Figure 9. Resonance Raman spectra ($\nu_0 = 5145$ Å) of $\{[Si(hp)O]I_{1.51}\}_n$ (A) and $\{[Ge(hp)O]I_{1.48}\}_n$ (B).

weak scattering at 113 and 165 cm^{-1}. From past experience,[2] it appears qualitatively that the amount of polyiodides (I_3^-, I_5^-, $I_2 \cdot I_3^-$)[2] present is rather small.

Conclusions

This contribution extends significantly what is known about cofacially linked $[M(hp)O]_n$ hemiporphyrazinato polymers. The series now includes M = Si, and the vibrational and solid-state NMR data along with the X-ray diffraction results expand the existing structural information. The tritium-labeling experiments provide the first accurate data on the degrees of polymerization. Interestingly, however, straightforward partial oxidation procedures do not lead to electrically conductive arrays of cofacial π-radical cations but to insulating materials in which the polymeric M–O–M backbone is no longer intact.

was attributed to destruction of the Sn–O–Sn backbone. X-ray powder diffraction studies of $[M(hp)O]_n$ doping reveal not only the appearance of several new reflections but also the presence of substantial quantities of the starting materials in even the most heavily iodinated materials. Resonance Raman spectra of typical $\{[M(hp)O]I_y\}_n$ samples (Figure 9) exhibit surprisingly

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Contribution from the Department of Chemistry,
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Kinetics of Reduction of Ferrichrome and Ferrichrome A by Chromium(II), Europium(II), Vanadium(II), and Dithionite

S. ARIF KAZMI,[1] A. LEE SHORTER,[2] and JAMES V. McARDLE*[3]

Reduction of ferrichrome (Fc) by europium(II) and vanadium(II) follows the rate law $-d[\text{Fc}]/dt = k[\text{Fc}][\text{M(II)}]$ with $k = (8.64 \pm 0.06) \times 10^2$ M^{-1} s^{-1} at 25 °C, pH 4.1, and $\mu = 0.5$ for europium(II) and $k = 24.8 \pm 0.1$ M^{-1} s^{-1} at 25 °C, pH 4.0, and $\mu = 1.0$ for vanadium(II). The rates are nearly independent of pH between 2.6 and 4. For europium(II), $\Delta H^* = 2.7 \pm 0.5$ kcal mol^{-1} and $\Delta S^* = -36 \pm 1$ cal K^{-1} mol^{-1}; for vanadium(II), $\Delta H^* = 3.9 \pm 0.5$ kcal mol^{-1} and $\Delta S^* = -39 \pm 1$ cal K^{-1} mol^{-1}. Reduction of ferrichrome by chromium(II) is an inner-sphere process rate limited by dissociation of one hydroxamate from iron(III). Dissociation occurs by an acid-independent pathway (k_1) and an acid-dependent pathway (k_2). The rate of formation of intact ferrichrome from the dissociated, protonated bis complex is given by k_{-2}, and the rate of electron transfer is given by k_3. The rate law for reduction by chromium(II) is $-d[\text{Fc}]/dt = k_3[\text{Cr(II)}][\text{Fc}](k_1 + k_2[\text{H}^+])/(k_{-2} + k_3[\text{Cr(II)}])$, and $k_1 = 0.108 \pm 0.020$ s^{-1}, $k_2 = 296 \pm 15$ M^{-1} s^{-1}, and $k_3/k_{-2} = 188 \pm 26$ M^{-1} for pH 2.6–4.0, 25 °C, and $\mu = 0.5$. Reduction by dithionite occurs only by the SO$_2^-$ radical according to rate constant k_0. The rate law is $-d[\text{Fc}]/dt = k_0 K^{1/2}[\text{Fc}][\text{S}_2\text{O}_4^{2-}]^{1/2}$ where K is the equilibrium constant for dissociation of $\text{S}_2\text{O}_4^{2-}$. At 25 °C, pH 7.8, and $\mu = 0.5$, $k_0 = (2.12 \pm 0.03) \times 10^4$ M^{-1} s^{-1}. The value of k_0 is nearly independent of pH from 5.8 to 7.8. At pH 7.8, $\Delta H^* = 6.0 \pm 0.5$ kcal mol^{-1} and $\Delta S^* = -19 \pm 1$ cal K^{-1} mol^{-1}. Reduction of ferrichrome A (FcA) by chromium(II), europium(II), or vanadium(II) follows the rate law $-d[\text{FcA}]/dt = (k_4 + k_5 K_a/[\text{H}^+])[\text{FcA}][\text{M(II)}]$ over the pH range 2–4. K_a is the acid-dissociation constant for loss of one proton from ferrichrome A. The parameters k_4 (M^{-1} s^{-1}) and $k_5 K_a$ (s^{-1}), respectively, at 25 °C are 11 ± 1 and $(15 \pm 1) \times 10^{-3}$ for chromium(II) ($\mu = 0.5$), 322 ± 5 and $(146 \pm 3) \times 10^{-3}$ for europium(II) ($\mu = 0.5$), and 31.1 ± 0.4 and $(12.7 \pm 0.2) \times 10^{-3}$ for vanadium(II) ($\mu = 1.0$). Values of ΔH_4^* (kcal mol^{-1}) and ΔS_4^* (cal K^{-1} mol^{-1}), respectively, for the rate constant k_4 are 21 ± 3 and -16 ± 8 for chromium(II), 3.7 ± 0.3 and -34 ± 1 for europium(II), and 2.6 ± 0.2 and -43 ± 1 for vanadium(II). Reduction by all three M(II) ions is outer sphere. Reduction of ferrichrome A by dithionite occurs only by the SO$_2^-$ radical according to the same rate law found for ferrichrome. At 25 °C, pH 7.6, and $\mu = 0.5$, $k_0 = (8.6 \pm 0.6) \times 10^3$ M^{-1} s^{-1}. The rate is nearly independent of pH from 5.7 to 7.6. At pH 7.6, $\Delta H^* = 4 \pm 1$ kcal mol^{-1} and $\Delta S^* = -26 \pm 3$ cal K^{-1} mol^{-1}.

Introduction

Siderophores are powerful iron(III) chelators that are synthesized by a wide variety of microorganisms and excreted in response to low-iron stress. In the microbial medium ex-

terior to the cell, the siderophore solubilizes and binds iron, and the iron is then delivered to the interior of the microorganism. These general features of iron(III) siderophore transport have been presented in more detail elsewhere,[4] and

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(4) Neilands, J. B. In "Bioinorganic Chemistry II"; Raymond, K. N., Ed.; American Chemical Society: Washington, DC, 1977; Adv. Chem. Ser. No. 162, pp 3–32.

the structures and the coordination chemistry of a number of siderophores also have been reviewed.[5,6]

The formation constants of the iron(III) siderophore complexes are extremely high and thereby present the microbe with the problem of removing the iron for utilization by the cell. For example, iron(III) enterobactin, in which iron is coordinated by three catecholate groups, has a formation constant of 10^{52},[7] and its iron(III)/iron(II) redox couple is estimated to be −0.70 V vs. NHE.[8] NHE is the normal hydrogen electrode. All potentials cited in this paper refer to the NHE. Other abbreviations used are as follows: Fc, ferrichrome; FcA, ferrichrome A; sid, siderophore.

Removal of iron from iron(III) enterobactin probably involves degradation of the ligand.[9,10] Iron(III) siderophore complexes of the ferrichrome or ferrioxamine families, which coordinate iron with hydroxamate groups, have formation constants of about 10^{35} and iron(III)/iron(II) redox couples of about −0.45 V. In contrast to iron(III) enterobactin, removal of iron from hydroxamate-type siderophores may not require degradation of the ligand, and the ligand may be used again in another cycle of excretion, complexation, transport, and dissociation.[11]

Because the siderophores display great specificity for complexing iron(III), all of the various schemes proposed for removal of iron from the complexes involve reduction of iron(III) to iron(II). The iron(II) is held much more weakly and may be removed from the complex for incorporation into the various iron-containing enzymes and proteins.[4] Enzyme systems that catalyze the reduction of iron(III) siderophores have been described for a number of organisms.[12-15] The redox characteristics of iron(III) siderophore complexes are therefore crucial to evaluating and understanding mechanisms of release of iron from the siderophore complexes. Thus, it is important to answer the following questions pertaining to the reduction of a particular iron(III) siderophore complex: (1) Is inner-sphere or outer-sphere reduction favored? (2) Is remote or adjacent attack favored? (3) Are hydrophobic or hydrophilic reductants favored? (4) What effect does pH have on kinetic and thermodynamic properties of reduction? (5) Are the reactivity characteristics similar to those of related iron(III) siderophore complexes?

