[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY]

Stability of Metal Chelates. VIII. 3-Hydroxypropyliminodiacetic and 2-Hydroxyethyliminodipropionic Acids

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The acid dissociation constants of 3-hydroxypropyliminodiacetic acid and of 2-hydroxyethyliminodipropionic acid have been measured by potentiometric measurements of *p*H. The same method, applied to the interaction of the corresponding amino acid anions with various divalent metals, showed the relative stabilities to vary in the order: Cu > Ni > Co, Zn > Cd >> Mg for both ligands, with a much higher order of stability for the diacetate derivatives. The metal chelate stability constants are tabulated and compared with those of structurally-related substances. The two ligands investigated showed varied behavior with the iron(III) ion, forming chelates generally stable in acid solutions, but resulting in precipitation of iron(III) hydroxide in alkaline solution.

Recent investigations of the chelating properties of synthetic hydroxyl-containing amino acids[2a,b] indicated that hydroxyethyl groups are definitely involved in metal chelate formation. The presence of these groupings in a chelating structure increases markedly the affinity of the resulting complexing agent for ferric ions. For example, dihydroxyethylglycine[2] forms iron(III) chelates of sufficient stability that the effect of metal hydrolysis is greatly reduced, even in strong alkaline solutions. In order to elucidate further the role of the hydroxyl group in metal ion coördination, especially with regard to the complexing of iron(III) ions, interaction studies have been extended to 3-hydroxypropyliminodiacetic and 2-hydroxyethyliminodipropionic acids. Both compounds are potentially tetradentate chelating agents capable of forming five- and six-membered chelate rings.

Experimental

Apparatus and Procedure.—The experimental method used in this investigation is similar to that described in detail in an earlier publication.[3] Measurements were made at a temperature of 30 ± 0.05° and at a constant ionic strength of 0.1 which was maintained with KCl. Titrations were carried out in a nitrogen atmosphere, and the *p*H was recorded with the aid of a Beckman model G *p*H meter. The *p*H values measured by the glass electrode–calomel cell corresponded to hydrogen ion activities, since the experimental system was periodically calibrated against values determined by the hydrogen–silver–silver chloride cell under conditions which were the same as those used in the metal titrations.

Materials.—The 3-hydroxypropyliminodiacetic and 2-hydroxyethyliminodipropionic acids were prepared and purified by methods to be described in a subsequent publication.[4]

Experimental Data.—Potentiometric data for solutions of the amino acids and divalent heavy metal ions containing acid to metal ratios of 2/1 are presented graphically in Figs. 1 and 2. Similar data for various acid to iron(III) ion ratios are plotted in Figs. 3 and 4. The corrected *p*H values are shown, and the volume of standard base, usually given as the abscissa in potentiometric plots of this type has been converted to *m*, moles of base per mole of divalent or trivalent metal ion.

Calculations.—The acid dissociation constants of 3-hydroxypropyliminodiacetic and 2-hydroxyethyliminodipropionic acids were calculated by the adaptation of Bjerrum's method described previously.[5] Metal chelate stability constants were determined by the modified Bjerrum method described in detail for 2-hydroxyethyliminodiacetic acid.[2] The final equations which were utilized are

$$\bar{n} = \frac{1}{C_{\mathrm{M}}}\left[C_{\mathrm{A}} - \frac{(\mathrm{H}^{+})^2}{k_1k_2} + \frac{(\mathrm{H}^{+})}{k_2} + 1\right](\mathrm{A}^{-2})$$

where

$$(\mathrm{A}^{-2}) = \frac{(2-a)C_{\mathrm{A}} - (\mathrm{H}^{+}) + (\mathrm{OH}^{-})}{(2(\mathrm{H}^{+})^2/k_1k_2) + ((\mathrm{H}^{+})/k_2)}$$

and C_{A} and C_{M} are the total concentrations of amino acid and metal ion species, respectively, k_1 and k_2 are the successive acid dissociation constants, and a = moles of KOH added per mole of amino acid.

