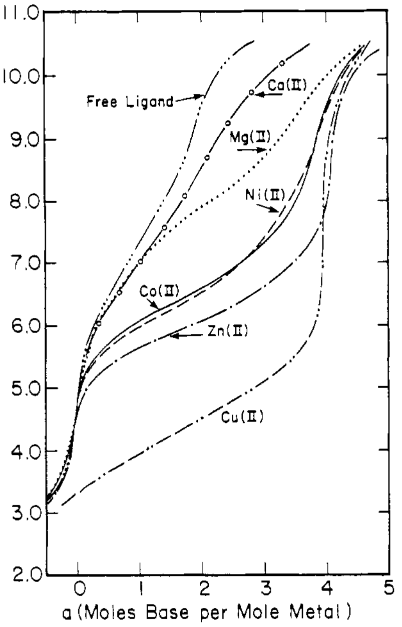

Figure 5. Potentiometric equilibrium curves of 3,4,3-LICAMS free ligand and 1:2 3,4,3-LICAMS to divalent metal. $[M^{2+}] \approx 1.80 \times 10^{-3}$ M; $\mu = 0.10$ M (KNO_3); $T = 25$ °C.

Qualitatively, the Mn(II) complexes were slightly less stable than those formed with Co(II).

Although one can directly compare β values of a series of divalent metals with the *same* ligand (e.g., β_{110} of Cu[4-LICAMS] vs. β_{110} or Co [4-LICAMS]), problems arise when one attempts to compare β values of divalent metals with *different* ligands (e.g., β_{110} of Cu[4-LICAMS] vs. β_{111} of Cu[MECAMS]). This is because the ligands differ in acidity and proton dependence. In addition, one cannot compare β values of divalent metal complexes to those of ferric complexes of the same or different ligands (e.g., β_{110} or Fe[MECAMS] vs. β_{111} of Cu[MECAMS]). In this case, the coordination around the metal differs: bis(catecholate) vs. tris(catecholate) coordination. As a standard by which to measure and compare the effectiveness of a potential chelating agent for a metal at physiological pH, one can calculate the concentration of the uncomplexed, aquated ion in a solution which is 10 μM in ligand, 1 μM in metal, at pH 7.4. These calculations are performed by using refined β values or, when β values are not directly obtainable, by using conditional formation constants as in the case of Fe^{III}[MECAMS][15] and Fe^{III}[3,4,3-LICAMS].[25] The concentrations that are calculated are expressed as pM, where pM = $-\log [M(H_2O)_x{}^{N+}]$. The pM values for the divalent metals and ferric ion with 4-LICAMS, MECAMS, 3,4,3-LICAMS, EDTA, DTPA, and desferrioxamine B (DFO), the current chelating agent used for treatment of iron overload, are tabulated in Table III. With use of these numbers direct comparisons can be made: the larger the pM value, the greater the affinity of the chelate for the metal under the defined conditions. Under the conditions specified, the minimum pM value that is possible is 6.0.

Analysis of Table III reveals several important points regarding these chelating agents. None of the poly(catechoylamides) bind the important biological ions Ca(II) or Mg(II) to any significant extent, whereas the amine polycarboxylates, EDTA and DTPA, have an enhanced affinity for Ca(II) and Mg(II). Generally, EDTA and DTPA do not bind ferric ions as tenaciously as do the poly(catechoylamides), nor do they demonstrate specificity in binding.

Table III. Equilibrium Free Metal Ion Concentrations Expressed as pM[a]

	4-LICAMS	MECAMS	3,4,3-LICAMS	EDTA[b]	DTPA[b]	DFO[c]
Cu(II)	13.6	16.9	14.7	16.9	18.2	11.8
Zn(II)	8.3	11.3	8.7	14.6	15.1	7.2
Ni(II)	6.8	8.0	7.2	16.7	17.0	7.0
Co(II)	6.5	7.7	7.0	14.5	16.0	6.5
Mg(II)	6.0	6.0	6.0	7.0	6.4	6.0
Ca(II)	6.0	6.0	6.0	8.8	7.6	6.0
Fe(III)	23.3	29.3	31.1	22.2	24.7	26.6

[a] pM = $-\log [M(H_2O)_x{}^{N+}]$; calculated for 10 μM ligand, 1 μM metal, pH 7.4 at 25 °C, and 0.1 M KNO_3. [b] Reference 4. [c] Anderegg, G.; L'Eplattenier, F.; Schwarzenbach, G. *Helv. Chim. Acta* **1963**, *46*, 1400.

