an ASP ligand. To test this hypothesis, the same synthetic procedure used to link two ASP units was used to prepare the analogous ligands prepared from either (*S*)-alanine or (*S*)-glutamic acid. It has been shown that the two carboxylate groups of glutamic acid are too far apart to form a simple chelate ring,[32] and of course alanine only contains a single carboxyl. Neither compound was observed to yield appreciable optical activity at low pH at any metal:ligand ratio, even though significant metal–ligand bonding is known to take place.[18]

It has also been shown that observation of strong optical activity requires the presence of a conformational effect (where the asymmetric atom of the ligand is bound in a chelate ring),[33] and such effects cannot exist in the ligands derived from alanine or glutamic acid. On the other hand, the CPL spectra observed for the Tb/ASP and Tb/EDDS complexes were both of a type indicative of conformational effects.[32,33] The CPL data thus provide very strong evidence for concluding that, under low-pH conditions, the EDDS ligand forms complexes via its two carboxylate groups. There apparently is no tendency for the two carboxylate groups of an ASP functionality on EDDS to bind metal centers independently.

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G. Summary. The luminescence techniques used during the course of the present work have proved to be capable of providing rather detailed information regarding the nature of the Ln/EDDS complexes. The presence of polymeric and monomeric complexation was deduced from energy-transfer experiments, and water-counting experiments were used to obtain information on the inner coordination sphere of the lanthanide ions. CPL spectroscopy could be used to obtain further information regarding how the various functionalities of the EDDS ligand could be used to bind a metal ion, and taken together, all the techniques provide a detailed look into this aspect of lanthanide solution chemistry.

It is undoubtably true that the nature of the Ln/EDDS binding might allow for the presence of more than one type of compound under any given set of experimental conditions. However, the specific nature of the information obtained within certain well-defined pH regions indicates that the conclusions obtained pertain to a majority species in solution. Thus, effects due to small amounts of other species may be neglected. The strengths of the luminescence techniques as means for the study of lanthanide complexes in solution are self-evident, and further work along these lines is currently being pursued.

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Iron(III) Complexation by Desferrioxamine B in Acidic Aqueous Solutions. Kinetics and Mechanism of the Formation and Hydrolysis of the Binuclear Complex Diferrioxamine B

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Ferrioxamine B ($Fe(HDFB)^+$), a complex of iron(III) with the linear trihydroxamic acid siderophore desferrioxamine B (H_4DFB^+), yields in the presence of an excess of ferric ions in aqueous acid the binuclear complex diferrioxamine B ($Fe_2(HDFB)^{4+}$) by two parallel pathways involving fully aquated (Fe^{3+}) and hydrolyzed ($FeOH^{2+}$) iron(III) ions. The observed rate constants for two paths at 25 ± 0.1 °C and 1.00 M ionic strength (NaCl) are k_4 = 52 M^{-1} s^{-1} and k_4' = 3500 M^{-1} s^{-1}, respectively. When the ferrioxamine B acid solution is mixed with a ferric ion solution of acidity higher than that of the ferrioxamine B solution, the binuclear complex formation reaction is preceded by a reversible process in which the partial unraveling of the desferrioxamine B ligand from the inner coordination sphere of the iron(III) center occurs. The acid hydrolysis of diferrioxamine B complex to the ferrioxamine B complex proceeds also by two parallel pathways: an acid-dependent and an acid-independent path exhibiting the rate constants k_{-4} = 0.91 M^{-1} s^{-1} and k_{-4}' = 0.105 s^{-1}, respectively. Mechanistic implications are discussed.

Introduction

Naturally occurring iron chelating agents called siderophores have attracted a remarkable interest because of their role in iron bioavailability in microorganisms,[1-3] where three limiting types among many mechanisms for siderophore-mediated microbial iron transport have been advanced.[4] Of prime importance for the understanding of the molecular basis for iron bioavailability continues to be the kinetic and thermodynamic information relating to the complexation of iron(III) by various siderophore chelating agents. The three types of siderophores—the hydroxamates, thiohydroxamates, and catecholates—have been recognized to form extremely stable, highly specific, high-spin d^5 octahedral coordination compounds with iron(III). The hydroxamate group ($HON(R_1)(C(=O)R_2)$) is considered to be the most common functional group of siderophores produced by molds, fungi, and yeasts.[5]

Particularly important appears to be the linear trihydroxamic acid siderophore desferrioxamine B (H_4DFB^+) with the molecular formula $^+NH_3(CH_2)_5[N(OH)C(O)(CH_2)_2C(O)$-

