

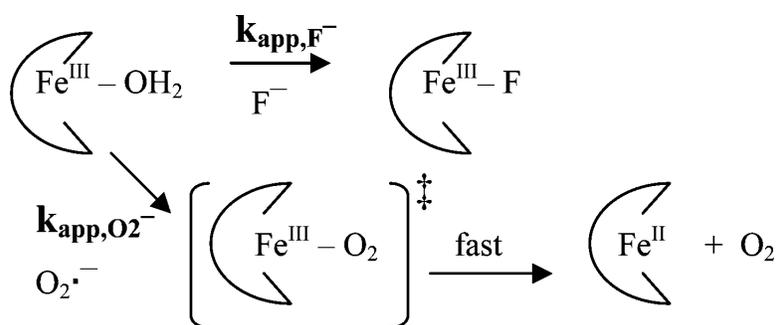
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Measured Rates of Fluoride/Metal Association Correlate with Rates of Superoxide/Metal Reactions for Fe^{III}EDTA(H₂O)⁻ and Related Complexes

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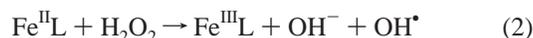
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Abstract: The effects of 10 paramagnetic metal complexes (Fe^{III}EDTA(H₂O)⁻, Fe^{III}EDTA(OH)²⁻, Fe^{III}PDTA⁻, Fe^{III}DTPA²⁻, Fe^{III}O(TTHA)²⁻, Fe^{III}(CN)₆³⁻, Mn^{II}EDTA(H₂O)²⁻, Mn^{II}PDTA²⁻, Mn^{II}β-EDDADP²⁻, and Mn^{II}PO₄⁻) on F⁻ 19F NMR transverse relaxation rates ($R_2 = 1/T_2$) were studied in aqueous solutions as a function of temperature. Consistent with efficient relaxation requiring formation of a metal/F⁻ bond, only the substitution inert complexes Fe^{III}(CN)₆³⁻ and Fe^{III}EDTA(OH)²⁻ had no measured effect on T_2 relaxation of the F⁻ 19F resonance. For the remaining eight complexes, kinetic parameters (apparent second-order rate constants and activation enthalpies) for metal/F⁻ association were determined from the dependence of the observed relaxation enhancements on complex concentration and temperature. Apparent metal/F⁻ association rate constants for these complexes (k_{app,F^-}) spanned 5 orders of magnitude. In addition, we measured the rates at which O₂^{•-} reacts with Fe^{III}PDTA⁻, Mn^{II}EDTA(H₂O)²⁻, Mn^{II}PDTA²⁻, and Mn^{II}β-EDDADP²⁻ by pulse radiolysis. Although no intermediate is observed during the reduction of Fe^{III}PDTA⁻ by O₂^{•-}, each of the Mn^{II} complexes reacts with formation of a transient intermediate presumed to form via ligand exchange. These reactivity patterns are consistent with literature precedents for similar complexes. With these data, both $k_{app,O_2^{•-}}$ and k_{app,F^-} are available for each of the eight reactive complexes. A plot of $\log(k_{app,O_2^{•-}})$ versus $\log(k_{app,F^-})$ for these eight showed a linear correlation with a slope ≈ 1 . This correlation suggests that rapid metal/O₂^{•-} reactions of these complexes occur via an inner-sphere mechanism whereas formation of an intermediate coordination complex limits the overall rate. This hypothesis is also supported by the very low rates at which the substitution inert complexes (Fe^{III}(CN)₆³⁻ and Fe^{III}EDTA(OH)²⁻) are reduced by O₂^{•-}. These results suggest that F⁻ 19F NMR relaxation can be used to predict the reactivities of other Fe^{III} complexes toward reduction by O₂^{•-}, a key step in the biological production of reactive oxygen species.

Introduction

Iron polyaminocarboxylate complexes are widely used to model reactivities of catalytic species involved in generating reactive oxygen species (ROS) in biological systems. The most studied of these are iron complexes of ethylenediamine tetraacetate (EDTA⁴⁻) and diethylenetriamine pentaacetate (DTPA⁵⁻, Figure 1).¹ These two complexes display substantially different behaviors in ROS generating systems: Whereas Fe^{III}EDTA(H₂O)⁻ catalyzes the production of ROS from superoxide and hydrogen peroxide according to eqs 1 and 2, Fe^{III}DTPA²⁻ does not.²



This difference in behavior arises due to the difference in the rates at which the complexes are reduced by O₂^{•-} (eq 1).² Whereas Fe^{III}EDTA(H₂O)⁻ reacts rapidly,³ reaction with Fe^{III}DTPA²⁻ is too slow to compete with O₂^{•-} dismutation.⁴ Because the Fe^{II} complex of DTPA⁵⁻ reacts with H₂O₂ to form ROS (eq 2),⁵ it is the Fe^{III} reduction step that limits the catalytic activity of this complex. If reduction of Fe^{III} complexes by O₂^{•-} is the limiting step in biological ROS production, then Fe^{III}/biomolecule complexes may be reasonable targets for therapeutic intervention in diseases where oxidative stress is a contributing factor.⁶ Targeting Fe^{III} reduction, however, will require knowl-

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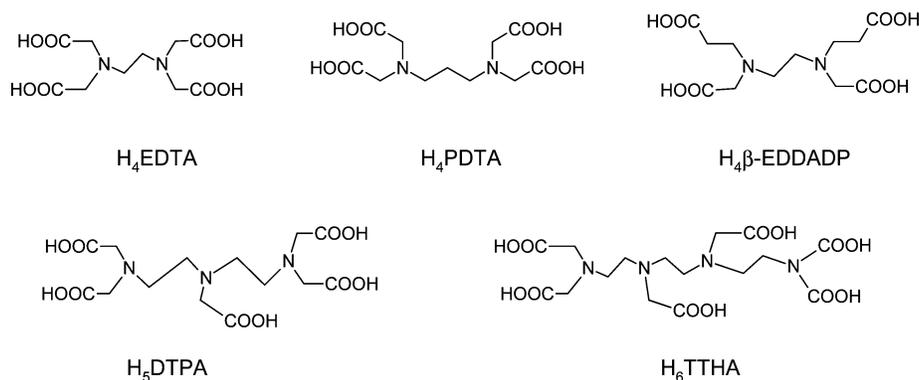


Figure 1. Structural formulas of chelating agents; H₄EDTA, H₄PDTA, H₄β-EDDADP, H₅DTPA, and H₆TTHA.