We previously published a spectroelectrochemical study of the iron(III) siderophore complexes ferrioxamine B, ferrichrome, and ferrichrome A,[16] and another paper reported the kinetics of reduction of ferrioxamine B.[17] We have taken the approach of using small-molecule reductants of well-defined and varying redox properties to examine the redox characteristics of the iron(III) siderophore complexes. This report presents a kinetic study of the reduction of ferrichrome (Figure 1a) and ferrichrome A (Figure 1b). These three siderophores
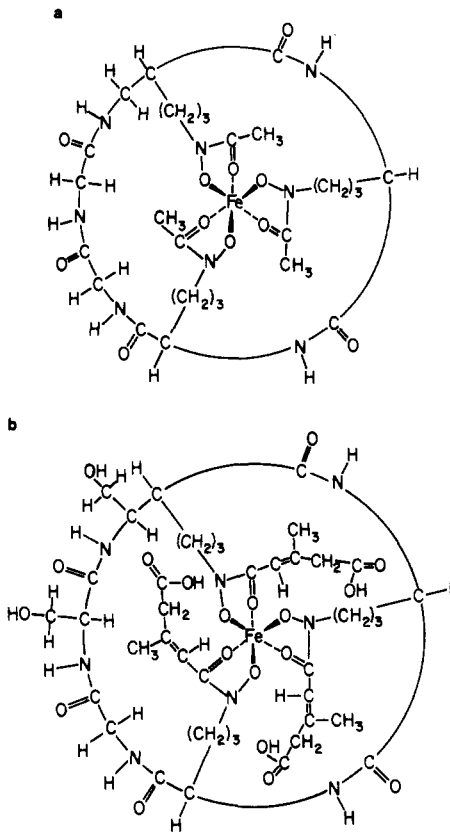
Figure 1. (a) Ferrichrome. (b) Ferrichrome A.

are similar in that each binds iron with three hydroxamates and in that they all have similar formation constants and redox potentials.[16] The hydroxamates of ferrioxamine B are incorporated into the main chain, but the hydroxamates of the ferrichromes are on appendages to the main chain. Ferrioxamine B and ferrichrome[18] are true ferric ionophores. They are transported intact into the cell where the iron is released by a process that involves reduction to iron(II). Desferrichrome A binds iron with a higher formation constant than does desferrichrome,[19] but ferrichrome A does not cross the cell membrane.[18] The iron of ferrichrome A is given up at the membrane in a process that involves reduction of iron(III) to iron(II).[18] Both ferrichromes are produced by the same organism (*Ustilago sphaerogena*). The present study will complement the previous kinetic studies of ferrioxamine B[17] and the thermodynamic study of the reduction of the three siderophores.[16] In addition, the three complexes present very similar coordination geometries yet incorporate significant structural differences. Thus, apart from gaining insight into the in vivo processes, the comparisons of kinetic behavior will be of theoretical interest.

Experimental Section

Reagents. Reagent grade chemicals and deionized distilled water were used throughout the study. Solutions of chromium(II), vanadium(II), and dithionite were prepared and analyzed as previously described.[17] Europium(II) carbonate and europium(II) perchlorate were prepared from europium(III) oxide (Alfa Products) according to the method of Cooley and Yost.[20] Europium(II) solutions were analyzed by the method of Carlyle and Espenson,[21] using chloropentaaminecobalt(III).[22] Ferrichrome was obtained from Porphyrin

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(10) Langman, L.; Young, G. I.; Frost, G. E.; Rosenberg, H.; Gibson, F. *J. Bacteriol.* **1972**, *112*, 1142–1149.
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(17) Kazmi, S. A.; Shorter, A. L.; McArdle, J. V. *J. Inorg. Biochem.* **1982**, *17*, 269–281.

(18) Ecker, D. J.; Lancaster, J. R., Jr.; Emery, T. *J. Biol. Chem.* **1982**, *257*, 8623–8626.
(19) Ecker, D. J.; Passavant, C. W.; Emery, T. *Biochim. Biophys. Acta* **1982**, *720*, 242–249.
(20) Cooley, R. A.; Yost, D. M. *Inorg. Synth.* **1946**, *2*, 9.
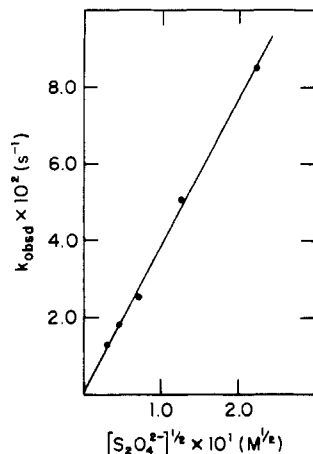(21) Carlyle, D. W.; Espenson, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 2272–2278.

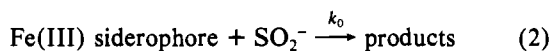**Figure 2.** Plot of k_{obsd} vs. $[S_2O_4^{2-}]^{1/2}$ for the reduction of ferrichrome at 25 °C, pH 7.8.

Products and was used without further purification. One sample of ferrichrome A was a generous gift of Professor T. Emery (Utah State University) and another sample was isolated from cultures of *U. sphaerogena* by the published procedure[11] by J. P. Robinson of this laboratory. Chromium(II), europium(II), and dithionite reactions were done at an ionic strength of 0.5 M, and vanadium(II) reactions were done at an ionic strength of 1.0 M. Ionic strength was maintained with $NaClO_4$ for chromium(II) and europium(II) solutions, whereas NaCl was used for vanadium(II) and dithionite solutions.

Physical Measurements. A stopped-flow spectrophotometer assembled inside an inert-atmosphere box as described[17] was used. Some of the slower reactions of dithionite were monitored on a Perkin-Elmer 552 spectrophotometer using standard anaerobic techniques. Pseudo-do-first-order conditions were maintained with ferrichrome or ferrichrome A as the deficient reagent in all experiments. The iron(III) siderophore concentration was typically 5×10^{-5} M. The ferrichrome reactions were followed at 425 nm ($\Delta\epsilon = 2850$ M^{-1} cm^{-1}),[23] and the ferrichrome A reactions were followed at 440 nm ($\Delta\epsilon = 3700$ M^{-1} cm^{-1}).[23]

Results

For reduction of either siderophore by any of the reagents employed in this study, plots of ln $(A_t - A_\infty)$ vs. t are linear for at least 90% of the reaction. Thus, in all cases the reaction rates exhibit first-order dependence on iron(III) siderophore.

Reduction by Dithionite. Reduction by dithionite is not first order in the concentration of $S_2O_4^{2-}$. As is the case with ferrioxamine B,[17] the SO_2^- radical is the only significant reductant of ferrichrome or ferrichrome A. The mechanism for reduction of ferrichrome or ferrichrome A by dithionite is

$$S_2O_4^{2-} \rightleftharpoons 2SO_2^- \quad K \quad (1)$$

$$Fe(III) \text{ siderophore} + SO_2^- \xrightarrow{k_0} \text{products} \quad (2)$$

$$\text{rate} = k_0 K^{1/2}[Fe(III)sid][S_2O_4^{2-}]^{1/2} \quad (3)$$

A plot of k_{obsd} vs. $[S_2O_4^{2-}]^{1/2}$ is linear with $r^2 > 0.99$ and with the intercept within one standard deviation of zero for the reaction from pH 5.7 to 7.8. The data at pH 7.8 for ferrichrome are shown in Figure 2. The rate of reaction is practically independent of pH. A temperature-dependence study yielded $\Delta H_0^* = 6.0 \pm 0.5$ kcal mol^{-1} and $\Delta S_0^* = -19 \pm 1$ cal K^{-1} mol^{-1} for ferrichrome at pH 7.8 and $\Delta H_0^* = 4 \pm 1$ kcal mol^{-1} and $\Delta S_0^* = -26 \pm 3$ cal K^{-1} mol^{-1} at pH 7.6. (See ref 17 for the temperature dependence of K.) The data for the reduction of ferrichrome or ferrichrome A by dithionite are given in Table I.

(22) Gould, E. S.; Taube, H. *J. Am. Chem. Soc.* **1964**, *86*, 1318–1328.
(23) Bickel, H.; Gaumann, W.; Keller-Schierlein, W.; Prelog, V.; Visher, E.; Wettstein, A.; Zahner, H. *Experientia* **1960**, *16*, 129–133.

Table I. Rates of Reduction

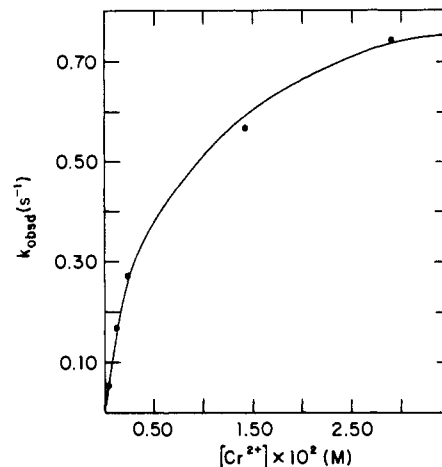| pH	T, °C	$10^{-4}k_0$, M^{-1} s^{-1}	pH	T, °C	$10^{-4}k_0$, M^{-1} s^{-1}
(a) Ferrichrome by SO_2^-					
5.8	25	1.81 ± 0.04	7.8	30	2.42 ± 0.06
6.8	25	2.00 ± 0.04	7.8	35	3.03 ± 0.04
7.8	25	2.12 ± 0.03			
(b) Ferrichrome A by SO_2^-					
5.7	25	11.6 ± 0.6	7.6	30	11 ± 1
6.6	25	9.8 ± 0.4	7.6	37	12.2 ± 0.2
7.6	25	8.6 ± 0.6			

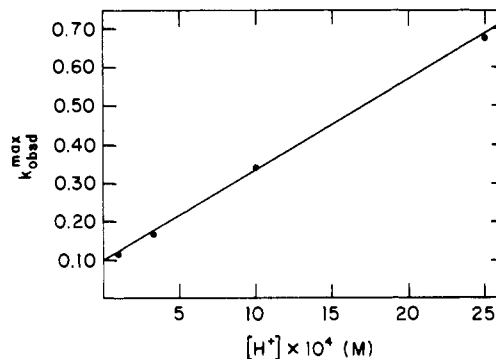**Figure 3.** Plot of k_{obsd} vs. $[Cr^{2+}]$ for the reduction of ferrichrome at 25 °C, pH 3.0.

Figure 4. Plot of k_{obsd}^{max} vs. proton concentration at 25 °C for the reduction of ferrichrome by chromium(II).