(1) Neilands, J. B. In "Inorganic Biochemistry"; Eichhorn, G., Ed.; Elsevier: New York, 1973; p 167.
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(3) Kehl, H., Ed. "Biology and Chemistry of Hydroxamic Acids"; Karger: New York, 1982.
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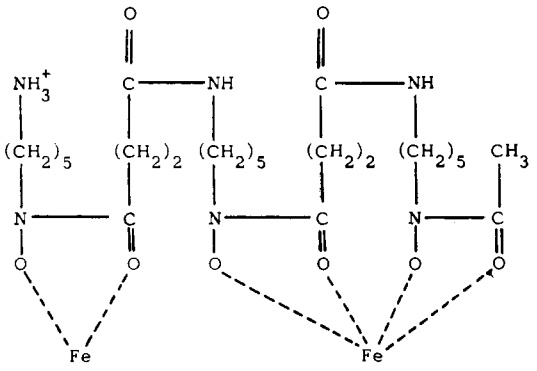
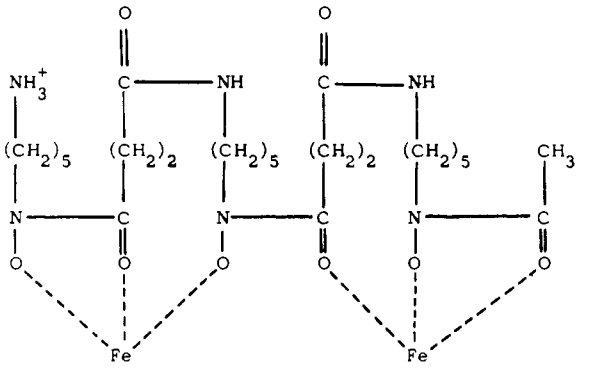
Chart I. Tentative Structures of Diferrioxamine B[a]



FORMULA I



FORMULA II

$Fe_2(HDFB)^{4+}$

[a] Possible hydroxo and/or chloro bridging is not shown.

$NH(CH_2)_5]_2N(OH)C(O)CH_3$. The great interest in current research in desferrioxamine B arises from its specific mediation in iron bioavailability and its worldwide use in the treatment of both iron toxicity and iron storage diseases.[6] In addition to its biological significance, desferrioxamine B is an important agent as a representative of hydroxamic acids which are excellent ligands for use in probing the intimate mechanism of ligand substitution at an iron(III) center.[7] Therefore, the kinetic data from chelation studies of the desferrioxamine B ligand have application to an understanding of the fundamentals of ligand-substitution processes at aqueous high-spin iron(III).[8]

The three hydroxamate moieties linearly linked in the desferrioxamine B molecule provide the three modes of coordination to ferric ion: bidentate, tetradentate, and fully coordinated hexadentate bonded ferrioxamine B ($Fe(HDFB)^+$). Because of this fact the formation and dissociation of the ferrioxamine B complex is expected to proceed in a stepwise manner including intermediates of the ferrioxamine B complex of various degrees of denticity. The four kinetically distinguishable stages in perchlorate media[8] and three in chloride media[9] have been reported.

It is reasonable to expect that under favorable conditions each intermediate of the ferrioxamine B complex may react with other chelating agents present in solution or with iron(III) ions when present in excess over desferrioxamine B ligand concentration. Hence, an important feature of the ferrioxamine B intermediates is the partial unwrapping of the hexadentate trihydroxamic ligand and the presence of the labile unidentate aquo ligands. The open primary coordination sphere about the iron(III) center may therefore be relatively exposed either to subsequent attack by the competing ligand or to the complexation of other iron(III) ions by the uncoordinated hydroxamate group. The first case was exemplified by the study of the iron exchange and iron removal from ferrioxamine B complex using ethylenediaminetetraacetic acid.[10] The second case, involving an excess of ferric ion over desferrioxamine B concentration, would lead to the production of polynuclear hydroxamate complexes.

The first evidence of formation of the binuclear diferrioxamine B complex ($Fe_2(HDFB)^{4+}$) was presented in our preliminary communication,[11] and recently the synthesis has been reported[12] as well as the spectrophotometric characterization of the diferrioxamine B complex.[13] Two possible structures of the binuclear complex that are consistent with our results are shown by formulas I and II (Chart I). In the present paper we report the details of the kinetics and mechanism of the formation and hydrolysis of the diferrioxamine B complex.

Experimental Section

Materials. Ferric chloride stock solution (0.15 M in 0.1 M HCl) was prepared from ferric chloride hexahydrate (Merck) and standardized both spectrophotometrically and gravimetrically as Fe_2O_3. The methanesulfonate salt of desferrioxamine B (Desferal) was kindly supplied by the Ciba-Geigy Corp. The salt was recrystallized from methanol and was stored in a vacuum desiccator over P_4O_{10} (mp 149–151 °C).

Reagent iron(III) solutions were prepared by dilution of the stock solution with aqueous HCl/NaCl, with the H^+ ion concentration kept high enough to prevent extensive hydrolysis and precipitation of iron(III) ions.