Discussion of Results

Potentiometric Curves.—The free acid titration curve of 3-hydroxypropyliminodiacetic acid (3-HIMDA) is similar to that of 2-hydroxyethyliminoacetic acid[1] and is characterized by the presence of a strong inflection at one equivalent of base corresponding to the formation of the monopotassium salt. A second inflection corresponding to the formation of the dipotassium salt is absent, probably because of extensive hydrolysis of the divalent anion, (A^{-2}). Although the low *p*H buffer region of the 2-hydroxyethyl and 3-hydroxypropyl derivatives are roughly coincident, the displacement of the high *p*H buffer region of the latter to higher *p*H values indicates a smaller ionization constant for the amino proton.

The addition of copper(II), nickel(II), cobalt(II) and zinc(II) ions (moles amino acid/moles metal ion = 2/1) results in a shift of the first inflection to an *m* value of 3. Thus 1:1 chelates are formed as separate and stable compounds in solution. The titration curves may be explained by the reactions

$$\mathrm{H_2A} + \mathrm{M}^{+2} + 2\mathrm{OH}^{-} \longrightarrow \mathrm{MA} + 2\mathrm{H_2O}$$
$$\mathrm{H_2A} + \mathrm{OH}^{-} \longrightarrow \mathrm{HA}^{-} + \mathrm{H_2O}$$

These metal amino acid titration curves all indicate 2:1 complex formation, which is accompanied by a second inflection at $m = 4$, corresponding to the reaction

$$\mathrm{MA} + \mathrm{HA}^{-} + \mathrm{OH}^{-} \longrightarrow \mathrm{MA_2}^{-2} + \mathrm{H_2O}$$

In the presence of the cadmium(II) ion, the corresponding titration curve is characterized by two inflections occurring at *m* values of 2 and 4. Interaction occurs therefore with the monohydrogen acid species, HA^{-}, according to the reaction

$$\mathrm{M}^{+2} + \mathrm{HA}^{-} + \mathrm{OH}^{-} \longrightarrow \mathrm{MA} + \mathrm{H_2O}$$

Further interaction resulting in the formation of the 2:1 chelate occurs with considerable overlapping of the chelate formation reactions corresponding to the successive stability constants K_1 and K_2.

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[1] Bersworth Postdoctoral Fellow, Clark University, 1951–1952.

[2] (a) S. Chaberek, R. C. Courtney and A. E. Martell, THIS JOURNAL, **74**, 5057 (1952); (b) **75**, 2185 (1953).

[3] S. Chaberek, Jr., and A. E. Martell, *ibid.*, **74**, 5052 (1952).

[4] S. Chaberek, Jr., A. E. Martell and F. C. Bersworth, unpublished work.

[5] S. Chaberek and A. E. Martell, THIS JOURNAL, **74**, 5052 (1952).

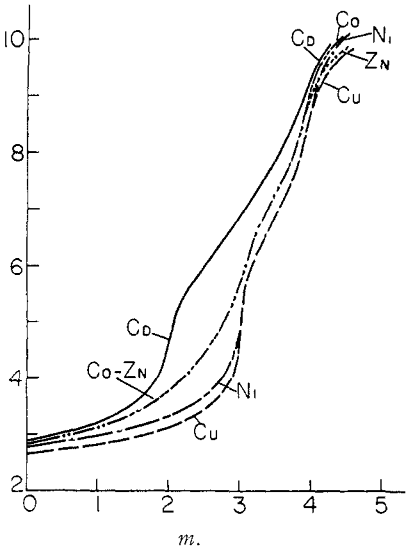

Fig. 1.—Potentiometric titrations of solutions containing two moles of 3-hydroxypropyliminodiacetic acid per mole of various divalent metal chlorides: *m*, moles of KOH added per mole of divalent metal; μ, 0.1; *t*, 30°.

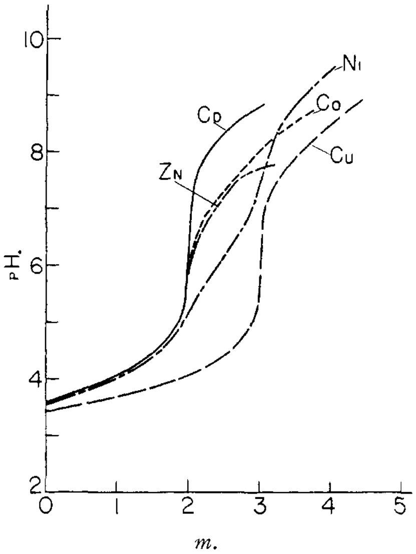

Fig. 2.—Potentiometric titrations of solutions containing two moles of 2-hydroxyethyliminodipropionic acid per mole of various divalent metal chlorides: *m*, moles of KOH added per mole of divalent metal; μ, 0.1; *t*, 30°.

