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Mary J. Kappel and Kenneth N. Raymond

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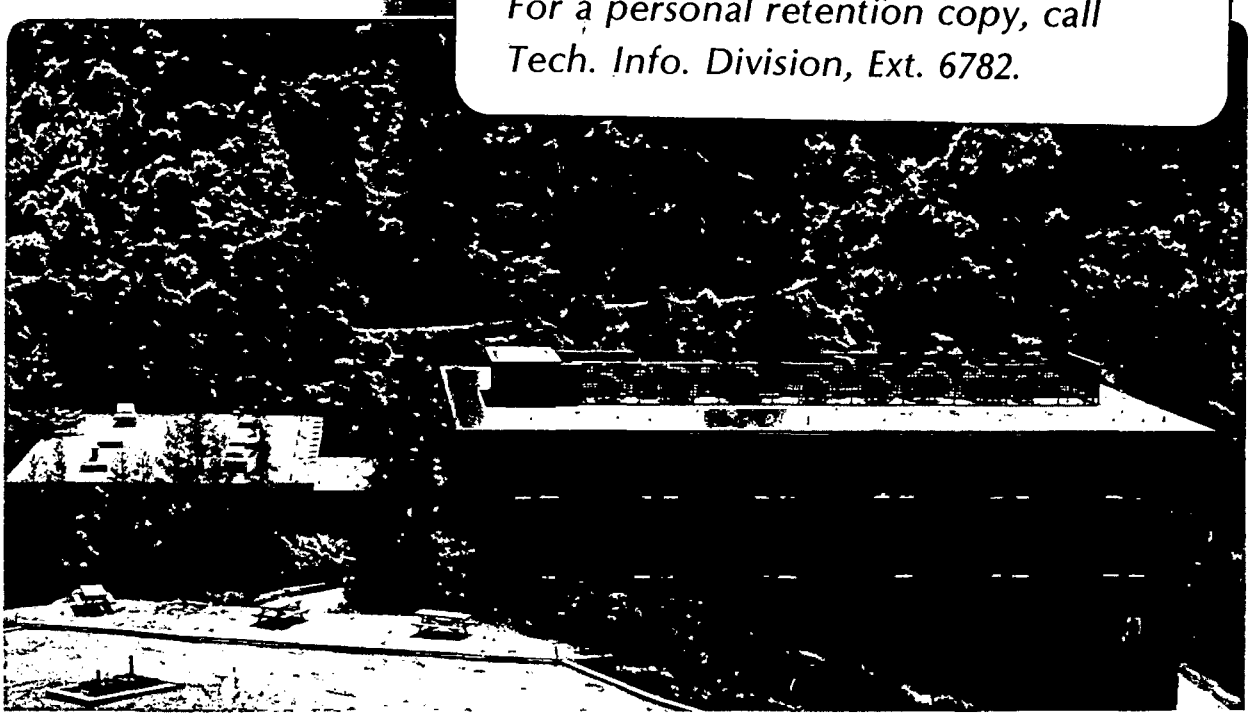

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Ferric Ion Sequestering Agents. 10. Selectivity of Sulfonated Polycatechoylamides for Ferric Ion[1]

By

Mary J. Kappel and Kenneth N. Raymond*

Contribution from Materials and Molecular Research Division, Lawrence Berkeley Laboratory, and Department of Chemistry, University of California, Berkeley, California 94720

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*Address correspondence to this author, Chemistry Department, University of California.

Abstract

Complexation equilibria have been evaluated by potentiometric titration of several biologically significant divalent metals as well as Fe(III) with the sulfonated polycatecholate ligands N,N'-bis(2-3-dihydroxy-5-sulfobenzoyl)-1,6-diazahexane [4-LICAMS], 1,3,5-N,N',N"-tris(2,3-dihydroxy-5-sulfobenzoyl)triaminomethylbenzene [MECAMS], and N,N',N",N"'-tetra(2,3-dihydroxy-5-sulfobenzoyl)-1,5,10,14-tetraazadecane [3,4,3-LICAMS]. For all ligands studied the titrations demonstrate the following relative stabilities

