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Complexes of Hydroxamates. Part 1. Interaction of Methioninehydroxamic Acid with Iron(III) in Aqueous Solution

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Abstract

The binding affinity of Fe(III) to methioninehydroxamate (MX) has been studied spectrophotometrically at $I = 0.15$ M NaCl and $T = 25$ °C. Equilibrium data have been assessed by the program SQUAD(II) in the wavelength range 400–550 nm and pH range 1.5–5.0. Five formation constants were determined for the species $Fe(MX)(H)^{3+}$, $Fe(MX)^{2+}$, $Fe(MX)_2(H)_2^{3+}$, $Fe(MX)_2(H)^{2+}$ and $Fe_2(MX)_3^{3+}$. The stopped-flow kinetic data studied at 470 nm and in the pH range 1.0–3.0 is collectively expressed by the following rate equation at a given pH

$$\text{Rate} = (A + BT_{MX})T_{MX}$$

where T_{MX} = the analytical concentration of MX and the parameters A and B are both functions of pH in the range 1.7–3.0, but only A in the range 1.2–1.7. A proposed mechanism was discussed, based on the equilibrium study, where the role of the chloro species of $Fe(OH)^{2+}$ and $Fe(OH)_2^+$ in the complex formation of Fe(III) with MX has been emphasized. Correlation of the results with pertinent systems has also been discussed.

Introduction

Hydroxamic acids have important and diverse functions in chemistry as well as in biology. They have been used as colorimetric and gravimetric reagents in analytical chemistry and have been shown to be antibiotics, growth factors, antibiotic antagonists, tumour inhibitors and cell division factors for natural products [1, 2]. Complexation with transition metal ions is involved in the chemistry of these areas [3–5].

Hydroxamates form stable complexes with iron(III) which have been proved to donate the metal to apotransferrin in a biphasic reaction [3]. The chelate probably reacts initially with apotransferrin to form a ternary complex, which then decays in the second phase yielding iron transferrin and free ligand.

It has also been shown that $Fe(OH)^{2+}$ is the reactive iron(III) species in the complex formation of some hydroxamates with the metal ion [6, 7]. In addition, it has been pointed out that $Fe(OH)_2^+$ could also be a reactive species [5].

In this work the reaction of Fe(III) with methioninehydroxamate was studied spectrophotometrically to define the equilibria and their reaction kinetics. The investigation is essential to account for the iron exchange between its low molecular weight complexes and apotransferrin and the ability of the ligand to extract iron from ferritin.

Experimental

Solutions of acidic iron(III) chloride (E. Merck) and methioninehydroxamate (mX) (sigma > 98%) were obtained by subdilution processes from stock solutions. The concentration of the Fe(III) solutions (~0.1 M in 0.1 M HCl) was checked by EDTA titration using salicylate indicator at pH ≃ 1.5 [5]; that of MX was prepared by accurate weighing of the required amount of the solid (used as provided) and dissolved in 0.1 M HCl.

Measurements of pH were done using Radiometer pH-meter type 63 equipped with combined glass electrode type GK-2311C. The pH-meter was calibrated by the two buffers procedure (2.0 and 4.0 or 4.0 and 7.0) in the pH range used. The pH range was 1.0–3.0 in case of the equilibrium study and 1.0–5.0 in case of the kinetic study. Hydrogen ion concentration was taken to be 10^{-pH}.

Spectral measurements were made using Pye-Unicam model 8–100 in the wavelength range 400–550 nm at room temperature 25.0 ± 1 °C.

Kinetic measurements were performed using a Durrum Stopped-flow Spectrophotometer D-110. The optical path was 20.0 mm. The mixing syringes

