Hydrolysis of Ferrioxamine B in Aqueous Micellar Solution

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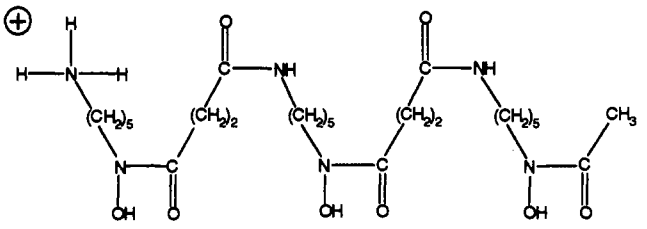
The association constant for the Fe(III) complex of the linear trihydroxamic acid siderophore ferrioxamine B ($FeHDFB^+$; $HDFB^{2-} = H_3N-[(CH_2)_5-N(O)C(O)-(CH_2)_2C(O)NH-)]_2(CH_2)_5-N(O)C(O)-CH_3$) binding to sodium dodecyl sulfate (SDS) micelles was determined by ultrafiltration and kinetic methods. Both methods are in agreement and yield an average value of the association constant $K_m = 98\ M^{-1}$. Association constants for the Al(III) analogue of ferrioxamine B, $AlHDFB^+$, and of the metal-free ligand deferriferrioxamine B, H_4DFB^+, were also determined by ultrafiltration and found to be $K_m = 90$ and $362\ M^{-1}$, respectively. Ion-exchange constants (K_{ex}) are calculated from K_m values [$K_{ex}(FeHDFB^+/Na^+) = K_{ex}(AlHDFB^+/Na^+) = 13$; $K_{ex}(H_4DFB^+/Na^+) = 46$] and are discussed in relation to K_{ex} for alkylammonium cations. Kinetic and thermodynamic parameters for the hydrolysis of ferrioxamine B in SDS solutions (0.01–0.15 M) at 25 °C have been obtained by stopped-flow and spectrophotometric titration methods at $I = 0.1$ M ($NaClO_4/HClO_4$, $NaNO_3/HNO_3$) over a $p[H^+]_{tot}$ range from 4.80 to 2.05. Good agreement is found between equilibrium constants determined by spectral and kinetic methods. Comparison with the parameters previously reported for the hydrolysis of $FeHDFB^+$ in aqueous acidic solution suggests that $FeHDFB^+$ resides in the Stern layer of the micelle, and consequently in a region of increased H^+ concentration. Once a correction is made for the higher $[H^+]$ in the Stern layer, kinetic and thermodynamic parameters obtained in the presence of SDS micelles agree well with those reported for the reaction in aqueous medium. This agreement also gives additional support to the K_m and K_{ex} values obtained by ultrafiltration and kinetics. Results reported here show that there is no micellar stabilization of the siderophore complex.

Introduction

Iron is an essential element for microbial growth. Microorganisms synthesize iron(III)-specific chelating agents (siderophores) that can solubilize iron from the environment by complexation and transport it to the cell. The mechanism for the release of the iron to the cell is still not fully understood and undoubtedly varies with siderophore structure and the microorganism. Iron may be released either at the cell wall or, after penetration into the cell, through exchange with other chelators, by means of molecular recognition through host–guest interaction, by hydrolysis of the siderophore ligand, and/or by reduction to a more labile iron(II) species.[1-4]

Biomimetic studies of membranes and membrane transport seek to illustrate fundamental principles governing the complex behavior of natural systems. This involves greatly simplified systems that either are derived from natural sources or are completely artificial.[5] Both types of models mimic either membrane structure or function in order to clarify the constraints placed on natural transport systems.[6] Micelles, by virtue of their structure, may be used to mimic aspects of both the structure and function of a biomembrane.[7] They may accommodate both hydrophobic chelators and host molecules. Iron–ligand exchange processes, and consequent release of the iron, may be facilitated through the cooperative action of the polar head groups in contact with the aqueous phase, hydrophobic contacts within the core of the micelle, or host–guest interactions.[8-11]

We recently undertook an investigation of iron(III) exchange between the hydrophilic siderophore deferriferrioxamine B (I)



deferriferrioxamine B, H_4DFB^+

I

and benzohydroxamic acid in aqueous micellar solution.[12] Parallel to this, experiments were done to establish and to characterize molecular recognition processes between the iron(III) complex and a crown ether host molecule leading to supramolecular assembly formation.[13] The combination of both of these processes, by introducing the supramolecular assembly into the micellar structure, may be used as a working model to elucidate a key feature of the biological iron-transport processes.

We have observed a shift in the equilibrium position and a rate enhancement relative to the corresponding reaction in aqueous medium for the iron(III)-exchange reaction between H_4DFB^+ and benzohydroxamic acid in the presence of SDS micelles.[12,14] The purpose of this report is to establish that in aqueous SDS micellar solutions the reactions of the iron(III) siderophore

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ferrioxamine B, $FeHDFB^+$, occur in the Stern layer of the micelle. In addition, we wish to establish whether the SDS micelle will influence the thermodynamic and kinetic stability of ferrioxamine B with respect to hydrolysis. The overall reaction of interest in this investigation is shown in eq 1. We have used ultrafiltration

$$Fe(H_2O)_6^{3+} + H_4DFB^+ \overset{SDS}{\rightleftharpoons} FeHDFB^+ + 3H_3O^+ + 3H_2O \quad (1)$$

techniques, and kinetics, to establish whether ferrioxamine B is associated with the SDS micellar surface, presumably within the Stern layer. We have also performed ultrafiltration experiments with the structurally similar Al(III) analogue of ferrioxamine B, $AlHDFB^+$, and the metal-free ligand, H_4DFB^+, in order to better understand the nature of the forces that cause the association of ferrioxamine B with the micellar surface. We have investigated the influence of pH on the equilibrium position and kinetics of eq 1. These data are interpreted in the context of the Hartley model[15,16] for micellar structure and the Bunton equation[17,18] to calculate the $[H^+]$ in the Stern layer. This enables us to establish whether the presence of the micellar pseudophase influences the thermodynamics and kinetics of eq 1.