edge of the reaction mechanism. Although the kinetics of the Fe^{III}EDTA(H₂O)⁻/O₂^{•-} reaction were established more than 20 years ago,^{3,7} ambiguity still exists as to whether this reaction proceeds via direct coordination of O₂^{•-} to the iron center or via an outer-sphere mechanism. The difference in reactivities of O₂^{•-} toward Fe^{III}EDTA(H₂O)⁻ and Fe^{III}DTPA²⁻ has been cited as evidence that the iron(III)/O₂^{•-} redox reaction proceeds via an inner-sphere mechanism.² On the basis of the kinetic data, however, Bull et al.³ suggested an outer-sphere mechanism for the Fe^{III}EDTA(H₂O)⁻/O₂^{•-} reaction. This assignment was made because the rate constant for the reaction was approximately 10-fold larger than that predicted from the Eigen-Wilkins model.⁸ According to this model, the maximum value of the apparent second-order rate constant for an inner-sphere reaction (k_{\max}) is the product of the rate constant for solvent exchange at the metal complex (k_s) and the equilibrium constant for outer-sphere association of the anion with the metal complex (K_{OS}), eq 3:⁸

$$k_{\max} = k_s K_{OS} \quad (3)$$

The measured value of the k_s for Fe^{III}EDTA(H₂O)⁻ used in the outer-sphere assignment⁹ has recently been shown to be low by a factor of ~100.¹⁰ Using the more recent value of k_s and a value for K_{OS} from an electrostatic model,¹¹ eq 3 gives a value of k_{\max} that is 10-fold larger than the measured rate constant for the O₂^{•-}/Fe^{III}EDTA(H₂O)⁻ reaction. Thus, the best available data do not discount the possibility that reduction of Fe^{III}EDTA(H₂O)⁻ by O₂^{•-} occurs via an inner-sphere mechanism. Support for the outer-sphere mechanism is further eroded by the inability of the Marcus cross relation to account for differences in the rates at which metal complexes are reduced by O₂^{•-}. According to Marcus theory, second-order rate constants for outer-sphere reactions are determined by a number of variables, including the self-exchange rate constants (k_{11}) for the reacting redox partners. Although the value of k_{11} for the O₂^{•-}/O₂ self-exchange should be independent of which complex is used in its calculation, values calculated from data for reactions with Fe^{III}EDTA(H₂O)⁻ and Fe^{III}(CN)₆³⁻ differ by 11 orders of

magnitude.¹² In light of these inconsistencies, we believe the mechanisms of metal/O₂^{•-} redox reactions should be reexamined.

If O₂^{•-} reduces Fe^{III}EDTA(H₂O)⁻ and similar complexes via inner-sphere mechanisms, it is likely that ligand exchange is rate limiting. Under this condition, the rate of reaction is equal to the rate at which the metal comes into inner-sphere contact with O₂^{•-}. We set out to determine whether rates of metal/anion association correlate with rates of their reactions with O₂^{•-}. To this end, we have measured rates at which a variety of metal complexes associate with the redox-innocent anion, F⁻ (the forward reaction in eq 4) using paramagnetic NMR relaxation methods.



The effects of metal/ligand exchange on the relaxation of ligand nuclei were originally studied by Swift and Connick in 1962.¹³ Since that time, paramagnetic relaxation enhancement of solvent nuclei has been widely used to measure rates of solvent exchange at paramagnetic metal complexes.^{9,13-15} We recently reported metal/anion association kinetics for a variety of phosphate analogs measured using ³¹P NMR relaxation.^{16,17} We note that ¹⁹F relaxation enhancement has been used to determine F⁻ association kinetics at diamagnetic metal complexes.^{18,19}

We expected that F⁻ would be a suitable probe for studying metal/anion association kinetics at complexes of iron(III) and manganese(II). Because the ¹⁹F nucleus in transient metal/F⁻ complexes would be bound directly to the paramagnetic center, strong magnetic coupling between the observed nucleus and the paramagnetic center is expected to give rise to efficient transverse nuclear relaxation.^{14,20,21} This efficient relaxation is necessary for kinetic factors to govern relaxation rates by labile

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metal complexes.¹³ It has been demonstrated that ¹⁹F NMR resonance is extremely sensitive to transverse relaxation by superoxide dismutases enzymes (SODs).²² Because SODs are thought to act via inner-sphere coordination of O₂^{•-} to paramagnetic metal centers,²³ rapid T₂ NMR relaxation of the ¹⁹F nucleus by the enzymes is likely due to transient metal/F⁻ coordination at the active site of the enzyme.

Complexes of polyamine carboxylates were chosen for this study because of the availability of rate data for their reactions with O₂^{•-} and because of the significant variation in their reported ligand exchange reaction rates.¹⁰ Rate constants have been reported for reactions of O₂^{•-} with a variety of metal complexes, including: Fe^{III}CN₆³⁻,²⁴ Fe^{III}EDTA(H₂O)⁻,³ FeEDTA(OH)²⁻,^{3,25} Fe^{III}DTPA²⁻,⁴ Fe^{III}₂O(TTHA)²⁻,²⁶ Mn^{II}EDTA²⁻,^{27,28} and Mn^{II}PO₄⁻.²⁹ Recently aquo ligand exchange rates for a variety of Fe^{III} polyamine carboxylates have been measured by ¹⁷O NMR.¹⁰ This report indicated that aquo ligand exchange rates at Fe^{III} complexes of EDTA⁴⁻ and PDTA⁴⁻ (Figure 1) are very different despite the structural similarity of the complexes. We have measured the rates of metal/F⁻ association for each complex listed above and have measured rates at which both F⁻ and O₂^{•-} react with Fe^{III}PDTA⁻, Mn^{II}EDTA(H₂O)²⁻, Mn^{II}PDTA²⁻, and Mn^{II}EDDADP²⁻ (structural formulas of the chelates are presented in Figure 1). Our results support an inner-sphere mechanism for rapid reactions of these complexes with O₂^{•-}.