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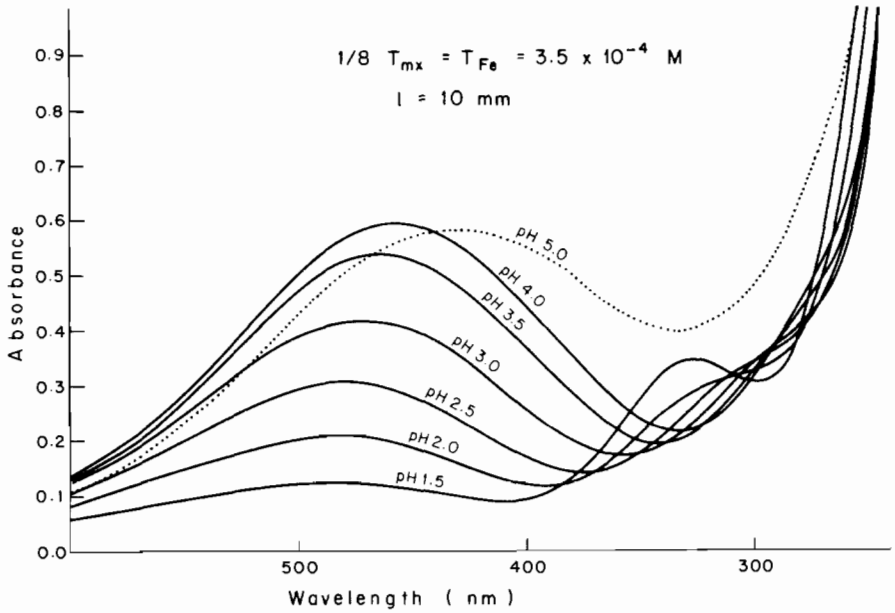


Fig. 1. The spectra of the Fe(III)–GX system at various pHs taken overnight.

and cuvette were thermostated at 25 °C. The wavelength used was 470 nm.

In the equilibrium study, the ranges of liquid and metal ion concentration were $(3.0–4.0)10^{-3}$ M and $(2.0–5.0)10^{-4}$ M, respectively. In the kinetic study, the concentration was in the range of $(1.0–4.0)10^{-3}$ M for the ligand and only 1×10^{-4} M for the metal ion. The ionic strength was kept constant at 0.15 M (NaCl).

Equilibrium data were assessed by the programs TRIANG (to determine the number of absorbing species) and SQUAD II (to determine the stability constants of the complexes) [8, 9].

Results and Discussion

Two sets of spectra were taken for the Fe(III)–MX system, one directly after mixing the reactants at various pHs and the other after being left overnight. The spectra in both cases were identical only in the pH range 1.0–2.5, but not at pHs greater than 2.5 where spectral changes were observed for those left overnight. These findings were also obtained in a previous pertinent work: the Fe(III) glycine-hydroxamic acid (GX) system [5]. Figure 1 shows typical overnight spectra of Fe(III)–MX at different pHs in the wavelength range 270–600 nm. MX, similar to GX, has no characteristic spectra in the same wavelength range in the pH-range 1.0–7.0. However, iron(III) chloride solution has spectral characteristics under identical experimental conditions. Two major absorption peaks were observed in acidic medium (1.0 M HCl), one at 335 nm and the other at 225 nm. They were appreciably affected by change in the pH where both bands lost their identities. This observation was reported previously for iron(III) perchlorate solutions [10]. A major change in $FeCl_3$ spectra occurred in presence of MX. A new band, probably of the charge transfer type, appeared at ~480 nm, which showed hypsochromic shift as well as hyperchromism as the pH increased from 1.5–5.0. The $FeCl_3$ band at 335 nm decreased in absorbance while that at 225 nm increased considerably as the pH varied from 1.5 to 5.0 in the presence of MX. The band at 335 nm vanished at pH = 5.0. As a consequence, the spectral variations with pH serve as an indication of the presence of more than one absorbing species. The test of the number of absorbing species [8] revealed the existence of three species, if errors in absorbances were taken in the range 0.001–0.006 absorbance units. This result does not actually reflect the number of species in solution if protonated and nonprotonated species are considered as different species.

Equilibrium Study

The program SQUAD(II) has been used to calculate the stability constants of the various Fe(III)–MX species. Different equilibrium models have been tried. The one which converged successfully with the least value of standard deviation in the absorbance data (within experimental error) at various wavelengths, initial concentration of ligand and metal ions and pHs was selected to be the best model. In these trials the protonation constants of the ligand as well as the hydrolysis constants of Fe(III) were introduced as fixed constants. The log β_{pqr} values

TABLE I. Summary of the Stepwise Formation Constants (log β_{pqr}) of Fe(III)–MX (or GX) Complexes $L_pM_qH_r$ (L = MX or GX M = Fe(III) at I = 0.15 M NaCl and 25 °C