The free acid titration curve of 2-hydroxyethyliminodipropionic acid (2-HIMDP) is similar to that of the 3-hydroxypropyliminodiacetic acid. One inflection occurs at one equivalent of base, corresponding to the formation of the monopotassium salt. A second very weak inflection occurs at 2 equivalents of base. It is interesting to note, however, that both the low and high *p*H buffer regions are displaced to *lower* *p*H values than are those of iminodipropionic acid.[5] This indicates that substitution of a hydroxyethyl group on the amino group results in a considerable increase in the acidity of the amino proton (k_2) and a smaller increase in the ionization constant of the carboxyl proton (k_1).

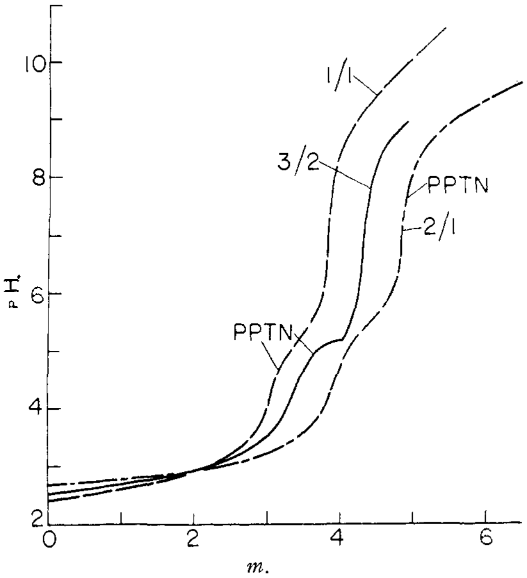

Fig. 3.—Potentiometric titrations of solutions containing various ratios of moles of 3-hydroxypropyliminodiacetic acid per mole of Fe(III) chloride: *m*, moles of KOH added per mole of ferric ion present; μ, 0.1; *t*, 30°.

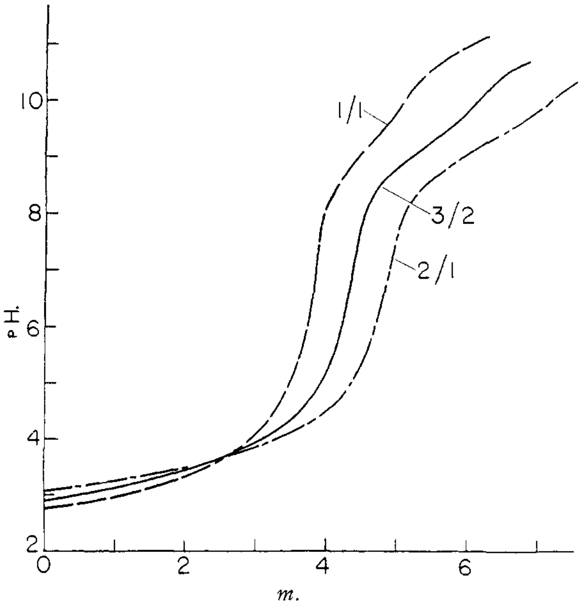

Fig. 4.—Potentiometric titrations of solutions containing various ratios of moles of 2-hydroxyethyliminodipropionic acid per mole of Fe(III) chloride: *m*, moles of KOH added per mole of ferric ion present; μ, 0.1; *t*, 30°.

Interaction of 2-hydroxyethyliminodipropionic acid with all metal ions investigated except that of copper(II) is considerably weaker than that occurring in the presence of the 3-hydroxypropyliminodiacetic acid. The occurrence of an inflection at an *m* value of 2 indicates that little, if any, interaction occurs with the undissociated acid species, H_2A.

A second inflection of the nickel(II) curve at $m = 3$ indicates distinct 1:1 chelate formation. Evaluation of the titration curves of cobalt(II), zinc(II) and cadmium(II) at *m* values greater than 3 is complicated by the precipitation of the corresponding metal hydroxides. However, the depression of the high pH buffer region to more acid values indicates some interaction between amino acid and ligand anions. In general, it was not possible to calculate $\bar{n}$ values greater than 1. Consequently K_2 values are not reported for this acid. The copper(II) titration curve is quite similar in shape to the corresponding 3-HIMDA plot. The displacement of the low pH buffer region to more acidic values is indicative of extensive interaction of the undissociated acid with the cupric ion.