Experimental Section

All materials were of reagent grade or better and were purchased from standard commercial sources. Disodium ethylenediamine-*N,N,N',N'*-tetraacetate (Na₂H₂EDTA) was from Fisher. Propylenediamine-*N,N,N',N'*-tetraacetate (H₄PDTA) was from Akzo Nobel. Ethylenediamine-*N,N'*-diacetic-*β-N,N'*-dipropionic acid (H₄β-EDDADP) and triethylenetetraamine-*N,N,N',N',N'',N'''*-hexaacetic acid (H₆TTHA) were from Sigma, and diethylenetriamine-*N,N,N',N',N'',N'''*-pentaacetic acid (H₅-DTPA) and potassium hexacyanoferrate (K₃FeCN₆) were from Alpha Aesar. Sodium trifluoroacetate was prepared by neutralizing trifluoroacetic acid (Fisher) with sodium hydroxide. Fe^{III}₂(OTTHA)²⁻ was prepared by aerobic oxidation of a solution containing Fe^{II}(NO₃)₂ and H₆TTHA as described by Shepherd et al.³⁰ KFe^{III}PDTA was prepared by the method of Kanamori et al.³¹

Transverse relaxation times (T₂) were determined by the CPMG technique using a JEOL Eclipse 300 MHz NMR spectrometer. For each complex, data was measured at a minimum of four complex concentrations. ¹⁹F NMR relaxation rates were measured in aqueous (90% H₂O, 10% D₂O) solutions containing sodium fluoride (20 mM), an appropriate buffer (either EDTA, succinate, citrate, PIPES, Tris, or borate,

depending on pH), and metal complex at varying concentrations. The buffer concentration was 25 mM in all cases except for Fe^{III}PDTA⁻, where buffer was 10 mM. Association reactions of Fe^{III}EDTA(H₂O)⁻, Fe^{III}PDTA⁻, Fe^{III}₂OTTHA²⁻, and Mn^{II}PO₄⁻ were studied at pH 6 (buffered with succinic acid/sodium succinate) to minimize the effects of complex hydrolysis. Reactions of Mn^{II}EDTA⁻, Mn^{II}PDTA⁻, and Mn^{II}EDDADP⁻ were studied at pH 7 (PIPES). For most complexes, the maximum metal concentration used was that necessary to decrease T₂ relaxation times to between 8 and 60 ms. Relaxation enhancement by Fe(CN)₆³⁻ was investigated at complex concentrations up to 0.5 M. Relaxation enhancement by Fe^{III}PDTA⁻ was studied at concentrations up to 0.65 mM due to aggregation of this complex at higher concentrations. For studies of Fe^{III}EDTA(H₂O)⁻, Mn^{II}EDTA²⁻, Mn^{II}PDTA²⁻, and Mn^{II}β-EDDADP²⁻, solutions also contained excess chelate (5 mM). Samples of Mn^{II}PO₄⁻ were prepared by adding aliquots of a stock Mn^{II}(H₂O)₆²⁺ solution to solutions containing 0.5 M NaH₂-PO₄ buffered at pH 6. The effects of the metal complexes on ¹⁹F transverse relaxation were measured as a function of temperature. For most complexes, the temperature ranged from 25 to 85 °C. For Fe^{III}DTPA²⁻, the temperature range was from 5 to 95 °C. The effects of Fe^{III}DTPA²⁻ on the ¹⁹F resonance of sodium trifluoroacetate (tfa, 5 mM) and NaF were measured separately and in solutions that contained both ions. Results of the two sets of experiments were in agreement. In addition, the effects of pH on ¹⁹F NMR transverse fluoride relaxation enhancement by Fe^{III}EDTA(H₂O)⁻ and Fe^{III}PDTA⁻ were studied at 25 °C. The effects of Fe^{III}EDTA(H₂O)⁻ on F⁻ ¹⁹F relaxation were measured at 13 different buffer conditions, covering the pH range of 4.0–9.2. The effects of Fe^{III}PDTA⁻ were measured at two pH values, 6.0 and 8.3. Paramagnetic relaxation enhancements for each metal complex were determined as the slope of plots of observed relaxation rate versus metal complex concentration (ΔR_{2,obs}/Δ[M], where R_{2,obs} = 1/T_{2,obs}).

To estimate the equilibrium binding constant for Fe^{III}EDTA(H₂O)⁻/F⁻ association, spectra of Fe^{III}EDTA(H₂O)⁻ (0.2 and 0.05 mM) were measured as a function of F⁻ concentration in aqueous solutions (succinate buffer, 20 mM, pH 6) at constant ionic strength. Solutions were prepared by mixing aliquots of two stock solutions, one containing 500 mM NaClO₄ and the other containing 500 mM NaF. Although changes in the absorbance spectrum of Fe^{III}EDTA⁻ provided evidence for coordination, the equilibrium was not saturated at 500 mM F⁻.

We performed potentiometric titrations to look for evidence of changes in metal speciation with pH. The pH of a solution containing 30 mM NaF and either 0 or 30 mM Fe^{III}EDTA(H₂O)⁻ was monitored as a function of added HNO₃. Results of the two titrations were compared to see if Fe^{III}EDTA(H₂O)⁻ affected F⁻ protonation. The hydrolytic behavior of Fe^{III}PDTA⁻ in 0.1 M KCl was studied by potentiometric titration with NaOH solution as a function of complex concentration. The titration procedure followed that described by Gustafson and Martell.³² The hydrolysis of Fe^{III}PDTA⁻ was also studied at lower concentration by monitoring absorbance spectra of solutions containing 0.1 mM Fe as a function of pH. For this experiment, absorbance spectra were recorded in a series of buffered 0.1 M KCl solutions, over the pH range of 6.8–12.0.

Pulse-Radiolysis. The pulse radiolysis experiments were carried out using the Varian 7715 linear electron accelerator of the Hebrew University of Jerusalem. The dose of fast electrons per pulse was controlled by varying the pulse duration of a 200 mA current of 5 MeV electrons. Pulse durations ranged from 0.1 to 1.5 μs. Absorbance data were collected by passing light from a 150 W xenon arc lamp three times through a 4 cm Suprasil cell to give a 12.3 cm path length. The experimental setup has been previously described.^{33,34}

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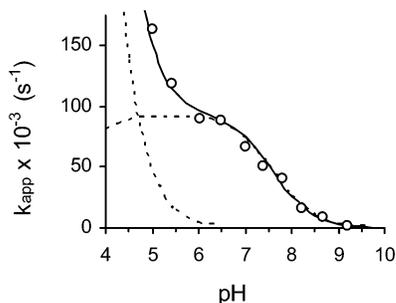


Figure 2. Effect of pH on observed $F^-/Fe^{III}EDTA(H_2O)^-$ association rates.

The exact dose was calibrated by quantifying the yield of $Fe^{III}(CN)_6^{3-}$ produced by pulsing a N_2O saturated solution containing 1×10^{-3} M $Fe^{II}(CN)_6^{4-}$. The dose per pulse was calculated using the molar extinction coefficient of $Fe^{III}(CN)_6^{3-}$ ($\epsilon_{420} = 1000 \text{ M}^{-1}\text{cm}^{-1}$) and assuming $G(Fe^{III}(CN)_6^{3-}) = 6.0$.³⁵ The dose per pulse was set to give an initial radical concentration of between 2 and 20 μM . Reactions were studied either in 0.00046 M O_2 or in air saturated solutions.