The results presented here are of relevance to our work on the kinetics and thermodynamics of iron exchange from the hydrophilic carrier ferrioxamine B to the hydrophobic carrier tris(benzohydroxamato)iron(III) complex, incorporated in the micellar interior.[12,14] On the basis of literature data,[17-21] rate enhancement of this exchange process is readily understandable in terms of the increased $FeHDFB^+$ and H^+ concentrations in the Stern layer of the micellar pseudophase, thus causing the dechelation of the hexacoordinate complex even though the H^+ concentration in the aqueous phase is still too low for the reaction to occur appreciably. Initial ring opening of the hexadentate chelate is the first and crucial step in an iron-exchange reaction between these chelators of different hydrophilicities. Once the tetracoordinated ferrioxamine B iron(III) complex is formed, the exchanging ligand benzohydroxamic acid can readily coordinate to the iron, with immediate subsequent coordination of a second and a third benzohydroxamic acid.[12,14] Thus it is of utmost importance to identify the location of the ferrioxamine B in the aqueous micellar solution and to consider the thermodynamic and kinetic parameters in comparison with those of the same reaction in aqueous solution.[22,23]

Experimental Section

Materials. Sodium perchlorate ($NaClO_4 \cdot H_2O$; Aldrich, 99.99%) was recrystallized twice from water. Perchloric acid solutions were obtained by dilution of 70% perchloric acid (Fisher, ACS reagent) and standardization with 0.1 M NaOH. Sodium dodecyl sulfate (ICN, ultrapure >99%) was washed several times with anhydrous ethyl ether (Fisher, ACS reagent) and recrystallized twice from methanol (Fisher, ACS Certificated reagent). Ferrioxamine B solutions were made by dissolving deferriferrioxamine B (Sigma, methanesulfonate salt) in water, followed by the addition of iron(III) stock solution[24] and acid (either $HClO_4$ or HNO_3). The $FeHDFB^+$ solution was then carefully (to avoid iron hydrolysis) neutralized by adding NaOH up to the desired pH. Ionic strength was maintained at 0.1 M ($HNO_3/NaNO_3$, $HClO_4/NaClO_4$). The same procedure was applied to the preparation of the solution of $AlHDFB^+$, the Al(III) analogue of ferrioxamine B.[25,26] $AlHDFB^+$ concentration was determined through an exchange reaction with Fe(III) at $p[H^+] = 2.6$.[23] Al(III) stock solution was prepared by dissolving $Al(ClO_4)_3 \cdot 6H_2O$, 99.9% (Alfa) in 0.1 M $HClO_4$. All solutions were prepared by using water that was purified by distilling conductivity water from acidic $K_2Cr_2O_7$ and then slowly from basic $KMnO_4$ in all-glass apparatus with Teflon sleeves and stopcocks.

Amicon Diaflo ultrafilters, YM 1 and YM 5 with >1000 and >5000 MW cutoffs, respectively, were used with an Amicon 8M Micro ultrafiltration system.

Methods. Ultrafiltration using an Amicon 8M system was carried out under a pressure of 50 psi. Aqueous 0.01, 0.04, and 0.15 M SDS solutions of $FeHDFB^+$ were filtered through >1000 and >5000 MW cutoff filters. $FeHDFB^+$ concentrations were in the range 75 μM–1.5 mM. $p[H^+]_{tot}$ was 4.80, and ionic strength was kept at 0.1 M by $NaNO_3$.[27] The total H^+ concentration, $[H^+]_{tot}$, corresponds to the sum of the H^+ concentrations in the aqueous phase and in the Stern layer of the micellar pseudophase. $FeHDFB^+$ molar absorptivity ($\epsilon_{425nm} = 2600\ cm^{-1}\ M^{-1}$ [22]) is not influenced by micelles, and its concentrations in the retentate and the filtrate were determined spectrophotometrically. SDS concentrations in the filtrate and retentate were determined by measuring the absorbance at 636 nm of Azure A sulfonate that was extracted from the aqueous to the chloroform layer due to its hydrophobicity.[29] All absorbance readings were recorded using a Hewlett-Packard 8451 diode-array spectrophotometer. Ultrafiltration of $AlHDFB^+$ and H_4DFB^+ was also performed using a >1000 MW cutoff filter in aqueous and in 0.01 M SDS solution, in the range of $AlHDFB^+$ concentrations from 0.15 to 1.5 mM and the range of H_4DFB^+ concentrations from 0.6 to 1.2 mM. $p[H^+]_{tot}$ was 6.88 in the case of $AlHDFB^+$ and 5.60 in the case of H_4DFB^+. The concentration of H_4DFB^+ in the filtrate was determined spectrophotometrically by measuring the $FeHDFB^+$ formed by reaction with Fe(III) at $p[H^+] = 2.6$.[22,23] The concentration of $AlHDFB^+$ in the filtrate was determined through an exchange reaction with Fe^{3+} at $p[H^+] = 2.6$.[23]

Spectrophotometric titrations were carried out by the continuous addition of 0.1 M $HClO_4$ to a solution containing 0.30 mM Fe^{3+}_{tot} and 0.33 mM $H_4DFB^+_{tot}$ at $p[H^+]_{tot} = 4.80$. Both titrand and titrant solutions were of the same SDS concentration, either 0.01, 0.04, or 0.078 M. Ionic strength was kept at 0.1 M ($NaClO_4/HClO_4$). The same experiment was done in both the absence and the presence of SDS over a $p[H^+]_{tot}$ range from 4.80 to 1.32. The total H^+ concentration was calculated on the basis of the added amount of 0.1 M $HClO_4$ (microburet) and the H^+ concentration of the initial solution determined by means of a glass electrode. The glass electrode system was calibrated in 0.1 M $NaClO_4/HClO_4$ using the computer program MAGEC.[30] The titration was carried out in a water-jacketed cell, from which the solution was run by a peristaltic pump through the thermostated 1-cm cell. Electronic spectra were taken after equilibration upon each addition of acid using a Beckman ACTA III spectrophotometer that was interfaced to an OLIS data acquisition system. The stability constants were refined using the computer program SQUAD.[31]

In the kinetic experiments, a solution containing 0.30 mM Fe^{3+}_{tot} and 0.33 mM $H_4DFB^+_{tot}$, at $p[H^+] = 4.80$ and $I = 0.1$ M ($NaNO_3/HNO_3$ and $NaClO_4/HClO_4$), was mixed with micellar aqueous acidic solutions. Total H^+ concentrations of the micellar aqueous acidic solutions were varied from 6 mM to 0.1 M, $I = 0.1$ M ($NaNO_3/HNO_3$ and $NaClO_4/$

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$HClO_4$), and [SDS] was 0.300, 0.156, 0.080, and 0.020 M. The cmc for SDS at 0.1 M electrolyte concentration was estimated to be 1.5 mM from our kinetic experiments, both for $FeHDFB^+$ hydrolysis and for $FeHDFB^+$ exchange with benzohydroxamic acid.[14] This is consistent with literature reports.[32,33] All experiments were performed at SDS concentrations above the cmc. Some kinetic experiments were performed in which the $FeHDFB^+$ concentration was half of that used in all other experiments (75 μM), $[H^+]_{tot}$ was 1.5×10^{-2} M, and [SDS] was 0.04 M.