All other reagents were of analytical grade and were used without further purification.

Water that was doubly distilled from alkaline $KMnO_4$ in an all-glass apparatus was used to prepare all the solutions.

Methods. Preparation of Solutions. The formation kinetics of diferrioxamine B were studied by mixing a solution containing 2×10^{-4} M $Fe(HDFB)^+$, 2×10^{-3} M $FeCl_3$, and 0.0402–0.6 M HCl with a solution of $(3–62) \times 10^{-3}$ M $FeCl_3$ in 0.0402–0.6 M HCl. The solutions mixed were of the same acidity, exhibiting increases in absorbance at 500, 440, and 425 nm. However, in some experiments an H^+ concentration jump occurred when solutions of different acidity were mixed. For example, a solution of 2×10^{-4} M $Fe(HDFB)^+$ in 1×10^{-4} M $FeCl_3$ and 8×10^{-3} M HCl was mixed with solutions of $(4–100) \times 10^{-3}$ M $FeCl_3$ in 0.4 M HCl. In the last experiments two-stage kinetics were observed at 440 nm where the increase in absorbance was preceded by fast absorbance decrease.

In diferrioxamine B hydrolysis experiments a water solution of 2×10^{-4} M H_4DFB^+ in 7.5×10^{-3} M $FeCl_3$ and 1×10^{-2} M HCl was mixed in a stopped-flow apparatus with 0.02–2 M HCl. In all experiments a decrease in absorbance was followed at 500 and 425 nm.

All of the reactions were studied in aqueous solutions of 1.00 M ionic strength maintained by NaCl. Ionic strength is defined as $I = 0.5\sum C_i z_i^2$, where C_i and z_i are total concentration and formal charge numbers of ions present in solution, respectively.

Kinetic Measurements. The kinetic experiments were performed on a Durrum D-110 stopped-flow spectrophotometer. The mixing chamber and drive syringes were thermostated at 25 ± 0.05 °C by

(6) Anderson, W. F., Hiller, M. C., Eds. "Development of Iron Chelators for Clinical Use"; Department of Health, Education and Welfare: Washington, DC, 1975; Publication No. NIH 77-994.
(7) Monzyk, B.; Crumbliss, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 6203–13.
(8) Monzyk, B.; Crumbliss, A. L. *Inorg. Chim. Acta* **1981**, *55*, L5. Monzyk, B.; Crumbliss, A. L. *J. Am. Chem. Soc.* **1982**, *104*, 4921–9.
(9) Biruš, M.; Bradič, Z.; Kujundžič, N.; Pribanič, M. *Croat. Chem. Acta* **1983**, *56*, 61–77.
(10) Tufano, T. P.; Raymond, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 6617–24.
(11) Biruš, M.; Bradič, Z.; Kujundžič, N.; Pribanič, M. *Inorg. Chim. Acta* **1981**, *56*, L43.
(12) Biruš, M.; Bradič, Z.; Kujundžič, N.; Pribanič, M. *Acta Pharm. Jugosl.* **1983**, *32*, 163–7.
(13) Biruš, M.; Bradič, Z.; Kujundžič, N.; Pribanič, M. *Inorg. Chim. Acta* **1983**, *78*, 87–92.

Table I. Rate and Equilibrium Constants of Complexes of Ferric Ions with Desferrioxamine B at 25 °C[a]

step 1					step 2				
$k_1/M^{-1}\ s^{-1}$	$k_{-1}/M^{-1}\ s^{-1}$	$k_1'/M^{-1}\ s^{-1}$	k_{-1}'/s^{-1}	K_1	k_2/s^{-1}	$k_{-2}/M^{-1}\ s^{-1}$	K_2/M	I/M	ref
282	0.65	4.1×10^3	0.016	430	9	2	5.8	1.0 (NaCl)	9

step 4					step 3				
$k_4/M^{-1}\ s^{-1}$	$k_{-4}/M^{-1}\ s^{-1}$	$k_4'/M^{-1}\ s^{-1}$	k_{-4}'/s^{-1}	K_4	k_3/s^{-1}	$k_{-3}/M^{-1}\ s^{-1}$	K_3/M	I/M	ref
52 (2)	0.91 (6)	$3.5\ (2) \times 10^3$	0.105 (5)	57	2.4 (1)	16.4 (1)	0.14	1.0 (NaCl)	this work
					2.2	18	0.12	1.0 (NaCl)	9
					3.4	34	0.10	0.2 (KNO_3)	10
							0.11	0.1 ($NaClO_4$)	16
							0.08	1.0 (NaCl)	13

[a] All constants are defined as in Scheme I.

water circulating from a constant-temperature bath. From the oscilloscope, tracings of photomultiplier output voltage (absorbance) as a function of time were collected and analyzed in terms of one- and/or two-stage pseudo-first-order kinetics.

