s cm^{-1}. ^{19}F NMR: ϕ −50.27 (CF_3, mult), −69.27 (CF_2Cl, mult), −88.96 (NCF_2, mult). Anal. Calcd for $C_5F_{11}Cl_2N$: C, 16.95; F, 59.04. Found: C, 16.93; F, 58.80.

Properties of $CF_3N(CF_2CFCl_2)_2$. This compound was found in the trap at −10 °C, having passed through a trap at 0 °C. It was obtained in 60% yield as a colorless liquid. Spectral data are as follows. EI MS (*m/e* (species), intensity): 286/284 ($C_4F_8NCl_2^+$), 5.98/9.53; 153/151 ($C_2F_3Cl_2^+$), 64.67/100; 137/135 ($C_2F_4Cl^+$), 5.22/16.18; 118/116 ($C_2F_3Cl^+$), 4.0/12.65, 103/101 ($CFCl_2^+$), 23.58/37.18; 87/85 (CF_2Cl^+), 4.65/14.23; 69 (CF_3^+), 22.20; 68/66 ($CFCl^+$), 1.49/4.61. IR (gas): 1324 vs, 1296 vs, 1239 s, 1213 s, 1149 s, 1105 vs, 982 vs, 899 vs, 829 vs, 765 vs, 737 vs, 657 s cm^{-1}. ^{19}F NMR: ϕ −49.06 (CF_3, pt), −69.73 ($CFCl_2$, qt), −83.74 (CF_2, qd); $J_{CF_3-CF_2}$ = 15.14 Hz, J_{CF_3-CF} = 20.39 Hz, J_{CF_2-CF} = 7.32 Hz. Anal. Calcd for $C_5F_9Cl_4N$: C, 15.5; F, 44.2. Found: C, 15.61; F, 44.30.

Properties of $CF_3CF_2N(CF_2CF_2Cl)_2$. This compound was found in the trap at −10 °C. It was obtained in ~55% yield as a colorless liquid. Spectral data are as follows. EI MS (*m/e* (species), intensity): 320/318 ($C_5F_{11}NCl^+$), 6.73/18.60; 232/230 ($C_4F_7NCl^+$), 7.53/23.78; 214 ($C_4F_8N^+$), 14.78; 164 ($C_3F_6N^+$), 31.22; 135 ($C_2F_4Cl^+$), 100; 119 ($C_2F_5^+$), 98.88; 114 ($C_2F_4N^+$), 10.17; 87/85 (CF_2Cl^+), 23.23/72.66; 69 (CF_3^+), 46.11; 50 (CF_2^+), 5.56. IR (gas): 1310 s, 1290 s, 1240 vs, 1185 s, 1167 s, 1006 s, 839 s, 796 vs, 710 vs, 697 s cm^{-1}. ^{19}F NMR ϕ −66.95 (CF_2Cl, mult), −79.63 (CF_3, mult), −86.19 (CF_2N, mult), −87.86 (CF_2N, mult). Anal. Calcd for $C_6F_{13}Cl_2N$: C, 17.82; F, 61.1. Found: C, 18.28; F, 60.7.

Synthesis and Properties of $CF_3N(CF_2CFCl_2)(CF_2CF_2Cl)$. Five mmoles of $CF_3N(CF_2CFCl_2)Cl$ and 6 mmol of CF_2=CF_2 were condensed in a thick-walled Pyrex vessel. The tube was sealed and heated at 95–100 °C for 12–14 h. The product was purified by trap-to-trap distillation. This compound was found in a trap at −30 °C. It was obtained in ~65% yield as a colorless liquid. Spectral data are as follows. EI MS (*m/e* (species), intensity): 286/284 ($C_4F_8NCl_2^+$), 3.64/5.64; 270/268 ($C_4F_9NCl^+$), 9.59/28.64; 182/180 ($C_3F_5NCl^+$), 6.21/19.45; 164 ($C_3F_6N^+$), 12.34; 153/151 ($C_2F_3Cl^+$), 60.70/96.75; 137/135 ($C_2F_4Cl^+$), 32.12/100; 119 ($C_2F_5^+$), 11.39; 114 ($C_2F_4N^+$), 417; 103/101 ($CFCl_2^+$), 30.01/47.65; 100 ($C_2F_4^+$), 13.02; 87/85 (CF_2Cl^+), 19.66/61.62; 69 (CF_3^+), 68.33; 50 (CF_2^+), 5.27. IR (gas): 1384 w, 1337 vs, 1312 vs, 1270 w, 1239 w, 1208 s, 1185 s, 1154 s, 1114 s, 1029 s, 1009 s, 907 s, 854 s, 780 vs, 744 s cm^{-1}. ^{19}F NMR: ϕ −49.81 (CF_3, mult), −68.28 (CF_2Cl, mult), −70.71 ($CFCl_2$), −84.84 (NCF_2CFCl_2), −87.74 (NCF_2CF_2Cl). Anal. Calcd for $C_5F_{10}Cl_3N$: C, 15.5; F, 44.2. Found: C, 15.61; F, 44.30.

Photolysis of $R_fN(CF_2CFXCl)Cl$. Five mmoles of $R_fN(CF_2CFXCl)Cl$ was condensed into a 500-mL quartz vessel and was photolyzed in the gas phase by using a Rayonet photochemical reactor at 3000 Å for 2–3 h. The products were separated by trap-to-trap distillation and identified by ^{19}F NMR and infrared spectral data. Photolysis of $CF_3N(CF_2CFXCl)Cl$ gave CF_3N=CF_2[27] and $CFXCl_2$. The azapropene (65–70% yield) was found in a trap at −120 °C, having passed through a trap at −100 °C. Photolysis of $CF_3CF_2N(CF_2CFXCl)Cl$ gave CF_3CF_2N=CF_2[27] and $CFXCl_2$. Perfluoro-2-aza-1-butene was found in the trap at −100 °C in ~80% yield.

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Registry No. CF_2=CF_2, 116-14-3; CF_2=$CFCl$, 79-38-9; CF_3NCl_2, 13880-73-4; $C_2F_5NCl_2$, 677-66-7; $CF_3N(CF_2CF_2Cl)Cl$, 120417-57-4; $CF_3N(CF_2CFCl_2)Cl$, 120417-58-5; $CF_3CF_2N(CF_2CF_2Cl)Cl$, 120417-59-6; $CF_3CF_2N(CF_2CFCl_2)Cl$, 120417-60-9; $CF_3N(CF_2CF_2Cl)_2$, 60940-98-9; $CF_3N(CF_2CFCl_2)_2$, 120417-61-0; $CF_3CF_2N(CF_2CF_2Cl)_2$, 63419-66-9; $CF_3N(CF_2CFCl_2)(CF_2CF_2Cl)$, 120417-62-1; CF_3N=CF_2, 371-71-1; CF_2Cl_2, 75-71-8; $CFCl_3$, 75-69-4; CF_3CF_3N=CF_3, 428-71-7.