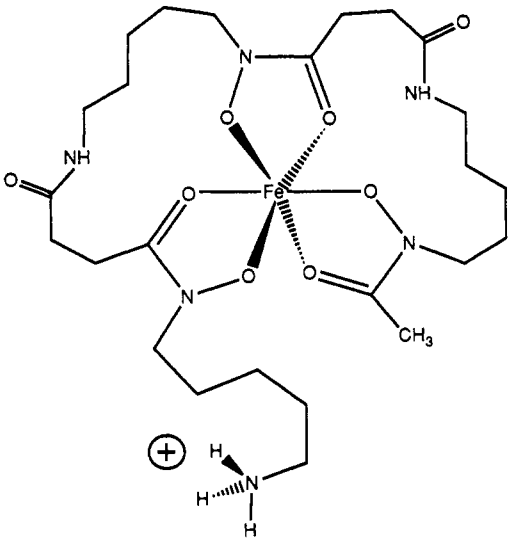
Kinetic experiments were also carried out to determine the $FeHDFB^+$ association constant for binding with the micellar phase, K_m. Kinetics of $FeHDFB^+$ hydrolysis were performed as described above at $[H^+]_{tot} = 1.5 \times 10^{-2}$ M and 3.5 mM in different [SDS] ranging from 0.01 to 0.09 M, $[Fe^{3+}]_{tot} = 0.15$ mM, $[H_4DFB^+]_{tot} = 0.165$ mM, and $I = 0.1$ M ($NaNO_3/HNO_3$).

Pseudo-first-order hydrolysis reactions were monitored by following the continuous decrease in absorbance at 425 nm using an Aminco stopped-flow apparatus interfaced to an OLIS data acquisition system. A nonlinear least-squares fitting program[34] was used to obtain the kinetic parameters reported. Parameters were calculated both by using kinetic data alone and by introducing the thermodynamic constants β_3/β_2, refined by SQUAD[31] calculations.

All data were obtained from at least three replicate experiments. Thermodynamic and kinetic experiments were done at 25 ± 0.1 °C, and ultrafiltration was done at 25 ± 0.5 °C.

Results

Micelle Association (K_m) and Exchange (K_{ex}) Constants. Ferrioxamine B, $FeHDFB^+$, due to its positive charge and structure which includes a free pendant protonated amine group (see **II**), may be expected to reside in the Stern layer of the SDS



ferrioxamine B, $FeHDFB^+$
(not intended to show stereochemistry)

II

micelle as a result of an electrostatic attraction to the negatively charged head group of the micellized dodecyl sulfate. This was qualitatively confirmed by ultrafiltration experiments of $FeHDFB^+$ solutions in the presence of SDS at concentrations above the cmc. Using a >5000 MW cutoff filter, the $FeHDFB^+$ was found in the retentate when the SDS concentration was above the cmc and in the filtrate when the SDS concentration was below the cmc. The cmc for SDS in 0.1 M $NaNO_3$, taken as 1.5 mM (see Experimental Section), was not affected by $FeHDFB^+$, as determined by measuring SDS concentrations in the filtrate and retentate. Also, no interaction of $FeHDFB^+$ with SDS monomers below the cmc (0.70 mM) was detected. This is consistent with equilibrium reaction 2 describing $FeHDFB^+$ association with the sulfate head groups of SDS micelles and presumably residing in the Stern layer.

$$FeHDFB^+_{aq} + SDS_{micelle} \overset{K_m}{\rightleftharpoons} (FeHDFB^+\cdot SDS)_{micelle} \quad (2)$$

The association between ferrioxamine B and micellized surfactant was quantified by measuring the ratio of ferrioxamine B concentration in the retentate to its concentration in the filtrate ($[FeHDFB^+]_{ret}/[FeHDFB^+]_{fil}$) as a function of [SDS] and [$FeHDFB^+$] using a >1000 MW cutoff filter. The same experiments were also performed to quantify $AlHDFB^+$ and H_4DFB^+ association with micellized surfactant.

In blank experiments (no SDS present) we observed that a certain amount of the species of interest was rejected by the >1000 MW cutoff filter. This may be due to the high molecular weights (MW = 803, 774, and 658 for $FeHDFB^+$, $AlHDFB^+$, and H_4DFB^+, respectively), bulky structure, and the possibility for intermolecular H-bonding. We determined retention factors of 2.00 for $FeHDFB^+$, 1.92 for $AlDFB^+$, and 1.75 for H_4DFB^+. The retention factor is defined as the ratio of initial concentration to filtrate concentration; *e.g.*, a retention factor 2.00 means that 50% of the molecules are allowed to pass through the filter and a retention factor of 1.00 means there is no retention. The retention factor was used as a correction factor in the experiments with micellar solutions. Namely, the experimentally obtained filtrate concentrations were multiplied by given retention factors in order to obtain the true $[FeHDFB^+]_{fil}$, $[AlHDFB^+]_{fil}$, and $[H_4DFB^+]_{fil}$. This correction worked best for the very dilute micellar solution, *i.e.* 0.01 M SDS, since the results obtained under these conditions correlate well with the micelle association constant (K_m) determined kinetically under a wide range of SDS concentrations.

The >1000 MW cutoff filter did not allow micellar aggregates to pass through, as determined by separate experiments using laurohydroxamic acid that is completely associated with the micellar phase. On the other hand, if a >5000 MW cutoff filter was used, the SDS concentration in the filtrate was found to be 4.5 mM, significantly above the cmc. This resulted in a difference between K_m values determined by >1000 and >5000 MW cutoff filters. It is difficult to distinguish accurately between free $FeHDFB^+$ in the filtrate and that which is associated with smaller micellar aggregates. Thus the use of >5000 MW cutoff filters was abandoned for quantitative K_m determinations.

The equilibrium constant (K_m) for reaction 2 may be expressed as eq 3, where $[SDS]_{micelle}$ corresponds to ($[SDS]_{total}$ – cmc) and

$$K_m = [FeHDFB^+\cdot SDS]_{micelle}/\{[FeHDFB^+]_{aq}[SDS]_{micelle}\} \quad (3)$$

$K_m = K/N$, where N is the aggregation number of the micelle and K is the binding constant in terms of micellar aggregates. A rearranged form of eq 3 predicts a plot of $[FeHDFB^+\cdot SDS]_{micelle}/[SDS]_{micelle}$ *vs* $[FeHDFB^+]_{aq}$ to be linear over a range of ferrioxamine B concentrations, as shown in Figure 1. After necessary corrections were made for retention of ferrioxamine B by the filter, the ferrioxamine B in the retentate corresponds to $[FeHDFB^+\cdot SDS]_{micelle}$ and that in the filtrate to $[FeHDFB^+]_{aq}$. This allows us to calculate an association constant (K_m) for ferrioxamine B binding with micellized surfactant from the slope of the plot in Figure 1 (see Table 1). Since the calculation includes the corrections for the retention of aqueous $FeHDFB^+$ by the >1000 MW cutoff filter in a 0.01 M micellar solution, the K_m value given in Table 1 may be considered as a lower limit for the

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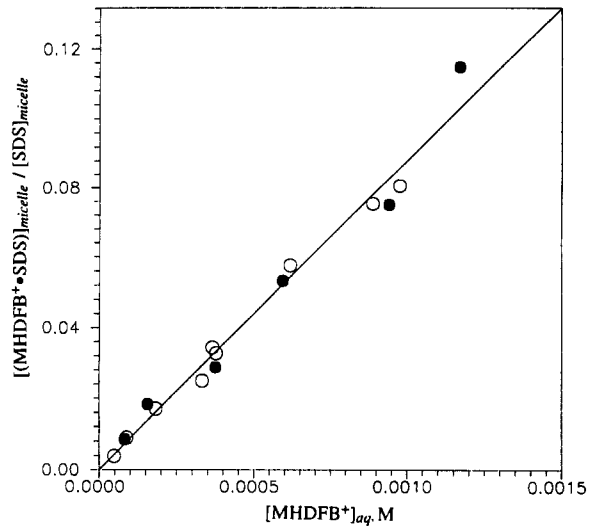