Reduction of Ferrichrome. By Europium(II) and Vanadium(II). Plots of k_{obsd} vs. [M(II)] are linear and feature zero intercepts for europium(II) ($r^2 = 0.99$) for five Eu(II) concentrations from 1.25×10^{-4} to 5.0×10^{-3} M and for vanadium(II) ($r^2 = 0.99$) for five V(II) concentrations from 9.0 $\times 10^{-4}$ to 1.75×10^{-2} M. The rate law for reduction of ferrichrome by either europium(II) or vanadium(II) is

$$-d[Fc]/dt = k[Fc][M(II)] \quad (4)$$

For reduction by europium(II), $k = (8.79 \pm 0.05) \times 10^2$ M^{-1} s^{-1} at 25 °C and pH 2.8 and $k = (8.64 \pm 0.06) \times 10^2$ M^{-1} s^{-1} at 25 °C and pH 4.1. For reduction by vanadium(II), $k = 28.5 \pm 0.1$ M^{-1} s^{-1} at 25 °C and pH 3.0 and $k = 24.8 \pm 0.1$ M^{-1} s^{-1} at 25 °C and pH 4.0. These reactions also were studied at 15, 20, and 30 °C. The Eyring plots of the temperature-dependence data yield $\Delta H^* = 2.7 \pm 0.5$ kcal mol^{-1} and $\Delta S^* = -36 \pm 1$ cal K^{-1} mol^{-1} for europium(II) ($r^2 = 0.95$) at pH 2.8 and $\Delta H^* = 3.9 \pm 0.5$ kcal mol^{-1} and $\Delta S^* = -39 \pm 1$ cal K^{-1} mol^{-1} for vanadium(II) ($r^2 = 0.98$) at pH 3.0.

By Chromium(II). The rate of reduction by chromium(II) is not first order in chromium(II). Plots of k_{obsd} vs. chromi-

Table II. Comparison of k_{obsd} to k_{calcd} for the Reduction of Ferrichrome by Chromium(II) at 25 °C ([Fc] = 5 × 10⁻⁵ M)

pH	10^3 [Cr(II)], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹
2.6	0.37	0.07	0.06
2.6	1.23	0.17	0.16
2.6	2.33	0.27	0.26
2.6	14.3	0.57	0.62
2.5	29.5	0.75	0.72
3.0	0.82	0.07	0.05
3.0	2.00	0.12	0.11
3.0	4.50	0.19	0.19
3.0	11.50	0.23	0.28
3.0	16.00	0.37	0.30
3.5	0.24	0.012	0.009
3.5	1.20	0.041	0.037
3.5	2.40	0.055	0.063
3.5	4.80	0.086	0.096
3.5	12.00	0.138	0.140
4.0	0.60	0.018	0.014
4.0	1.18	0.031	0.025
4.0	2.60	0.050	0.045
4.0	8.40	0.067	0.085
4.0	15.50	0.106	0.103

Table III. Least-Squares Parameters for the Reduction of Ferrichrome A by M(II)

M	T, °C	k_4, M⁻¹ s⁻¹	$10^3 k_5 K_a$, s⁻¹
Cr	21	8 ± 1	9.4 ± 0.9
Cr	25	11 ± 1	15 ± 1
Cr	30	24 ± 3	15 ± 2
Cr	35	34 ± 5	18 ± 2
Eu	15	285 ± 10	126 ± 6
Eu	20	306 ± 9	136 ± 5
Eu	25	332 ± 5	146 ± 3
Eu	35	448 ± 10	159 ± 5
V	15	27.5 ± 0.5	8.9 ± 0.2
V	20	29.4 ± 0.6	10.4 ± 0.2
V	25	31.1 ± 0.4	12.7 ± 0.2
V	35	38.0 ± 0.6	14.3 ± 0.2

um(II) concentration are not linear and clearly show rate-limiting behavior (Figure 3). Plots of $1/k_{obsd}$ vs. $1/[Cr^{2+}]$ do yield good straight lines. The reciprocal of the intercept of the double-reciprocal plot represents the rate-limiting k_{obsd} (k_{obsd}^{max}). The values of k_{obsd}^{max} are dependent upon hydrogen ion concentration as shown in Figure 4.

In the following mechanism, which accounts for the kinetic data, the notation Fe(hyd)₃ represents intact ferrichrome with all three hydroxamate groups coordinated to the iron, and Fe(hyd)₂–hydH represents iron coordinated by two hydroxamate groups of the ligand while the third hydroxamate is dissociated and protonated. Waters are assumed to occupy vacated ligand sites. The mechanism is given as

$$\text{Fe(hyd)}_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{Fe(hyd)}_2\text{-hyd} \underset{k_{-p}}{\overset{k_p, H_2O}{\rightleftharpoons}}$$
$$\text{Fe(hyd)}_2\text{-hydH}^+ + \text{OH}^- \quad (5)$$

$$\text{Fe(hyd)}_3 + \text{H}^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{Fe(hyd)}_2\text{-hydH}^+ \quad (6)$$

$$\text{Fe(hyd)}_2\text{-hydH}^+ + \text{Cr}^{2+} \overset{k_3}{\longrightarrow} \text{products} \quad (7)$$
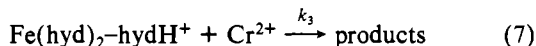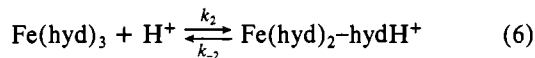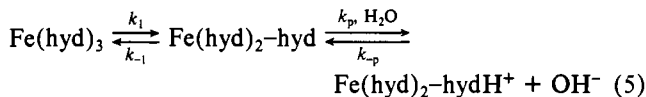
Applying the steady-state assumption to Fe(hyd)₂–hyd we obtain

$$[\text{Fe(hyd)}_2\text{-hyd}] = [k_1[\text{Fe(hyd)}_3] + k_{-p}[\text{Fe(hyd)}_2\text{-hydH}][\text{OH}^-]]/(k_{-1} + k_p) \quad (8)$$

The rate constant k_p is the rate of protonation of hydroxamate, and we therefore assume $k_p \gg k_{-1}$. We apply the steady-state assumption to Fe(hyd)₂–hydH and use eq 8 to obtain

$$\text{rate} = \frac{k_3[\text{Cr}^{2+}][\text{Fc}](k_1 + k_2[\text{H}^+])}{k_{-2} + k_3[\text{Cr}^{2+}]} \quad (9)$$

With ferrichrome present as the limiting reagent, the reciprocal of k_{obsd} is given by eq 10. The slope of the line plotted in

$$\frac{1}{k_{obsd}} = \frac{k_{-2}}{(k_1 + k_2[\text{H}^+])k_3[\text{Cr}^{2+}]} + \frac{1}{k_1 + k_2[\text{H}^+]} \quad (10)$$
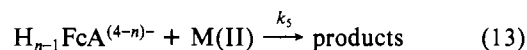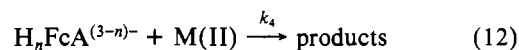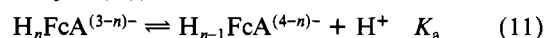
Figure 4 gives $k_2 = (2.4 \pm 0.2) \times 10^2$ M⁻¹ s⁻¹, and the intercept gives $k_1 = (7.7 \pm 0.8) \times 10^{-2}$ s⁻¹ with $r^2 = 0.98$. We use the slopes of plots of $1/k_{obsd}$ vs. $1/[Cr^{2+}]$ with the calculated values of k_1 and k_2 to determine an average value of $k_3/k_{-2} = (3.3 \pm 0.3) \times 10^2$ M⁻¹. These parameters were refined by a nonlinear least-squares program to yield as final values for the parameters (with standard errors) $k_1 = 0.108$ (0.020) s⁻¹, $k_2 = 296$ (15) M⁻¹ s⁻¹, $k_3/k_{-2} = 188$ (26) M⁻¹. Table II compares

k_{obsd} to the calculated value of the pseudo-first-order rate constant (k_{calcd}).

Reduction of Ferrichrome A by Metal Ions. Plots of observed rate constants vs. the concentration of M(II) are linear and have zero intercepts, and the reactions are first order in M(II). These plots yield an apparent second-order rate constant k', which is dependent upon pH. Plots of k' vs. $1/[H^+]$ are linear with nonzero intercepts and indicate that one acid-dependent and one acid-independent pathway is operating. We propose the following mechanism for the reduction of ferrichrome A (FcA) by chromium(II), europium(II), or vanadium(II) (each represented by M(II)):

$$\text{H}_n\text{FcA}^{(3-n)-} \rightleftharpoons \text{H}_{n-1}\text{FcA}^{(4-n)-} + \text{H}^+ \quad K_a \quad (11)$$

$$\text{H}_n\text{FcA}^{(3-n)-} + \text{M(II)} \overset{k_4}{\longrightarrow} \text{products} \quad (12)$$

$$\text{H}_{n-1}\text{FcA}^{(4-n)-} + \text{M(II)} \overset{k_5}{\longrightarrow} \text{products} \quad (13)$$

With M(II) in excess, the above mechanism predicts

$$\text{rate} = (k_4 + k_5 K_a/[\text{H}^+])[\text{M(II)}][\text{H}_n\text{FcA}]^{(3-n)-} \quad (14)$$

$$k_{obsd} = (k_4 + k_5 K_a/[\text{H}^+])[\text{M(II)}] \quad (15)$$

From the plots described above, estimates of k_4 and $k_5 K_a$ were obtained. The data were then refined by a nonlinear least-squares program. The refined values of k_4 and $k_5 K_a$ are given in Table III, and Table IV compares values of k_{obsd} to values of the observed rate constant calculated according to eq 15 (k_{calcd}). From the temperature dependence of k_4 we calculate $\Delta H_4^* = 21 \pm 3$ kcal mol⁻¹ and $\Delta S_4^* = -16 \pm 8$ cal K⁻¹ mol⁻¹ for the reduction of ferrichrome A by chromium(II), $\Delta H_4^* = 3.7 \pm 0.3$ kcal mol⁻¹ and $\Delta S_4^* = -34 \pm 1$ cal K⁻¹ mol⁻¹ for the reduction by europium(II), and $\Delta H_4^* = 2.6 \pm 0.2$ kcal mol⁻¹ and $\Delta S_4^* = -43 \pm 1$ cal K⁻¹ mol⁻¹ for the reduction by vanadium(II).