Results

Two-stage kinetics have been observed spectrophotometrically in both formation and hydrolysis reactions of the diferrioxamine B complex in acid media. However, the fast stage in hydrolysis, which exhibited a half-time of about 20 ms and was observed in some experiments, occurs also in the absence of any desferrioxamine B ligand under the same experimental conditions. This process might be due to the acid dissociation of the bridged binuclear iron(III) complexes, which have been studied under various conditions.[14] The rate of this process is about 50 times greater than the rate of the subsequent hydrolysis reaction. A detailed study of this fast absorbance change in the absence of the desferrioxamine B ligand is beyond the scope of this work.

It has been found that the rate of the fast stage in formation is more than 10 times higher than that of the slow one. Hence, the formation kinetics can be analyzed in terms of two well-separated reactions.

Fast Stage in Formation. The decrease in absorbance in the range 425–440 nm has been recorded to determine the pseudo-first-order rate constants. The rate acceleration with the increase in H^+ concentration is illustrated in Figure 1. This reaction can be easily followed in those experiments where the solution of the ferrioxamine B complex is mixed in the stopped-flow apparatus with the iron(III) ion solutions of higher acidity; i.e. an H^+ concentration jump should occur. Furthermore, the pseudo-first-order rate constants of the fast stage in formation are invariant with respect to the ferric ion concentrations.

These findings indicate the desferrioxamine B stepwise dissociation from the iron(III) center with the accompanying replacement by coordinated water. On the assumption that partial unwrapping of the hexadentate trihydroxamate ligand from the iron(III) center leads first to the formation of a diaquo(hydroxamato)iron(III) species, then the fast stage in formation represents the interconversion of completely coordinated ferrioxamine B to the tetradentate-bonded ferrioxamine B complex (step 3 of Scheme I). In that case the observed rate constant is described by eq 1.

$$k_{obsd} = k_{-3}[H^+] + k_3 \qquad (1)$$

The obtained values $k_{-3} = 16.4\ (1)\ M^{-1}\ s^{-1}$ and $k_3 = 2.38\ (1)\ s^{-1}$ are in excellent agreement with reported values (see Table I). The numbers in parentheses are standard deviations referring to the last significant digits.

Slow Stage in Formation. Coordination of ferric ions to the tetradentate-coordinated ferrioxamine B may proceed by two parallel pathways as illustrated in Scheme I by step 4. The observed rate constant corresponding to the reversible step 4 is given by eq 2. In eq 2, brackets denote molar concentrations, K_h is the thermodynamic equilibrium constant ($K_h = [Fe(H_2O)_5OH^{2+}][H^+]/[Fe(H_2O)_6^{3+}] = 1.65 \times 10^{-3}$ M at 25 °C[15]), and K_3 is the equilibrium quotient ($K_3 = 0.12$[9]).

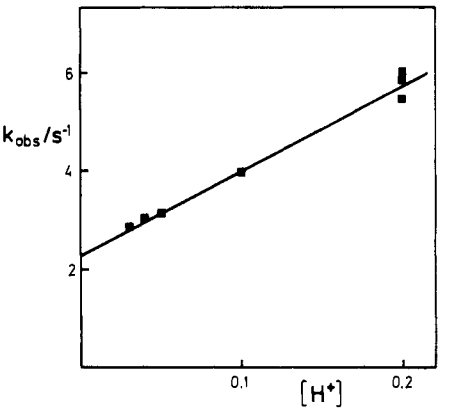


Figure 1. Observed first-order rate constants for the fast stage in formation plotted as a function of $[H^+]$ in the range 0.03–0.204 M HCl at 25 ± 0.1 °C and $I = 1.00$ M (NaCl). The starting concentrations of the reaction mixture are 0.1 mM $Fe(HDFB)^+$ and 7.7 mM $FeCl_3$.

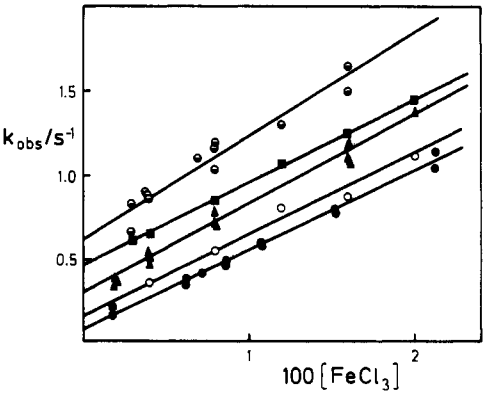


Figure 2. Observed first-order rate constants for the slow stage in formation plotted as a function of $FeCl_3$ (25 ± 0.1 °C; $I = 1.00$ M (NaCl); 0.1 mM $Fe(HDFB)^+$): (⊖) 0.60 M HCl; (■) 0.40 M HCl; (▲) 0.20 M HCl; (○) 0.10 M HCl; (●) 0.04 M HCl.