Figure 1. Plot of $[MHDFB^+{\cdot}SDS]_{micelle}$ / $[SDS]_{micelle}$ *vs* $[MHDFB^+]_{aq}$ according to eq 3. M = Fe(III) (open circles), and Al(III) (full circles). Data were obtained by ultrafiltration through a >1000 MW cutoff Amicon filter at 50 psi. Conditions: $[SDS]_{tot}$ = 0.01 M; I = 0.1 M ($NaNO_3$/HNO_3). The calculation of $[MHDFB^+]_{aq}$ and $[(MHDFB^+{\cdot}SDS)]_{micelle}$ includes a correction of the experimentally measured $[MHDFB^+]_{fil}$ by the retention factor defined under Results.

Table 1. Micelle Association (K_m) and Exchange (K_{ex}) Constants As Defined by Eqs 3 and 4[a]

cation	K_m/M^{-1}	K_{ex}(cation/Na^+)
Na^+, H^+	8[b]	1[c]
NH_4^+	14[b]	1.9[b]
$FeHDFB^+$	86(2)	13
	110(8)[d]	
$AlHDFB^+$	90(4)	13
H_4DFB^+	362(19)	46

[a] The values in parentheses represent one standard deviation. [b] Reference 38. [c] Reference 17. [d] Determined in this laboratory by kinetic measurement; all other values determined in this laboratory by ultrafiltration equilibrium measurements.

$FeHDFB^+$·SDS binding constant. Data are also shown in Figure 1 for $AlHDFB^+$, and K_m values for $AlHDFB^+$ and H_4DFB^+ are listed in Table 1.

These ultrafiltration experiments and resulting K_m values quantitatively demonstrate that $FeHDFB^+$, $AlHDFB^+$, and H_4DFB^+ reside in the Stern layer of the micelle. For example, at 0.04 and 0.078 M SDS concentrations at least 77 and 87%, 77 and 87%, and 93 and 97% of the total $FeHDFB^+$, $AlHDFB^+$, and H_4DFB^+ concentrations, respectively, reside in the Stern layer.

Micelles may be used to scavenge cations in several different ways in order to remove them from solution. Cation selectivity may be achieved in the removal process by complexation with a hydrophobic ligand that is incorporated into the micellar interior.[35-37] The micellar surface can also act as a selective ion exchanger.[7,38] For example, at the negatively charged head group of the micellized SDS surfactant, metal cations may be exchanged with Na^+ either as hydrated ions[39] or through the exchange of a positively charged metal–ligand complex. Thus, the association of $FeHDFB^+$ with the SDS micellar surface is essentially based on its exchange with Na^+ ions in the Stern layer. An exchange constant, K_{ex}, may be defined as shown in eq 4.[7,38] Assuming

$$K_{ex}(FeHDFB^+/Na^+) = K_{ex}(H^+/Na^+)/K_{ex}(H^+/FeHDFB^+) = ([FeHDFB^+]_m[Na^+]_{aq})/([Na^+]_m[FeHDFB^+]_{aq}) \quad (4)$$

$K_{ex}(H^+/Na^+) = 1$,[17] then eq 4 reduces to eq 5, where $K_{ex}(H^+/$

$$K_{ex}(FeHDFB^+/Na^+) = 1/K_{ex}(H^+/FeHDFB^+) \quad (5)$$

$FeHDFB^+$) is defined in eq 6. Equations 4–6 are also valid for

$$K_{ex}(H^+/FeHDFB^+) = ([H^+]_m[FeHDFB^+]_{aq})/([FeHDFB^+]_m[H^+]_{aq}) \quad (6)$$

Na^+-exchange processes involving $AlHDFB^+$ and H_4DFB^+. Equations 7a and 7b[17-20] were used to calculate both the H^+ and

$$[H^+]_m = 0.82[H^+]_{tot}/\{0.15([H^+]_{tot} + [Na^+]_{tot}]\} \quad (7a)$$

$$[H^+]_{aq} = [H^+]_{tot} - \{0.82[H^+]_{tot}([SDS] - cmc)/([H^+]_{tot} + [Na^+]_{tot})\} \quad (7b)$$

Na^+ concentrations in the micellar and aqueous pseudophases. Other cationic species such as $FeHDFB^+$, $AlHDFB^+$, and H_4DFB^+ are present at low concentrations compared to $[Na^+]_{tot}$ and do not appreciably influence the denominator term of eqs 7a and 7b. Therefore, they may be neglected when either $[H^+]_m$ and $[H^+]_{aq}$ or $[Na^+]_m$ and $[Na^+]_{aq}$ are calculated. The $[H^+]_m$ and $[H^+]_{aq}$ values from eqs 7a and 7b and K_m values from eq 3 needed to calculate the $FeHDFB^+$, $AlHDFB^+$, and H_4DFB^+ concentrations in both phases were used in order to obtain the K_{ex} values listed in Table 1. Literature values for $K_{ex}(NH_4^+/Na^+)$[38] and $K_{ex}(Na^+/H^+)$[17] were used to calculate K_m for NH_4^+, Na^+, and H^+ association with the micellar pseudophases. These literature values are included in Table I for the purpose of comparison.

Ferrioxamine B Hydrolysis Equilibria. The addition of solutions of $FeHDFB^+$ at neutral pH to solutions of various acidities (>0.005 M H^+) results in a shift in the absorbance maximum of ferrioxamine B to longer wavelength.[22,23] This is interpreted in terms of different degrees of overall ligand dissociation, as illustrated in eqs 8–10, where coordinated H_2O is omitted for

$$FeHDFB^+ + H^+ \rightleftharpoons FeH_2DFB^{2+} \quad (8)$$

$$FeH_2DFB^{2+} + H^+ \rightleftharpoons FeH_3DFB^{3+} \quad (9)$$

$$FeH_3DFB^{3+} + H^+ \rightleftharpoons Fe^{3+} + H_4DFB^+ \quad (10)$$

clarity.[22,23] This shift in ferrioxamine B absorption spectra to longer wavelengths is also observed in aqueous acidic solutions containing SDS micelles, as shown in Figures 2 and 3.