The value of K_a probably is in the range 10^{-3}–10^{-4} if the proton is dissociating from a carboxylic acid (see Discussion). Thus, k_5 at 25 °C is estimated to be in the range 15–150 M⁻¹ s⁻¹ for reduction by chromium(II), 146–1460 M⁻¹ s⁻¹ for reduction by europium(II), and 12.7–127 M⁻¹ s⁻¹ for reduction by vanadium(II).

Discussion

Reduction by Dithionite. The linearity and zero intercept of the plot of k_{obsd} vs. $[S_2O_4^{2-}]^{1/2}$ establish the SO_2^- radical as the only important reductant of ferrichrome or of ferrichrome A. The dithionite reduction of ferrioxamine B[17] also proceeds exclusively through the SO_2^- radical as do the reductions of a few others species.[24,25] The equilibrium concentration of SO_2^- is small, but the dissociation of $S_2O_4^{2-}$ is sufficiently rapid ($k = 1.7$ s⁻¹) to maintain the equilibrium concentration of SO_2^-.[26-28]

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Table IV. Comparison of k_{obsd} to k_{calcd} for the Reduction of Ferrichrome A by M(II)

pH	$10^3 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹	pH	$10^3 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹	pH	$10^3 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹	pH	$10^3 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹
	M = Cr, T = 35 °C								M = Eu, T = 35 °C						
2.4	0.90	0.029	0.034	3.3	0.78	0.075	0.053	2.2	0.26	0.116	0.121	2.8	1.03	0.514	0.566
2.4	4.80	0.16	0.18	3.3	2.95	0.20	0.20	2.2	1.32	0.625	0.625	3.5	0.30	0.274	0.284
2.4	8.20	0.26	0.31	3.3	8.25	0.88	0.57	2.2	2.78	1.30	1.32	3.5	1.90	2.00	1.81
2.4	18.50	0.59	0.71	3.3	19.25	1.50	1.33	2.2	5.85	2.79	2.77	3.5	2.39	2.28	2.28
2.8	1.40	0.056	0.063	3.6	0.61	0.068	0.064	2.8	0.22	0.104	0.118	3.5	2.99	2.78	2.85
2.8	2.25	0.10	0.10	3.6	1.27	0.16	0.13	2.8	0.13	0.067	0.071	3.5	3.78	3.56	3.60
2.8	6.35	0.22	0.28	3.6	6.85	0.57	0.71	2.8	0.50	0.225	0.273				
2.8	8.50	0.37	0.38	3.6	13.75	1.30	1.43		M = Eu, T = 25 °C						
	M = Cr, T = 30 °C							2.2	0.26	0.084	0.090	2.8	3.65	1.46	1.55
2.4	0.90	0.021	0.025	3.3	0.78	0.056	0.043	2.2	0.56	0.199	0.201	3.5	0.074	0.050	0.058
2.4	4.80	0.11	0.14	3.3	2.95	0.12	0.16	2.2	1.32	0.465	0.469	3.5	0.15	0.104	0.117
2.4	8.20	0.18	0.23	3.3	8.25	0.59	0.47	2.2	2.78	1.01	0.99	3.5	0.33	0.253	0.263
2.4	18.20	0.43	0.52	3.3	19.25	1.24	1.07	2.2	5.85	2.12	2.08	3.5	0.63	0.464	0.501
2.8	1.40	0.046	0.048	3.6	0.61	0.050	0.053	2.8	0.13	0.049	0.055	3.5	0.88	0.708	0.699
2.8	2.25	0.076	0.077	3.6	1.27	0.11	0.11	2.8	0.22	0.080	0.091	3.5	2.39	1.94	1.90
2.8	6.35	0.18	0.22	3.6	6.85	0.51	0.59	2.8	0.50	0.196	0.211	3.5	3.78	3.00	3.00
2.8	8.50	0.29	0.29	3.6	13.75	1.08	1.18	2.8	1.03	0.403	0.437				
	M = Cr, T = 25 °C								M = Eu, T = 20 °C						
2.4	0.90	0.016	0.013	3.3	0.78	0.040	0.032	2.2	0.56	0.173	0.185	2.8	1.03	0.378	0.510
2.4	4.80	0.087	0.070	3.3	2.95	0.10	0.12	2.2	1.32	0.428	0.433	3.5	0.88	0.660	0.647
2.4	8.20	0.14	0.12	3.3	8.25	0.40	0.34	2.2	2.78	0.841	0.911	3.5	1.90	1.41	1.40
2.4	18.50	0.30	0.27	3.3	19.25	1.00	0.78	2.2	5.85	1.98	1.92	3.5	2.39	1.72	1.76
2.8	1.40	0.027	0.028	3.6	0.61	0.032	0.043	2.8	0.22	0.072	0.084	3.5	2.98	2.22	2.19
2.8	2.25	0.059	0.046	3.6	1.27	0.078	0.090	2.8	0.50	0.180	0.195				
2.8	6.35	0.15	0.13	3.6	3.79	0.42	0.27		M = Eu, T = 15 °C						
2.8	8.50	0.23	0.17	3.6	13.75	0.88	0.97	2.2	0.26	0.071	0.078	2.8	1.30	0.431	0.474
2.8	19.10	0.40	0.39	4.0	0.49	0.057	0.078	2.2	0.56	0.158	0.172	3.5	0.33	0.175	0.227
2.8	32.50	0.63	0.66	4.0	1.91	0.27	0.31	2.2	1.32	0.404	0.402	3.5	0.63	0.408	0.431
2.8	77.50	1.51	1.57	4.0	3.55	0.48	0.57	2.2	5.85	1.81	1.78	3.5	0.88	0.708	0.603
	M = Cr, T = 21 °C							2.8	0.13	0.043	0.047	3.5	3.78	2.58	2.59
2.4	0.90	0.015	0.009	2.8	3.25	0.37	0.44	2.8	0.50	0.162	0.182				
2.4	4.80	0.077	0.048	3.6	0.61	0.030	0.028								
2.4	8.20	0.12	0.08	3.6	3.79	0.16	0.17								
2.4	18.50	0.26	0.19	3.6	6.85	0.28	0.31								
2.8	2.25	0.041	0.031	3.6	13.75	0.66	0.62								
2.8	8.50	0.16	0.12												

pH	$10^2 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹	pH	$10^2 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹	pH	$10^2 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹	pH	$10^2 \times$ [M²⁺], M	k_{obsd}, s⁻¹	k_{calcd}, s⁻¹
	M = V, T = 35 °C								M = V, T = 20 °C						
2.4	0.21	0.085	0.087	3.2	1.33	0.829	0.807	2.4	0.21	0.065	0.067	3.2	1.33	0.613	0.610
2.4	0.37	0.155	0.152	3.2	3.22	1.96	1.95	2.4	0.37	0.112	0.117	3.2	3.22	1.53	1.48
2.4	0.68	0.309	0.284	4.0	0.060	0.106	0.108	2.4	0.68	0.206	0.218	4.0	0.039	0.057	0.052
2.4	1.36	0.588	0.566	4.0	0.085	0.186	0.154	2.4	1.36	0.432	0.435	4.0	0.085	0.126	0.113
2.4	2.57	1.03	1.07	4.0	0.23	0.446	0.424	2.4	2.57	0.777	0.822	4.0	0.23	0.320	0.312
3.2	0.12	0.080	0.071	4.0	0.72	1.26	1.30	3.2	0.12	0.060	0.054	4.0	0.47	0.620	0.627
3.2	0.33	0.222	0.202	4.0	1.10	2.00	1.99	3.2	0.33	0.151	0.153	4.0	1.10	1.45	1.47
3.2	0.71	0.438	0.431					3.2	0.71	0.298	0.326				
	M = V, T = 25 °C								M = V, T = 15 °C						
2.7	0.062	0.024	0.023	3.2	0.71	0.376	0.365	2.4	0.21	0.052	0.062	3.2	1.33	0.564	0.554
2.7	0.13	0.048	0.049	3.2	1.33	0.680	0.682	2.4	0.37	0.095	0.109	3.2	3.22	1.38	1.34
2.7	0.25	0.094	0.093	3.2	3.22	1.65	1.65	2.4	0.68	0.187	0.203	4.0	0.039	0.055	0.046
2.7	0.66	0.239	0.249	4.0	0.039	0.063	0.062	2.4	1.36	0.401	0.404	4.0	0.085	0.110	0.100
2.7	1.25	0.442	0.468	4.0	0.085	0.145	0.134	2.4	2.57	0.734	0.764	4.0	0.23	0.260	0.274
2.7	3.01	1.14	1.12	4.0	0.23	0.381	0.371	3.2	0.12	0.052	0.049	4.0	0.47	0.511	0.550
3.2	0.12	0.067	0.060	4.0	0.47	0.789	0.745	3.2	0.33	0.134	0.139	4.0	1.10	1.29	1.29
3.2	0.33	0.178	0.171	4.0	1.10	1.72	1.74	3.2	0.71	0.266	0.296				

The rate and the activation parameters for the dithionite reduction of ferrichrome A ($k_0 = 8.9 \times 10^3$ M⁻¹ s⁻¹; $\Delta H_0^* = 4$ kcal mol⁻¹; $\Delta S_0^* = -26$ cal K⁻¹ mol⁻¹) are very similar to those of ferrioxamine B ($k_0 = 4.6 \times 10^3$ M⁻¹ s⁻¹; $\Delta H_0^* = 6.8$ kcal mol⁻¹; $\Delta S_0^* = -19$ cal K⁻¹ mol⁻¹) and those of ferrichrome ($k_0 = 2.1 \times 10^4$ M⁻¹ s⁻¹; $\Delta H_0^* = 6.0$ kcal mol⁻¹; $\Delta S_0^* = -19$ cal K⁻¹ mol⁻¹). The values of the pertinent redox couples are -0.44 V for ferrichrome A,[16] -0.45 V for ferrioxamine B,[8,29] and -0.40 V for ferrichrome.[16] Thus, the ferrichrome reaction is expected to be somewhat faster than the other two due to a larger driving force.