L	Stoichiometric coefficients			log β_{pqr} ($\pm\sigma$)	Wavelength range, no. of wavelengths, no. of solutions, pH range[a]
	p	q	r		
MX	1	0	1	9.033[b]	
	1	0	2	15.803[b]	
	0	1	−1	−3.05	
	0	1	−2	−6.31	
	1	1	0	12.73(0.003)	400–550, 16,
	1	1	1	16.26(0.007)	19, 1.5–5.0
	2	1	1	26.12(0.18)	
	2	1	2	30.94(0.08)	
	3	2	0	38.24(0.12)	
GX[c]	1	0	1	9.55	
	1	0	2	17.15	
	1	1	0	14.14	
	1	1	1	17.30	
	2	1	0	22.72	
	2	1	1	28.94	

[a]The standard deviation in absorbance data did not exceed 4.4×10^{-3} absorbance unit. [b]Ref. 11. [c]Ref. 5.

(p, q and r are the stoichiometric coefficients of MX, Fe^{3+} and H^+) are listed in Table I. The presence of the unprotonated species (1:1:0) in the acidic region may indicate the possible involvement of the amino group in complex formation, emphasizing the bidentate or tridentate nature of the ligand where the amino group and the hydroxamate group are chelating Fe(III). However, this conclusion does not rule out the participation of the sulfur atom in ligation. In such case the ligand acts as a tridentate. In the 2:1:1 species the metal ion is likely to be pentacoordinated with respect to MX, while in the 2:1:2 it is tetra-coordinated with respect to MXs. Since MX has various legating sites and Fe(III) has the tendency to dimerize and/or polymerize, no wonder that the species 3:2:0 could

The distribution diagram of the iron(III) complexes is shown in Fig. 2. It is clear that only three complex species (of the stoichiometries 1:1:1, 1:1:0 and 2:1:2) together with the free Fe^{3+} and $FeOH^{2+}$ species exist in the pH range 1.0–3.0. Actually, the complex formation started at pHs as low as one. This conclusion, however, is dependent on the relative concentration of MX to Fe(III).

Kinetic Study

Two rate steps were observed in the kinetic study of the Fe(III) reaction with MX in the pH range

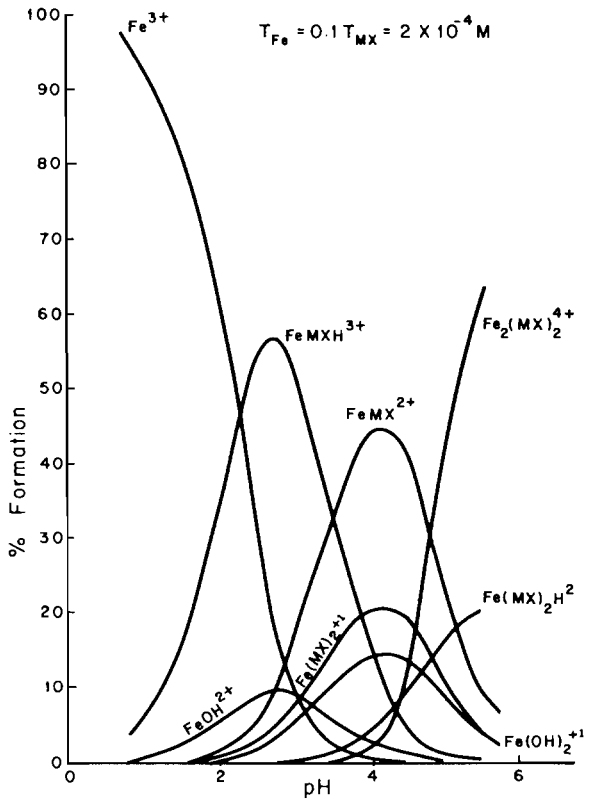


Fig. 2. Distribution diagram of different complexes as function of pH.

1.2–3.0. Both steps were dependent on the pH and the initial concentration of MX (T_{MX}). The speed of the slow step was in the one-hour range, while the fast one was in the millisecond range. The fast step may be attributed to the formation of metal chelate preceeded by the deprotonation of the ligand. Only this step will be analyzed in this work.