Results

Speciation of $Fe^{III}EDTA^-$. Our results indicate that F^- complexes (such as $Fe^{III}EDTA(F)^{2-}$) are not a significant fraction of total metal under the conditions of the NMR experiments (10–20 mM NaF). From the effects of F^- concentrations on the UV–vis spectrum of $Fe^{III}EDTA(H_2O)^-$, we estimate the equilibrium association constant of $Fe^{III}EDTA(F)^{2-}$ is on the order of 2 M^{-1} (0.5 M $NaClO_4$ at 25 °C, data not shown). Likewise, our potentiometric titration data did not support significant metal/ F^- binding under the conditions of our experiments; The presence of 30 mM $Fe^{III}EDTA(H_2O)^-$ had no measurable effect on titration of NaF with HNO_3 . Of the complexes in this study, $Fe^{III}EDTA(H_2O)^-$ is the most likely to form a stable F^- adduct. Only $Fe^{III}EDTA(H_2O)^-$ and $Mn^{II}EDTA(H_2O)^{2-}$ bind an exogenous ligand (H_2O) in the solid state, and $Fe^{III}EDTA(F)^{2-}$ is likely to be more stable than $Mn^{II}EDTA(F)^{3-}$ due to electrostatic effects. Thus, metal/ F^- complexes are not likely to contribute significantly to the speciation of the complexes in this study.

Speciation of $Fe^{III}PDTA^-$. Unlike $Fe^{III}EDTA(H_2O)^-$, the iron in $Fe^{III}PDTA^-$ does not bind a water molecule in the solid.³⁶ Instead, it is six coordinate, forming bonds with the six donor atoms of the chelate. The six coordinate complex is also believed to be the dominant species in acidic solution.³⁷ Our observations, however, indicate that $Fe^{III}PDTA^-$ aggregates in aqueous solutions. At concentrations higher than a few mM, the electronic spectrum of $Fe^{III}PDTA^-$ deviates strongly from Beer's law. With increasing concentration, the UV absorbance spectrum of $Fe^{III}PDTA^-$ shifts to longer wavelengths and extinction coefficients decrease markedly. Although absorbance and titration experiments indicate that both $Fe^{III}PDTA^-$ and $Fe^{III}PDTA(OH)^{2-}$ form dimers (or higher aggregates) at concentrations higher than a few millimolar, NMR and pulse radiolysis experiments used to determine rate constants for reactions of this complex (described below) were conducted under conditions where monomeric $Fe^{III}PDTA^-$ was the dominant species. Maximum complex concentrations were 0.20 mM

(pH 8.3) and 0.65 mM (pH 6.0) for the pulse radiolysis and NMR experiments, respectively.

The hydrolysis of $Fe^{III}PDTA^-$ was investigated by potentiometric titration and by UV spectroscopy. Our observations are consistent with earlier reports that $Fe^{III}PDTA^-$ undergoes hydrolysis (presumably to give $Fe^{III}PDTA(OH)^{2-}$) and further reactions at higher pH, leading to precipitation.³⁷ Although the earlier study reported hydrolysis occurred with a pK_a of 7.3, the apparent pK_a of this complex depends strongly on both the complex concentration and ionic strength. At 26 mM $KFe^{III}PDTA$ (25 °C, 0.1 M KCl), the apparent pK_a of this complex was 7.2. At lower concentrations, the complex was measurably less acidic by titration (at 5 mM complex, 0.1 M KCl, 25 °C the pK_a increased to 7.4). Under conditions where the absorbance spectra of $Fe^{III}PDTA^-$ obey Beer's law (0.1 mM complex and 10 mM buffer), the effects of pH on the electronic absorbance spectra of $Fe^{III}PDTA^-$ were consistent with the monomeric complex having a pK_a of 9.0. Thus, both $Fe^{III}PDTA^-$ and $Fe^{III}PDTA(OH)^{2-}$ aggregate at mM concentrations, with the latter having the larger association constant.³⁸ This behavior differs from that of the analogous EDTA complexes where $Fe^{III}EDTA(OH)^{2-}$ aggregates but $Fe^{III}EDTA(H_2O)^-$ does not.³²

^{19}F NMR Relaxation Enhancement Studies. With the exceptions of $Fe^{III}(CN)_6^{3-}$, $Fe^{III}PDTA(OH)^{2-}$, and $Fe^{III}EDTA(OH)^{2-}$, each metal complex caused significant enhancement of the F^- ^{19}F transverse NMR relaxation rates ($R_{2,obs} = 1/T_2$). At concentrations up to 500 mM, $Fe^{III}(CN)_6^{3-}$ had no measurable effect on F^- relaxation. For each of the eight reactive complexes, observed ^{19}F relaxation rates ($R_{2,obs}$) increased linearly with complex concentration. Relaxation enhancements by seven of the eight reactive complexes ($Fe^{III}EDTA(H_2O)^-$, $Fe^{III}PDTA^-$, $Fe^{III}_2O(TTHA)^{2-}$, $Mn^{II}EDTA^{2-}$, $Mn^{II}PDTA^{2-}$, $Mn^{II}EDDADP^{2-}$, and $Mn^{II}PO_4^-$) obeyed Arrhenius behavior, indicating that relaxation enhancement was governed by the kinetics of metal/fluoride association (eq 5):

$$R_{2,obs} - R_{2,dia} = k_{app,F^-}[M] \quad (5)$$

where $R_{2,dia}$ is the relaxation rate in diamagnetic solution and k_{app,F^-} is the apparent second-order rate constant for metal/ F^- association (the assumptions leading to eq 5 are discussed elsewhere¹⁶). The temperature dependence of relaxation enhancement by the eighth complex, $Fe^{III}DTPA^{2-}$, was more complex. Treatment of the data from this complex is described below. Observed 25 °C rate constants and activation enthalpies for F^- association with Fe^{III} and Mn^{II} are presented in Tables 1 and 2, respectively.