According to the mechanism presented above, the reduction of ferrichrome by dithionite must be an outer-sphere process.

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It was shown that the rate-limiting first-order dissociation of an hydroxamate group from ferrichrome proceeds with $k_1 =$ (0.108 ± 0.020) s^{-1} (eq 5). Values of k_{obsd} for reduction of ferrichrome by dithionite as large as 0.084 s^{-1} were measured at 25 °C, but no indication of rate-limiting behavior is seen. (Figure 3 demonstrates that rate-limiting behavior is obvious at 80% of k^{max}.)

The absence of rate-limiting behavior in the reduction of ferrichrome by dithionite establishes that reaction as outer sphere, and the similarity of rate and activation parameters of all three ferric siderophore reductions by dithionite suggests that a common mechanism is employed. An exception to the similarity of behavior in the three reactions is the following: the rate of reduction of ferrichrome A decreases with increasing pH whereas the rates of the other two reactions increase with increasing pH. In all case, the pH dependence is very slight. The small decrease in rate in the case of ferrichrome A may be due to the slight increase in the negative charge of the complex as the pH is raised. We calculate (see below) the complex to be 95% as the trianion at pH 5.7, 99% at pH 6.6, and essentially 100% at pH 7.6.

The Marcus equation[30]

$$\log k_{12} = 0.5(\log k_{11} + \log k_{22} + 16.9\Delta E°) \quad (16)$$

can be used to obtain an apparent self-exchange rate constant (k_{11}) for ferrichrome and for ferrichrome A in its reaction with dithionite. The self-exchange rate for SO$_2^-$ (k_{22}) is 1×10^{-3} M^{-1} s^{-1},[31] and that of the S(III)/S(IV) redox couple of SO$_2^-$ is -0.72 V.[32] The value of k_{11} calculated for ferrichrome is 8×10^5 M^{-1} s^{-1} (pH 7.8) and that for ferrichrome A is 1×10^6 M^{-1} s^{-1} (pH 7.6). These values are close to that calculated for ferrioxamine B $(3 \times 10^5$ M^{-1} s^{-1}, pH 7.8).[17]

We now assume that k_{11} for ferrichrome and for ferrichrome A is independent of pH (as is apparently true for ferrioxamine B)[17] in order to calculate the Fe(III)/Fe(II) redox potential for ferrichrome and for ferrichrome A at low pH where the potential cannot be measured directly.[16] The calculated potentials for ferrichrome are -0.29 V at pH 6.8 and -0.25 V at pH 5.8, and for ferrichrome A they are -0.34 V at pH 6.6 and -0.28 V at pH 5.6.

Reduction of Ferrichrome. By Vanadium(II) and Europium(II). Reduction of ferrichrome by vanadium(II) or europium(II) is outer sphere. For reduction at pH 4.0, k_{obsd} values greater than 0.50 s^{-1} were measured for reduction by vanadium(II) and values greater than 4.0 s^{-1} were measured for reduction by europium(II). Inner-sphere processes for ferrichrome are limited to less than 0.15 s^{-1} (Figure 4). Neither inner-sphere remote nor bridged outer-sphere electron transfer is ruled out by these comparisons, but the lack of available binding sites on the ligand makes these processes unlikely. Furthermore, inner-sphere processes involving substitution at vanadium(II) typically occur with enthalpies of activation greater than 11 kcal mol^{-1}.[33,34] The activation parameters obtained here ($\Delta H^{\ddagger} = 3.9$ kcal mol^{-1}; $\Delta S^{\ddagger} = -40$ cal K^{-1} mol^{-1}) are similar to those obtained for the reduction of ferrioxamine B by vanadium(II) ($\Delta H^{\ddagger} = 1.7$ kcal mol^{-1}; $\Delta S^{\ddagger} = -40$ cal K^{-1} mol^{-1}).[17] The reduction of ferrioxamine B by vanadium(II) must be an outer-sphere process because the electron-transfer rate (680 M^{-1} s^{-1})[17] exceeds the rate of substitution into the vanadium coordination sphere (40 M^{-1} s^{-1}).[33] The increase in $\Delta H^{\ddagger}$ for reduction of ferrichrome compared to reduction of ferrioxamine B implies that the

former complex requires greater activation in its reduction by vanadium(II). The greater size, the cyclic ligand, and the three ornithine side chains of ferrichrome all may contribute to the decrease in kinetic access to the active site and to the increase in activation enthalpy that is responsible for the greater than 24-fold decrease in rate of reduction compared to ferrioxamine B. The smaller reductant SO$_2^-$ has nearly equal access to either siderophore as evidenced by very similar rates and activation parameters.

The Marcus equation may be applied to the reduction of ferrichrome by vanadium(II). For vanadium(II) $k_{22} = 1.5 \times 10^{-2}$ M^{-1} s^{-1} and $E° = -0.23$ V,[35] and for ferrichrome $k_{11} = 8 \times 10^5$ M^{-1} s^{-1} as calculated from the SO$_2^-$ data. The Marcus equation predicts $E° = -0.35$ V for ferrichrome at pH 4.0. Such a value is very unlikely considering the potentials calculated above from the dithionite data for pH 5.8 and 6.8 and considering also the potential of ferrioxamine B at low pH (-0.12 V).[29] The apparent failure of the Marcus equation in this calculation compared to the success of the Marcus equation is the case of ferrioxamine B is another indication that vanadium(II) and SO$_2^-$ have equal acess to the active site in ferrioxamine B but that vanadium(II), compared to SO$_2^-$, has only hindered access to the active site in ferrichrome.

Low values of $\Delta H^{\ddagger}$ and large negative values of $\Delta S^{\ddagger}$ are also characteristic of outer-sphere electron-transfer reactions of europium(II).[36] The Marcus equation may be applied to the reduction of ferrichrome by europium(II) by using $k_{22} = 4 \times 10^{-4}$ M^{-1} s^{-1} and $E° = -0.38$ V.[35] A prediction of $E° = -0.18$ V at pH 4.0 is obtained. This is a reasonable value and indicates that simple Marcus theory is followed. This result at first is perplexing considering the conclusions reached in the preceding paragraph. One might expect that the larger Eu(II)(aq) ion would have even less access to the ferrichrome active site than V(II)(aq) (see below).

The Marcus correlations also may be considered by assuming a value of $E°$ for ferrichrome. The cross relationships will be corrected for work terms in order to account for the effects of charge on the reagents. An analogous treatment was used recently by Bennett et al.[37] to evaluate the reaction between hexaammineruthenium(II) and (ethylenediaminetetraacetato)iron(III). To proceed, we assume a value of $E°$ for ferrichrome at pH 4.0. We will use $E° = -0.16$ V as a reasonable estimate based on the results above and the value for ferrioxamine B at pH 3.0. However, the qualitative conclusions do not depend on the chosen value of $E°$ from -0.11 to -0.25 V (see below). The parameters given here were calculated according to ref 35. For the self-exchange reaction of ferrichrome $(\Delta G^{\ddagger})_{cor} = (\Delta G^{\ddagger})_{app}$, and for cross reaction involving ferrichrome it is essentially true $(\Delta G_{12}^{\ddagger})_{cor} = (\Delta G_{12}^{\ddagger})_{app}$ because the charge on ferrichrome is zero. For ferrichrome, $(\Delta G_{11}^{\ddagger})_{cor} = 6.6$ kcal mol^{-1}; for vanadium(II), $(\Delta G_{22}^{\ddagger})_{cor} = 16.8$ kcal mol^{-1}; and for europium(II), $(\Delta G_{22}^{\ddagger})_{cor} = 19.3$ kcal mol^{-1}. Using the equations of Weaver and Yee[35]

$$(\Delta G_{12}^{\ddagger})_{cor} = 0.5[(\Delta G_{11}^{\ddagger})_{cor} + (\Delta G_{22}^{\ddagger})_{cor} + \Delta G_{12}° + \alpha\Delta G_{12}°] \quad (17)$$

with

$$\alpha = \Delta G_{12}°/4[(\Delta G_{11}^{\ddagger})_{cor} + (\Delta G_{22}^{\ddagger})_{cor} - 2\Delta G_s^w] \quad (18)$$

and

$$\Delta G_{12}° = -23.06 \text{ kcal mol}^{-1} \text{ V}^{-1} (E°_{ox} - E°_{red}) \quad (19)$$

we calculate for vanadium(II) $0.5\alpha\Delta G_{12}° = 1.9$ kcal mol^{-1} and $0.5\alpha_0\Delta G_{12}° = 0.0$ kcal mol^{-1} and for europium(II) $0.5\alpha\Delta G_{12}°$