Figure 3 shows the dependence of the observed pseudo-first-order rate constant, k_{obs}, on both pH and T_{MX} ($T_{MX} \gg T_{Fe}$). The rate constant first decreases as pH increases from 1.2 to ~1.7 or 2.0 (depending on the value of T_{MX}) and then increases as the pH increases from 1.7 or 2.0 to 3.0. At a given pH the rate constant is a linear function of T_{MX}, Fig. 4 (a and b). Actually, two sets of curves are observed. The first set of curves (below pH 2.0) has approximately the same slope and different intercepts, Fig. 4a. The second set of curves shows significant slopes and small variation in the intercepts (above pH 2.0), Fig. 4b. Empirically both sets of curves could be represented as follows:

$$k_{obs} = A_i + B_i T_{MX} \quad (1)$$

where A_i and B_i are the intercepts and slopes of the linear plots shown in Fig. 4a and 4b; their values

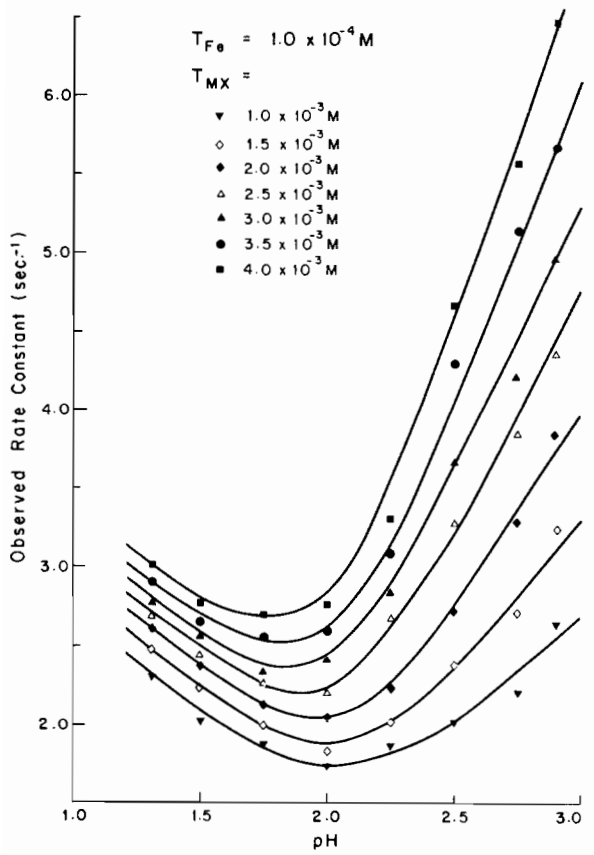


Fig. 3. The dependence of the observed rate constants (k_{obs}) on pH and initial concentration of MX at constant iron(III) concentration.

are listed in Table II. It is obvious that both A and B are pH dependent at pHs greater than 1.7, but only A at pHs lower than 2.0.

In the pH range used (1.2–3.0), the solution of MX exhibits only one species, the diprotonated one, MXH_2^+, while that of Fe(III) exhibits several chloro

TABLE II. Summary of the Values of A and B at Different Interpolated pHs Used in the Determination of k_i and k_{-i}

pH	A (s^{-1})	$B \times 10^{-2}$ (s^{-1} mol^{-1} l)	$A\frac{([H]+K_{HC})}{K_{HC}} \times 10^{-2}$	$BQ_1Q_3 \times 10^{-2}$
1.25	2.08	2.60	4.00	2.64
1.37	1.94	2.60	2.80	2.66
1.50	1.80	2.60	1.95	2.67
1.62	1.70	2.60	1.39	2.70
1.75	1.60	2.60	1.10	2.72
2.00	1.34	3.60	0.469	3.94
2.12	1.24	4.60	0.329	5.19
2.25	1.16	5.70	0.234	6.70
2.37	1.08	7.30	0.166	9.06
2.50	1.06	8.40	0.125	11.20
2.62	1.04	10.20	0.096	14.96
2.75	1.14	11.20	0.080	18.61
2.87	1.26	12.40	0.070	24.18
3.00	1.38	13.40	0.061	32.03

complexes of the metal ion together with the aquated form and the different hydroxy species, Table I. The dimeric species of Fe(III) was excluded due to the presence of a high concentration of chloride ions ($T_{Cl} \gg T_{Fe}$) and the low pH of the medium.

The mechanism of Fe(III) interaction with MX can be summarized in the following Scheme 1*. Where k_i and k_{-i} are the forward and backward rate constants and K_{1OH}**, K_{2OH}* and K_{HC}*** are the first and second hydrolysis constants of Fe^{3+} and deprotonation constant of $FeMXH^{3+}$, respectively.