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Metal Ion Recognition in Ligands with Negatively Charged Oxygen Donor Groups. Complexation of Fe(III), Ga(III), In(III), Al(III), and Other Highly Charged Metal Ions

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The existence of good linear relationships between the formation constant log values of complexes of ligands containing negative oxygen donor groups only and log $K_1(OH^-)$ values for the metal ions is demonstrated for a variety of ligands containing phenolate, carboxylate, and hydroxamate donor groups. The formation constants of DFB (desferriferrioxamine-B), BAMTPH (a synthetic trihydroxamate), and several dihydroxamic acids of the type $HONHCO(CH_2)_nCONHOH$ (n = 4, 6, 7, 8) with several metal ions are reported and used to demonstrate the general existence of linear relationships of the above type. The DFB constants are reported for Al(III), Ga(III), and In(III) and considered in relation to possible use of DFB for treating aluminum intoxication. The selectivity patterns of negatively charged oxygen donor ligands for metal ions are discussed in relation to the effect of chain length of the bridging groups connecting the donor groups, the presence of sulfonic acid groups, and how the selectivity patterns might be altered by the inclusion of other donor groups such as neutral oxygen and nitrogen donor groups.

Introduction

There is concurrently considerable interest in designing ligands for the complexation of metal ions that have in common a high affinity for the negatively charged oxygen donor atom. Types of donor groups of interest have been catecholates,[1,2] phenolates,[3] hydroxamates,[4,5] and phosphonates.[6] Areas of application of this type of ligand are removal of Fe(III) in the treatment of Cooley's anemia,[1-5] complexation of Al(III) in the treatment of aluminum intoxication,[7] development of complexes of In(III) and Ga(III) as imaging agents,[8] and complexation of actinide elements.[2] Also of interest here is use of complexes of lanthanide(III) ions as NMR imaging agents.[9]

In this paper the aim is to highlight some of the factors of importance in designing ligands that have predominantly negatively charged oxygen donor atoms. A consideration of importance in this regard is the type of correlation briefly discussed[10,11] for

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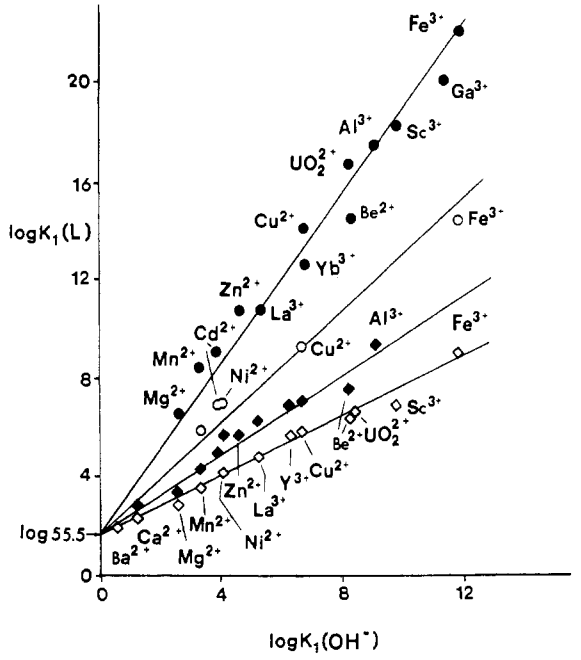

Figure 1. log K_1 values for catecholate (●), 5-nitrosalicylate (○), kojate (◆), and malonate (◇) versus log $K_1(OH^-)$ values for the metal ions. Formation constants are from ref 14. The log 55.5 intercept is the theoretical value of the entropy contribution to the chelate effect on the basis of the asymmetry of the standard reference state.[12,13]

negatively charged oxygen donor ligands. In Figure 1 are seen examples of this type of correlation, where log K_1 for a selection of oxygen donor ligands has been plotted against log $K_1(OH^-)$ for each metal ion. Such correlations appear to apply to a wide variety of ligands containing negatively charged oxygen donor (RO^-) groups. Examples include oxalate, di- and tripolyphosphates, β-diketonates, tropolonates, variously substituted salicylates and catecholates, and a variety of hydroxamic acids.

The correlations shown in Figure 1 are for catecholate, 5-nitrosalicylate, kojate, and malonate. Such linear correlations suggest that the affinity which a metal ion has for an O-donor chelating ligand is directly related to the affinity of the metal ion for the archetypal RO^- ligand, the OH^- ion. The slopes of such correlations are dependent on the basicity of the RO^- donors of the chelating ligand.[11] Of interest here is the fact that the intercepts of these correlations are (Figure 1) close to log 55.5, which is the magnitude of the chelate effect[12] expected from eq 1.

$$\log K_1(\text{polydentate}) = \log \beta_n(\text{unidentate}) + (n - 1) \log 55.5 \quad (1)$$

Equation 1 relates log K_1 for the complexes of a n-dentate polydentate ligand to log β_n for a complex containing n unidentate analogues of the polydentate ligands.[12,13]

In this paper correlations of the type seen in Figure 1 are extended to ligands of higher denticity than two and, in particular, to ligands of interest in the complexation of Fe(III), Al(III), In(III), Ga(III), actinides, and lanthanides. Use is made of data available in the literature,[14] supplemented by a study of the complexation of Al(III), Ga(III), In(III), and Fe(III) with desferriferrioxamine-B (DFB, Figure 2). Of particular interest is the proposal[15] that DFB, with an estimated log K_1 for Al(III) of 28, be used for the treatment of aluminum poisoning. Correlations drawn up by the present authors for log K_1 for DFB versus log $K_1(OH^-)$ suggest a value of log K_1 of about 23. A determination of log K_1 for the DFB complex of Al(III) is thus also a test of the predictive ability of correlations such as those in Figure 1. Also studied was the ligand BAMTPH (Figure 2), a trihydroxamate investigated[4] as being of potential use in the complexation of Fe(III). Other ligands studied here are the dihydroxamates C_nDHA (n = 4, 6, 7, 8) seen in Figure 2, which have four, six, seven, and eight methylene groups in the connecting chain. The variation of chain length should indicate the optimum chain length for connecting hydroxamate groups together and also factors controlling the size of intercepts in correlations such as those in Figure 1.