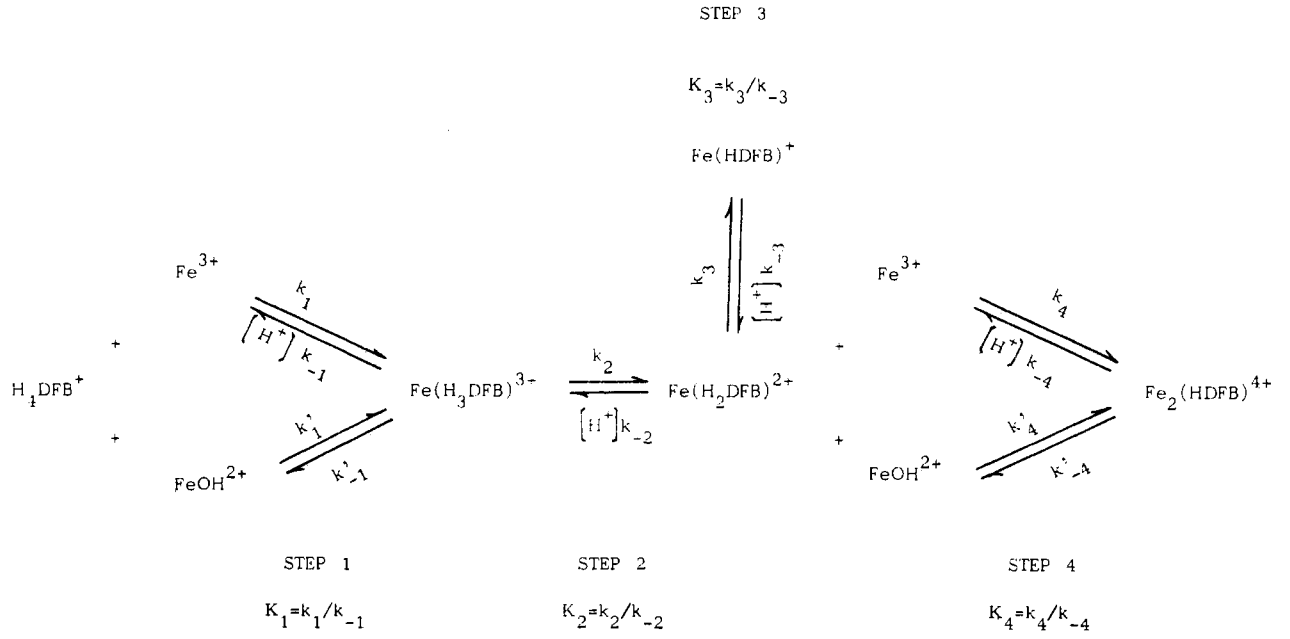
$$k_{obsd} = \frac{k_4[H^+] + k_4'K_h}{[H^+] + K_h}\,\frac{[H^+]}{K_3 + [H^+]}[Fe_{tot}] + k_{-4}[H^+] + k_{-4}' \qquad (2)$$

(14) Po, H. N.; Sutin, N. *Inorg. Chem.* **1971**, *10*, 428–31.

(15) Milburn, R. M.; Vosburgh, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 1352–5.

(16) Schwarzenbach, G.; Schwarzenbach, K. *Helv. Chim. Acta* **1963**, *46*, 1390–400.

Scheme I



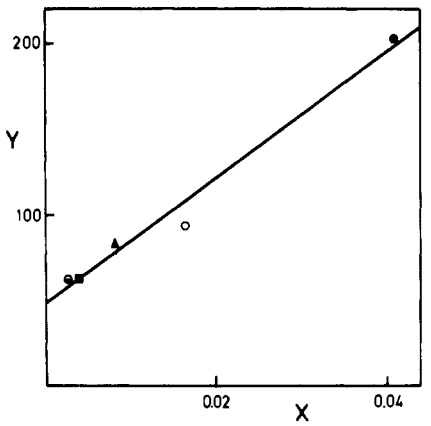


Figure 3. Linear relationship between the quantities y and x of eq 3. Conditions are given in the legend of Figure 2.

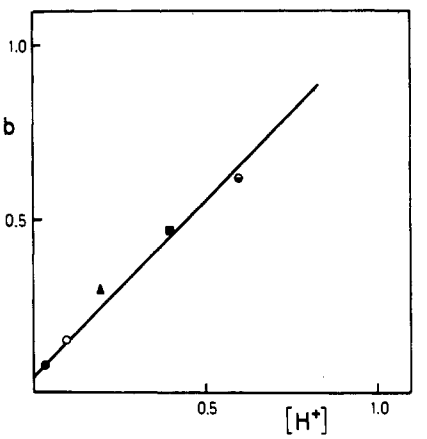


Figure 4. Plot of the data shown in Figure 2 according to the equation $b = k_{-4}[H^+] + k_{-4}'$, where b is the intercept in Figure 2 of eq 2. Conditions are given in the legend of Figure 2.