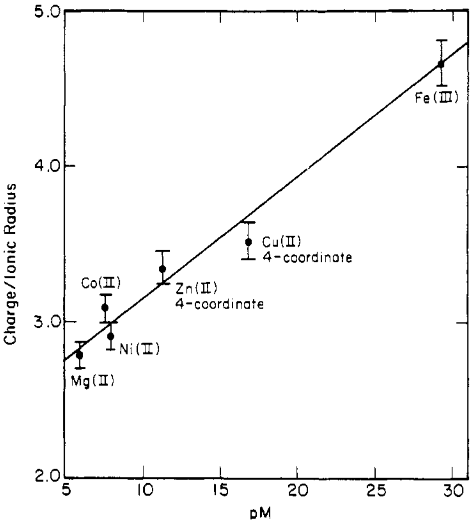

Figure 6. Graph of charge to ionic radius ratio vs. pM for MECAMS.

The specificity of desferrioxamine B for ferric ion is impressive. However, it does not show as great an affinity for ferric ion as do MECAMS and 3,4,3-LICAMS; also, the difference in the Cu(II) pM value and the ferric ion pM value (ΔpM = 14.8) is less than that demonstrated by 3,4,3-LICAMS (ΔpM = 16.4). Desferrioxamine B also does not bind Ca(II) or Mg(II) to any great extent.

Just as MECAMS was designed to bind ferric ion, the ligand 3,4,3-LICAMS has been designed to complex tetravalent actinides, in particular Pu(IV). The ligand is octadentate, which satisfies the eight-coordinate nature of Pu(IV), via four catecholate moieties. The length and substitution pattern of the linear backbone have been determined from the structure of simple tetrakis(catecholato)actinide(IV) complexes[29] to allow for the best fit of the large Pu(IV) ion. In view of the similarities between Fe(III) and Pu(IV) (vide supra), 3,4,3-LICAMS is expected to effectively bind Pu(IV). In vivo tests of 3,4,3-LICAMS show it is very effective in removing plutonium from mice.[30] In addition, in vivo tests of a related compound, 3,4,3-LICAMC, a carboxylated rather than sulfonated catechoylamide derivative, has shown it to be more effective in plutonium removal at low dosages than any other sequestering agent tested to date.[31]

It is apparent from this study that 3,4,3-LICAMS demonstrates greater selectivity and greater affinity for metals of high charge to radius ratio than does DTPA, the current chelating

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agent used for plutonium decorporation. The difference in specificity between DTPA and 3,4,3-LICAMS confirms that catechoylamides may provide a promising alternative to DTPA for chelation therapy of plutonium contamination.

An interesting correlation is observed if one compares the pM value of each metal to its charge to ionic radius ratio. Figure 6 is a graph of charge to ionic radius ratio vs. pM for MECAMS. A similar correlation exists for 4-LICAMS and 3,4,3-LICAMS. The ionic radii used for Zn(II) and Cu(II) were those listed by Shannon[11] for four-coordinate species. The other ions were assumed to be six-coordinate. Copper(II) is the smallest of the divalent metals studied, and it demonstrates the greatest affinity for the catechoylamide. Ferric ion, with its high charge and small size, demonstrates the greatest stability. Plutonium(IV) also exhibits a high charge to ionic radius ratio, and this explains the qualitative observation of its high affinity for poly(catechoylamide) ligands. Work in progress includes titrations of trivalent lanthanides with 3,4,3-LICAMS to analyze the extent to which the correlation mentioned above can be extended.