Reactions of F^- with $Fe^{III}EDTA(H_2O)^-$ and $Fe^{III}PDTA^-$ were also studied as a function of pH. For $Fe^{III}EDTA(H_2O)^-$, relaxation enhancements were measured for 13 buffer conditions, having pH values ranging from 4.0 to 9.2. For $Fe^{III}PDTA^-$, relaxation enhancements were measured at two pH values, 6.0 and 8.3. Figure 2 shows the effect of pH on relaxation enhancement by $Fe^{III}EDTA(H_2O)^-$ (data at pH 4.0, 4.3, and 4.7 conformed to the solid trend line but were omitted for clarity). In this pH range, F^- ^{19}F relaxation enhancement is governed by two protic equilibria, hydrolysis of $Fe^{III}EDTA(H_2O)^-$

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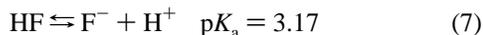
(38) Data not presented. This behavior will be described elsewhere.

Table 1. Kinetic Parameters for Reactions of Iron(III) Complexes with Superoxide and Fluoride in Aqueous Solution

complex	superoxide reaction		fluoride association reaction
	k_{app,O_2^-} ($M^{-1}s^{-1}$)	k_{app,X^-} ($M^{-1}s^{-1}$) ^a	ΔH^\ddagger (kJ/mol)
$Fe^{III}CN_6^{3-}$	2.7×10^{2b}	—	—
$Fe^{III}DTPA^{2-}$	6×10^{3c}	4.8×10^2	22
$Fe^{III}_2O(TTHA)^{2-}$	1.2×10^{4d}	$1.2 (\pm 0.2) \times 10^2$	39
$Fe^{III}PDTA^-$	$4.4 (\pm 1.3) \times 10^{5e}$	$2.5 (\pm 0.2) \times 10^4$	37
$Fe^{III}EDTA(H_2O)^-$	1.9×10^{6f}	$9.3 (\pm 1.6) \times 10^4$	39

^a Rate constants (25 °C) measured in 90% H₂O/10% D₂O solution, pH 6 except where indicated. ^b From Zehavi and Rabani, ref 24. ^c From Egan et al., ref 4. ^d From Rush and Cabelli, ref 26. ^e Reported here, pH 8.3. ^f From Bull et al., ref 3.

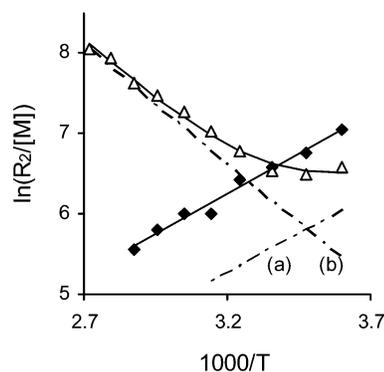
and protonation of F⁻ (eqs 6 and 7).³⁹ The solid trend line in Figure 2 represents the behavior predicted for the case where HF and F⁻ associate with Fe^{III}EDTA(H₂O)⁻ with apparent rate constants of 9.3×10^4 and $4 \times 10^6 M^{-1}s^{-1}$, and where F⁻ is unreactive toward Fe^{III}EDTA(OH)²⁻.⁴⁰



The dashed lines in Figure 2 show the individual contributions of HF and F⁻ association to the observed relaxation enhancement. These results indicate that HF is a much more reactive nucleophile toward Fe^{III}EDTA(H₂O)⁻ than is F⁻. This order of reactivity has also been reported for association reactions of Al^{III}EDTA⁻; HF is reportedly ~22 times more nucleophilic toward this complex than is F⁻.¹⁹

Relaxation enhancements by Fe^{III}PDTA⁻ and its hydrolysis products were analogous to those of the EDTA complexes: Relaxation enhancement under conditions where Fe^{III}PDTA(OH)²⁻ aggregates are the dominant metal containing species (pH 8.6, 10 mM complex) was greatly attenuated relative to relaxation enhancement under conditions where Fe^{III}PDTA⁻ dominates. Thus, Fe^{III}PDTA⁻ undergoes association reactions with exogenous ligands whereas Fe^{III}PDTA(OH)²⁻ aggregates do not.

We considered the possibility that the acceleration of ¹⁹F relaxation enhancement by Fe^{III}EDTA(H₂O)⁻ at pH < 6 (Figure 2) was due to protonation of the metal complex. Although there have been reports that Fe^{III}EDTA(H₂O)⁻ participates in other protic equilibria in this range,^{41,42} the accepted pK_a for protonation of Fe^{III}EDTA(H₂O)⁻ is 1.3.⁴³ Our potentiometric titration data did not support protonation of the complex at a higher pH. The attribution of the behavior to an enhanced reactivity of HF and not to protonation of the metal complex is further supported by experiments with another NMR reactivity probe, methylphosphite anion (MeOPH⁻). From the temperature dependence of the relaxation enhancement of the ³¹P resonance of MeOPH⁻

**Figure 3.** Effects of temperature on relaxation of tfa (◆) and fluoride (△) ¹⁹F NMR resonances by Fe^{III}DTPA²⁻.

by Fe^{III}EDTA(H₂O)⁻, we determined that transverse relaxation is governed by metal/MeOPH⁻ association kinetics (data not presented). MeOPH⁻ is not protonated under the conditions employed (pK_a = 0.86¹⁷), and relaxation enhancement of the ³¹P nucleus of MeOPH⁻ by Fe^{III}EDTA(H₂O)⁻ does not increase with [H⁺] at pH between 4 and 6.

Although the k_{app,F^-} for reaction at Fe^{III}PDTA⁻ is similar to that for reaction at Fe^{III}EDTA(H₂O)⁻, a recent study indicated that exchange of solvent water into the inner coordination sphere of Fe^{III}PDTA⁻ is much slower than at Fe^{III}EDTA(H₂O)⁻.¹⁰ The solvent exchange experiments, however, were conducted at Fe^{III}PDTA⁻ concentrations that were much greater than those in the present study. Significant aggregation is expected under this condition, which may retard solvent exchange.