Experimental Section

Materials. Ligands. The ligand DFB was supplied in the crystalline methanesulfonate salt by Ciba-Geigy. Potentiometric titration confirmed the calculated molecular weight of 656 Da. The synthesis of the ligand BAMTHP has been described previously.[3] The dihydroxamic acids were synthesized by a standard general procedure involving formation of the diester from the commercially available dicarboxylic acids,[16] followed by reaction in methanol with excess hydroxylamine to give the dihydroxamate.[16] Analysis of the ligand BAMTPH (Figure 2) and the dihydroxamates by potentiometric titration confirmed the purity of the ligands. The analyses for the dihydroxamic acids of the general formula $HONHCO(CH_2)_nCONHOH$ (C_nDHA, n = 4, 6, 7, 8) were as follows. Calcd for n = 4: C, 40.91; H, 6.82; N, 15.91. Found: C, 40.63; H, 6.98; N, 16.25. Calcd for n = 6: C, 47.05; H, 7.84; N, 13.73. Found: C, 47.15; H, 7.99; N, 13.63. Calcd for n = 8: C, 51.69; H, 8.68; N, 12.06. Found: C, 51.78; H, 8.90; N, 11.98. Calcd for n = 7: C, 49.51; H, 8.31; N, 12.83. Found: C, 49.19; H, 8.30; N, 12.71.

Solutions of metal nitrates were prepared from the AR metal nitrate salts and standardized by usual procedures. These were used in the potentiometric titrations of the dihydroxamate ligands and BAMTPH, which were carried out in 0.100 M KNO_3 at 25 °C. The titrations involving the DFB ligand were carried out in 0.100 M KCl at 25 °C. A stock solution of iron(III) chloride was made by employing excess HCl to keep hydrolysis in check. The Ga(III) solution was prepared from the weighed metal. After complete dissolution in HCl, excess acid was driven off by repeated evaporation. Residual excess acid was estimated with Dowex 50-W X-8 cation-exchange resin in the acid form.

Equipment. Titrations of the DFB complexes were carried out in a jacketed potentiometric cell with an O-ring-seal-equipped cap containing a high-pH glass extension electrode and a calomel reference extension electrode, inert-gas inlet and outlet, and a sealed-in buret tip driven by means of a Metrohm 10-mL-piston screw-type buret. The potential changes were monitored by means of a Corning Model 150 digital meter and printer. The meter was calibrated to read -log [H^+] directly with standard strong acid solution at an ionic strength of 0.100 M (KCl). The equipment for carrying out the titrations on the dihydroxamic acids and BAMTPH was similar, except that potential changes were monitored on a Radiometer PHM84 pH meter, and a Radiometer G202B glass electrode was used to measure the potentials. It was found that the Fe(III) and Th(IV) complexes of the C_8DHA dihydroxamate ligand was of such stability that complex formation was still largely complete at pH 2, rendering use of potentiometry to measure the stability of these complexes rather difficult. Accordingly, complex formation of these metal ions with dihydroxamates was studied spectrophotometrically. The electronic spectra of solutions of the C_8DHA (Figure 2) complexes of Fe(III) and Th(IV) were thus recorded on a Cary 2300 UV–visible spectrophotometer as a function of acid concentration in the pH range 1–2 in quartz cells thermostated at 25 °C.

Generalized Procedure for DFB Complexes. A sample of about 0.1 mmol of DFB was weighed directly and placed in the cell. The appropriate metal salt solution and a 5.00-mL aliquot of 1.000 M KCl were then added. The final volume was made up to 50.00 mL with water. The vessel was sealed, and after an initial equilibration of 1–2 h under inert-gas flow, the standard 0.100 M KOH solution was added incrementally with suitable allowance of time for equilibrium to be established. Procedures for the complexes of BAMTPH and the dihydroxamates were similar, except that titrations were carried out in 0.10 M KNO_3, with 1.00 mmol solutions of the metal ion being titrated with 1.00–2.00-mmol solutions of the dihydroxamic acid.

Data Reduction. The potentiometric data were processed by using the programs BEST[17] and MINIQUAD.[18] The metal ion titrations for DFB were

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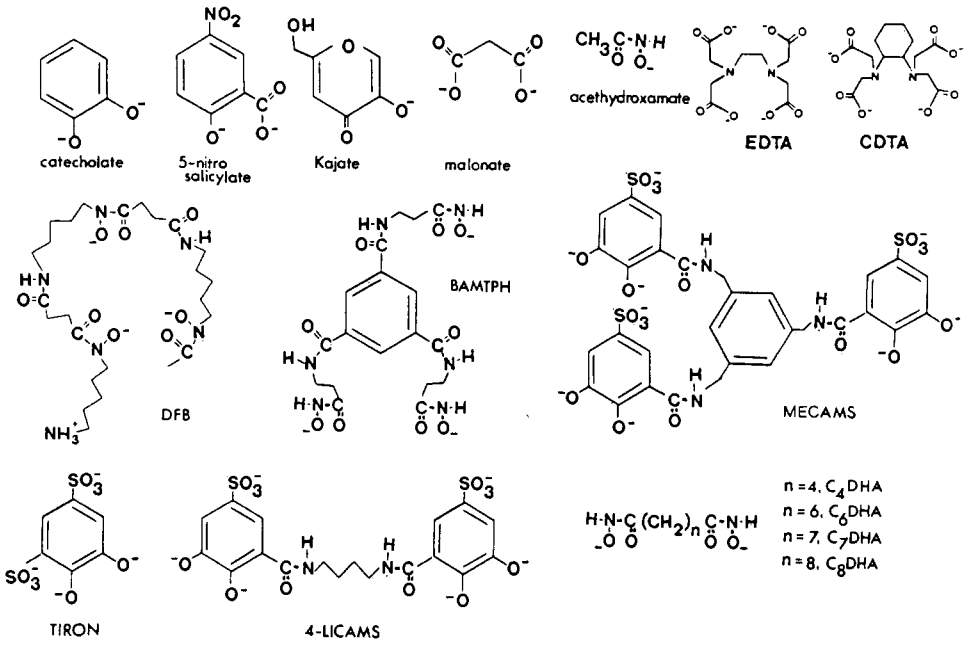

Figure 2. Structure of ligands discussed in this paper.