Summary

The synthetic poly(catechoylamide) ligands generally form very stable complexes with ferric ion and other ions of high charge to ionic radius ratios including Pu(IV) and Th(IV).[10] The common divalent metals that are present in the body, e.g., Mg(II) and Ca(II), are large enough and are of sufficiently low charge not to be chelated effectively by the poly(catechoylamides). The effectiveness of the ligands as a whole can be attributed not only to the intrinsic affinity of the phenolic oxygens for ligation of highly charged ions but also can be attributed to the structural design of the entire complex for encapsulation of the desired ion. It is the combination of these two factors which contributed to the excellent selectivity of the poly(catechoylamides) to sequester Fe(III) or Pu(IV).

Acknowledgment. We wish to thank Dr. V. L. Pecoraro for helpful discussions, Dr. W. R. Harris for the Fe^{III}[3,4,3-LICAMS] data, and Dr. F. L. Weitl for samples of 3,4,3-LICAMS and 4-LICAMS. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy, under Contract No. W-7405-ENG-48.

Registry No. 4-LICAMS, 73630-97-4; MECAMS, 71353-06-5; 3,4,3-LICAMS, 82044-95-9; Fe, 7439-89-6; Cu, 7440-50-8; Zn, 7440-66-6; Ni, 7440-02-0; Co, 7440-48-4; Mg, 7439-95-4; Ca, 7440-70-2.

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Kinetics and Mechanism of the Oxidation of Hydroquinone and Catechol by $[Ni^{III}cyclam]^{3+}$ in Aqueous Perchlorate Media

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Received November 23, 1981

Detailed rate studies have been made of the oxidation of hydroquinone (H_2Q) and catechol (H_2Cat) by Ni^{III}cyclam, $[Ni^{III}L]^{3+}$, complexes. Over the pH range 0–2.9, the rate of loss of Ni(III) may be represented by the equation $-d[Ni(III)]/dt = \{2(k_1 + k_2K_h/[H^+] + k_3K_aK_h/[H^+]^2)K_3[H^+][Ni(III)]_t[H_2Q]_t\}/\{([H^+] + K_h)([H^+] + K_3)\}$, where K_h and K_3 represent hydrolysis and dissociation constants of $[Ni^{III}cyclam]^{3+}$ and protonated dihydroxybenzene, respectively. The rate constants are k_1([Ni(III)] + [H_2Q]) = 1.09×10^4 (H_2Q) and 6.98×10^2 (H_2Cat) $M^{-1}\ s^{-1}$, respectively ($T = 25$ °C), and other constants involving $[Ni(OH)L]^{2+} + H_2Q$ have been evaluated from hydrogen ion dependence measurements. There is also evidence for a pathway involving $H(Cat)^-$ as a reductant. Sulfate ion has a marked effect on the rates, showing pronounced retardation owing to the formation of sulfate complexes with lower redox potentials. The data have been interpreted with a Marcus cross correlation and are considered outer sphere in character. Self-exchange rates for Ni(II)/Ni(III) macrocycles are discussed.

Introduction

With recent observations[2,3] that the nickel(III) state can be stabilized with nitrogen-donor macrocyclic ligands, several reports have been published[4-8] describing various ligand types and some chemical and physical properties of the nickel(III) complexes. The broader aspects of the chemistry of this oxidation state have also been the subject of a recent review.[9]

The nickel(III) species offer a wide range of oxidizing potentials,[10] but to date there have been relatively few data describing the kinetics and mechanisms of reaction with reducing substrates. In some systems where the transient nickel(III) complexes were generated at relatively high pHs (2–5) with pulse radiolysis[11] or flash photolysis[12] techniques, the reactions with Br^-, SCN^-, and H_2O_2 have been monitored. In general, the rate data show a second-order dependence on metal complex and first or second order on substrate, suggesting the involvement of inner-sphere complexes. The rate, however, varies with both pH and reductant concentration.

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