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2,3-Dihydroxyterephthalamides: Highly Efficient Iron(III)-Chelating Agents[1]

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The synthesis and ferric ion complexation of a general series of 2,3-dihydroxyterephthalamides are described. These ligands are more acidic than other catechol ligands and are much more effective sequestering agents at neutral pH. The proton association constants are as follows: 2,3-dihydroxy-*N*,*N*'-dimethylterephthalamide log β_{011} = 11.1 (1), log β_{012} = 17.2 (1); 2,3-dihydroxy-*N*,*N*'-diethylterephthalamide log β_{011} = 11.1 (1), log β_{012} = 17.1 (1); 2,3-dihydroxy-*N*,*N*'-dipropylterephthalamide log β_{011} = 11.0 (1), log β_{012} = 17.0 (1); 2,3-dihydroxy-*N*,*N*'-dibutylterephthalamide log β_{011} = 11.0 (1). Formation constants of the ferric complexes were determined by potentiometric and spectrophotometric studies: 2,3-dihydroxy-*N*,*N*'-dimethylterephthalamide log β_{130} = 41.8 (1), log β_{120} = 30.9 (1), log β_{110} = 16.4 (1); 2,3-dihydroxy-*N*,*N*'-diethylterephthalamide log β_{130} = 42.2 (1), log β_{120} = 30.7 (1), log β_{110} = 16.3 (1); 2,3-dihydroxy-*N*,*N*'-dipropylterephthalamide log β_{130} = 43.1 (1), log β_{120} = 31.2 (1). The resultant equilibrium free metal ion concentrations (-log [Fe^{3+}] = pM, a direct measure of a ligand's ability to bind a metal at physiological pH; for 10^{-5} M total ligand and 10^{-6} M total iron(III)) are as follows: 2,3-dihydroxy-*N*,*N*'-dimethylterephthalamide, 21.1; 2,3-dihydroxy-*N*,*N*'-diethylterephthalamide, 21.6; 2,3-dihydroxy-*N*,*N*'-dipropylterephthalamide, 22.7. These are the highest pM values yet observed in a bidentate ligand for Fe(III), making these ligands effective iron(III)-chelating agents by themselves and promising constituent subunits for multidentate sequestering agents.

Introduction

The naturally occurring, low molecular weight iron(III)-sequestering agents (siderophores) produced by microbes typically possess three bidentate ligating subunits in order to accommodate the preferred octahedral coordination geometry of iron(III).[2] The most powerful of the siderophores is enterobactin (log $K_f \simeq 52$),[3] which contains three 2,3-dihydroxybenzamide binding subunits (subunit type A in Figure 1) pendant from a triserine backbone. Recently, Vögtle,[4,5] Martell,[6] and we[7-9] have produced macrobicycles such as **12** and **13** and macrocycles such as **14** (Figure 2) based not on the 2,3-dihydroxybenzamide moiety A found in enterobactin but on the 2,3-dihydroxyterephthalamide B as the binding subunit. Entropic considerations have been the dominant rationale behind this work. Margerum[10] and others[11-13] have used the term "macrocyclic effect" to describe the increased stability gained by a chelating agent when all binding subunits are incorporated into a macrocycle or macrobicycle. However, in this strategy toward a more effective chelating agent, the enthalpic properties of the new binding subunit have not been considered. This is perhaps surprising, since addition of another electron-withdrawing group onto the aromatic ring is predicted to lower significantly the catechol protonation constants. The first solution thermodynamic studies on the new sequestering agents have not shown a macrocyclic effect. The formation constant for the ethane trimer, **14**, is 5 log units less than that for TRENCAM, **11**, a tripodal ligand with three 2,3-dihydroxybenzamide binding subunits.[7] More recently, however, Vögtle and co-workers have claimed a formation constant of 10^{59} for **12**, a value 7 orders of magnitude higher than that for enterobactin.[5] This stability constant represents a dramatic departure from results obtained by this laboratory, as well as by Martell's[6] laboratory. In all of these new macrocyclic ligands both the ligand topology and the binding subunit have been varied. Thus, it is unclear what effects are dominant in the binding of iron by the new chelating agents. Knowledge of the complexation behavior of the new binding subunits individually, without any skeletal macrocyclic structure, is crucial to an understanding of the effect of ligand topology on the hexadentate chelating agents. We report here a detailed investigation of the coordination chemistry of the bidentate 2,3-dihydroxyterephthalamide ligands.