Acid titration experiments were carried out by adding increments of H^+ to an aqueous solution of $FeHDFB^+$ containing 0.00, 0.01, 0.04, and 0.078 M SDS. A sample plot in Figure 2 shows the spectral shift which occurs upon addition of acid to an $FeHDFB^+$ solution containing 0.04 M SDS to change the total $[H^+]$ of the solution from 15.8 μM to 8.95 mM $HClO_4$. The isosbestic point at 475 nm in Figure 2 corresponds to that observed for the hydrolysis reaction in aqueous solution[22,23] and illustrates a shift in equilibrium 8 between the hexacoordinate and tetracoordinate ferrioxamine B complexes with a change in total $[H^+]$. Spectral changes similar to those shown in Figure 2 were also observed in the presence of 0.01 and 0.078 M SDS. Figure 3 represents an overlay of spectral traces obtained after 0.4 mL

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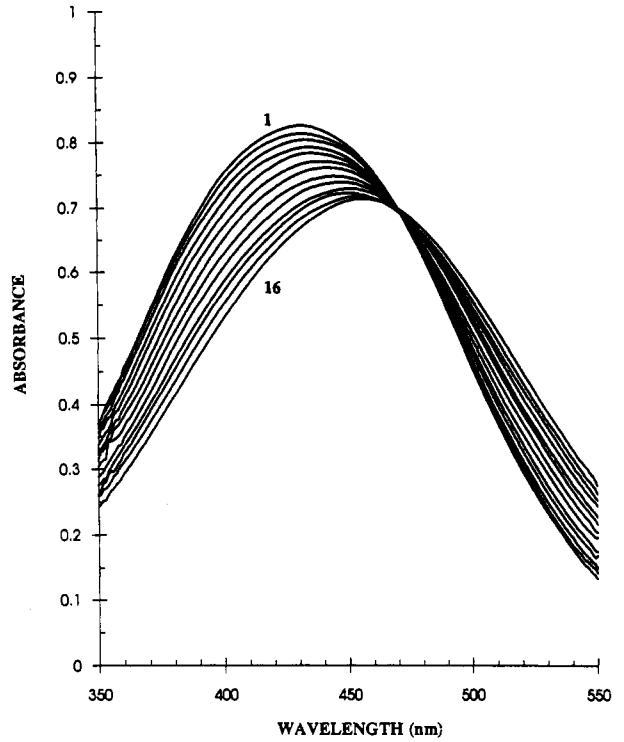

Figure 2. Equilibrium spectra obtained by the addition of $HClO_4$ to $FeHDFB^+$ in the presence of 0.04 M SDS. Conditions: $[Fe^{3+}]_{tot}$ = 0.30 mM, $[H_4DFB^+]_{tot}$ = 0.33 mM, I = 0.1 M ($NaClO_4/HClO_4$), optical path length = 1 cm. Different curves represent different equilibrium total $[H^+]$ from 15.8 μM (curve 1) to 8.95 mM (curve 16).

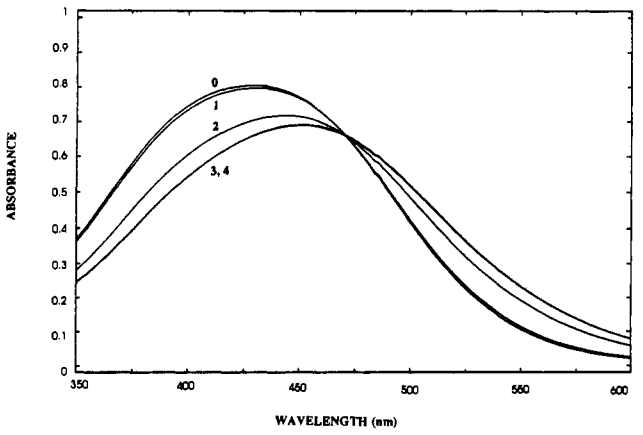

Figure 3. Equilibrium spectra obtained by the addition of 0.4 mL of 0.10 M $HClO_4$ to $FeHDFB^+$ in the absence of SDS micelles (curve 1) and in 0.01 M SDS (curve 2), 0.04 M SDS (curve 3), and 0.078 M SDS (curve 4). Conditions: $[Fe^{3+}]_{tot}$ = 0.29 mM, $[H_4DFB^+]_{tot}$ = 0.32 mM, $p[H^+]_{tot}$ = 2.40; I = 0.1 M ($NaClO_4/HClO_4$), optical path length = 1 cm. Spectrum 0 corresponds to the same conditions as curve 1, except $p[H^+]_{tot}$ = 4.80.

of 0.10 M $HClO_4$ was added to a $p[H^+]_{tot}$ 4.80 solution of $FeHDFB^+$ in the presence of 0.00, 0.01, 0.04, and 0.078 M SDS.

Comparison of Figures 2 and 3 confirms that the spectral shift and isosbestic point observed upon addition of H^+ to $FeHDFB^+$ in the presence of constant SDS concentration (Figure 2) may also be observed by the addition of SDS to a $FeHDFB^+$ solution at a constant total H^+ concentration (Figure 3). By increasing the total H^+ concentration at a constant SDS concentration, we are increasing the H^+ concentration at the micellar pseudophase, where a constant fraction of the total $FeHDFB^+$ is located (Figure 2). By increasing the SDS concentration from 0.010 to 0.078 M (Figure 3), we are increasing the fraction of micellar-bound $FeHDFB^+$ from 42 to 87% as given by K_m = 86 M^{-1}, while at the same time decreasing the micellar-bound-H^+ concentration from 0.19 to 0.12 M (eq 7a). These are two opposing effects, but the increased association of $FeHDFB^+$ with the micellar surface is dominant, which accounts for the position of the spectra shown in Figure 3. Both series of experiments thus illustrate that the equilibrium position of reaction 8 may be shifted by a change in total $[H^+]$ at a constant [SDS] or by a change in [SDS] at a constant total $[H^+]$.

Table 2. Equilibrium Parameters for Eqs 11–13[a]

	solution		
		micellar[c]	
param	aqueous[b]	$[H^+]_{tot}$[d]	$[H^+]_m$[e]
$\log \beta_3$	30.60[f]	28.20(3)	30.5(2)
$\log \beta_2$	31.54[f]	30.60(2)	31.2(1)
$\log K_a$	−0.94,[f] −1.01(4)[g]	−2.40(4)	−0.7(2)

[a] The values in parentheses represent one standard deviation. [b] Data obtained in aqueous solution in the absence of SDS micelles. [c] Data obtained in the presence of 0.04 M SDS over the $p[H^+]_{tot}$ range 4.80–0.17, $[Fe^{3+}]_{tot}$ = 0.30 mM, $[HDFB^+]_{tot}$ = 0.33 mM, I = 0.1 M ($NaClO_4/HClO_4$). [d] Parameters calculated using total $[H^+]$. [e] Parameters calculated using eq 7a to calculate the $[H^+]_m$ in the Stern layer. [f] Reference 40. [g] Data from Table 3.