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= 0.3 kcal mol^{-1} and $0.5\alpha_0\Delta G_{12}° = 0.3$ kcal mol^{-1}. (Note that eq 17 does not include the terms $\Delta G_{12}{}^w$ [=0] and $\Delta G_{21}{}^w$ [=0.2 kcal mol^{-1}]. Inclusion of $\Delta G_{21}{}^w$ has no perceptile effect.) The difference between these two terms is the quantity $0.5\Delta G_{12}°$ $(\alpha - \alpha_0)$, which is equal to the difference between the experimental and the calculated values of $(\Delta G_{12}{}^*)_{cor}$. If this difference is less than 1 kcal mol^{-1}, then the agreement between experiment and the prediction of eq 16 is considered good.[35] For the reduction of ferrichrome by europium(II), the only work terms that are required are the Debye–Huckel terms. For reduction by vanadium(II), the term $\Delta G_s{}^w$ clearly is not negligible. It is surprising that this reaction, which involves a dication and a neutral molecule and proceeds with a low driving force, should involve such a large Debye–Huckel corrected work term. It is not likely that the explanation lies in any intrinsic component of ΔG^w as postulated for reactions with large $-\Delta G_{12}°$.[35] It is more useful to view these calculations as demonstrating the inapplicability of $(\Delta G_{22}{}^*)_{cor}$ for vanadium(II) to this reaction. An effective $\Delta G_{22}{}^*$ of 21 kcal mol^{-1} is required of vanadium(II) in the present reaction. That is, considerably more activation (about 4 kcal mol^{-1}) of vanadium(II) is required in its reaction with ferrichrome than is required in its reaction with vanadium(III) or with ferrioxamine B. Of course, it is not proper to assign all of the increase in activation to either reagent, but this treatment facilitates comparisons. On the other hand, europium(II) already faces a very large activation energy for reduction of europium(III), and a similar activation energy is required for reduction of ferrichrome. By this same argument, one would predict that the reduction of ferrioxamine B by europium(II) would go faster than predicted by the Marcus calculation. That indeed is observed ($k_{calcd} = 1.4 \times 10^3$ M^{-1} s^{-1}; $k_{exptl} = 6.3 \times 10^4$ M^{-1} s^{-1}).[38a] Thus, the reduction of ferrichrome by europium(II) also requires more activation energy than the corresponding reduction of ferrioxamine B. The insensitivity of these conclusions toward the assumed value of $E°$ for ferrichrome simply reflects the small contribution of $\Delta G_{12}°$ to $(\Delta G_{12}{}^*)_{cor}$. For example, if we assume $E° = -0.11$ V or $E° = -0.25$ V, the difference between the parameters $0.5\alpha\Delta G_{12}°$ and $0.5\alpha_0\Delta G_{12}°$ is 2.4 or 1.3 kcal mol^{-1}, respectively, for reduction by vanadium(II) and 0.6 or -0.7 kcal mol^{-1}, respectively, for reduction by europium(II).

By Chromium(II). Reduction of ferrichrome by chromium(II) proceeds by an inner-sphere mechanism that is rate limited by dissociation of an hydroxamate from the complex (eq 5–7). This mechanism is similar to that proposed for the reduction of ferrioxamine B by chromium(II)[17] except that dissociation in the latter case is rapid ($k_2 > 1.6 \times 10^4$ M^{-1} s^{-1}) and is not rate limiting.

Figure 4 clearly demonstrates that there are two pathways to the dissociated siderophore complex. Monzyk and Crumbliss[38b] proposed a similar mechanism of acid-dependent and acid-independent pathways for the dissociation of the third hydroxamate in the aquation reaction of ferrioxamine B. The value of pK_a for Fe(hyd)$_2$–hydH is given as 1.49 by Schwarzenbach.[39] Thus, according to our mechanism

$$\frac{[Fe(hyd)_3]}{[Fe(hyd)_2\text{-}hydH]} = \frac{k_{-2}}{k_1 + k_2[H^+]} = 1 \qquad (20)$$

at pH 1.49. The calculated value of k_{-2} is 9.7 ± 0.5 s^{-1}, and therefore $k_3 = (1.8 \pm 0.3) \times 10^3$ M^{-1} s^{-1}. The value of k_3 is within a factor of 7 of the corresponding rate for the reduction of ferrioxamine B.[17] No data on the temperature dependence of pK_a exist, and no activation parameters are given for k_3.

The very large difference in rate of dissociation of one hydroxamate from ferrichrome compared to ferrioxamine B must be due to structural differences between the ligands since the coordination geometries in the two cases are very similar. Ferrichrome has a cyclic base whereas ferrioxamine B has a linear base, and the hydroxamates of ferrichrome are appendages of the cyclic base whereas the hydroxamates of ferrioxamine B are integral parts of the main chain. Perhaps one or both of these features confer less freedom of motion to the hydroxamates in ferrichrome. The X-ray crystal structures of ferrichrome[40] and ferrichrome A[41] and the NMR of the gallium(III) and aluminum(III) analogues[42] have determined that a strong intramolecular hydrogen bond exists between N–H of one of the ornithine residues and the N–O hydroxamate oxygen of the same ornithine residue. This hydrogen bond could confer decreased lability upon the complexes. Another factor may be that the solution conformation of ferrichrome allows less access to iron by solvent molecules, thereby impeding the displacement reaction.

Our data do not exclude the possibility that chromium(II) is bound in a rate-limiting step at some site other than a hydroxamate. Electron transfer then could occur to the intact tris(hydroxamato)iron(III) center. However, such a "bridged outer-sphere" mechanism as has been proposed for other chromium(II) reductions[43] is very unlikely considering the magnitude of k_3. The small amounts of ferrichrome that were available for this study involving four reductants and the apparent instability of the chromium(III) product precluded an in-depth analysis of the product of reduction of ferrichrome by chromium(II).

Reduction of Ferrichrome A by M(II). Reduction of ferrichrome A by chromium(II), europium(II), or vanadium(II) is outer sphere and occurs by a mechanism that is common to all three reductants. The mechanism features two parallel paths (eq 11–13), one of which is acid dependent. The studies of Gould and co-workers are most relevant to establishing these reactions as outer sphere. One study[44] of the reduction of a number of pentaaminecobalt(III) derivatives of heterocyclic bases gave the ratio of outer-sphere rates $k_{Eu^{2+}}/k_{Cr^{2+}}$ to be in the range of 8–25. Another study[45] of the reduction of some pentaamminecobalt(III) carboxylate complexes gave $k_{Eu^{2+}}/k_{Cr^{2+}}$ as 19. In the present study the ratio $k_{Eu^{2+}}/k_{Cr^{2+}}$ is 30 for the rate constant k_4 and 10 for the rate constant k_5. The work of Gould and others[46] has shown that when an inner-sphere electron-transfer pathway is available, the rate of reduction by chromium(II) is greatly enhanced. Such is not the case here, and these reactions are established as outer sphere.

Gould and co-workers[45,46] and others[47,48] also have studied ratios of outer-sphere electron-transfer rates for vanadium(II) and chromium(II). Ratios of $k_{V(II)}/k_{Cr(II)}$ from 60 to 0.4 have been found. The ratios in the present study are on the low side of this range (3 for rate constant k_4 and 0.8 for rate constant k_5). Furthermore, the low $\Delta H_4{}^*$ and negative $\Delta S_4{}^*$ for the reduction of ferrichrome A by vanadium(II) and europium(II) are characteristic of outer-sphere electron transfer.[34,49]

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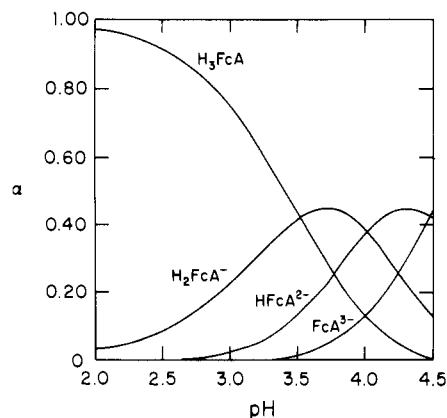
Figure 5. Distribution of ferrichrome A species assuming $pK = 4.0$ for each carboxylic acid and assuming that the acids are independent of each other. The quantity α is the fraction of total ferrichrome A present as a specific species.

The origin of the acid dependence clearly lies with ferrichrome A because the studies of the reduction of the similar complexes ferrichrome and ferrioxamine B[17] by these same reductants show no such acid dependence. We will discuss the two most likely sites for the interaction of ferrichrome A with protons, and we will consider the mechanistic implications of each of those interactions. The two sites are the carboxylates and the hydroxamates. An obvious possible source of the acid dependence is the *trans*-β-methylglutaconic acid substituents of the hydroxamic acid. An earlier titration of the ferrichrome A ligand revealed an average pK_a of 4.0 for the three carboxylic acid residues but was not able to resolve individual values of pK_a.[50] In order to estimate the distribution of ferrichrome A species as a function of pH, we have assumed that each carboxylic acid has a pK_a of 4.0 and that the three acids are independent of each other. The resulting distribution curve is shown in Figure 5. This treatment suggests that at pH 3.5 the only species present in significant concentration are H_3FcA and H_2FcA^- and that these may be the species represented as $H_nFcA^{(3-n)-}$ and $H_{n-1}FcA^{(4-n)-}$, respectively, in eq 11–13. However, at pH 4.0 the species $HFcA^{2-}$ also should be present in large concentration, and about 12% of the complex should be FcA^{3-}. The kinetic data clearly show only a $[H^+]^{-1}$ dependence and thereby rule out the participation of more than two ferrichrome A species. If the pH dependence for the reduction of ferrichrome A by M(II) arises from deprotonation of carboxylic acid, then the species $HFcA^{2-}$ and FcA^{3-} appear to be unreactive. Reaction of H_2FcA^- could involve binding of M(II) at the carboxylate prior to electron transfer in a bridged outer-sphere mechanism.[43] In this mechanism, substitution on the M(II) ion occurs but electron-transfer proceeds via overlaps of the first coordination spheres of the metal ions. The M(II) ion bound by one carboxylate still might possess enough flexibility to encounter iron(III) at a distance short enough to allow electron transfer. The species $HFcA^{2-}$ and FcA^{3-} could bind M(II) with two or three carboxylates, respectively. An M(II) ion bound by more than one carboxylate might lack the necessary flexibility to approach iron(III) closely enough to permit electron transfer. These species would be redox inactive.