*For simplicity $Fe(OH)_iCl_{n-i}(H_2O)_{6-n-1}$ species will be represented as Fe^{3+} or $Fe(OH)^{2+}$ species (if $i > 0$).
**$K_{1OH} = 9 \times 10^{-4}$ for $Fe^{3+} + H_2O \rightleftarrows Fe(OH)^{2+} + H^+$; K_{1OH} $K_{2OH} = 4.9 \times 10^{-7}$ for $Fe^{3+} + 2H_2O \rightleftarrows Fe(OH)_2^+ + 2H^+$.
***K_{HC} is for $FeMXH^{3+} \rightleftarrows FeMX^{2+} + H^+$ and can be obtained from the equilibrium study.

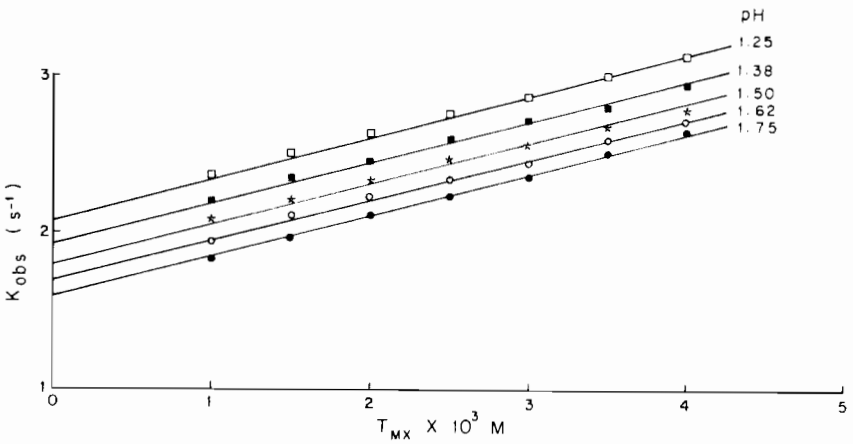


Fig. 4a. Interpolated values of k_{obs} at interpolated constant values of pH (at pHs < 1.7).

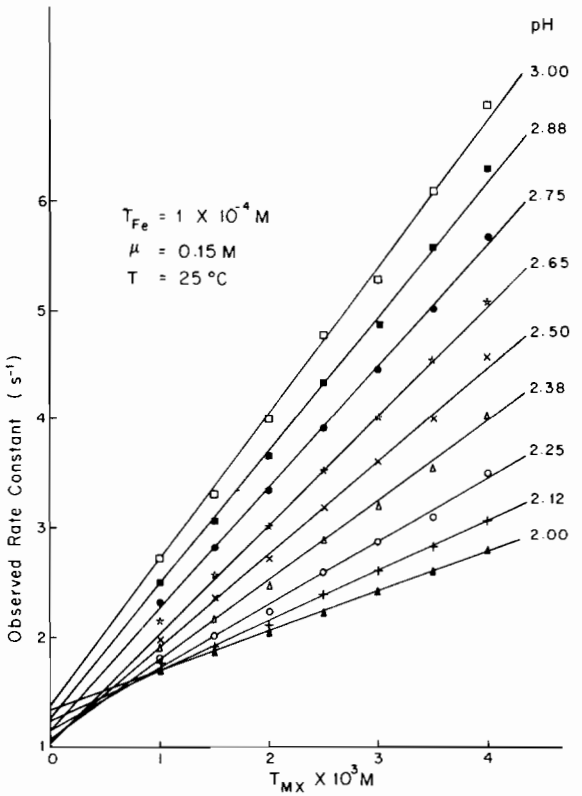


Fig. 4b. Interpolated values of k_{obs} at interpolated constant values of pH (at pHs > 1.7).

(a) $Fe^{3+} + MXH_2^+ \rightleftharpoons FeMXH^{3+} + H^+$; k_1, k_{-1}

$\uparrow\downarrow K_{1OH}$

(b) $Fe(OH)^{2+} + MXH_2^+ \rightleftharpoons FeMXH^{3+} + H_2O$; k_2, k_{-2}

$\uparrow\downarrow K_{2OH}$

(c) $Fe(OH)_2^+ + MXH_2^+ \rightleftharpoons FeMXH^{3+} + H_2O + OH^-$; k_3, k_{-3}

$K_{HC} \uparrow\downarrow$

(d) $Fe^{3+} + MXH_2^+ \rightleftharpoons FeMX^{2+} + 2H^+$; k_4, k_{-4}

(e) $Fe(OH)^{2+} + MXH_2^+ \rightleftharpoons FeMX^{2+} + H_2O + H^+$; k_5, k_{-5}

(f) $Fe(OH)_2^+ + MXH_2^+ \rightleftharpoons FeMX^{2+} + 2H_2O$; k_6, k_{-6}

Scheme 1.