DETERMINATION OF K_{APP,F^-} FOR Fe^{III}DTPA²⁻. The F⁻ ¹⁹F relaxation enhancement by Fe^{III}DTPA²⁻ did not display Arrhenius temperature dependence (△, Figure 3). The curvature of the plot most likely arises from a similarity in the magnitudes of outer-sphere and inner-sphere contributions to relaxation ($R_{2,OS}$ and $R_{2,IS}$).^{13,20,21} It has been suggested that when $R_{2,IS}$ and $R_{2,OS}$ are of similar size, k_{app} can be estimated by subtracting $R_{2,OS}$ from $R_{2,obs}$.²¹ To estimate the contribution of $R_{2,OS}$, we measured relaxation enhancement of the ¹⁹F resonance of the trifluoroacetate anion (tfa) by Fe^{III}DTPA²⁻. We reasoned that $R_{2,IS}$ for the tfa resonance would be negligible due to the low basicity of this anion and the absence of a through bond pathway for magnetic interaction between the paramagnetic center and the ¹⁹F nuclei. For the tfa resonance, $R_{2,obs}$ decreased with increasing temperature, consistent with an outer-sphere interaction (◆, Figure 3).^{13,14,21} If $R_{2,obs}$ for the tfa ¹⁹F resonance were equal to the outer-sphere contribution to the $R_{2,obs}$ for F⁻, however, then $R_{2,obs}$ for the F⁻ resonance should asymptotically approach that of the tfa resonance with decreasing temperature. Surprisingly, relaxation of the tfa nuclei at low temperatures (<25 °C) was more sensitive to Fe^{III}DTPA²⁻ concentration than was relaxation of the F⁻ nucleus. Although this effect could arise if the lifetime of a transient tfa complex (Fe^{III}DTPA(tfa)²⁻) is greater than that of Fe^{III}DTPA(F)²⁻, this behavior is more likely due to differences in factors that determine the outer-sphere relaxation rates (outer-sphere correlation times and distance of closest approach). Whereas $R_{2,IS}$ should obey Arrhenius temperature dependence, $R_{2,OS}$ decays with temperature (eq 8):

$$\Delta R_{2,obs}/T \Delta[M] = \alpha \exp(-\Delta H^\ddagger/RT) + \beta \exp(\gamma/T) \quad (8)$$

(39) Although Fe^{III}EDTA(OH)²⁻ dimerizes at higher concentrations, the extent of this reaction is minimal at the concentrations of this study (maximum total Fe = 150 μM).

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(41) Kennard, C. H. L. *Inorg. Chim. Acta* **1967**, *1*, 347.

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Table 2. Kinetic Parameters for Reactions of Manganese(II) Complexes with Superoxide and Fluoride in Aqueous Solution

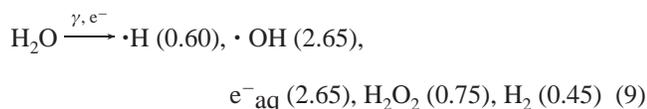
complex	superoxide reaction data		anion binding data	
	$k_{\text{app},\text{O}_2,\text{A}}$ ($\text{M}^{-1}\text{s}^{-1}$)	$k_{\text{app},\text{O}_2,\text{B}}$ (s^{-1})	$k_{\text{app},\text{X}^-}$ ($\text{M}^{-1}\text{s}^{-1}$) ^a	ΔH^\ddagger (kJ/mol)
Mn ^{II} EDTA(H ₂ O) ²⁻	$1.24 (\pm 0.24) \times 10^7$	$4.0 (\pm 0.8) \times 10^2$	$5.46 (\pm 0.19) \times 10^4$	31
Mn ^{II} PDTA ²⁻	$1.33 (\pm 0.26) \times 10^7$	$2.0 (\pm 0.4) \times 10^2$	$2.85 (\pm 0.06) \times 10^5$	19
Mn ^{II} β -EDDADP ²⁻	$1.95 (\pm 0.40) \times 10^7$	$3.5 (\pm 0.7) \times 10^2$	$1.52 (\pm 0.02) \times 10^5$	22
Mn ^{II} PO ₄ ⁻	$5.0 \times 10^{7b,c}$		$5.34 (\pm 0.15) \times 10^{6b}$	42
Mn ^{III} TM-2-PyP ⁵⁺	6.2×10^{7d}		2.1×10^{6e}	36 ^e
Mn ^{II} (H ₂ O) ₆ ²⁺	1.1×10^{8f}		5.8×10^{6e}	47 ^e

^a Rate constants (25 °C) measured in 90% H₂O/10% D₂O solution, pH 7 except where noted. Except for Mn^{III}TM-2-PyP⁵⁺ and Mn^{II}(H₂O)₆²⁺ (note e), data are for metal/F⁻ association. ^b Measured at pH 6. ^c From Cabelli and Bielski, ref 29. ^d From Batinic-Haberle et al., ref 58. ^e Rate data for MeOPH⁻ association, ref 16. ^f From Pick-Kaplan and Rabini, ref 62.

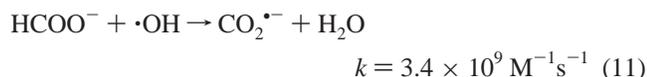
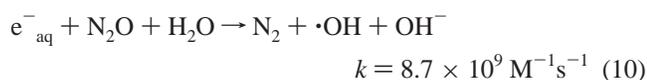
where α , β , and γ are constants. The γ term for F⁻ relaxation in eq 8 was set equal to the slope of the least-squares line for the tfa data,⁴⁴ and ΔH^\ddagger , α , and β were refined to give the curved trend line following the F⁻ data in Figure 2. Dashed lines a and b in Figure 3 represent the predicted outer-sphere and inner-sphere contributions to the relaxation rate, respectively. The 25 °C association rate constant and activation enthalpy in Table 1 are from this refinement.

Rate Constants of O₂^{•-} Reactions. The reactions of O₂^{•-} with the complexes Fe^{III}PDTA⁻, Mn^{II}EDTA(H₂O)²⁻, Mn^{II}PDTA²⁻, and Mn^{II} β -EDDADP²⁻ were studied in aqueous solutions containing 0.1 M NaHCO₂ and 0.018 M N₂O. These reactions were studied at pH 8.3 to minimize interference by the reaction of HO₂[•] with O₂^{•-} ($k = 9.7 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$).⁴⁵

The O₂^{•-} radicals were prepared by irradiating the solutions with fast electrons. When ionizing radiation is absorbed by a dilute aqueous solution, the following initial products are formed:⁴⁶



where the G values (defined as the yield of product per 100 eV absorbed by the solution) are given in parentheses. In solutions containing N₂O and O₂, the following reactions yield the desired O₂^{•-} radical anion:⁴⁷



Absorbance data were acquired at times greater than 1×10^{-6} s because radiolysis product distributions are homogeneous after 1×10^{-7} s.⁴⁶

(44) We felt that γ values for tfa and F⁻ should be similar because the temperature dependencies of the electron spin relaxation time of the metal complex are not anion dependent and the correlation times for motions of the ions should be similar.