The data for Figure 5 were obtained by assuming that each carboxylic acid has the same pK_a of 4.0 and that the acids are independent of each other. It is likely that the carboxylic acids are not independent of each other and that $pK_{a_1} < pK_{a_2} < pK_{a_3}$. If the difference between pK_{a_1} and pK_{a_2} is large, then Figure 5 may not be a good approximation to the species distribution and the only important species in the pH range 2–4 would be

H_3FcA and H_2FcA^-. If that is the case, no information is obtained about the reactivity of $HFcA^{2-}$ and FcA^{3-}.

The increase in rate with increasing pH also may be due to simple electrostatic interactions. The increase in rate due to the appearance of H_2FcA^- may be estimated according to[51]

$$\Delta G_{12}^* = \Delta G_{12}^{**} + \Delta G^w \qquad (21)$$

where ΔG_{12}^* is the free energy change for the measured cross-reaction rate, ΔG_{12}^{**} is the sum of the average free energy changes for the self-exchange reactions corrected for electrostatic work terms and ΔG_{12}° corrected for work terms, and ΔG_{12}^w is the work term for the assembly of the reagents in the cross reaction. From 7×10^{-8} cm as the distance between reactive centers, $\Delta G_{12}^w = -0.12$ kcal mol^{-1} at an ionic strength of 1.0 M. The acceleration of rate due to electrostatic effects is small and means that k_5 should be only slightly greater than k_4. For example, k_4 for reduction by europium(II) is 332 M^{-1} s^{-1}. On the basis of these arguments and assuming parameters other than charge on ferrichrome A remain constant, k_5 is calculated to be 5×10^2 M^{-1} s^{-1}. Comparing this value to the measured parameter k_2K_a yields $pK_a = 3.5$, which is a reasonable value. The same calculation done for the vanadium and chromium data yields $pK_a = 3.5$ and 3.0, respectively. Simple electrostatic effects are a plausible cause of the increase in rate of reduction of ferrichrome A by M(II) as the pH is increased over the range 2–4.

The pH dependence also may be due to protonation of an hydroxamate. This suggestion accounts for the presence of only two species in the pH range studied. Protonation of an hydroxamate of ferrioxamine B[17] or ferrichrome permits inner-sphere attack by chromium(II) and rapid electron transfer. The inner-sphere reactions of ferrioxamine B and ferrichrome are accelerated at lower pH. In contrast, the rate of reduction of ferrichrome A is accelerated at higher pH. Protonation of an hydroxamate of ferrichrome A apparently is not sufficient disruption of the complex to enable inner-sphere attack by even chromium(II). The decrease in rate with decreasing pH of the outer-sphere reaction then is ascribed to the decrease in thermodynamic driving force as an hydroxamate dissociates. Dissociation of an hydroxamate from the closely related ferrichrome complex occurs by an acid-independent pathway ($k = 0.11$ s^{-1}) and an acid-dependent pathway ($k = 3.0 \times 10^2$ M^{-1} s^{-1}). Ferrichrome A might be expected to dissociate an hydroxamate according to a similar mechanism with similar rate constants. Thus, rate-limiting behavior should be observed for the reaction in eq 5 under certain conditions. For example, at pH 3.5 formation of a protonated, dissociated hydroxamate of ferrichrome A should have a rate of about 0.2 s^{-1}. However, with a europium(II) concentration of 3.78 mM at 25 °C, the reaction of eq 5 proceeds at 1.25 s^{-1} with no indication of a rate-limiting process. This observation makes protonation of an hydroxamate an unlikely cause of the pH dependence of the rate of reduction of ferrichrome A by M(II) and leaves protonation of glutaconic acid as the likely explanation.

The Marcus equation[30] may be applied to the reaction of eq 12 by using a self-exchange rate of 1×10^6 M^{-1} s^{-1} for ferrichrome A as calculated above from the dithionite data. The self-exchange rates and E° values, respectively, are 2×10^{-6} M^{-1} s^{-1} and -0.42 V for chromium(II)/chromium(III), 4×10^{-4} s^{-1} and -0.38 V for europium(II)/europium(III), and 1.5×10^{-2} M^{-1} s^{-1} and -0.23 V for vanadium(II)/vanadium(III) (all of these values are taken from ref 35 and references cited therein). The Marcus equation is used to calculate E° for the iron(III)/iron(II) couple in ferrichrome A and yields -0.31, -0.24, and -0.30 V for the reactions with chromium(II), europium(II), and vanadium(II), respectively. However, the

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Table V. Effective Values of $(\Delta G_{11}{}^*)_{app}{}^{red}$

oxidant[a]	reductant	$(\Delta G_{11}{}^*)_{app}{}^{red}$, kcal mol^{-1}	$(\Delta G_{22}{}^*)_{app}{}^{ox}$, kcal mol^{-1}
V^{3+}	V^{2+}	16.8	16.8
FOB	V^{2+}	16.9	7.3
Fc	V^{2+}	20.6	6.6
FcA	V^{2+}	20.9	6.4
Eu^{3+}	Eu^{2+}	19.3	19.3
V^{3+}	Eu^{2+}	19.3	16.8
FOB	Eu^{2+}	15.0	7.3
Fc	Eu^{2+}	19.8	6.6
FcA	Eu^{2+}	21.6	6.4
Cr^{3+}	Cr^{2+}	22.5	22.5
Eu^{3+}	Cr^{2+}	22.5	19.3
FcA	Cr^{2+}	26.2	6.4

[a] Abbreviations: FOB = ferrioxamine B; Fc = ferrichrome; FcA = ferrichrome A.

reduction of ferrichrome A by a 10-fold excess of vanadium(II) goes to completion and indicates that E° for ferrichrome A must be more positive than that for vanadium(II). If, for example, we assume that the vanadium reaction goes to 99% completion, then the relationship

$$\Delta E^\circ = (RT/nF) \ln K \qquad (22)$$

predicts $E^\circ = -0.09$ V for ferrichrome A. This value is comparable to $E^\circ = -0.12$ V measured for ferrioxamine B at low pH.[29] Furthermore, an E° of about -0.30 V at pH 3 is unlikely considering $E^\circ = -0.28$ V at pH 5.7 as estimated from the dithionite data above and the increase in E° with proton concentration seen for other hydroxamate siderophores.[17,29] It therefore appears that the Marcus equation fails as applied to the reduction of ferrichrome A by M(II).

A more useful approach to Marcus correlations may be to write the Marcus equation in the form[35]

$$(\Delta G_{12}{}^*)_{app} = 0.5[(\Delta G_{11}{}^*)_{app} + (\Delta G_{22}{}^*)_{app} + \Delta G_{12}{}^\circ] \qquad (23)$$

This equation is applicable when $\Delta E^\circ < 0.5$ V. Corrections for charge effects are difficult to determine because of the uncertainty about the ferrichrome A species but should be small and will be ignored. This treatment requires that a value of E° for ferrichrome A at low pH be assumed. According to the same arguments advanced in the treatment of ferrichrome, we assume $E^\circ = -0.16$ V for ferrichrome A, but again the important conclusions are not dependent upon the exact value of E°. Equation 23 is solved to obtain an effective value of $(\Delta G_{11}{}^*)_{app}$ for the reductant. The values of $(\Delta G_{22}{}^*)_{app}$ for

the ferric siderophores are obtained from the reactions with $SO_2{}^-$. Table V gives the effective values of $(\Delta G_{11}{}^*)_{app}$ for the three metal ion reductants in their outer-sphere reactions with the ferric siderophores and includes data on metal ion self-exchange and cross reactions taken from ref 35 and references therein. The data for ferrichrome A refer to the rate constant k_4.

Table V shows that vanadium(II) has the same effective $(\Delta G_{11}{}^*)_{app}$ in its reduction of vanadium(III) as in its reduction of ferrioxamine B. This simply says that the Marcus equation works well in predicting the rate of reduction of ferrioxamine B by vanadium(II). The vanadium(II) reduction of ferrichrome or ferrichrome A, however, requires an increase of about 4 kcal/mol in $(\Delta G_{11}{}^*)_{app}$ for vanadium(II). The Marcus equation fails in these cases and demonstrates that considerably more activation is required. It is, of course, not proper or meaningful to assign all of that increase in activation energy to one of the reagents as in the present treatment, but again we find it is instructive to do so. Thus, compared to $SO_2{}^-$ (upon which the value of $(\Delta G_{22}{}^*)_{app}$ depends), vanadium(II) is an efficient reductant of ferrioxamine B but not a ferrichrome or ferrichrome A. The same is true for reduction by europium(II). The required activation energy for the reduction of ferrichrome or ferrichrome A increases by about 5 kcal/mol compared to the reduction of ferrioxamine B. Kinetic access by these metal ions to the outer-sphere electron-transfer active site in these two ferrichromes is significantly hindered compared to that in ferrioxamine B. There are two major structural differences between these ferrichromes and ferrioxamine B. The first is that each of the former has a cyclic base and the latter has a linear base, and the second difference is that in the former the hydroxamates are on appendages to the cyclic base and in the latter the hydroxamates are an integral part of the main chain. The strong peptide ring to chelate hydrogen bond referred to above may be an important factor. All of these differences may contribute to the differences in reactivity. The larger ion, Eu(II)(aq), also requires almost 2 kcal/mol more activation in its reduction of ferrichrome A than ferrichrome. The bulkier hydroxamate substituents on ferrichrome A presumably are responsible. Chromium(II) reduces only ferrichrome A by an outer-sphere mechanism so comparisons as made above are not possible. However, the very large value of $(\Delta G_{11}{}^*)_{app}$ for that reaction is about 3.5 kcal/mol larger than that for the chromium(II) reduction of chromium(III) or europium(III) and again indicates hindered access to the outer-sphere electron-transfer active site of ferrichrome A.