Table I. Protonation Constants and Formation Constants for Desferriferrioxamine-B[a]

metal ion	quotient[b]	log K[c]	σ-fit[d]
H^+	HL/H·L	10.79	0.001
	H_2L/HL·H	9.55	
	H_3L/H_2L·H	8.96	
	H_4L/H_3L·H	8.32	
Al^{3+}	MHL/M·HL[c]	24.14	0.011
	MH_2L/MHL·H	1.18	
	MHL/ML·H	9.43	
	ML/M·L	24.50	
Ga^{3+}	MLH/M·HL	28.17	0.014
	MHL/ML·H	10.31	
	ML/M·L	28.65	
In^{3+}	MHL/M·HL	20.60	0.007
	MH_2L/MHL·H	3.15	
	MHL/ML·H	10.00	
	ML/M·L	21.39	
Fe^{3+}	MHL/M·HL	30.60	ref 29
	MH_2L/MHL·H	0.94	ref 29
	MHL/ML·H	10.40	0.026 (this work)
	ML/M·L	30.99	this work

[a] Constants as determined in this work in 0.100 M KCl at 25.0 °C, except where indicated, by glass-electrode potentiometry. [b] The quotient in the equilibrium constant K, as indicated, where H is the proton, M is the metal ion indicated, and L is the deprotonated ligand DFB^{3-}. [c] This constant is that referred to here and in the work of Schwarzenbach,[29] as "log K_1", and refers to the complex that has the apparently noncoordinated amine group protonated. [d] σ-fit is the standard deviation computed from calculated pH values relative to those observed experimentally.[30]

processed by also including the protonation constant of the methane sulfonate and all of the applicable metal ion hydrolysis constants. Of particular relevance is the $[Ga(OH)_4]^-$ formation constant, which allows the formation constant for DFB to be evaluated[19] at high pH, even though the complex of DFB does not break up appreciably at the lowest pH values attained in the titrations.

The dihydroxamate ligands form ML and MLH type complexes with the metal ions studied. This includes the Fe(III) system, for which no indication of complexes of the type M_2L_3 was found, in contrast to Raymond et al.[20] in their study of *N*-alkyl-substituted dihydroxamic acids of differing chain lengths. The nonobservation of M_2L_3 type complexes in this study undoubtedly is related to the fact that ligand to metal ratios much in excess of one were not achieved in the concentration ranges employed here.

Table II. Protonation Constants and Formation Constants for Dihydroxamate Ligands and for BAMTPH[a]

	C_4DHA	C_6DHA	C_7DHA	C_8DHA	BAMTPH
log K_1[b]	9.38 (2)	9.61 (2)	9.65 (1)	9.52 (2)	
log K_2	8.81 (2)	8.92 (2)	9.02 (1)	8.82 (2)	
log K for					
$Cu^{II}L$[c]	13.11 (2)	13.40 (5)	13.60 (7)	13.54 (4)	
$Cu^{II}LH$[d]	17.06 (6)	17.53 (3)			
UO_2L	13.27 (4)	12.95 (2)	13.07 (4)	13.28 (6)	
UO_2LH	17.50 (5)	17.50 (1)	17.48 (2)	16.92 (8)	
$Ni^{II}L$	7.63 (1)		8.92 (2)	8.78 (3)	
$Ni^{II}LH$	14.43 (2)		14.89 (4)		
$Zn^{II}L$	7.76 (1)	8.05 (1)		8.80 (3)	
$Zn^{II}LH$	14.51 (2)	14.92 (2)			
$Mg^{II}L$	3.33 (1)	3.73 (1)	4.37 (2)	4.34 (2)	6.42 (6)
$Mg^{II}LH$	12.43 (3)	12.53 (2)	12.64 (6)	12.47 (9)	15.11 (6)
$Co^{II}L$	7.35 (2)			7.40 (3)	
$Co^{II}LH$	14.37 (3)				
$Cd^{II}L$	6.16 (2)			6.22 (3)	
$Cd^{II}LH$	13.73 (2)				
$Ca^{II}L$				4.94 (7)	
$Fe^{III}L$	17.60 (3)	18.01 (2)	20.08 (6)	20.30 (8)	
$Th^{IV}L$	16.36 (1)			18.44 (8)	
$Al^{III}L$	14.20 (1)	14.59 (1)	15.55 (1)	15.29 (3)	
$In^{III}L$	14.86 (1)	15.32 (1)	15.93 (1)	16.08 (1)	22.83 (3)
$La^{III}L$	9.01 (4)	9.59 (3)	9.98 (3)	10.33 (3)	14.42 (2)
$Yb^{III}L$					18.08 (2)

[a] All constants measured at 25.0 °C in 0.100 M $NaNO_3$. Numbers in parentheses are the standard deviations indicated by the program MINIQUAD.[18] [b] The protonation constants refers to the following equilibria. log K_1: $H^+ + L^{2-} = HL^-$. log K_2: $HL^- + H^+ = H_2L$. [c] The constants indicated as ML, where M is the metal ion and L is the ligand, refer to the equilibrium M + L = ML. [d] The constants indicated as MLH refer to the equilibrium M + L + H = MLH, where M is the metal ion, L the ligand, and H the proton (charges omitted for simplicity).

Results and Discussion

The formation constants for the complexes of DFB, BAMTPH, and the dihydroxamic acids determined here are presented in Tables I and II. The formation constant of the Al(III) complex of DFB is log K_1 = 24.14, considerably lower than that of Fe(III) at 30.60.[14] It is not clear whether this low selectivity of DFB for Al(III) relative to that for Fe(III) would be enough to allow for

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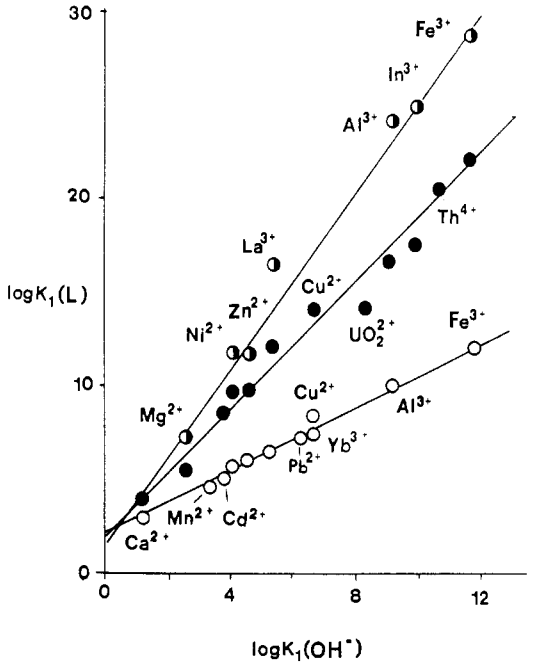

Figure 3. Correlation of log K_1 values for the hydroxamic acid ligands acetohydroxamate (○), C_8DHA (●), and BAMTPH (◑) against log $K_1(OH^-)$ values for the same set of metal ions. log K_1 values are from ref 14 and this work.