Table 3. FeH_2FDB^{2+} Dissociation Constants ($-\log K_a$) for Reaction 13 in Aqueous Solution and Aqueous SDS Solution[a]

	[SDS]/M			
	0.01	0.04	0.078	0
$-\log K_a$ calcd using $[H^+]_{tot}$	2.09(2)	2.39(1)	2.43(1)	1.01(4)
$-\log K_a$ calcd using $[H^+]_m$	0.35(2)	0.78(1)	1.01(2)	

[a] Conditions: $[Fe^{3+}]_{tot}$ = 0.30 mM, $[H_4DFB^+]_{tot}$ = 0.33 mM, I = 0.1 M ($NaClO_4/HClO_4$). All data were obtained in the $p[H^+]_{tot}$ range from 4.80 to 1.32. The total H^+ concentration was calculated on the basis of the added amount of 0.1 M $HClO_4$ (microburet) and the H^+ concentration of the initial solution determined by means of a glass electrode which was calibrated in 0.1 M $NaClO_4/HClO_4$ using the computer program MAGEC. The values in parentheses represent one standard deviation.

The hexacoordinate to tetracoordinate ferrioxamine B hydrolysis step (eq 8) may be described by eqs 11–13. Due to the

$$Fe^{3+} + HDFB^{2-} \rightleftharpoons FeHDFB^+ \quad \beta_3 \qquad (11)$$

$$Fe^{3+} + H^+ + HDFB^{2-} \rightleftharpoons FeH_2DFB^{2+} \quad \beta_2 \qquad (12)$$

$$FeH_2DFB^{2+} \rightleftharpoons FeHDFB^+ + H^+ \quad K_a = \beta_3/\beta_2 \qquad (13)$$

high stability of the ferrioxamine B complex, the dissociation to the dicoordinate species (eq 9), and to the free metal (eq 10) requires an extremely high $[H^+]$. However, the micelle can provide such conditions within the Stern layer at moderately high aqueous $[H^+]$. Experimental conditions necessary to produce sufficient uncomplexed Fe^{3+} (0.04 M SDS over a $p[H^+]_{tot}$ range from 4.80 to 0.17) were used so that β_2 and β_3 could be estimated without significant inaccuracy due to the increased ionic strength (Table 2). Literature values for these same parameters obtained in aqueous acidic solution in the absence of micelles are also listed in Table 2.[22,23,40] In all other experiments the titrations were carried out in the $p[H^+]_{tot}$ region from 4.80 to 2.05 in aqueous micellar solutions and from $p[H^+]_{tot}$ 4.80 to 1.32 in aqueous solution, and the calculations of K_a values were done by keeping β_2 at a fixed value while β_3 was refined. The K_a values (listed as $-\log K_a$) obtained at various [SDS] are presented in Table 3.

Significantly lower values were calculated for β_3, β_2, and K_a in aqueous micellar solutions than in aqueous solution when the total $[H^+]$ was assumed to be the environment for dechelation of $FeHDFB^+$ (column 3, Table 2). Due to the negative charge on the dodecyl sulfate head groups which comprise the micelles,

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H^+ ions are expected to be attracted to the micellar surface, into the Stern layer.[17-21,41,42] Consequently, the H^+ concentration may be significantly higher in the Stern layer than in the aqueous phase.

The Stern layer H^+ concentration is affected by the presence of cations in the aqueous phase ($FeHDFB^+$, H^+, Na^+), particularly Na^+ in our system, since it is present in excess over other cations. The empirical eq 7a has been proposed to calculate the $[H^+]_m$ in the Stern layer of an aqueous micellar solution.[17-20] The validity of this equation is based on the following assumptions:[17] (1) that 82% of the surfactant head group charge for an anionic micelle is neutralized by the counterions in the Stern layer, (2) that there is essentially no difference in binding Na^+ and H^+ ions in the Stern layer, and (3) that low concentrations of $FeHDFB^+$ will not influence Na^+ and H^+ binding in the Stern layer. Hydrogen ion concentrations in the Stern layer, calculated from eq 7a, were used to refine the stability constants given in Table 2 (column 4). These refined constants are in excellent agreement with parameters found in our laboratory in aqueous solution and reported in the literature.[22,23,40] These observations lead us to conclude that $FeHDFB^+$ is exposed to an increased $[H^+]$ in SDS micellar solution relative to the aqueous solution. Therefore, this suggests that, at a given SDS concentration well above the cmc, the complex resides in the Stern layer.

Table 3 presents our results for the equilibrium constant calculations for reaction 13 in the presence of various SDS concentrations. The differences between the pK_a value for eq 13 obtained in aqueous solution in the absence of SDS (1.01; Table 3) and that calculated in the presence of SDS using the $p[H^+]_{tot}$ are consistent with (1) the $p[H^+]$ difference between the aqueous phase and that calculated for the Stern layer using eqs 7a and 7b and (2) the fraction of micellar-bound $FeHDFB^+$. Comparison of the pK_a values for reaction 13 (Table 3) in the presence of micellized surfactant suggests that, at 0.01 M SDS, a significant amount of $FeHDFB^+$ is not associated with micellar surface, while, at SDS concentrations >0.04 M, essentially all of the $FeHDFB^+$ complex resides in the Stern layer where hydrolysis is occurring. This is consistent with the results of our ultrafiltration experiments. These observations support the application of eqs 7a and 7b[17-20] to our experimental conditions.

Ferrioxamine B Hydrolysis Kinetics. The kinetics of ferrioxamine B hydrolysis was found to proceed up to 30 times faster when SDS micelles were added to the aqueous acidic solution, depending on acidity and SDS concentration. Four kinetically distinguishable stages were observed for the hydrolysis of $FeHDFB^+$ in aqueous solution containing micellized surfactant. This is consistent with the four stages which were also observed for this reaction in the absence of micelles.[22,23] The first step, which is represented by reaction 14 and which is the reverse of

$$FeHDFB^+ + H^+ \rightleftharpoons FeH_2DFB^{2+} \qquad k_1, k_{-1}, K_a^{-1} \quad (14)$$

$$FeH_2DFB^{2+} \rightleftharpoons FeH_2DFB^{2+*} \qquad k_2, k_{-2}, K_2 \quad (15)$$

reaction 13, is very fast on the stopped-flow time scale and thus cannot be determined without a significant experimental error. Reaction 15 corresponds to the $[H^+]$-independent path previously reported in aqueous solution.[22,23] The product of reaction 15 is an intermediate between tetracoordinate and dicoordinate ferrioxamine B, whose structure has been discussed previously.[22,23,43]

The combination of reactions 14 and 15 was monitored by the pH jump method to establish the influence of SDS micelles on $FeHDFB^+$ dechelation kinetics. The approach to equilibrium is first order. The k_{obs} vs $[H^+]_m$ profile is given in Figure 4 for the reaction in the presence of 0.04, 0.078, and 0.15 M SDS. The data shown in Figure 4 are consistent with eq 16, which is expected

$$k_{obs} = \{k_2 K_a^{-1}[H^+]/(1 + K_a^{-1}[H^+])\} + k_{-2} \quad (16)$$

for the combination of reactions 14 and 15.[22,23] As illustrated in Figure 4, the same kinetic profile was obtained when the SDS concentrations were 0.04, 0.078, and 0.15 M, when either nitrate or perchlorate ions were present as the supporting electrolyte anion, and when the $[FeHDFB^+]$ was varied by a factor of 2 over the range from 75 μM to 0.15 mM.