$$Fe(III) \gg Cu(II) > Zn(II) > Ni(II), \quad Co(II) > Mg(II) > Ca(II) \quad .$$

These polycatechoylamide 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 anti-Lewisite (2,3-dimercaptopropanol) was discovered to be an effective sequestering agent for arsenic in the early 1940's.[2] Subsequent development of poly(carboxylate)amines 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 which 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. Using 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. Plutonium(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; and (3) Pu(IV) is known to follow biological iron transport pathways.[12] With these similarities 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 tetracatechoylamides 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 dicatechoylamide, N,N'-bis(2,3-dihydroxy-5-sulfobenzoyl)-1,6-diazahexane [4-LICAMS]; a tricatechoylamide, 1,3,5-N,N',N"-tris(2,3-dihydroxy-5-sulfobenzoyl)triaminomethylbenzene [MECAMS]; and a tetracatechoylamide N,N',N",N"' -tetra(2,3-dihydroxy-5-sulfobenzoyl)-1,5,10,14-tetraazadecane [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 ethylenediaminetetraacetic acid (EDTA) using Eriochrome Black T as an indicator. Stock solutuons of $Ca(NO_3)_2$,

$Co(NO_3)_2$, and $Ni(NO_3)_2$ were standardized by back titration of a measured excess of disodium EDTA with a standardized solution of $Zn(NO_3)_2$ using Eriochrome Black T as the indicator. The $Cu(NO_3)_2$ solution was standardized with Pyrocatechol Violet by direct titration with disodium EDTA. Details of the standardization procedures are presented elsewhere.[17] Stock solutions of 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.

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 non-linear least-squares refinement in which the log β's were varied to minimize the sum of the differences between the observed and calculated pH at each point in the titration curve.[20]

Results and Discussion

4-LICAMS Titrations. The potentiometric titration curve of the free di-catechol ligand, 4-LICAMS, is shown in Figure 2. [The abscissa of the graph in this titration is moles base per mole ligand.] The curve shows a break at two equivalents. This is indicative of the deprotonation

of the two phenolic oxygens which 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 catechoylamides 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 four equivalents due to formation of a biscatecholate 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 assuming dimeric complexes present had errors ten to twenty times greater than the stability constants obtained assuming formation of monomeric complexes. In addition, titrations were performed varying the metal concentration while keeping the ligand concentration 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.

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.[26] The refined value of log β_{230} for the dimeric Fe(III) complex is 76(1), where $\beta_{m\ell h}$ is the formation constant written in terms of free metal, ligand, and hydrogen concentrations. The subscript mℓh denotes the number of metal, ligand, and hydrogen ions incorporated in the complex.[26]

MECAMS Titrations. The titration of the free tri-catechol 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 (moles base per mole 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 biscatecholate complex followed by deprotonation of the remaining phenol ortho to the carbonyl. A distinct inflection at a = 4 following the formation of the biscatecholate 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 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 ferric MECAMS titration curve (Figure 3) indicates formation of a triscatecholate 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 tetracatechol ligand 3,4,3-LICAMS [a is moles base per mole ligand] is shown in Figure 4. This curve shows an inflection at a = 4. Analogous to the 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 biscatecholate 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 biscatecholate 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 biscatecholate 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 phenol 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.

The ferric ion titration with 3,4,3-LICAMS breaks at a = 7. This is in keeping with the formation of a triscatecholate 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 moles base per 1/2 mole 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 be 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] 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 <u>same</u> ligand (e.g., β_{110} of Cu[4-LICAMS] vs. β_{110} of Co [4-LICAMS]), problems arise when one attempts to compare β values of divalent metals with <u>different</u> 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 ferric complexes of the same or different ligands (e.g., β_{110} of 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 using refined β values, or when β values are not directly obtainable, by using conditional formation constants as in the case of ferric MECAMS[15] and ferric 3,4,3-LICAMS.[25] The concentrations which 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. Using 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 polycatechoylamides bind the important biological ions Ca(II) or Mg(II) to any significant extent; whereas the polycarboxylateamines, EDTA and DTPA, have an enhanced affinity for Ca(II) and Mg(II). Generally, EDTA and DTPA do not bind ferric ion as tenaciously as do the polycatechoylamides, nor do they demonstrate specificity in binding.