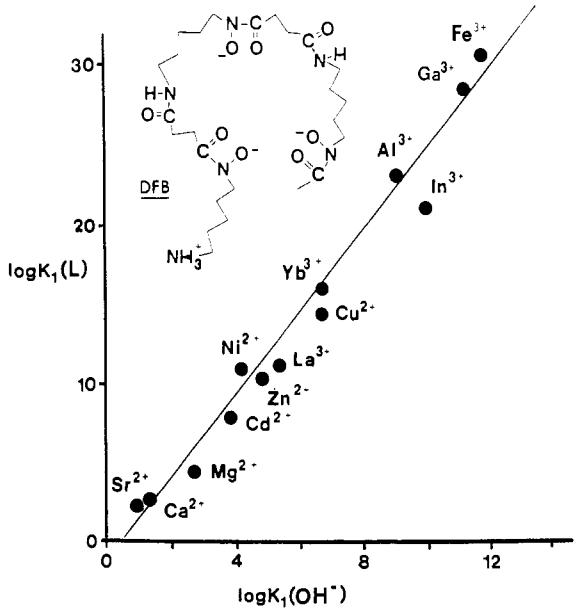

Figure 4. Correlation of log K_1 values for DFB against log $K_1(OH^-)$ values for a variety of metal ions. Data are from ref 14 and this work.

use of DFB as proposed[15] for the treatment of Al(III) intoxication.

In Figure 3 is seen a correlation of log K_1 for acetohydroxamate, C_8DHA, and BAMTPH versus $K_1(OH^-)$ for the same metal ions. For all three ligands, excellent linear relationships result. The slopes of these relationships increase with increasing numbers of hydroxamate groups. In Figure 4 is seen the relationship of log K_1 for the complexes of DFB against log K_1 for the hydroxo complexes. A good linear relationship results, and log K_1 for the Al(III) complex of DFB as predicted by the correlation (23 log units) is in close agreement with that finally determined. In Figure 5 is seen a plot of log K_1 for the ligand 4-LICAMS of Kappel and Raymond,[21] versus log $K_1(OH^-)$ for the hydroxo complexes. Also included in Figure 5 is the correlation involving log K_1 for the ligand TIRON.[11] Although not reproduced here, the pM value

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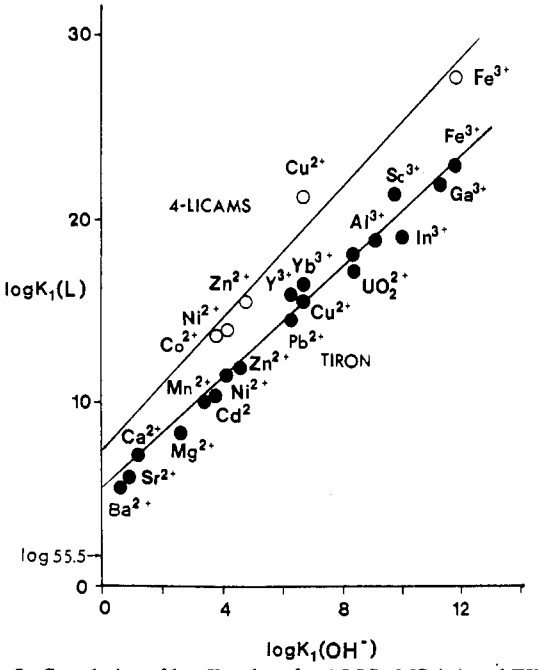


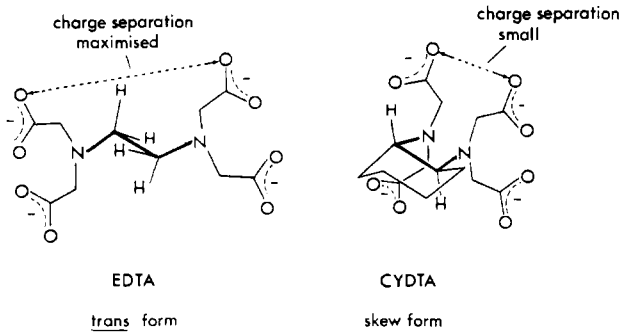
Figure 5. Correlation of log K_1 values for 4-LICAMS (○) and TIRON (●) against log $K_1(OH^-)$ values. Data are from ref 1 and 14. The intercepts are higher than expected for TIRON (log 55.5 for a bidentate ligand) and for 4-LICAMS (3 log 55.5 for a tetradentate ligand) on the basis of theories of the chelate effect discussed[12,13] in the text, which is typical of sulfonated ligands.

(which is the negative log of the free metal ion concentration in the presence of 0.01 mM excess ligand at biological pH 7.4) for the MECAMS complexes[21] also gives an excellent correlation with log $K_1(OH^-)$. The impression that one gains is that correlations such as those in Figures 1 and 3–5 are fairly typical for ligands with negatively charged donors, even those as complex as DFB, BAMTPH, and probably MECAMS. This simple behavior means that it should be fairly simple to predict the stability of complexes of ligands with negative oxygen donors. However, if the order of complex stability is fixed as the order of affinity for the hydroxide ion, it will be difficult to engineer the selectivity order away from that established in Figures 1 and 3–5.

As pointed out in the Introduction, for ligands containing two negatively charged O-donors, or a single negative oxygen donor and a carbonyl group, the value of the intercept is (Figure 1) usually very close to log 55.5, as required by eq 1. It is not clear at this stage why neutral carbonyl groups (reviewer's query) have the same effect on the intercept as a negative O-donor, except that they may acquire some negative charge from the adjacent RO^- group. Equation 1 predicts that for tetradentate ligands such as C_8DHA, or hexadentate ligands such as BAMTPH and DFB, the intercepts should be, respectively, 3 log 55.5 (5.22 log units) or 5 log 55.5 (8.7 log units). As seen in Figures 3 and 4, the intercepts fall short of these expectations. It has been established[10] that where the size of the chelate ring exceeds a ring size of six, the intercepts fall below the expected value of log 55.5 for bidentate ligands. The log 55.5 contribution to the chelate effect is[12] an entropy effect. Increase in length of the bridge connecting the donor atoms causes an unfavorable entropy contribution to the free energy of complex formation[10] and is manifested as a drop in the intercept in correlations such as Figures 3–5. It is suggested that the drop in the intercepts in Figures 3 and 4 relates to the greater "chelate ring size" produced by the long connecting bridges between the hydroxamate or catecholate groups, where, for example, the "chelate rings" that involve the connecting bridges between the hydroxamate groups in the DFB are of ring size 14.