Linear dependence of the observed first-order rate constants on the ferric ion concentration expected from eq 2 is shown in Figure 2.

Determination of the slopes "a" from Figure 2 allows the simple relationship

$$y = k_4'x + k_4 \tag{3}$$

where

$$y = a\frac{(K_3 + [H^+])([H^+] + K_h)}{[H^+]^2} \tag{4a}$$

$$x = K_h/[H^+] \tag{4b}$$

The linear plot of the quantity y vs. the quantity x (eq 3) is shown in Figure 3. The values of the rate constants calculated from the intercepts (k_4) and slopes (k_4') of Figure 3 are k_4 = 52 (2) M^{-1} s^{-1} and k_4' = 3.5 (2) × 10^3 M^{-1} s^{-1}.

The intercepts "b" of the straight lines of Figure 2, according to eq 2, should be linearly dependent on the concentration of H^+ ($b = k_{-4}[H^+] + k_{-4}'$). From the linear relationship shown in Figure 4 the following values of the rate constants are calculated:

$$k_{-4} = 0.91\ (6)\ M^{-1}\ s^{-1} \qquad k_{-4}' = 0.105\ (5)\ s^{-1}$$

The concentrations of iron(III) ions employed were less than 0.02 M. The linear dependence of the rate constants on ferric ion concentration fades away gradually in iron(III) solutions of concentration higher than 0.01 M Fe^{3+}, and the lines of Figure 2 would show leveling off. The higher ferric ion concentrations require lower concentrations of sodium chloride to maintain the constant ionic strength, which in turn reduces the concentration of chloride complexes of iron(III). The ferric ions involving coordinated chloride are known to react in substitution reactions much faster than the completely aquated iron(III) ions.[17] The accelerating effect of the coordinated chloride on the rate of chelation of iron(III) by desferrioxamine B has been discussed.[9] The possibility of the formation of polynuclear iron(III) complexes other than diferrioxamine B should not be ruled out. The existence of such species may make the kinetic study of the diferrioxamine B complex more complicated.

Hydrolysis of the Diferrioxamine B Complex. The kinetic data of the slow stage of the hydrolysis of diferrioxamine B have been analyzed also in terms of eq 2, since the slow stage in hydrolysis is considered to be a reverse reaction of the formation slow stage. Figure 5 shows nonlinear dependence of the observed rate constant on the pH values. The curve was calculated according to eq 2 by using the calculated rate

(17) Connick, R. E.; Coppel, C. P. *J. Am. Chem. Soc.* **1959**, *81*, 6389–94.

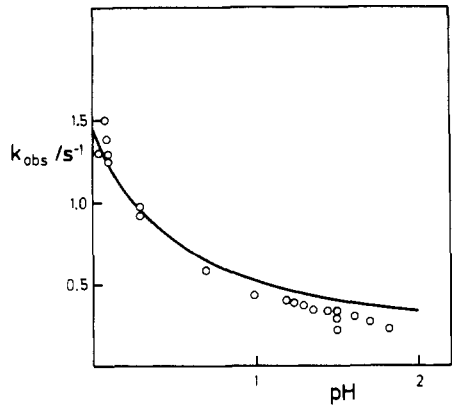


Figure 5. Nonlinear relationship between the observed first-order rate constants of the slow stage in hydrolysis and the acidity of the reaction solution (25 ± 0.1 °C; I = 1.00 M (NaCl); 1 × 10^{-4} M $Fe_2(HDFB)^{4+}$; 3.6 × 10^{-3} M $FeCl_3$; 0.01–1.00 M HCl).

constants from the formation experiments.

Discussion

The overall reaction scheme is developed from an analysis of the kinetic and equilibrium data of our previous[9,11-13] and present studies of the complexation of iron(III) ions by desferrioxamine B in aqueous acid chloride media. The fast stage in formation, described here, has been interpreted on the basis of its linear dependence on H^+ concentration and invariance on [$FeCl_3$] in terms of the dissociation of the first hydroxamate chelate group of the linear trihydroxamate chain ligand coordinated to iron(III). Furthermore, the rate constant values obtained are in excellent agreement with the reported rate constants[9,10] for the interconversion of tetradentate- to hexadentate-coordinated ferrioxamine B complex (see Table I), confirming that our interpretation of the fast stage in formation is correct.