The specificity of desferrioxamine B for ferric ion is impressive. However, it does not show as great an affinity for ferric ion as does MECAMS and 3,4,3-LICAMS: also, the differences in the Cu(II) pM value and the ferric ion pM value ($\Delta pM = 14.8$) is less than that demonstrated by 3,4,3-LICAMS ($\Delta pM = 16.4$). 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 has 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 shows 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 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 versus 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 polycatechoylamide 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 polycatechoylamide 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 which are present in the body, e.g. Mg(II) and Ca(II), are large enough and

of sufficiently low charge not to be chelated effectively by the polycatechoylamides. 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 polycatechoylamides to sequester Fe(III) or Pu(IV).

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20. Given 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 $r_i = (1/\sigma_i)(pH_{obs} - pH_{calc})_i$. 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:

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

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

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

where σ_{meter} = 0.003 pH unit, σ_{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.

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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

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

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Table I

Protonation constants[a] of sulfonated catecholate ligands[b]

Ligand	$\log K_3^H$	$\log K_4^H$	$\log K_5^H$	$\log K_6^H$	$\log K_7^H$	$\log K_8^H$	$\log K_{ave}^H$
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

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[a] $K_N^H = \frac{[H_nL]}{[H_{n-1}L][H]}$

[b] Measurements were made at 25°C and 0.10 M (KNO_3) ionic strength.

[c] See Ref. 22.

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] $\beta_{m\ell h} = \frac{[M_m L_\ell H_h]}{[M]^m [L]^\ell [H]^h}$; [b] Measurements were made at 25°C and 0.10 M (KNO_3) ionic strength; [c] See Ref. 22; [d] See Ref. 10.

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

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[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] Ref. 4

[c] Anderegg, G.; L'Eplattenier, F.; Schwarzenbach, G. Helv. Chim. Acta 1963, 46, 1400.

Figure Captions

Figure 1. Structural formulas of sulfonated catechoylamide ligands.

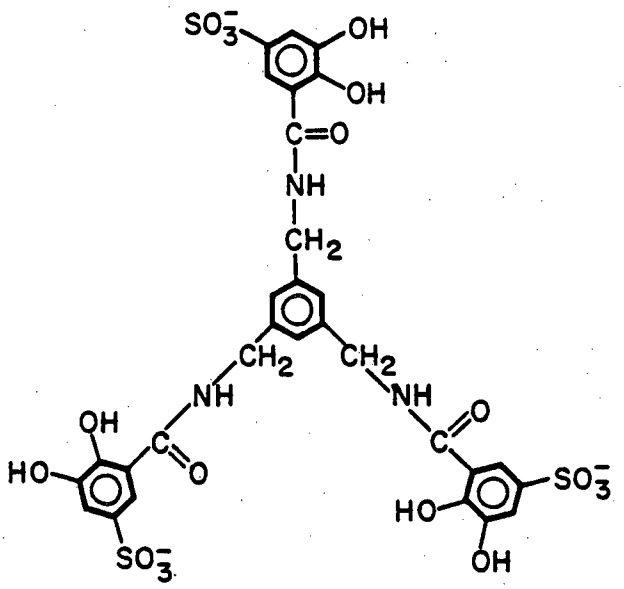
Figure 2. Potentiometric equilibrium curves of 4-LICAMS free ligand, 1:1 4-LICAMS to divalent metal, and 3:2 4-LICAMS to ferric ion. $[M^{2+}] \approx 1.1 \times 10^{-3}$ M; $[Fe^{3+}] = 6.6 \times 10^{-4}$ M; $\mu = 0.10$ M (KNO_3); T = 25°C.

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.

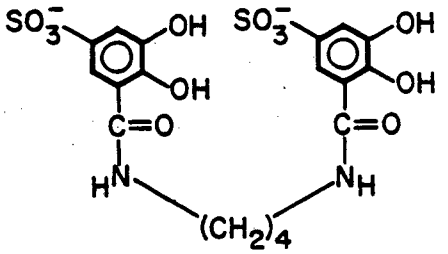
Figure 4. Potentiometric equilibrium curves of 3,4,3-LICAMS free ligand, and 1:1 3,4,3-LICAMS to metal. $[M^{2+}] = [Fe^{3+}] \approx 1.1 \times 10^{-3}$ M; $\mu = 0.10$ M (KNO_3); T = 25°C.

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.