Table VI. Summary of Kinetic Data for Reduction of Iron(III) Siderophores

reductant	oxidant[a,b]	rate law	parameters[c]	proposed mech[d]
$SO_2{}^-$	FOB	$k[S_2O_4{}^{2-}]^{1/2}[FOB]$	$k = 3.5 \times 10^3$ M^{-1} s^{-1}	OS
$SO_2{}^-$	Fc	$k[S_2O_4{}^{2-}]^{1/2}[Fc]$	$k = 2.0 \times 10^4$ M^{-1} s^{-1}	OS
$SO_2{}^-$	FcA	$k[S_2O_4{}^{2-}]^{1/2}[FcA]$	$k = 9.8 \times 10^3$ M^{-1} s^{-1}	OS
Cr(II)	FOB	$k[Cr(II)][FOB]$	$k = 1.2 \times 10^4$ M^{-1} s^{-1}	IS
Cr(II)	Fc	$[(k_1 + k_2[H^+])k_3[Cr(II)][Fc]]/ [k_{-2} + k_3[Cr(II)]]$	$k_1 = 0.11$ s^{-1} $k_2 = 3.0 \times 10^2$ M^{-1} s^{-1} $k_3/k_2 = 1.9 \times 10^2$ M^{-1}	IS
Cr(II)	FcA	$(k_4 + k_5 K_a/[H^+])[Cr(II)][FcA]$	$k_4 = 11$ M^{-1} s^{-1} $k_5 K_a = 1.5 \times 10^{-2}$ s^{-1}	OS
Eu(II)	FOB	$k[Eu(II)][FOB]$	$k = 6.3 \times 10^4$ M^{-1} s^{-1}	OS
Eu(II)	Fc	$k[Eu(II)][Fc]$	$k = 8.6 \times 10^2$ M^{-1} s^{-1}	OS
Eu(II)	FcA	$(k_4 + k_5 K_a/[H^+])[Eu(II)][FcA]$	$k_4 = 3.3 \times 10^2$ M^{-1} s^{-1} $k_5 K_a = 0.15$ s^{-1}	OS
V(II)	FOB	$k[V(II)][FOB]$	$k = 6.3 \times 10^2$ M^{-1} s^{-1}	OS
V(II)	Fc	$k[V(II)][Fc]$	$k = 25$ M^{-1} s^{-1}	OS
V(II)	FcA	$(k_4 + k_5 K_a/[H^+])[V(II)][FcA]$	$k_4 = 31$ M^{-1} s^{-1} $k_5 K_a = 1.3 \times 10^{-2}$ s^{-1}	OS

[a] Abbreviations: FOB, ferrioxamine B; Fc, ferrichrome; FcA, ferrichrome A. [b] Ferrioxamine B data from ref 17, except FOB + Eu(II): Shorter, A. L., unpublished results. All other data are from this work. [c] 25 °C, pH ~6.8 for $SO_2{}^-$ reductions and pH ~2.6–4.0 for metal ion reductants. [d] OS, outer sphere; IS, inner sphere.

Note also that these deductions are not dependent upon the assumed value of $E°$ for ferrichrome or ferrichrome A. If we assume $E° = -0.23$ V (an impossibly low value because the reduction by vanadium(II) goes to completion) rather than $E° = -0.16$ V, then the values of $(\Delta G_{11}{}^*)_{\text{app}}$ for the metal ion reductions of the ferrichromes decrease by 1.6 kcal mol⁻¹. The demonstrated differences in reactivity remain. If we assume $E° = -0.12$ V (the measured value for ferrioxamine B at low pH), then the values of $(\Delta G_{11}{}^*)_{\text{app}}$ for the metal ion reductions of the ferrichromes increase by almost 1 kcal mol⁻¹.

Thus, the three hydroxamate siderophores ferrioxamine B, ferrichrome, and ferrichrome A display an interesting variety of electron-transfer reactivities even though their coordination geometries and redox potentials are quite similar. Table VI summarizes the kinetic data. Ferrioxamine B undergoes efficient outer-sphere electron transfer at a rate that is very well predicted by Marcus theory. This complex is also very labile and is susceptible to rapid reduction by chromium(II) via inner-sphere attack. The redox active site of ferrichrome is kinetically less accessible than that of ferrioxamine B to metal ion reductants. Outer-sphere electron transfer requires greater activation, and inner-sphere reduction is rate limited by slow dissociation of an hydroxamate from iron(III). Ferrichrome A has the least accessible redox active site. Even greater activation energies are required, and the inner-sphere pathway is unavailable. Parallel paths are operating in the reduction of ferrichrome A. Two species, which probably are H₃FcA and H₂FcA⁻, are reduced at similar rates. The different reactivity may be due to simple charge effects, or it may be due to association of M(II) with one carboxylate to produce a bridged outer-sphere redox mechanism. The small reductant SO₂⁻ interestingly shows similar reactivity with all three siderophore complexes. It apparently has nearly equal access to each of the three redox active sites.

The pH range employed in this study is somewhat limited. Reactions involving metal ion reductants were performed below pH 4.5 due to the insolubility and unknown reducing properties of M(II) at higher pH. The lower limit of pH is dictated by the pK_a of about 1.5 for the dissociated bis(hydroxamato) complex.[39] The lower limit of pH is 2.6 so that the fully coordinated tris(hydroxamato)iron(III) siderophore complex was kept in at least 12-fold excess over the bis(hydroxamato) ferric siderophore complex. Nevertheless, we can provide partial characterization of the redox properties of the three iron(III) siderophore complexes. The reductant SO₂⁻ reduces each of the iron(III) siderophores with equal efficiency and suggests that if a common in vivo reductant exists, it is a small highly reactive species. Each of the complexes is capable of fast outer-sphere electron transfer with such a species. The effect of pH is most interesting. The iron(II)/iron(III) redox couple for each complex becomes more positive with increasing proton concentration. Reductive release of iron from the complexes therefore might be assisted by a mechanism that involves proton transfer or a high local proton concentration. Protonation also renders ferrioxamine B and ferrichrome susceptible to inner-sphere attack. In contrast, ferrichrome A is well insulated against inner-sphere reduction. Ferrichrome A carries a large charge that may contribute significantly to its redox characteristics.

Registry No. Cr, 7440-47-3; Eu, 7440-53-1; V, 7440-62-2; Fc, 15630-64-5; FcA, 15258-80-7; dithionite, 14844-07-6.

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High-Pressure Stopped-Flow Study of Complex Formation on Nickel(II) Ion in Dimethylformamide. Possible Existence of a 5-Coordinate Intermediate

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The complex formation of (thiocyanato)nickel(II) and bis(diethyldithiocarbamato)nickel(II) in dimethylformamide (DMF) has been studied as a function of temperature and pressure. The kinetic parameters obtained are $k_f{}^{298} = (3.1 \pm 0.2) \times 10^4$ M⁻¹ s⁻¹, $\Delta H_f{}^* = 66.0 \pm 1.0$ kJ mol⁻¹, $\Delta S_f{}^* = +62.7 \pm 3.7$ J K⁻¹ mol⁻¹, and $\Delta V_f{}^* = +8.8 \pm 0.5$ cm³ mol⁻¹ for the SCN⁻ reaction and $k_f{}^{298} = (3.03 \pm 0.03) \times 10^4$ M⁻¹ s⁻¹, $\Delta H_f{}^* = 62.0 \pm 0.4$ kJ mol⁻¹, $\Delta S_f{}^* = +48.8 \pm 1.3$ J K⁻¹ mol⁻¹, and $\Delta V_f{}^* = +12.4 \pm 0.2$ cm³ mol⁻¹ for Et₂DTC⁻. The discussion centers on whether to assign I_d or D mechanisms to nickel(II) complexation in DMF. Earlier work has shown that the DMF exchange rate is invariant with DMF concentration for exchange on Ni(DMF)₆²⁺ in DMF/nitromethane mixtures.[1] This fact and the above results are indicative of a D mechanism.

Introduction

In recent years, our kinetic interests have been mainly focused on the elucidation of the mechanisms that govern solvent exchange on divalent and trivalent transition-metal centers, in both aqueous[2,3] and nonaqueous media,[4,5] using high-

pressure NMR.[6] For the first-row transition-metal ions, it is now apparent that the mechanism for solvent exchange is not unique for all cations but changes from an associative activation mode for the early elements to a dissociative activation mode for the later ones.

We have recently extended our interests to the wider class of complex formation reactions on divalent cations. To this purpose, a high-pressure stopped-flow spectrophotometer was built and the formation of V(H₂O)₅SCN⁺ from V(H₂O)₆²⁺

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