Experimental Section

Thionyl chloride was purified by distillation from triphenyl phosphite. All liquid amines were purified by distillation from sodium. Water was deionized, distilled, and further purified by a Millipore cartridge system (resistivity 18 × 10^6 Ω cm). Water for titrations was also degassed and put under an inert atmosphere. All other compounds used were reagent grade and were not further purified. Spectra were collected on the following instruments: NMR, a custom built 200-MHz FT[14] spectrometer; IR, a Nicolet 5/DX FT spectrometer. Melting points were taken on a Büchi apparatus and are uncorrected. Microanalyses were performed by the Analytical Services Laboratory, University of California, Berkeley, CA. Mass spectra were recorded by the Mass Spectrometry Laboratory, University of California, Berkeley, CA.

Titration data were collected on a custom-built automatic spectrophotometric titration apparatus composed of an HP 8450 UV/vis spectrophotometer (with stirring and constant-temperature apparatus for 1-cm cell), a Fisher Accumet pH meter with a Corning calomel combination electrode, a Metrohm 655 Dosimat automatic buret, a custom-blown water-jacketed 10-cm quartz cell, a Brinkman Lauda K-2/R constant-temperature bath, and a computer equivalent to an IBM-XT. BASIC programs COYOTE (1-cm cell) and TIMBERWOLF (10-cm cell) were used to run the apparatus.[15] Data analysis was performed on an IBM-AT computer using the REFSPEC[16] spectral componentization and least-squares program. Due to limited aqueous solubility, the ligands were added as CH_3OH solutions with a calibrated Gilmont pipet to high-pH

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(1) Ferric Ion Sequestering Agents. 20. Part 19: Scarrow, R. C.; Raymond, K. N. *Inorg. Chem.* **1988**, *27*, 4140.
(2) Raymond, K. N.; Müller, G.; Matzanke, B. F. *Top. Curr. Chem.* **1984**, *123*, 50-102.
(3) Harris, W. R.; Carrano, C. J.; Cooper, S. R.; Sofen, S. R.; Avdeef, A.; McArdle, J. V.; Raymond, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 6097-6104.
(4) Wolfgang, K.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 714.
(5) Stutte, P.; Kiggen, W.; Vögtle, F. *Tetrahedron* **1987**, *43*, 2065-2074.
(6) Sun, Y.; Martell, A. E.; Motekaitis, R. J. *Inorg. Chem.* **1986**, *25*, 4780.
(7) Rodgers, S. J.; Ng, C. Y.; Raymond, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 4094-4095.
(8) McMurry, T. J.; Rodgers, S. J.; Raymond, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3451-3453.
(9) McMurry, T. J.; Hosseini, M. W.; Garrett, T. M.; Hahn, F. E.; Reyes, Z. E.; Raymond, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 7196-7198.
(10) Cabbiness, D. K.; Margerum, D. W. *J. Am. Chem. Soc.* **1969**, *91*, 6540-6541.
(11) Busch, D. H.; Farmery, K.; Goedken, V.; Katovic, V.; Melnyk, A. C.; Sperati, C. R.; Tokel, N. *Adv. Chem. Ser.* **1971**, *No. 100*, 44.
(12) Lehn, J.-M. *Science (Washington, D.C.)* **1985**, *227*, 849-856.
(13) Martell, A. E. *Development of Iron Chelators for Clinical Use*; Elsevier North Holland: New York, 1981; pp 67-104.
(14) Abbreviations and symbols used in the text include: FT, Fourier transform; DMF, *N*,*N*-dimethylformamide; EDTA, ethylenediaminetetraacetic acid; DMB, 2,3-dihydroxy-*N*,*N*-dimethylbenzamide; MTA, 2,3-dihydroxy-*N*,*N*'-dimethylterephthalamide; ETA, 2,3-dihydroxy-*N*,*N*'-diethylterephthalamide; PTA, 2,3-dihydroxy-*N*,*N*'-dipropylterephthalamide; BTA, 2,3-dihydroxy-*N*,*N*'-dibutylterephthalamide; DTA, 2,3-dihydroxy-*N*,*N*'-didecylterephthalmide; p[H^+] = -log [H^+]; pH = -log a_H; s = singlet; d = doublet; t = triplet; q = quintet; m = multiplet; br = broad; $R = [\sum(Y_{obs} - Y_{calc})^2/\sum Y_{obs}^2]^{1/2}$, where Y is the dependent variable. Definitions for the equilibrium constants used in the text include the following. (a) Stepwise constant K_{rst}: (i) for $t = 0$, $K_{rst} = [M_rL_s]/[M_rL_{s-1}][L]$, representing $M_rL_{s-1} + L \rightleftarrows M_rL_s$; (ii) for $r = 0$, $K_{rst} = [L_sH_t]/[L_sH_{t-1}][H]$, representing $L_sH_{t-1} + H \rightleftarrows L_sH_t$. (b) Cumulative constant $\beta_{rst} = [M_rL_sH_t]/[M]^r[L]^s[H]^t$.
(15) Loomis, L. D. Ph.D. Dissertation, University of California at Berkeley, 1986.
(16) Scarrow, R. C. Ph.D. Dissertation, University of California at Berkeley, 1985.