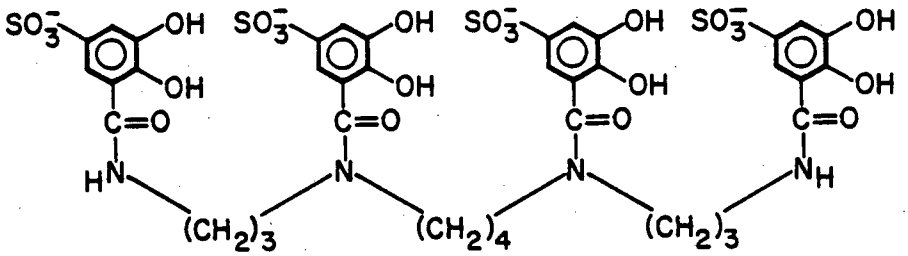
Figure 6. Graph of charge to ionic radius ratio versus pM for MECAMS.



MECAMS



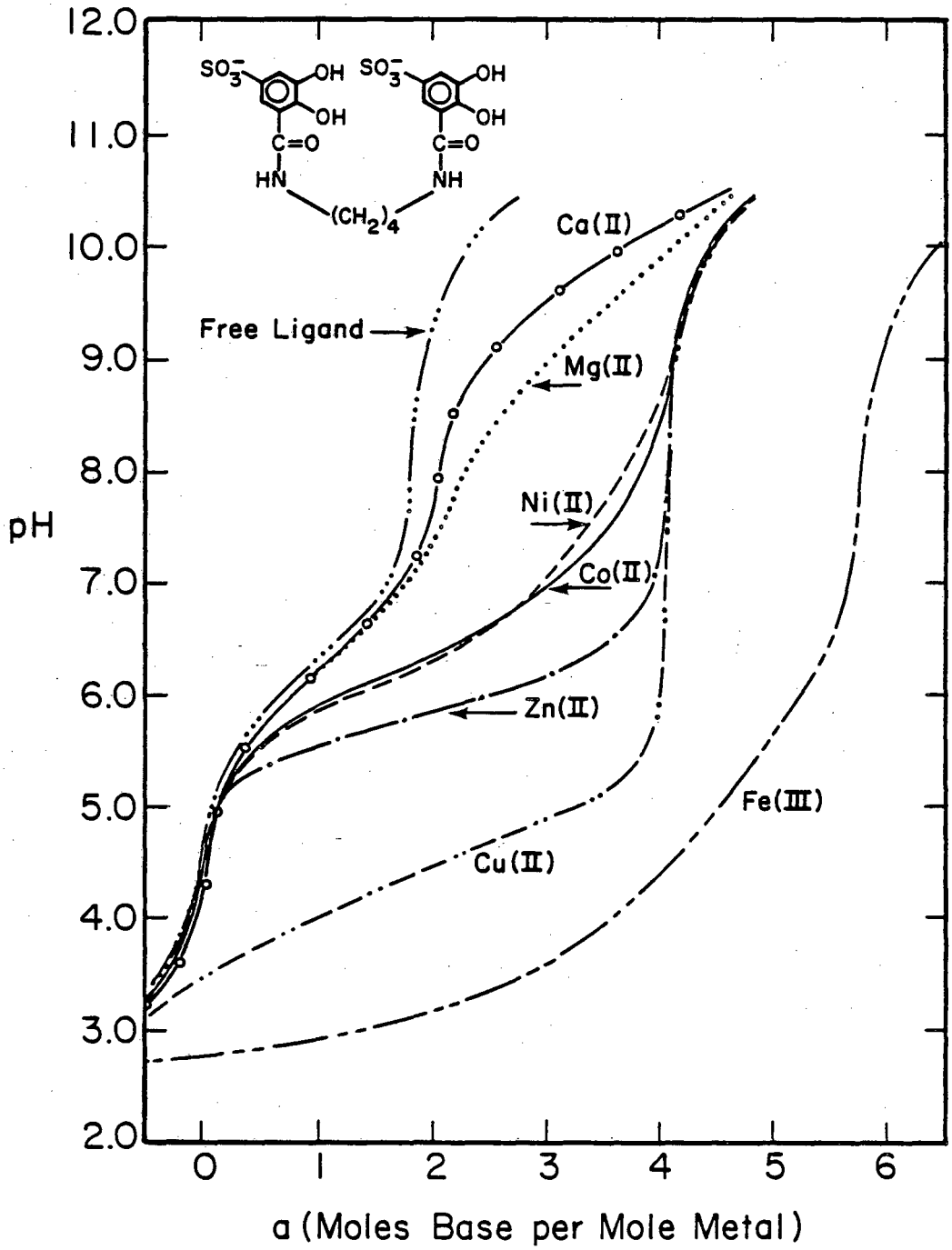
4-LICAMS



3,4,3-LICAMS