In a recent study[18] of the reduction of ferrioxamine B by chromium(II), an inner-sphere mechanism was proposed. The chromium(III) produced may be bound to one hydroxamate group of ferrioxamine B or to the ligand at some other site. For the first case the dissociation of an hydroxamate chelate from iron(III) was considered to be the rate-limiting step requiring the value of at least 1.6 × 10^4 M^{-1} s^{-1} at pH 2.6 for the rate constant of hydrolysis of hexadentate- to tetradentate-bonded ferrioxamine B. In spite of different conditions it seems that the similarity of the values for the rate constant obtained in three independent studies (k_{-3} = 16.4 (this work), 34,[10] and 18 M^{-1} s^{-1} [9]) rules out the above assumption and the second alternative involving bonding of chromium(III) to the non-hydroxamate site of the ligand appears more reasonable.

It has been shown[8] that the unwrapping process begins at the protonated amine end of the desferrioxamine B ligand. This means that the tetradentate-bonded ferrioxamine B complex containing one uncoordinated hydroxamate chelate group at the amine terminus point is produced in the formation fast stage. The generated species features both free coordination sites on the iron(III) center and free sites on the desferrioxamine B ligand. On one hand, this species can exhibit the reverse reaction, i.e. the formation of ferrioxamine B. On the other hand, the species produced represents the starting material for the formation of the diferrioxamine B complex which occurs in the subsequent formation slow stage. The reaction of the bidentate segment of the partially unwrapped linear trihydroxamate siderophore ligand in the ferrioxamine B complex with the free ferric ions proceeds by two parallel pathways involving fully aquated Fe^{3+} ions and hydrolyzed $FeOH^{2+}$ ions. This is well-known and typical of many ligation reactions of ferric ions. The obtained kinetic results allow comparison of the reactivity of the uncomplexed hydroxamate chelate group of the polydentate-coordinated ligand system with the reactivity of the free hydroxamate ligand. In Scheme I this comparison is illustrated by the rate constants of steps 1 and 4. This comparison may also be extended to the free mono(hydroxamate) ligand.

Fe^{3+} ions react with the free desferrioxamine B ligand by a rate (k_1 = 282 M^{-1} s^{-1})[9] not significantly higher than with partially unwrapped desferrioxamine B in the ferrioxamine B complex (k_4 = 52 M^{-1} s^{-1}). The rate values of the corresponding reverse reactions are even more similar in magnitude: k_{-1} = 0.65 M^{-1} s^{-1} [9] and k_{-4} = 0.91 M^{-1} s^{-1}.

A similar conclusion can be made for the pathway involving hydrolyzed $FeOH^{2+}$ ions. The rate constants of the formation and hydrolysis of the diferrioxamine B complex are k_4' = 3500 M^{-1} s^{-1} and k_{-4}' = 0.105 s^{-1}, respectively. These values should be compared with the rate constants for the formation (k_1' = 4100 M^{-1} s^{-1}) and hydrolysis (k_{-1}' = 0.016 s^{-1}) of the bidentate-bonded ferrioxamine B complex.[9] The difference in the hydrolysis constants (k_{-4}'/k_{-1}' = 6.6) probably reflects a small rate-accelerating effect of the positive charge of the protonated amine end of the desferrioxamine B ligand, where hydrolysis begins as discussed above.

All the rate constants are measured under the same conditions in chloride media. It should be noted that k_4' appears in the product $k_4'K_h$ in eq 2 and therefore cannot be measured directly[9,19] since the value of K_h in chloride media is not reported in the literature. However, it does not mean that the comparison of the rate constants of steps 1 and 4 in Scheme I is not possible, because both steps are studied under the same experimental conditions.

The observed k_4'/k_4 = 67 is less than one might expect for comparing reactivity at $Fe(H_2O)_5OH^{2+}$ and $Fe(H_2O)_6^{3+}$. However, the lower value of the ratio k_1'/k_1 = 15 reported in ref 9 has been discussed in terms of high accelerating effect of the coordinated chloride via the labilization of the water molecule coordinated to iron(III). The effect is higher in the aquo complex ($FeCl(H_2O)_5^{2+}$) than in the hydroxo complex ($FeCl(H_2O)_4OH^-$), making the reactivity of the ferric aquo and hydroxo species more comparable. An analogous explanation has been presented for formate media.[19] A detailed study of chloride effect on the substitution rate on iron(III) is in progress in our laboratory.

The obtained equilibrium constant $K_4 = k_4/k_{-4}$ = 57 is not in agreement with the value K_4 = 100 determined by spectrophotometric titration.[13] The difference may result from various facts such as the existence of a small fraction of a trinuclear complex of desferrioxamine B, providing that trinuclear and binuclear complexes exhibit similar spectra. In addition, dinuclear species of ferric ions may also interfere in the kinetic studies. Other speculation may involve preequilibrium of the complexes represented by formulas I and II, which are not expected to exhibit different visible spectra.