Formation Functions.—The Bjerrum formation functions for the various metal chelates of 3-HIMDA and 2-HIMDP are given in Figs. 5 and 6. With the exception of the nickel(II) plot, all 3-HIMDA curves indicate considerable overlapping in the formation of the 1:1 and 2:1 metal chelates. The curves are considerably different in this respect from the corresponding interactions of metal ions with 2-hydroxyethyliminodiacetic acid, where little overlapping occurs. Both the nickel (II)- and copper(II)-2-HIMDP plots show pronounced inflections, which are indicative of appreciable separation factors between the successive stability constants K_1 and K_2.

Equilibrium Constants.—The acid dissociation and chelate formation constants of 3-hydroxypropyliminodiacetic (3-HIMDA) and 2-hydroxyethyliminodipropionic (2-HIMDP) acids are compared in Table I with corresponding values for 2-hydroxyethyliminodiacetic (2-HIMDA), iminodiacetic (IMDA) and iminodipropionic (IMDP) acids. It is interesting to note that while the introduction of a 2-hydroxyethyl group into the iminodiacetate structures decreases the basicity of the amino group, the pk_2 values of 3-HIMDA and IMDA are roughly equivalent. The introduction of an additional methylene group greatly reduces the inductive effect of hydroxyl on the amino group. From the relative basicities of the ammonium nitrogens of IMDA and 3-HIMDA, it would be expected that both would have roughly the same affinities for metal ions. However, the fact that the introduction of a 3-hydroxypropyl group to the iminodiacetate structure increases the log K_1 values by 1.0–1.3 units for the nickel(II), cobalt(II) and zinc(II) chelates, and 0.5 unit for the cadmium(II) chelate indicates that the hydroxypropyl group takes part in complex formation, and that the γ-hydroxyamino acid acts as a tetradentate ligand for these metal ions. Further comparison of the 2-HIMDA and 3-HIMDA values illustrates the decrease in stability of the 1:1 chelates resulting from chelate ring enlargement from five to six members, in that corresponding log K_1 values for the hydroxyethyl derivative are 0.4–0.9 log K unit higher. Also, the separation factors between log K_1 and log K_2 for 3-HIMDA are considerably decreased. An increase in the degree of overlapping of the 1:1 and 2:1 chelates is in line with the observed decreased stability of the 1:1 complex.

The introduction of a β-hydroxyethyl group to the iminodipropionate structure greatly decreases the basicity of the amino group. Since a decrease in the basicity of the ligand results in a corresponding lower affinity for metal ions, one would expect for similar chelating structures, a decrease in the magnitude of the stability constants. However,

TABLE I

COMPARISON OF CHELATION TENDENCIES OF 2-HIMDA, 3-HIMDA, IMDA, 2-HIMDP, IMDP

t, 30°; μ, 0.1; γ_{H^+}, 0.78

	2-HIMDA[a] pk		3-HIMDA pk		IMDA[b] pk		2-HI-MDP pk	IM-DP[b] pk
$H^+(pk_1)$	1.96		2.06		2.54		3.93	4.11
$H^+(pk_2)$	8.78		9.24		9.13		8.91	9.61
	log K_1	log K_2	log K_1	log K_2	log K_1	log K_1	log K_1	log K_1
Cu^{+2}	>10	4.2	>10	5.7	10.6	5.7	8.4	9.4
Ni^{+2}	9.5	5.2	9.1	5.7	8.3	6.4	5.7	6.1
Co^{+2}	8.3	4.4	7.8	5.4	7.0	5.3	4.4	4.9
Zn^{+2}	8.6	4.1	7.7	5.3	7.0	5.1	4.6	5.0
Cd^{+2}	7.1	5.1	6.2	4.7	5.3	4.2	2.9	3.5
Mg^{+2}	3.5	...	3.3	...	3.6[c]	...	...	...

[a] Chaberek, Courtney and Martell[2a] 30°, μ 0.1. [b] Chaberek and Martell,[5] 30°, μ 0.1. [c] G. Schwarzenbach, E. Kampitsche and R. Steiner, *Helv. Chim. Acta*, **34**, 1133 (1945), 30°, μ 0.1.