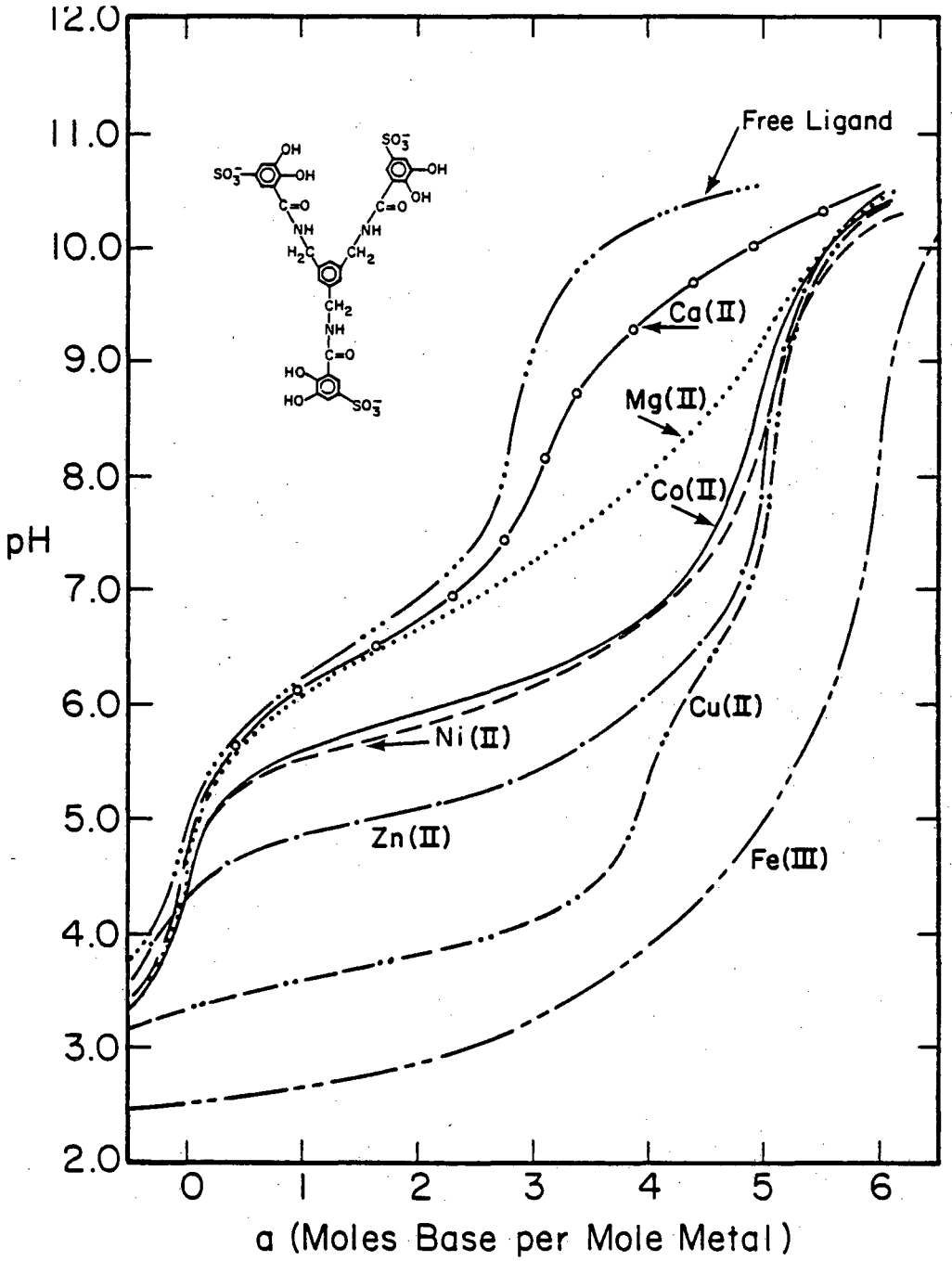
XBL 8010-12608

Fig. 1



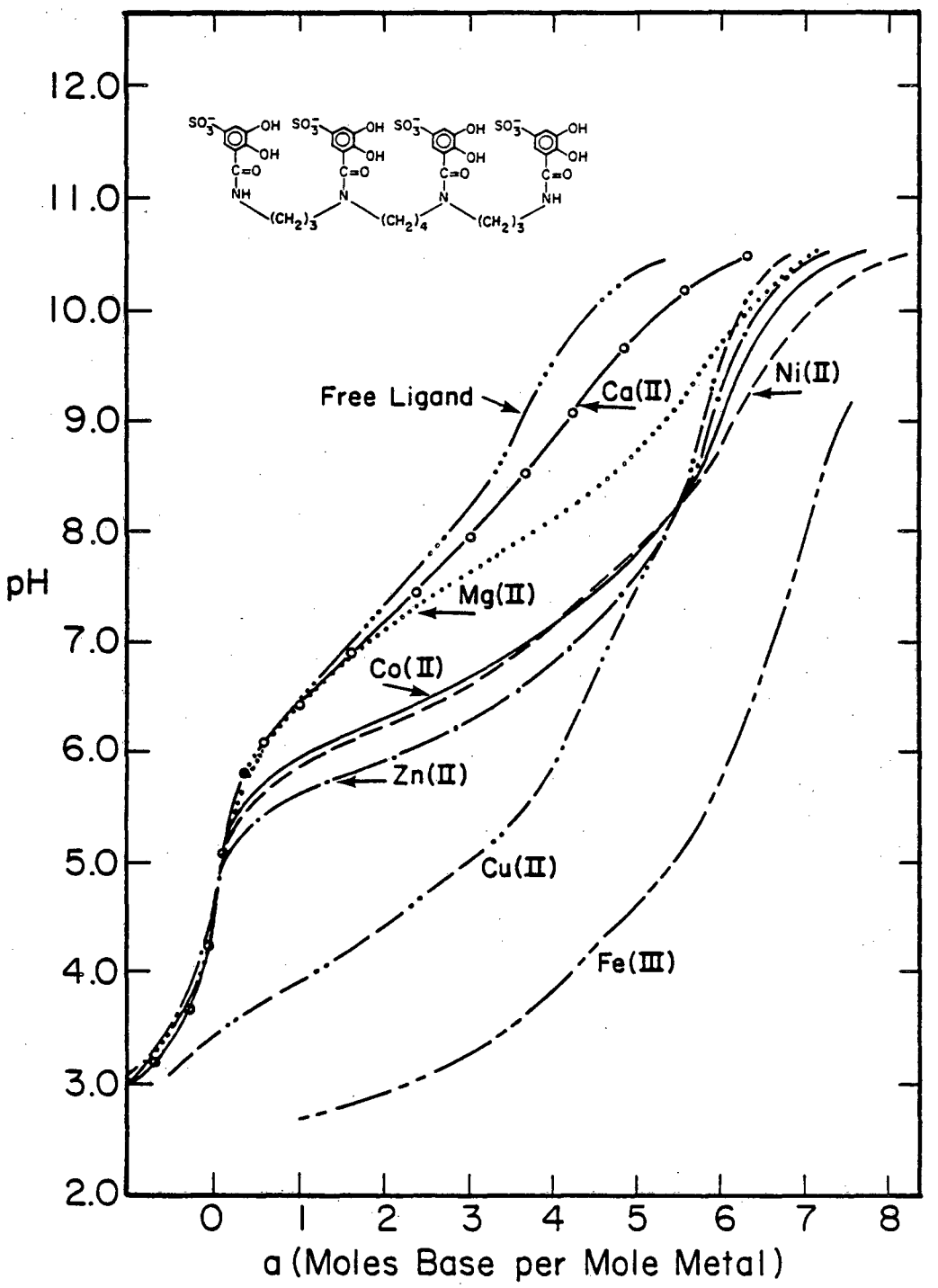
XBL 8010-12615

Fig. 2



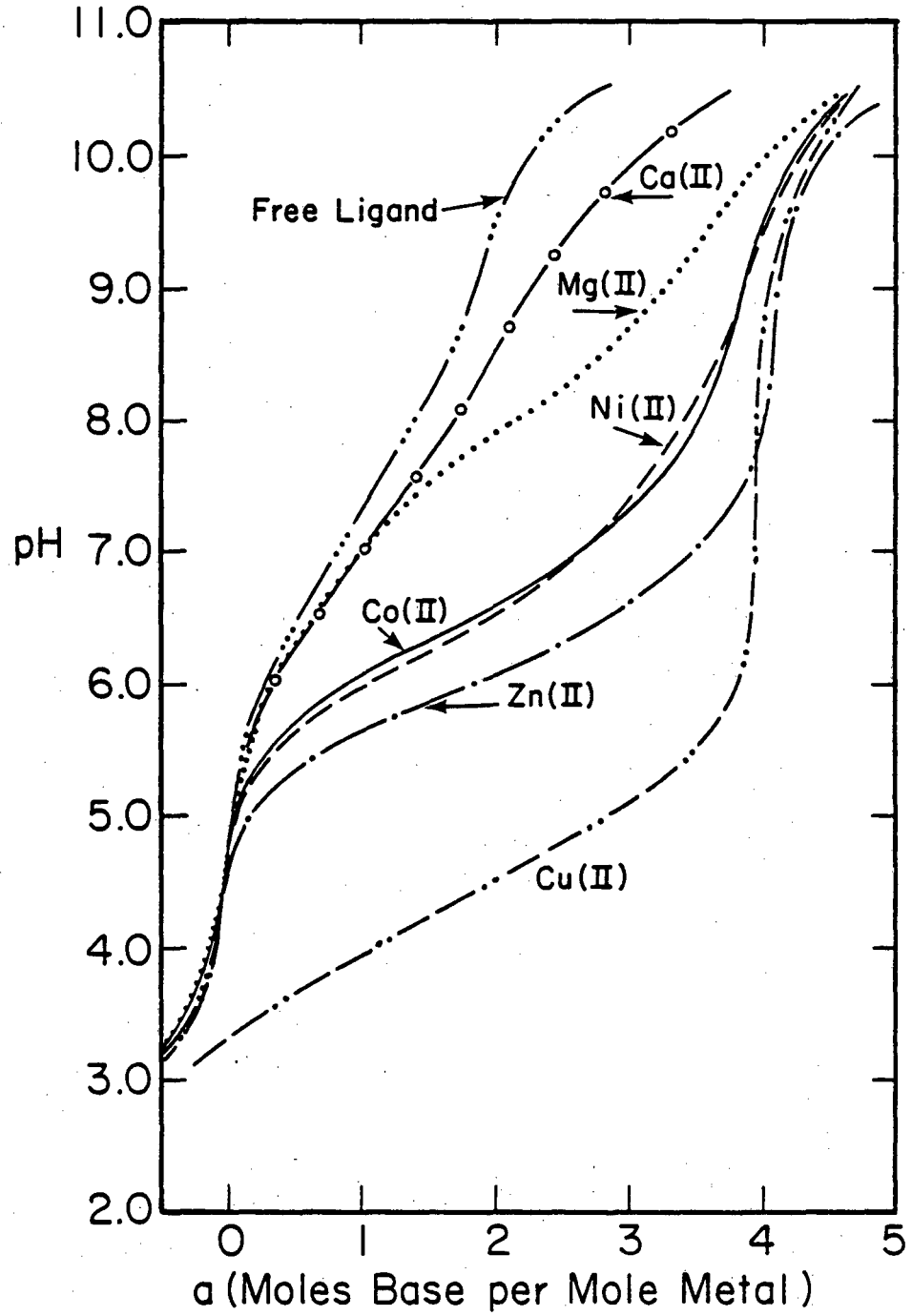
XBL 8010-12614

Fig. 3



XBL 8010-12616

Fig. 4