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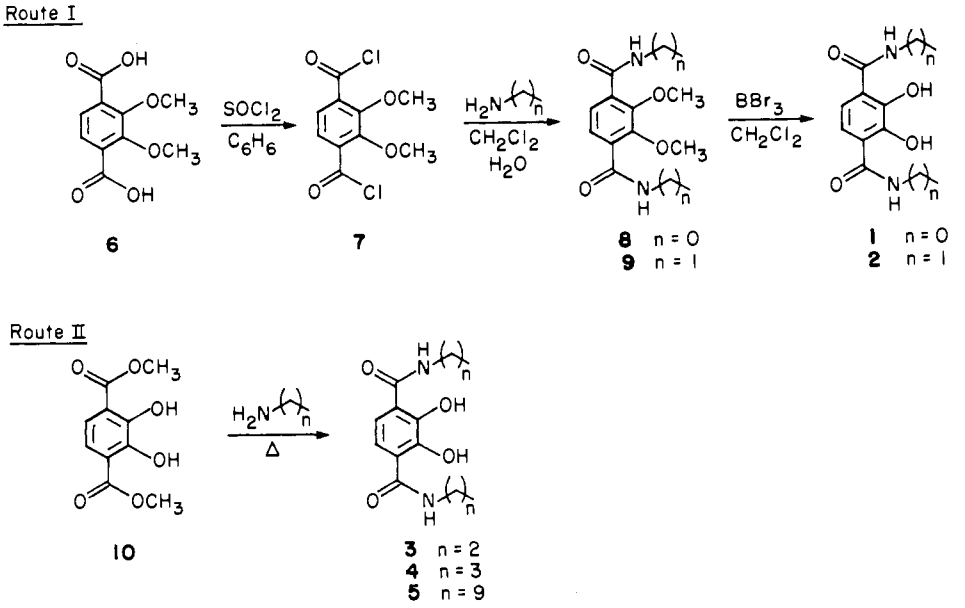
Scheme I



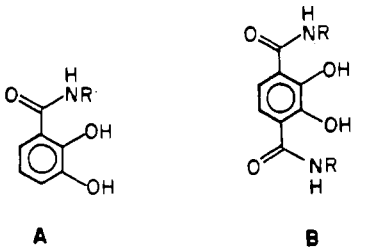


Figure 1. Bidentate binding subunits used in catechoylamide (A) and 2,3-dihydroxyterephthalamide (B) Fe(III)-sequestering agents.

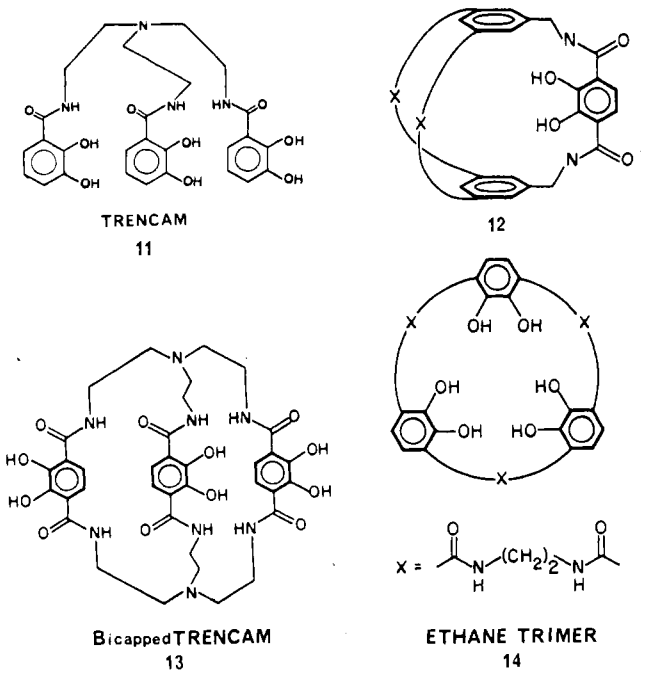


Figure 2. Recently synthesized catechoylamide Fe(III)-sequestering agents.

aqueous solutions at 0.1 M ionic strength (KCl electrolyte) held at 25 °C (resulting in less than 0.4% methanol) to give a final concentration of 2.40×10^{-5} M. The iron solution (1.00×10^{-5} M Fe^{3+} and 3.00×10^{-5} M ligand), standardized by EDTA titration with variamine blue as an indicator, was added as a weak HCl solution, also with a calibrated Gilmont pipet. The solution was titrated to low pH with 0.1 M HCl. After the titration the solution was back-titrated to high pH with concentrated KOH to check for hysteresis (i.e. irreversible behavior); none was found. All experiments were run under an argon atmosphere, excluding O_2. The electrode was calibrated in concentration units with degassed solutions of $10^{-2.30}$ M HCl and $10^{-2.295}$ M KOH at 0.1 M ionic strength (KCl). The appropriate value of $10^{-13.78}$ for K_w was used.[17]

Compounds **6** and **10** were prepared in four steps (37% yield)[7] and three steps (47% yield),[18] respectively, by previous methods from commercially available starting materials.