At fixed pH, the rate equation can be expressed as follows:

$$Q_2 \frac{d(FeMX)}{dt} = \left\{\frac{T_{Fe} - (FeMX)Q_2}{Q_3}\right\}\left\{\frac{T_{MX}}{Q_1}\right\} Q_4 - (FeMX)Q_5 \quad (2)$$

where:

$Q_1 = 1 + K_{1h}/(H^+) + K_{1h}K_{2h}/(H^+)^2$

K_{1h} and K_{2h} are the stepwise deprotonation constants of the species MXH_2^+

$Q_2 = \{(H^+)/K_{HC}\} + 1$

K_{HC} is the deprotonation constant of the species $FeMXH^{3+}$

$Q_3 = 1 + K_{1OH}/(H^+) + K_{1OH}K_{2OH}/(H^+)^2$

K_{1OH} and K_{2OH} are the hydrolysis constants of Fe^{3+}

$$Q_4 = k_1 + k_2K_{1OH}/(H^+) + k_3K_{1OH}K_{2OH}/(H^+)^2 + k_4 + k_5K_{1OH}/(H^+) + k_6K_{1OH}K_{2OH}$$

and

$$Q_5 = \{(k_{-3}K_w/K_{HC}) + k_{-6}\} + \{(k_{-2}/K_{HC}) + k_{-5}\}(H^+) + \{(k_{-1}/K_{HC}) + k_{-4}\}(H^+)^2$$

The integrated form of eqn. (2) is where $(FeMX)_\infty$

$$\ln \frac{(FeMX)_\infty}{(FeMX)_\infty - (FeMX)_t} = kt \quad (3)$$

and $(FeMX)_t$ are the concentration of the species at infinite time and time t (both are directly proportional to absorbance at a given wavelength), and k stands for

$$k = Q_5/Q_2 + Q_4T_{MX}/Q_3Q_1 \quad (4)$$

Equation (1) is correlated to eqn. (4) such that

$$A = Q_5/Q_2 \quad (5)$$

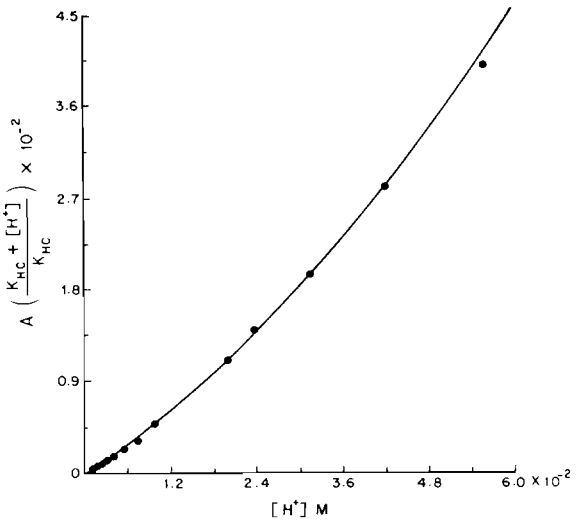
and

$$B = Q_4/Q_3Q_1 \quad (6)$$

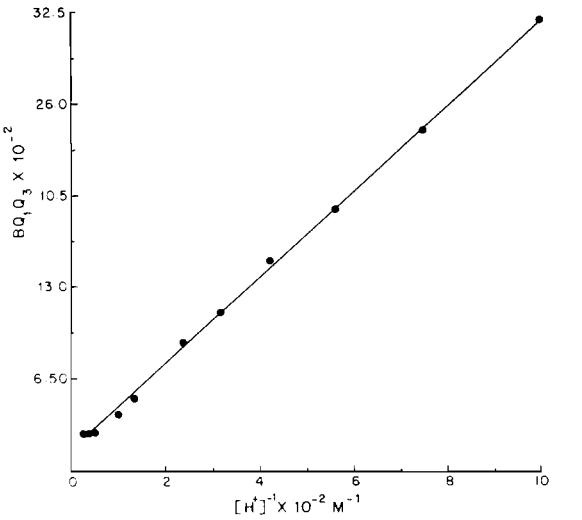
Upon rearrangement of eqns. (5) and (6), one gets the following equations:

$$A\left(\frac{H^+}{K_{HC}} + 1\right) = k_{-6} + k_{-3}K_w/K_{HC} + (k_{-2}/K_{HC} + k_{-5})(H^+) + (k_{-1}/K_{HC} + k_{-4})(H^+)^2 \quad (7)$$

and



(a)