The data shown in Figure 4 were used to calculate kinetic parameters using both total ($[H^+]_{tot}$) and Stern layer ($[H^+]_m$) hydrogen ion concentrations in the same manner as described above for the equilibrium experiments. The calculated parameters are given in Table 4. The parameters k_2, k_{-2}, and K_2 in micellar solution, which are calculated assuming that the $[H^+]$ which is operative is that given by eq 7a for the Stern layer, are in reasonable agreement with those obtained in aqueous solution, considering the multiple dechelation steps that are difficult to time resolve at higher $[H^+]$. Again, the K_a given in the literature[22,23] for

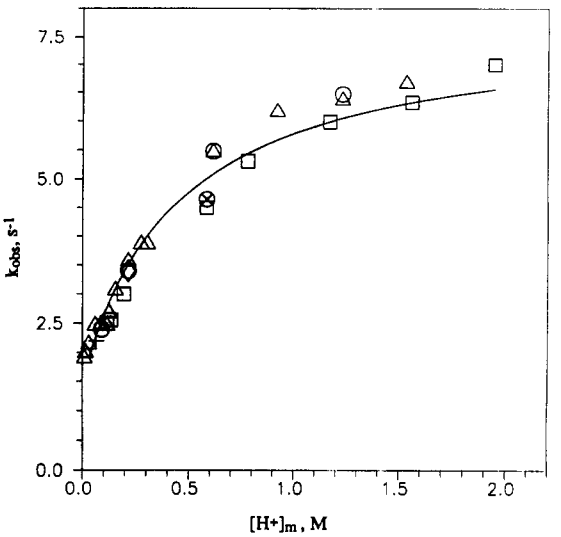

Figure 4. Plot of the observed pseudo-first-order rate constant, k_{obs}, for reactions 14 and 15 as a function of Stern layer $[H^+]_m$, calculated by eq 7a. Solid line represents a nonlinear least-squares fit of eq 16 to the data. Conditions: T = 25.0 °C, λ = 425 nm. For point ×, $[Fe^{3+}]_{tot}$ = 75 μM, $[H_4DFB^+]_{tot}$ = 83 μM, [SDS] = 0.04 M, and I = 0.1 M ($(HNO_3/NaNO_3)$). In all other experiments, $[Fe^{3+}]_{tot}$ = 0.15 mM, $[H_4DFB^+]_{tot}$ = 0.165 mM, [SDS] = 0.040 M (squares), 0.078 M (triangles), and 0.15 M SDS (cross), and I = 0.1 M ($HNO_3/NaNO_3$), except I = 0.1 M ($HClO_4/NaClO_4$) in both 0.04 M SDS (circles) and 0.078 M SDS (diamond).

Table 4. Kinetic Parameters for Reactions 14 and 15[a]

	solution		
		micellar[c]	
param	aqueous[b]	$[H^+]_{tot}$[d]	$[H^+]_m$[e]
K_a^{-1}/M^{-1}	5(1)/ 4.5(9)[g] 3.6(3)[h]	92(12)	2.2(2)
k_2/s^{-1}	14(5)/ 9.9(9)[g]	5.0(5)	6.7(5)
k_{-2}/s^{-1}	<3/ 2.6(1)[g]	1.7(5)	1.6(2)
K_2	4.7/ 3.9(9)[g]	2.9(3)	4.2(5)

[a] The values in parentheses represent one standard deviation. [b] Data obtained in aqueous solution in the absence of SDS micelles. [c] Data obtained in the presence of SDS micelles at concentrations described in the caption to Figure 4. [d] Parameters calculated using total $[H^+]$ as defined in the footnote to Table 3 and the Experimental Section. [e] Parameters calculated using eq 7a to calculate the $[H^+]_m$ in the Stern layer. [f] Reference 22; value obtained from kinetic data. [g] Reference 23; value obtained from kinetic data. [h] References 22 and 23; value obtained from spectral data.

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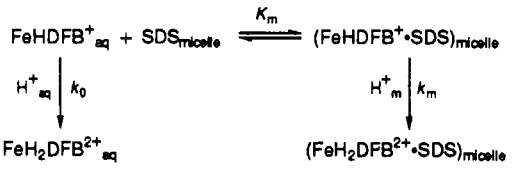
Scheme 1



aqueous solution differs on average by *ca.* 1.4 log units from the value obtained from our kinetic experiments in micellar solution when the total $[H^+]$ is assumed to be applicable. This difference corresponds to the $[H^+]$ increase in the Stern layer calculated using eq 7a. Consequently, good agreement between K_a obtained in the presence of SDS micelles and that obtained in aqueous solution is found when the Stern layer $[H^+]_m$ calculated from eq 7a is assumed to be applicable (see Table 4). The kinetic data are also in agreement with the equilibrium experiments and lead to the same conclusion that the hydrolysis reaction is actually occurring in a region where the H^+ concentration is higher than that measured in the aqueous phase, *i.e.* in the Stern layer. The fact that our kinetic results are independent of the electrolyte anion ($NaClO_4/HClO_4$ and $NaNO_3/HNO_3$) is consistent with the assumption that the hydrolysis reaction is occurring exclusively in the Stern layer, where no electrolyte anion influence is expected.

The reaction amplitudes in 0.04, 0.078, and 0.15 M SDS were essentially the same, and differences in k_{obs} correspond to a decrease in micellar H^+ concentration due to the increase in SDS concentration. In 0.01 M SDS a significant decrease in both the observed rate constant and amplitude (approximately 2-fold) was found. These observations are in agreement with the data obtained in both the equilibrium and ultrafiltration studies; that is, that at 0.01 M SDS less than 50% of $FeHDFB^+$ is in the aqueous phase while at ≥0.04 M SDS essentially all of the $FeHDFB^+$ is in Stern layer. The observed 2-fold increase in reaction amplitude upon going from 75 μM to 0.15 mM $FeHDFB^+$ further suggests that, at the conditions of our total $FeHDFB^+$ concentrations, the Stern layer can accommodate almost all of the aqueous $FeHDFB^+$.

A standard kinetic scheme has been proposed for micellar catalysis (Scheme 1),[44] where k_0 and k_m are the observed pseudo-first-order rate constants for $FeHDFB^+$ hydrolysis in the aqueous phase and micellar pseudophase, respectively. This scheme leads to eq 17, where k_1 is the observed pseudo-first-order rate constant

$$1/(k_0 - k_1) = 1/(k_0 - k_m) + \{N/(K(k_0 - k_m))\}\{1/([SDS]_{tot} - cmc)\} \quad (17)$$

for the reaction in aqueous micellar solutions of different SDS concentrations, K_m is K/N where K is the association constant expressed in terms of micellar aggregates, N is the aggregation number of the micelle, and $[SDS]_{tot}$ is the total surfactant concentration. The parameter k_0 is calculated from eq 16 using the kinetic parameters given in Table 4. A plot of $1/(k_0 - k_1)$ *vs* $1/([SDS]_{tot} - cmc)$, in which the cmc was taken as 1.5 mM and SDS was in the range 0.01–0.09 M, is linear and is shown in Figure 5. The rate parameter k_m was determined from the intercept of the plot. A K_m value calculated from the slope is given in Table 1 and agrees well with values obtained by equilibrium ultrafiltration measurements. This kinetic determination of K_m, together with the kinetic and equilibrium data, supports our conclusions concerning the location of $FeHDFB^+$ in the Stern layer.