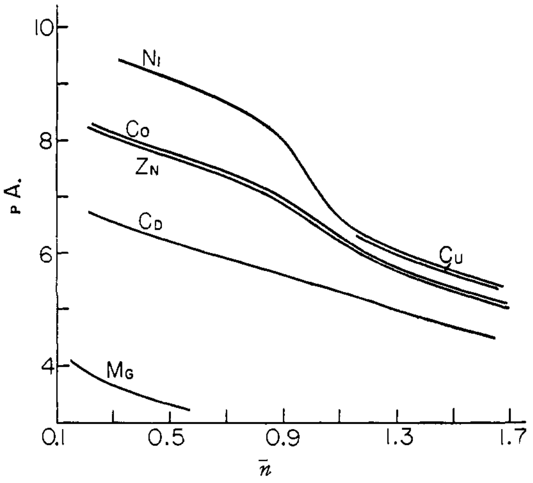

Fig. 5.—Bjerrum formation functions for 3-hydroxypropyliminodiacetic acid and divalent metal ions: $\bar{n}$, moles of ligand bound per mole of metal ion.

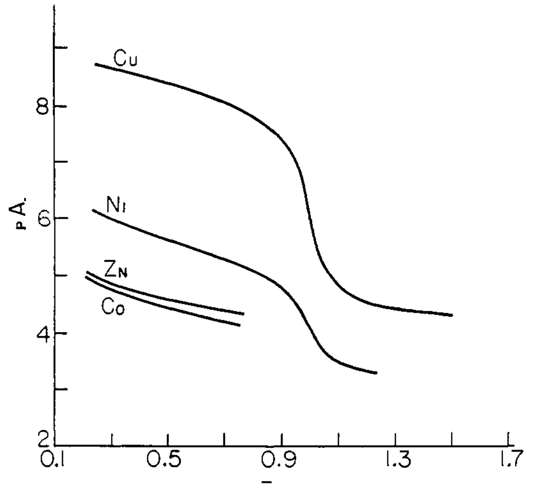

Fig. 6.—Bjerrum formation functions for 2-hydroxyethyliminodipropionic acid and divalent metal ions: $\bar{n}$, moles of ligand bound per mole of metal ion.

with the exception of the copper(II)–2-HIMDP chelate the decrease seems to be considerably less than would be expected for such a relatively large decrease in the ligand basicities. It is quite probable, therefore, that coördination of the β-hydroxyethyl group occurs in the presence of the hexacovalent metals. The ligand basicity effect, which results in a decrease in chelate stability is counterbalanced at least in part, by the 2-hydroxyethyl group, which increases the chelate stability by the formation of an additional five-membered chelate ring.

Chelation of Ferric Ions by 2-HIMDP and 3-HIMDA.—The first inflection of the 1:1 titration curves of 3-HIMDA in the presence of varying ratios of ferric ions, shown in Fig. 5, occurs at $m = 3$. This behavior indicates, as in the case of dihydroxyethylglycine,[2b] the formation of a 1:1 chelate accompanied by the simultaneous ionization of the ethanolic proton. Thus, if H_2AOH denotes the amino acid, the over-all reaction may be written as

$$Fe^{+3} + H_2AOH + 3OH^- \longrightarrow FeAO + 3H_2O$$

The formation of the 1:1 chelate is substantiated by the stoichiometry involved in the 3:2 and 2:1 titration curves. Thus, the first inflection of the 3:2 curve at $m = 3.5$ corresponds to the formation of the 1:1 complex and the neutralization of the first strongly acidic proton of the excess amino acid according to the reactions

$$\left.\begin{array}{l} 2Fe^{+3} + 2H_2AOH + 6OH^- \longrightarrow 2FeAO + 6H_2O \\ H_2AOH + OH^- \longrightarrow HAOH^- + H_2O \end{array}\right\} 3.5 \text{ moles } OH^-/Fe^{+3}$$

In the case of the 2:1 curves, chelate formation is accompanied by neutralization of excess amino acid

$$Fe^{+3} + 2H_2AOH + 4OH^- \longrightarrow FeAO + HAOH^- + 4H_2O$$

Second inflections occur at m values of approximately 4, 4.5 and 5 for amino acid to metal ratios of 1:1, 3:2 and 2:1, respectively. This behavior suggests the formation of a 3:2 binucleate chelate similar to that formed with dihydroxyethylglycine[2] according to the following reactions, all of which require one additional mole of base per mole of ferric ion.