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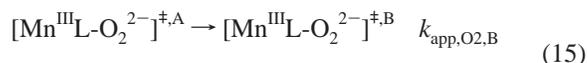
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Reaction of O₂^{•-} with Fe^{III}PDTA⁻ proceeds directly to the ferrous complex (eq 13). The reaction was run under pseudo-first-order conditions. The observed second-order rate constant for this reaction ($3.7 \pm 0.8 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$) was determined from the dependence of the pseudo-first-order rate constants on complex concentrations. The rate constant reported in Table 1 ($4.6 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$) was calculated from this value using the measured p*K* for hydrolysis of Fe^{III}PDTA⁻ (reported above; 9.0) and assuming that only Fe^{III}PDTA⁻ (and not Fe^{III}PDTA(OH)²⁻) is reactive toward O₂^{•-}. This assumption is reasonable because the analogous complex Fe^{III}EDTA(OH)²⁻ is reportedly unreactive toward O₂^{•-} and because both Fe^{III}PDTA(OH)²⁻ and Fe^{III}EDTA(OH)²⁻ are unreactive toward F⁻ association. This assumption has relatively little effect on the value of the rate constant, as only ~20% of the available iron was present as Fe^{III}PDTA(OH)²⁻ under the conditions of the pulse radiolysis experiment (pH 8.3).



In contrast to the reaction with Fe^{III}PDTA⁻, reactions of O₂^{•-} with Mn^{II}EDTA(H₂O)²⁻, Mn^{II}PDTA²⁻, and Mn^{II} β -EDDADP²⁻ displayed more complicated kinetics. The experimental observations indicate that these reactions proceed through two short-lived intermediates (formulated as [Mn^{III}L-O₂²⁻]^{•,A} and [Mn^{III}L-O₂²⁻]^{•,B}):



The initial reactions (eq 14) proceed with pseudo-first-order kinetics. Apparent second-order rate constants for formation of the first intermediate [Mn^{III}L-O₂²⁻]^{•,A} ($k_{\text{app},\text{O}_2,\text{A}}$, reported in Table 2) were determined from the dependence of the pseudo-first-order rate constants on complex concentrations. Rearrangements of the initial intermediates (eq 15) obey first-order kinetics with the rate constants ($k_{\text{app},\text{O}_2,\text{B}}$) reported in Table 2. Rates of the subsequent decomposition reactions (eq 16) will be reported elsewhere. Each of these three reactions is analogous to reactions reported for similar Mn^{II} complexes.²⁷⁻²⁹

Discussion

Comparing the Fe^{III}EDTA(H₂O)⁻/F⁻ association rate constant to that for Fe^{III}EDTA(H₂O)⁻/SO₃²⁻⁴⁰ indicates that ligand association reactions at Fe^{III}EDTA(H₂O)⁻ are not purely dis-

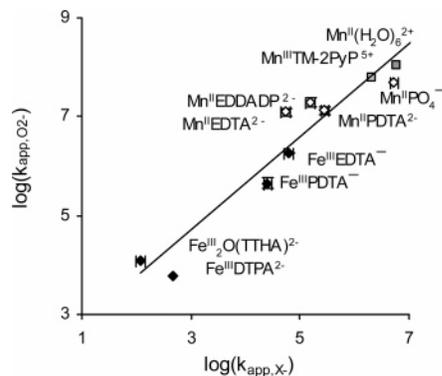


Figure 4. Apparent second-order rate constants for metal/anion association (k_{app,X^-}) correlate with rate constants of metal/ $\text{O}_2^{\bullet-}$ reactions ($k_{\text{app},\text{O}_2^{\bullet-}}$). \blacklozenge represent $\text{Fe}^{\text{III}}/\text{F}^-$ association, \diamond represent $\text{Mn}^{\text{II}}/\text{F}^-$ association, and \blacklozenge represent reactions of $\text{Mn}^{\text{III}}\text{TMPyP}^{5+}$ and $\text{Mn}^{\text{II}}(\text{H}_2\text{O})_6^{2+}$ with MeOPH^- .

sociative. The effects of nucleophile identity on rates of dissociative reactions should be limited to the factors that modulate electrostatic pre-association (factors that affect the rates of metal/anion complexation have been reviewed^{8,48–50}). Although electrostatic considerations predict the anionic metal complex would react more slowly with SO_3^{2-} than with F^- , the rate constant reported for SO_3^{2-} is approximately 40 times that for F^- .⁴⁰ We also found that $\text{Fe}^{\text{III}}\text{EDTA}(\text{H}_2\text{O})^-$ reacts more rapidly with SCN^- ⁵¹ than with F^- . This same reactivity order was reported previously for $\text{Fe}^{\text{III}}(\text{H}_2\text{O})_6^{3+}$.^{52,53} We note that aquo ligand exchange at $\text{Fe}^{\text{III}}(\text{H}_2\text{O})_6^{3+}$ proceeds by an associative interchange mechanism, as indicated by its small negative activation volume ($\Delta V^\ddagger = -5.4$ mL/mol).⁵⁴ Although dissociation of coordinated water from the seven-coordinate $\text{Fe}^{\text{III}}\text{EDTA}(\text{H}_2\text{O})^-$ is likely to precede anion association, the association of an anionic ligand with the anionic complex must present a second energy barrier.

The order of reactivity we observed ($\text{SO}_3^{2-} > \text{SCN}^- > \text{F}^-$) has been observed in other systems as well⁵⁶ and is consistent with the Swain-Scott/Pearson nucleophilicities of the ions.⁵⁵ We attribute differences in the nucleophilic reactivities to differences in the energies required to break nucleophile/solvent hydrogen bonds. Nucleophile/solvent hydrogen bonding is well-known to diminish nucleophilic reactivity.^{17,52,53,56}

Implications for the Mechanisms of Metal/ $\text{O}_2^{\bullet-}$ Redox Chemistry. Our results suggest that rapid reactions of Fe^{III} complexes with $\text{O}_2^{\bullet-}$ occur via inner-sphere mechanisms where metal/ $\text{O}_2^{\bullet-}$ association is rate limiting. Under this scenario, rates of metal/ $\text{O}_2^{\bullet-}$ reactions are expected to correlate with rates at which the metal complexes coordinate F^- . We were able to obtain both $k_{\text{app},\text{O}_2^{\bullet-}}$ and $k_{\text{app},\text{F}^-}$ for 8 of the 10 complexes studied. A plot of $\log(k_{\text{app},\text{O}_2^{\bullet-}})$ versus $\log(k_{\text{app},\text{F}^-})$ for these 8 complexes (Figure 4) displays a linear correlation extending 5 orders of magnitude. In addition to metal/ F^- association data, Figure 4