XBL 8010-12610

Fig. 5

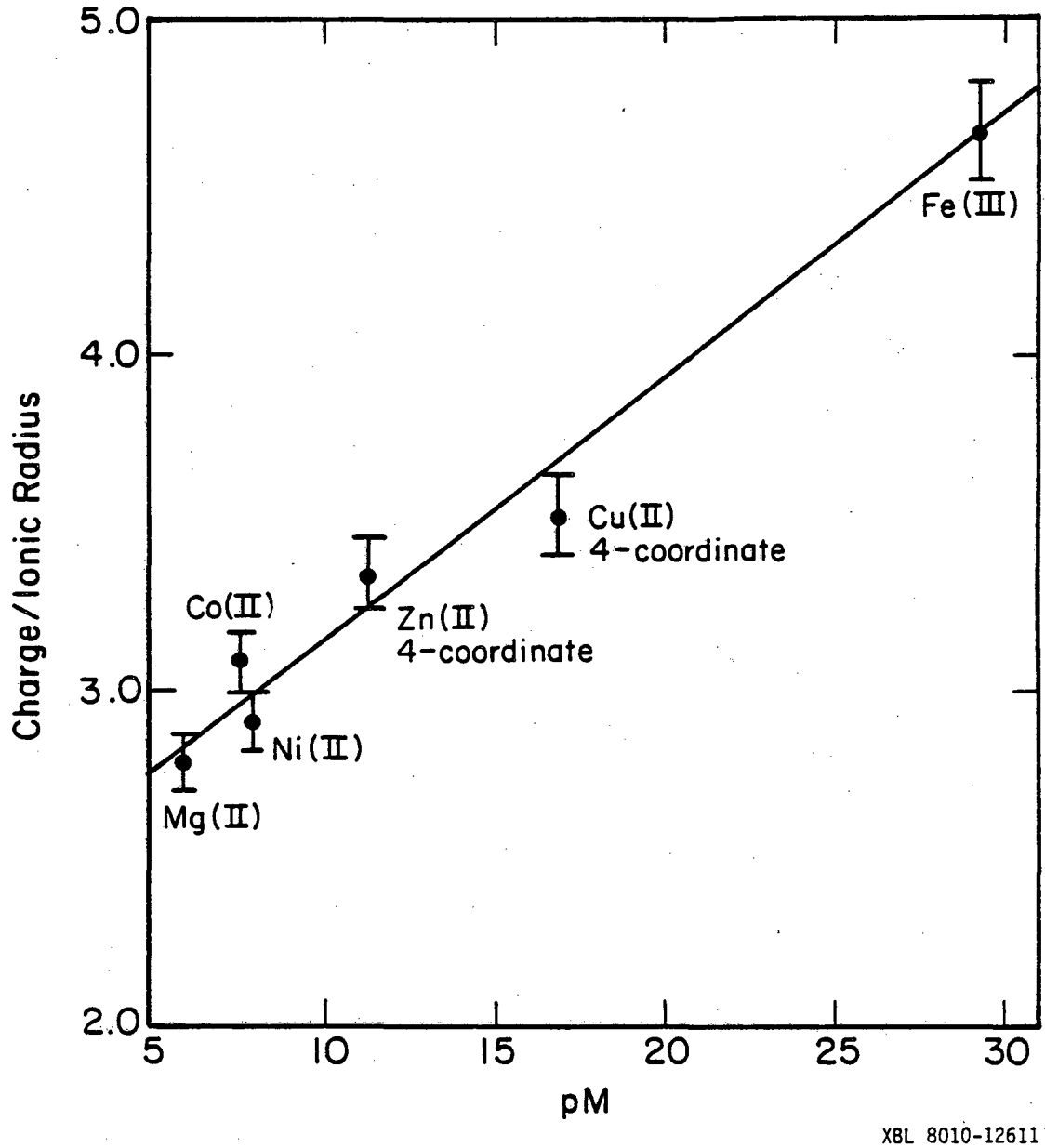

5.0
4.0
3.0
2.0
Charge/Ionic Radius
5
10
15
20
25
30
pM
Fe(III)
Cu(II)
4-coordinate
Co(II)
Zn(II)
4-coordinate
Ni(II)
Mg(II)
XBL 8010-12611

Fig. 6

This report was done with support from the Department of Energy. Any conclusions or opinions expressed in this report represent solely those of the author(s) and not necessarily those of The Regents of the University of California, the Lawrence Berkeley Laboratory or the Department of Energy.

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LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA 94720