Discussion

We have obtained data which demonstrate that $FeHDFB^+$ is attracted to the SDS Stern layer by electrostatic and possibly hydrophobic forces. Ultrafiltration and corresponding kinetic determination of micelle association and exchange constants are consistent with the interpretation that above 0.04 M SDS essentially all of the $FeHDFB^+$ resides in the Stern layer. Both equilibrium and kinetic data support this interpretation. When eq 7a is used to calculate the $[H^+]_m$ in the Stern layer, the kinetic and thermodynamic parameters are in agreement with the same parameters obtained in aqueous medium in the absence of micelles.

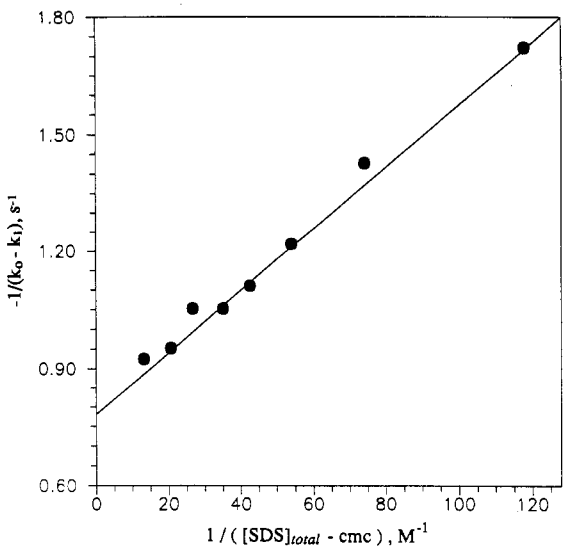


Figure 5. Plot of $1/(k_0 - k_1)$ *vs* $1/([SDS]_{tot} - cmc)$ according to eq 17. k_0 = observed pseudo-first-order rate constant for the reaction in the aqueous phase calculated using eq 16 and kinetic parameters from Table 4. k_1 = observed pseudo-first-order rate constant for the reaction in aqueous micellar solutions of different SDS concentrations. k_m = observed pseudo-first-order rate constant for the reaction in micellar phase determined from the intercept. Slope of the plot gives $N/(K(k_0 - k_m))$. Conditions: $[H^+]_{tot}$ = 3.5 mM, $[Fe^{3+}]_{tot}$ = 0.15 mM, $[H_4DFB^+]_{tot}$ = 0.165 mM, I = 0.1 M ($NaNO_3/HNO_3$).

Since $FeHDFB^+$, $AlHDFB^+$, and H_4DFB^+ are all structural derivatives of a substituted ammonium cation (see **I** and **II**), it is instructive to compare the K_{ex} values reported here with exchange constants for alkylammonium cations and Na^+ ions in SDS micelles. Alkylammonium ions bind more strongly to micelles than the parent ammonium or sodium ions. This may be seen by comparing $K_{ex}(RNH_3^+/Na^+)$ values for R = H (1.9), CH_3 (3.3), C_2H_5 (8.2), C_3H_7 (20), and C_4H_9 (70).[38] This trend may be rationalized by suggesting that a hydrophobic interaction between the alkylammonium chain and the micelle enhances K_{ex}.

The fact that $K_{ex}(FeHDFB^+/Na^+)$ and $K_{ex}(AlHDFB^+/Na^+)$ are equivalent is consistent with the similar structural features of the two complexes. The fact that $K_{ex}(MHDFB^+/Na^+) > K_{ex}(NH_4^+/Na^+)$ (Table 1; M = Fe, Al) suggests that hydrophobic interactions with the micelle contribute to $K_{ex}(MHDFB^+/Na^+)$. Any micellar model includes alkyl chains in intimate contact with water molecules. In the Menger and Doll model,[45] "rough" micelles are considered to have patches of different sizes and shapes which are rich in water and irregularly distributed along the surface. The transfer of an alkyl chain bearing counterion from the aqueous phase to the micellar surface will reduce unfavorable water–hydrophobic ion contacts by expelling water from the micelle, thereby decreasing water–surfactant alkyl chain interactions. The fact that $K_{ex}(MHDFB^+/Na^+)$ (M = Fe, Al) is intermediate between $K_{ex}(RNH_3^+/Na^+)$ for R = C_2H_5 and R = C_3H_7 (Table 1) suggests that the hexadentate complex at the end of a pentyl chain diminishes K_{ex}, perhaps because of steric factors or the hydrophilicity of the complex or because of both.

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At the micellar surface, complexes are probably hydrated in their second coordination shell.[46] However, the micelle does not distinguish between $FeHDFB^+$ and $AlHDFB^+$ as is observed for dicyclohexano-18-crown-6,[13] possibly due to the differences in the mechanism of association.

The fact that $K_{ex}(H_4DFB^+/Na^+) > K_{ex}(MHDFB^+/Na^+)$ may be viewed as being a consequence of H_4DFB^+ having a less sterically demanding linear structure, which compensates for the fact that we find the metal-free ligand to be less hydrophobic than the metal complex.[13] $K_{ex}(H_4DFB^+/Na^+)$ is intermediate between K_{ex} reported for propyl- and butylammonium cations.[38] That is less than expected for a pentyl chain bearing an ammonium cation, probably as a consequence of the hydrophilicity of the hydroxamate groups.[13] The fact that the metal-free ligand has a higher affinity for the Stern layer than the iron complex ($K_{ex}(H_4DFB^+/Na^+) > K_{ex}(FeHDFB^+/Na^+)$) also makes it reasonable to conclude that the entire hydrolysis process takes place in the Stern layer.

Since the stability constants β_3 and β_2 obtained in SDS micellar solution agree with data reported for aqueous solution[22,23,40] (see Table 2), there is apparently no stabilization or destabilization of the $FeHDFB^+$ complex due to hydrophobic or electrostatic interactions in Stern layer. In addition, the good agreement between kinetic and equilibrium parameters obtained in micellar solution (when corrected for Stern layer H^+ concentration) and corresponding parameters obtained in aqueous solution[22,23] suggests that the same mechanism for the hydrolysis of $FeHDFB^+$ is operative in both aqueous and micellar solution. Micellar catalysis of the process is thus solely due to the increase in H^+ concentration in the Stern layer (where metal complex and parent ligand are strongly attracted by the means of electrostatic and hydrophobic interactions), causing an increase in the hydrolysis rate of approximately 30-fold relative to that found in aqueous solution. This suggests that biomembranes, by virtue of their exterior polar groups, may attract metal complexes by electrostatic and/or hydrophobic interactions, and depending upon the nature of the possible receptors, ligand-exchange reactions may be initiated at the surface or within the membrane.

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