(b)

Fig. 5. (a) The plot of $\{A((H^+) + K_{HC})/K_{HC}\}$ as function of $(H^+)M$. (b) The plot of BQ_1Q_3 as function of $(H^+)^{-1}$ M^{-1}.

$$BQ_3Q_1 = (k_1 + k_4) + K_{1OH}(k_2 + k_5)/(H^+) + K_{1OH}K_{2OH}(k_3 + k_6)/(H^+)^2 \quad (8)$$

The dependence of $A([H^+]/K_{HC}) + 1$ on $[H^+]$ has been confirmed to follow eqn. (7), Fig. 5a with:

$k_{-6} + k_{-3} K_w/K_{HC} \simeq 0$

$k_{-5} + k_{-2}/K_{HC} = (4.93 \pm 0.16) \times 10^3$

and

$k_{-4} + k_{-1}/K_{HC} = (4.04 \pm 0.30) \times 10^4$

On the other hand, the plot of BQ_1Q_3 *vs.* $[H^+]^{-1}$ is linear, Fig. 5b, indicating that:

$k_1 + k_4 = (1.54 \pm 0.14) \times 10^2$

$K_{1OH}(k_2 + k_5) = 3.05 \pm 0.03$ or $(k_2 + k_5) = 3.39 \times 0^3$

and

$K_{1OH}K_{2OH}(k_3 + k_6) \simeq 0$

These findings indicate that reactions a, b, d, and e are the major paths in the complex formation of $FeMXH^{3+}$ and $FeMX^{2+}$. Although it seems that $FeCl_{n-i}(H_2O)_{6-n-i}$ and $FeOHCl_{n-i}(H_2O)_{6-n-i}$ are the most reactive species of iron(III) in these reactions, yet it is not possible to differentiate between them. However, if $k_{-1}/K_{HC} > k_{-4}$ and $k_{-1} > k_4$ one can conclude that $k_1/k_{-1} = 13.2$ and consequently $\log \beta_{111} = 16.92$. The value so obtained for β_{111} from this approach is greater than that obtained from equilibrium approach, which indicates that the above assumption is not entirely correct and k_4 and k_{-4} may have significant magnitude. On the other hand, if $k_{-2}/K_{HC} > k_{-5}$ and $k_2 > k_5$ one may obtain a value for k_2/k_{-2} which amounts to 2.4×10^3 and $\log \beta_{111} = 16.12$. This value is actually much closer to that obtained from the equilibrium study, a conclusion which validates the assumption. However, if we assume that $k_2 < k_5$ and $k_{-2}/K_{HC} < k_{-5}$, one gets a value for $k_5/k_{-5} = 0.69$ and $\log \beta_{111} = 12.59$, which is also close to the equilibrium value.

Conclusion

It has been concluded that interaction of Fe(III) with MX to form stable complexes takes place in acidic medium. Monomeric as well as polymeric species may form in the pH range 2–5; but only monomeric species are formed at $pH < 2$. This conclusion does not agree with the results obtained previously in case of the Fe(III)–glycinehydroxamate (GX) system, except at $pHs < 2$ [5]. Similar complexes in both systems show that Fe(III)–GX complexes are more stable than those in the Fe(III)–MX system (with 1–2 log units difference in log βs, Table I). The presence of polymeric species in the Fe(III)–MX system may be explained as due to the presence of various equivalent sites of the ligand to complex the metal ion. This has been confirmed in a recent study where it has been found that this ligand is able to ligate two different metal ions [11].

The mechanism in both systems is similar except that $Fe(OH)_iCl_{n-i}(H_2O)_{6-n-i}$ (where $i = 0$ and 1 respectively) has been found to be the only active metal species in the Fe(III)–MX system, whereas $Fe(OH)_iCl_{n-i}(H_2O)_{6-n-i}$ (where $i = 2$) is also active in the Fe(III)–GX system.

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