The comparisons referred to above indicate that both ferric ions Fe^{3+} and $FeOH^{2+}$, at least to a great extent, do not kinetically discriminate between the free and partially unwrapped desferrioxamine B complexes. The thermodynamic similarity of the processes illustrated by steps 1 and 4 of Scheme I has also been suggested[13] since the second iron bonded into the diferrioxamine B complex has essentially the same formation quotient as the iron that is bound bidentate into the $Fe(H_3DFB)^{3+}$ ion.

Our data suggest that the coordination of one iron(III) ion to two neighboring hydroxamate moieties of the linear tri-

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hydroxamic acid ligand does not significantly affect the chelation reactivity of the third uncoordinated hydroxamate group. Hence, we propose that the mechanism already described for the formation and hydrolysis of the bidentate-coordinated ferrioxamine B complex[8,9] is probably operative in the interconversion of the fully coordinated binuclear diferrioxamine B to the mononuclear tetradentate-linked ferrioxamine B complex.

The hydrolysis of the diferrioxamine B complex proceeds by two parallel acid-dependent and acid-independent pathways exhibiting rate constants of magnitude similar to those of the hydrolysis of the bidentate-bonded ferrioxamine B. These observations indicate a release, during hydrolysis, of ferric ion bound to only one hydroxamate group, since to propose otherwise, one would expect one pathway and the rate constant corresponding to the hydrolysis rate constant either of fully bound ferrioxamine B (k_{-3} = 16.4 M^{-1} s^{-1}) or of tetradentate-linked ferrioxamine B (k_{-2} = 2 M^{-1} s^{-1}).

The obtained data indicate that one hydroxamic acid group of the trihydroxamic acid also exhibits a high specificity for chelating iron(III) when the remaining hydroxamate functions are coordinated to the ferric ion. The spherically symmetric +3 oxidation state is the most important feature of ferric ions related to the the high biological selectivity of hydroxamic acid for high-spin iron(III) since the other biologically important metal ions are mainly in the +2 oxidation state.[7,20] In addition Monzyk and Crumbliss have shown in their excellent studies[7] that the enhanced thermodynamic and kinetic stability of (hydroxamato)iron(III) complexes is due to the delocalization of the N atom lone pair into the carbonyl functionality. This delocalization is strongly influenced by the electron donor ability of the organic substituents, such as alkyl, bound to the N atom.

The similarity of steps 1 and 4 of Scheme I suggests that the coordination of two hydroxamate groups of desferrioxamine B to iron(III) does not influence the electronic properties of the free hydroxamate functionality. This is a reasonable assumption since the hydroxamate groups are separated in desferrioxamine B by nine atoms. For the same reason the steric factors probably do not play an important role in the formation of the 14-membered ring when two or three hydroxamate groups of desferrioxamine B are coordinated to ferric ion.

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Electrochemical and Spectrophotometric Studies of Iron Complexes with a Pentaaza Macrocyclic Ligand

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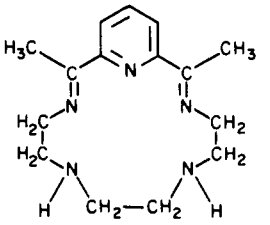
Aqueous solutions of complexes of iron(III) and iron(II) and the macrocyclic ligand 2,13-dimethyl-3,6,9,12,18-pentaazabicyclo[12.3.1]octadeca-1(18),2,12,14,16-pentaene (B) were investigated by voltammetry, chronocoulometry, and controlled-potential coulometry. Standard potentials for redox reactions involving species in this system, which include FeB^{3+}, $FeB(OH)^{2+}$, and FeB^{2+}, as well as binuclear species such as $(FeB)_2O^{4+}$, were obtained, and reactions involving decomposition of these at different pHs were investigated. Spectrophotometric measurements were also employed in the elucidation of the chemistry of this system.

Introduction

The desire to find highly water soluble and stable redox couples based on inexpensive materials for use as components in photoelectrochemical cells and redox storage batteries has led us to investigate bipyridine and phenanthroline complexes of iron and cobalt.[1,2] We have also investigated macrocyclic compounds as ligands with these metals in an attempt to determine the factors that govern the redox potentials, heterogeneous kinetics, and stabilities of these complexes. We report here results of studies of iron(II) and iron(III) complexes with the pentaaza macrocyclic ligand 2,13-dimethyl-3,6,9,12,18-pentaazabicyclo[12.3.1]octadeca-1-(18),2,12,14,16-pentaene (B). This ligand, which, in the presence of axial coordinating species, forms a seven-coordinate complex with iron, was first synthesized and characterized by



B

Busch and co-workers.[3-5] These species in solution probably involve water molecules in the axial positions and will be denoted as FeB^{3+} and FeB^{2+}. The solution chemistry is com-

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