A further factor destabilizing complexes of ligands with long connecting bridges between donor atoms is repulsion between electrostatically charged groups. Thus, for example, it is found that when the ethylene bridge of EDTA is immobilized as it is in CYDTA (Figure 2) by a cyclohexane ring as connecting bridge,

Chart I



there is a uniform entropy-related increase in log K_1 for all metal ions of about 3 log units.[14] This has been interpreted[22] in terms of stabilizing the skew form of CYDTA relative to the trans form, which is the more stable form of EDTA due to electrostatic repulsion between the charged acetate groups. (Chart I). In ligands such as C_8DHA, BAMTPH, DFB, or MECAMS, with their long connecting bridges, an important factor in destabilizing the complex, and contributing to a lowering of the intercepts in correlations such as those in Figures 3 and 4, is the fact that conformers of the ligand that are likely to be suitable for complex formation will be destabilized by electrostatic repulsion between charged hydroxamate or catecholate groups. It seems likely, by analogy with EDTA, that the most stable conformers for polydentate hydroxamate or catecholate ligands such as DFB or MECAMS will be those in which the distance between the charged donor atoms can be maximized, and an important factor in determining complex stability will be the increase in energy required to get the ligand into the right conformation for complex formation. This problem has recently been studied[23] with molecular mechanics (MM) calculations, in relation to the origin of the much higher[1] stability of the complexes of enterobactin than of ligands such as MECAM. It was concluded[23] that enterobactin is stabilized in the appropriate conformer for complex formation by hydrogen bonding between the amide hydrogens and the oxygens in the macrocyclic ring. In these calculations the energies of the free ligands were calculated with the donor atoms protonated. Thus, the question of how electrostatic repulsion would stabilize the equatorial conformers of the ligands relative to the axial conformers was not considered. The equatorial conformers of enterobactin are not able to coordinate completely to a single hexacoordinate metal ion, while the axial conformers are those observed in complexes of Fe(III). One would suggest that, by analogy with the example of EDTA and CYDTA, electrostatic repulsion would lead to the equatorial conformer of ligands such as enterobactin and MECAM being the more stable and that an important factor in producing ligands of greater binding strength would be structural changes in the ligands that would stabilize the axial conformers relative to the equatorial conformers. The importance of structural rigidity and preorganization is seen in the very high stability of the complexes with UO_2^{2+} of the calixarene-based ligand CALIX 6, seen in Figure 6, and the selectivity of CALIX-6 for the uranyl ion relative to other metal ions.[24] (Preorganization means that the ligand is restricted to the conformer required for complex formation.[25])

An interesting feature of Figure 5 is the high intercept observed for both the ligands TIRON and 4-LICAMS. This is generally observed[11] when sulfonic acid groups are present on aromatic donor groups and is also found with polyphosphates. The observed high

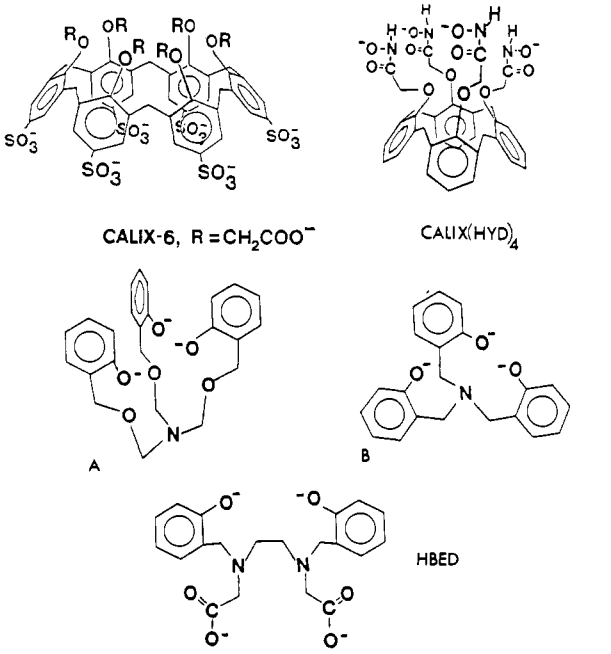


Figure 6. Newly emerging types of ligand discussed in this work.

intercepts are of a size that would be expected if all the sulfonic acid groups were also coordinated to the metal ion. Models suggest that in these ligands the simultaneous coordination of the sulfonic acid and the other donor groups present is sterically impossible,[11] so that the origin of the stabilization is not readily apparent. Electron-withdrawing sulfonic acid groups raise the intercept of correlations such as seen in Figures 1, 3, 4, and 5 but, as would be expected from the lowered basicity of the oxygen donor atoms, cause a flattening of the slope of the correlation.[11] Thus, in general, sulfonation of aromatic groups bearing phenolic type oxygen donors should lead to a loss of selectivity for metal ions such as Fe(III), or Al(III), relative to metal ions such as Ca(II), or Zn(II), which are usually more weakly coordinated. Sulfonation of ligands such as MECAM, which was carried out to promote water solubility,[1] is likely to lower selectivity for Fe(III) or Al(III) relative to biologically important metal ions such as Zn(II) or Ca(II).

The correlations in this paper have suggested that it will be difficult to control selectivity of ligands containing only negatively charged oxygen donor ligands away from the order of the log $K_1(OH^-)$ values of the metal ions concerned. One approach is to attach the negative oxygen donors to structurally rigid organic molecules, as with CALIX-6 discussed above, which is selective[24] for the uranyl ion because of the ability of the latter ion to accommodate the planar six-coordination demanded by the ligand. Such an approach is being followed by the present authors with ligands such as CALIX(HYD)$_4$ in Figure 6. Another approach is to introduce donor atoms other than the negative oxygen donor, which will then allow for an alteration of the ligand selectivity in the direction of the affinity of the metal ions under consideration for the new types of donor atom. One useful donor atom in this regard is the neutral oxygen donor, whose addition leads to a shift in selectivity of the ligand toward larger metal ions.[26] Thus, ligands such as A in Figure 6 should show a marked shift in selectivity toward large metal ions as compared with ligand B. Another useful alteration is the addition of the saturated neutral nitrogen donor. Both the saturated nitrogen and oxygen donors have a single advantage over negative oxygen donors in that the neutral oxygen or nitrogen donor can also serve as a point of connection for adjacent chelate rings, as in ligands such as polyethers or polyamines. The negative oxygen donor can, however, use only one valency for connection to the organic part of the ligand, and so cannot serve to connect adjacent chelate rings (see Chart II).