includes published data for reactions of another nucleophilic anion, methylphosphite (MeOPH^-). The gray squares in Figure 4 compare rate constants of metal/ MeOPH^- association¹⁷ to rate constants of metal/ $\text{O}_2^{\bullet-}$ reactions for $\text{Mn}^{\text{II}}(\text{H}_2\text{O})_6^{2+}$ and a water soluble manganese(III) porphyrin ($\text{Mn}^{\text{III}}\text{TM-2-PyP}^{5+}$, data in Table 2).^{57,58} For the case of $\text{Mn}^{\text{III}}\text{TM-2-PyP}^{5+}$, $k_{\text{app},\text{O}_2^{\bullet-}}$ is the catalytic rate constant for $\text{O}_2^{\bullet-}$ dismutation (k_{cat}). Values of k_{cat} for manganese(III) porphyrins are thought to be limited by rates of Mn^{III} reduction.⁵⁹ Thus, the fit of the $\text{Mn}^{\text{III}}\text{TM-2-PyP}^{5+}$ data to the trend line in Figure 4 suggests that the rate-limiting step in the catalytic dismutation of $\text{O}_2^{\bullet-}$ by this complex is the inner-sphere coordination of the two reactants. We note that complexes that were inert toward F^- exchange ($\text{Fe}^{\text{III}}(\text{CN})_6^{3-}$ and $\text{Fe}^{\text{III}}\text{EDTA}(\text{OH})^{2-}$) also react slowly with $\text{O}_2^{\bullet-}$.^{3,24} These results are all consistent with rapid metal/ $\text{O}_2^{\bullet-}$ reactions proceeding through inner-sphere mechanisms. This conclusion is in accord with the earlier report that redox reactions between transition metal complexes and radicals usually proceed via the inner-sphere mechanism.⁶⁰

If $\text{O}_2^{\bullet-}$ reacts with metal complexes by inner-sphere mechanisms, then Figure 4 compares the nucleophilicity of $\text{O}_2^{\bullet-}$ to that of F^- . The slope and intercept values for the trend line in Figure 4⁶¹ are reasonable for this interpretation. If the metal-dependent contributions to ΔG^\ddagger for coordination of metal complexes by F^- were identical to such contributions for reactions with $\text{O}_2^{\bullet-}$, then a plot of $\log(k_{\text{app},\text{O}_2^{\bullet-}})$ versus $\log(k_{\text{app},\text{F}^-})$ should be linear with a slope of 1. The slope of the trend line in Figure 4 is 0.94. The intercept of the trend line in this plot (1.9) indicates that $\text{O}_2^{\bullet-}$ is on average 74-fold more reactive than F^- toward metal complexes.

We attribute differences between $k_{\text{app},\text{O}_2^{\bullet-}}$ and $k_{\text{app},\text{F}^-}$ to differences in the nucleophilicities of the two anions and not to a contribution of an outer-sphere mechanism to electron-transfer reactions. A direct comparison of $\text{O}_2^{\bullet-}$ and F^- nucleophilicities is provided by rate data for reactions of Mn^{II} complexes. Whereas reactions of $\text{O}_2^{\bullet-}$ with each Fe^{III} complex proceed without a detectable intermediate to the corresponding Fe^{II} species, reactions with the Mn^{II} complexes do proceed through an intermediate.^{27–29} Values of $k_{\text{app},\text{O}_2^{\bullet-}}$ reported in Table 2 are rate constants for formation of these intermediates (typically formulated to contain the $\text{Mn}-\text{O}_2^+$ moiety).^{27–29} Because $\text{Mn}^{\text{II}}/\text{O}_2^{\bullet-}$ association is reversible for certain Mn^{II} complexes⁶² (including $\text{Mn}^{\text{II}}\text{PO}_4^{2-}$ ²⁹ and $\text{Mn}^{\text{II}}(\text{H}_2\text{O})_6^{2+}$ ⁶²), it is likely that $k_{\text{app},\text{O}_2^{\bullet-}}$ for those complexes (and presumably the other Mn^{II} complexes as well) are the rate constants for metal/ $\text{O}_2^{\bullet-}$ association. Because rate data for Mn^{II} complexes conform to the trend in Figure 4, it follows that the nucleophilicities of the two anions are related by $k_{\text{app},\text{O}_2^{\bullet-}}/k_{\text{app},\text{F}^-} \approx 74$. The magnitude of this ratio (corresponding to a difference in ΔG^\ddagger of ~ 11 kJ/mol) is reasonable given the difference in the solvation enthalpies of $\text{O}_2^{\bullet-}$ and F^- (-420 ⁶³ and -519 ⁶⁴ kJ/mol, respectively.).

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 (51) Unpublished results: Although relaxation enhancement of the ¹⁵N nucleus of SCN^- is not governed by kinetics at the magnetic field strength available to us, our measurements indicate that the rate constant for SCN^- association with $\text{Fe}^{\text{III}}\text{EDTA}(\text{H}_2\text{O})^-$ is greater than that for F^- association.
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The effects of nucleophile protonation on rates at which $O_2^{\bullet-}$ and F^- react with $Fe^{III}EDTA(OH)^{2-}$ are qualitatively similar. Rates of F^- relaxation dramatically accelerate in as the pH approached the pK_a of HF (3.17). Similarly, the reduction of $Fe^{III}EDTA(OH)^{2-}$ by $O_2^{\bullet-}$ reportedly accelerates at pH approaching the pK_a of HO_2^{\bullet} ^{3,7} (4.7⁶³). Acceleration of the reactions of HO_2^{\bullet} and HF compared to those of $O_2^{\bullet-}$ and F^- are likely to be due to a combination of factors, including: (1) decreased electrostatic repulsions of the metal complex and the protonated nucleophile, (2) decreased solvation energies of the nucleophiles, and (3) increased stability of the outer-sphere complex by hydrogen bonding between HF (or HO_2) and the anionic metal complex.

Conclusions

We have shown that rates of metal/ F^- association at Fe^{III} and Mn^{II} centers can be measured by paramagnetic relaxation enhancement of the F^- ^{19}F NMR resonance and report rate

constants and activation enthalpies for metal/ F^- association with eight metal complexes. We have also reported the rate constant for reaction of $O_2^{\bullet-}$ with $Fe^{III}PDTA^-$, $Mn^{II}EDTA^{2-}$, $Mn^{II}PDTA^{2-}$, and $Mn^{II}\beta$ -EDDADP²⁻. The correlation of metal/anion association rates with rates of metal/ $O_2^{\bullet-}$ reactions provides strong evidence for an inner-sphere mechanism for the reduction of Fe^{III} to Fe^{II} by $O_2^{\bullet-}$. Our findings suggest that ^{19}F NMR relaxation methods may be used to predict the reactivities of Fe^{III} containing biomolecules toward catalyzing the production of ROS relevant to oxidative stress and disease.

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