1:1 titration curve

$$3FeAO + 3OH^- \longrightarrow Fe(OH)_3 + Fe_2(AO)_3^{-3} + 3H_2O$$

3:2 titration curve

$$2FeAO + HAOH^- + 2OH^- \longrightarrow Fe_2(AO)_3^{-3} + 2H_2O$$

2:1 titration curve

$$2FeAO + 2HAOH^- + 2OH^- \longrightarrow Fe_2(AO)_3^{-3} + 2H_2O + HAOH^-$$

However, contrary to the behavior of dihydroxyethylglycine, disproportionation of the complex occurs with all three acid-to-metal ratios, resulting in the precipitation of ferric hydroxide. Hydroxide formation starts at a pH of about 5 for the 1:1 and 3:2 ratios, and at a pH of 8 for the 2:1 curve. Considerably less hydroxide was formed in the latter solution. This may be due to partial formation of a higher chelate (such as a 3:1 compound) stable at somewhat higher pH values.

Subsequent complex formation, therefore, may proceed along two different lines, both of which are consistent with the experimental data. The first is the formation of a weak 3:2 binucleate complex. It is possible, however, that this chelate is decomposed at higher pH values according to the reaction

$$Fe_2(AO)_3^{-3} + 6H_2O \longrightarrow 2Fe(OH)_3 + 3HAOH^-$$

It is interesting to note that this reaction involves no hydroxyl ions, and hence no change in the relative positions of the second inflection points of the titration curves would occur. This decomposition would also account for the precipitation of ferric hydroxide from solutions containing amino acid/metal ratios of 3:2 and 2:1.

However, the precipitation behavior suggests also the possible formation of a 2:1 metal chelate, FeAO(AOH). The second inflections correspond to the over-all reactions

1:1 titration curve

$$2Fe^{+3} + 2H_2AOH + 8OH^- \longrightarrow FeAO(AOH)^{-2} + Fe(OH)_3 + 5H_2O$$

inflection at $m = 4$

3:2 titration curve

$$4Fe^{+3} + 6H_2AOH + 18OH^- \longrightarrow 3FeAO(AOH)^{-2} + Fe(OH)_3 + 15H_2O$$

inflection at $m = 4.5$

2:1 titration curve

$$Fe^{+3} + 2H_2AOH + 5OH^- \longrightarrow FeAO(AOH)^{-2} + 5H_2O$$

inflection at $m = 5$

The available titration data, therefore, are insufficient to establish conclusively the nature of the second ferric–3-HIMDA complex, and final proof of the formula of the compound formed must await a study of additional information.

The addition of ferric ions to solutions of 2-HIMDP (Fig. 6) results in a strong acidification effect. The first inflection points occur at approximate m values of 4, 4.5 and 5 for the 1:1, 3:2 and 2:1 acid-to-metal ratios, and precipitation of ferric hydroxide occurred at the inflection points in all cases. Second weak inflections occurred at m values of 5, 6 and 7. Available data suggest the formation of a weak 1:1 metal chelate which disproportionates with increasing pH to the amino acid and ferric hydroxide according to the reactions

1:1 titration curve

$$Fe^{+3} + H_2AOH + 3OH^- \longrightarrow FeAO + 3H_2O$$

$$FeAO + 2H_2O + OH^- \longrightarrow Fe(OH)_3 + HAOH^-$$

3:2 titration curve

$$2Fe^{+3} + 3H_2AOH + 7OH^- \longrightarrow 2FeAO + HAOH^- + 7H_2O$$

$$2FeAO + 4H_2O + 2OH^- \longrightarrow 2Fe(OH)_3 + 2HAOH^-$$

2:1 titration curve

$$Fe^{+3} + 2H_2AOH + 4OH^- \longrightarrow FeAO + HAOH^- + 4H_2O$$

$$FeAO + 2H_2O + OH^- \longrightarrow Fe(OH)_3 + HAOH^-$$

The second weak inflections are probably due to the neutralization of the amino protons of the amino acid.

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