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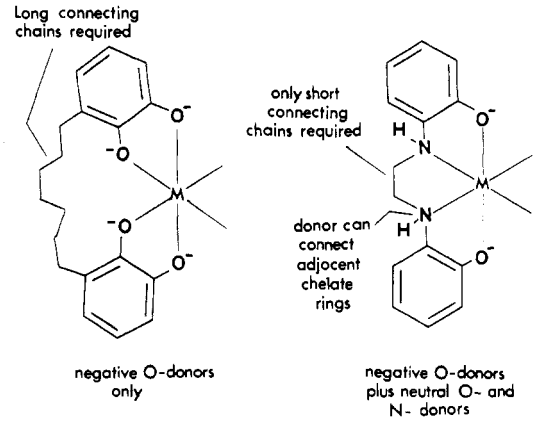
Chart II



It is this fact that leads to the need for very long connecting bridges in ligands with only negative oxygen donors. It is the long connecting bridges that lead to lowered complex stability because of the unfavorable entropy effects, and the elimination of long connecting bridges when phenolates are connected together as in HBED in Figure 6 means that ligands with a mixture of negative oxygen donors and nitrogen donors, placed so as to eliminate the need for long connecting bridges, must be considered very seriously in design of ligands for the selective complexation of metal ions such as Fe(III).

One is left to ask what effect the introduction of saturated nitrogen donors will have on selectivity. This can be answered in terms of the log $K_1(NH_3)$ values that have been estimated from models of the chelate effect.[27] The values of log $K_1(NH_3)$ for metal ions of interest in this paper are listed as follows:

metal ion	Ca(II)	Zn(II)	Cu(II)	La(III)	Gd(III)	Lu(III)
log $K_1(NH_3)$	−0.2	2.1	4.1	0.3	0.5	0.7
metal ion	Al(III)	Ga(III)	In(III)	UO_2^{2+}	Th(IV)	Fe(III)
log $K_1(NH_3)$	0.8	4.1	4.0	2.0	0.4	3.8

The effect on complex stability that the nitrogen donor has when incorporated into a ligand is very closely related to its log K_1 value with NH_3, the archetypal saturated nitrogen donor.[27] Thus, one would anticipate from the low estimated log $K_1(NH_3)$ for Al(III) that selectivity of ligands for Al(III) relative to Fe(III), which has a high affinity for NH_3, would be very adversely affected by the presence of nitrogen donors, as is indeed observed to be the case for EDTA.[14] The selectivities that ligands having negative O-donors display toward Ga(III), In(III), and Fe(III) relative to other metal ions are not adversely affected by the addition of one or two nitrogen donors, and it may thus indeed be true that ligands of the HBED type may ultimately prove to be the most successful for Ga(III), In(III), and Fe(III).

The effect of chain lengths on complex stability is seen in Figure 7, where log K_1 for a selection of metal ion complexes with dihydroxamic acids has been plotted as a function of the length of the hydrocarbon chain connecting the two hydroxamic acid groups. The response of the log K_1 values to variation in the length of the connecting chain in the dihydroxamate ligand is reasonably strong for most metal ions. This is in contrast to the situation found by Raymond et al.[20] in their study of *N*-isopropyl-substituted dihydroxamates of varying hydrocarbon chain length, where it was found that there was almost no variation of log K_1 for the Fe(III) complexes as a function of the length of the connecting hydrocarbon chain. One would suggest thus this situation possibly arises with the ligands of Raymond et al. because of a balance between improved fit of the ligand onto the Fe(III) as the chain length increased and steric crowding brought about by the presence of the *N*-isopropyl groups. It is seen that the variation of log K_1 as a function of chain length in Figure 7 differs somewhat from metal

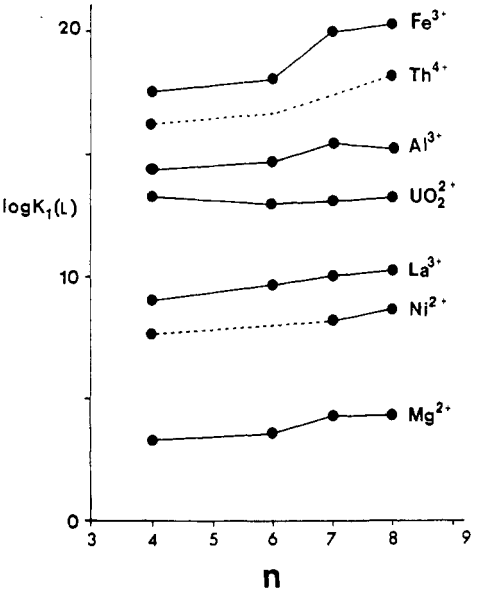


Figure 7. Stabilities of complexes of dihydroxamic acids, $HONHCO(CH_2)_nCONHOH$, as a function of n, the number of methylene groups in the alkane bridge, for a variety of metal ions. Data are from this work.

ion to metal ion, although the general tendency is for log K_1 to increase with increasing chain length and flatten as a chain length of seven is reached. This is a somewhat shorter chain length than found in DFB itself, which has connecting chains of nine atoms between the hydroxamate groups. This probably reflects the need for longer chain lengths in DFB brought about by the more sterically demanding presence of three rather than two hydroxamate groups. It is of interest to note that the response of log K_1 to increasing chain length in Figure 7 of a metal ion such as Fe(III) is much stronger than for most other metal ions and suggests that achieving adequate chain length will be of considerable importance in producing selectivity of the ligand for Fe(III) relative to other metal ions. The Al(III) ion response to increasing chain length is such that log K_1 peaks at a shorter chain length than does Fe(III), which possibly reflects the smaller size[28] of the Al(III) than the Fe(III) ion, and suggests that ligand selectivity for Al(III) relative to Fe(III) might be enhanced by shorter connecting chains between functional groups. The very flat response in log K_1 to increasing chain length in Figure 7 for metal ions such as Mg(II) possibly reflects the rather ionic nature of the metal to ligand bonding, which leads to greater insensitivity to steric effects, which lead to poor orientation of the hydroxamate groups for coordination to the metal ion.

The conclusions drawn from this work are the following: (1) the stability of complexes with negative oxygen donors only closely correlates with the affinity of the metal ion for the hydroxide ion, and this correlation extends to complex ligands of biological importance such as DFB and polycatecholate ligands; (2) the observation of the latter correlations means that it will be difficult to alter the observed selectivity orders but that these orders may be altered by steric means or the introduction of donor groups other than the negative oxygen donor; (3) the addition of sulfonic acid groups will probably lead to a flattening off of the selectivity for highly charged metal ions such as Fe(III) or Al(III) relative to metal ions of lower charge such as Ca(II) or Zn(II); (4) increasing the lengths of the chains connecting hydroxamate groups in dihydroxamate ligands produces maximum complex stability in the vicinity of chains consisting of eight methylene groups.

Acknowledgment. We thank the Council Research Grants Committee of the University of the Witwatersrand and the

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Registry No. C_4DHA, 4726-83-4; C_6DHA, 38937-66-5; C_7DHA, 18992-11-5; C_8DHA, 5578-84-7; DFB, 70-51-9; BAMTPH, 87834-24-0; Al, 7429-90-5.

Contribution from the Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

Electron-Transfer Reactions of Manganese(II) and -(III) Polyamino Carboxylate Complexes in Aqueous Media[1]

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The kinetics of electron-transfer reactions involving the manganese(II) and -(III) complexes of ethylenediaminetetraacetate ($edta^{4-}$) and *trans*-1,2-cyclohexanediaminetetraacetate ($cdta^{4-}$) have been investigated in aqueous media. The cross-reactants employed in this study are osmium and cobalt tris(polypyridine) complexes, $IrCl_6^{2-}$, and nickel polyaza complexes. The cross-reaction kinetic data have been correlated in terms of the Marcus relationship for outer-sphere electron-transfer reactions, and a self-exchange rate constant of 0.7 ± 0.4 M^{-1} s^{-1} was derived for the $Mn(edta)(OH_2)^{2-/-}$ and $Mn(cdta)(OH_2)^{2-/-}$ couples at 25 °C. Deviations from this correlation were observed for the metal tris(polypyridine) complexes (reduced rate constants attributed to poor orbital overlap and hydrophobic/hydrophilic repulsions) and for a nickel(II) dioxime species, $Ni(Hdiox)^+$ (enhanced reactivity related to a hydrogen-bonded precursor). The self-exchange rate constant is discussed in terms of the inner-sphere reorganization barriers to the exchange of an antibonding $d\sigma^*$ electron.

Introduction

Electron-exchange reactions of manganese(II/III) couples have received less attention in comparison with other metal(II/III) couples of the first transition row. While the $Mn(H_2O)_6^{3+}$ ion is unstable with respect to disproportionation except in strongly acidic solution, the Mn(III) oxidation state may be stabilized in neutral solutions by chelating ligands, such as Schiff bases and the polyamino carboxylates.[2,3] We have been interested recently in the electron-transfer reactions of octahedral Mn(II/III) complex couples containing oxygen donor ligands and have investigated reactions involving $Mn(H_2O)_6^{2+/3+}$,[4] $Mn(urea)_6^{2+/3+}$,[5a] and $Mn(bpyO_2)_3^{2+/3+}$ ($bpyO_2$ = 1,1′-dioxo-2,2′-bipyridine).[5b] The cross-reaction kinetic data were analyzed in terms of the Marcus relationship to yield relatively slow rates of electron exchange (10^{-4}–10^{-2} M^{-1} s^{-1}) for the Mn(II)/Mn(III) couples. This observation is consistent with the large barrier originating in the energy required to change the inner-sphere configuration prior to the exchange of an antibonding $d\sigma^*$ electron. In these high-spin d^5/d^4 complex couples the Mn–O bond distance difference between the Mn(II) and Mn(III) species is 0.18–0.20 Å.[4,5]

In order to extend these investigations to other Mn(II)/Mn(III) complexes, we have studied the electron-transfer reactions of ethylenediaminetetraacetate ($edta^{4-}$) and *trans*-1,2-cyclohexanediaminetetraacetate ($cdta^{4-}$) complexes of manganese. The redox reactions of the $Mn(edta)(OH_2)^{2-/-}$ (E° = 0.82 V)[7] and $Mn(cdta)(OH_2)^{2-/-}$ (E° = 0.81 V)[8] couples have previously been studied with a variety of cross-reactants, with the majority of these reactions believed to be proceeding via an inner-sphere mechanism.[6] Relatively few reactions have been identified as outer-sphere processes from which the Mn(II)/Mn(III) self-exchange rate constant may be derived.[9,10] The $Mn(cdta)(OH_2)^-$ ion has also recently been employed in electron-transfer kinetic studies with metalloproteins such as the high-potential iron–sulfur proteins,[11] the blue copper rusticyanin,[12] cytochrome c_{551},[13] and cytochrome oxidase.[13]

In this paper we report the results of kinetic studies of the reactions of the $Mn(cdta)(OH_2)^{2-/-}$ and $Mn(edta)(OH_2)^{2-/-}$ couples with a series of cross-reactants, $IrCl_6^{2-}$, osmium and cobalt tris(polypyridine), and nickel polyaza complexes, in aqueous solution. The kinetic data have been analyzed in terms of the Marcus relations, and self-exchange rate constants have been derived for the two couples. The exchange rate constants are discussed in terms of the structures of the manganese species in solution and the barriers to electron self-exchange. The rate constants for some of the reactions have been studied as a function of pH to determine the relative reactivities of protonated and deprotonated forms of the oxidized ($Mn(edta)(OH_2)^-$ and $Mn(edta)(OH)^{2-}$) and reducted ($Mn(Hedta)(OH_2)^-$ and $Mn(edta)(OH_2)^{2-}$) complexes.

Experimental Section

Materials. Manganous perchlorate (Alfa), ethylenediaminetetraacetic acid (BDH), and *trans*-1,2-cyclohexanediaminetetraacetic acid (BDH) were used as received. The manganese(II) complex ions, $Mn(edta)(OH_2)^{2-}$ and $Mn(cdta)(OH_2)^{2-}$, were generated in solution by the ad-

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