Compounds Prepared via Route I, Scheme I. 2,3-Dimethoxyterephthaloyl Chloride (7). To a 250-mL round-bottom flask containing 30 mL of benzene, 2 drops of DMF, and 15 mL of freshly distilled $SOCl_2$ (20.6 mmol, 15 equiv) was added 3.0 g (13.3 mmol, 1 equiv) of 2,3-dimethoxyterephthalic acid, and the mixture was heated at reflux overnight under nitrogen. The solvent was then coevaporated three times with 15 mL of benzene to give an oil, and the product solidified at −15 °C; yield 3.3 g (95%). An IR spectrum evinced an acyl chloride stretch at 1781 cm^{-1}. This product was used without further purification.

2,3-Dihydroxy-*N*,*N*'-dimethylterephthalamide (MTA, 1). Amide Formation (8). To 15 mL of CH_2Cl_2 was added 1.1 g (4.2 mmol) of the acid chloride **7**, and the solution was placed in an addition funnel. A 1-mL portion of a 40% aqueous solution (13 mmol) of NH_2CH_3 was added to 45 mL of H_2O in a 250-mL three-neck flask. The pH was maintained above 10 with 0.5 M NaOH in a second addition funnel. The acid chloride solution was added slowly, and the mixture was stirred vigorously with a mechanical stirrer for 9 h. The aqueous layer was extracted four times with 100 mL of CH_2Cl_2, the extract was combined with the organic layer of the reaction mixture, and the solvent was evaporated to give a solid. Recrystallization was accomplished by using a 1:6 ratio of CH_2Cl_2:hexanes; yield 0.977 g (93.5%). IR spectroscopy revealed an amide stretch at 1640 cm^{-1}. ^1H NMR[14] ($CDCl_3$): δ 7.95 (s, 2 H), 7.85 (br s, 2 H), 4.00 (s, 6 H), 3.00 (d, 6 H). Anal. Calcd (found) for $C_{12}H_{16}N_2O_4$: C, 57.19 (57.20); H, 6.39 (6.53); N, 11.10 (11.30).

Deprotection (1). In 45 mL of CH_2Cl_2 in a 250-mL three-neck flask was dissolved 0.967 g (4 mmol) of the amide **8**. After the apparatus was placed under N_2, 2.8 mL of BBr_3 (28 mmol) was added carefully, and the slurry was stirred for 24 h. The cloudy yellow mixture turned clear yellow upon the addition of 50 mL of MeOH via an addition funnel. After another 3 h of stirring, the solvent was evaporated, then the mixture was combined with another 50 mL of MeOH, and the solution was heated to a rolling boil. The solvent was evaporated again, and the procedure of heating with 50 mL of MeOH followed by evaporation was repeated 16 times: yield 0.68 g (75%); mp 224 °C. EIMS: parent ion at m/e 224. ^1H NMR (DMSO-d_6): δ 8.8 (br s, 2 H), 7.3 (s, 2 H), 2.8 (s, 6 H). Anal. Calcd (found) for $C_{10}H_{12}N_2O_4 \cdot H_2O$: C, 49.58 (50.01); H, 5.84 (5.51); N, 11.57 (11.64).

2,3-Dihydroxy-*N*,*N*'-diethylterephthalamide (ETA, 2). Amide Formation (9). To a 250-mL three-neck round-bottom flask were added 30

(17) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum: New York, 1976; Vol. IV, p 1.
(18) Weitl, F. L.; Raymond, K. N.; Durbin, P. W. *J. Med. Chem.* **1981**, *24*, 203–206.

mL of CH_2Cl_2, 40 mL of H_2O, and 0.323 mL (6.3 mmol, 2 equiv) of a 70% solution of ethylamine. The reaction flask was cooled to 0 °C by immersion in an ice bath. To this mixture, under N_2, was added a solution of 1 g (3.8 mmol, 1 equiv) of the acid chloride **7** in 15 mL of CH_2Cl_2 by dropwise addition with vigorous stirring (mechanical stirrer). A solution of 30 mL of 0.5 M NaOH was added concurrently by another addition funnel to maintain the pH above 10. After 3 h the stirring was stopped, the phases were allowed to separate, and the organic layers were extracted with 4 × 25 mL of CH_2Cl_2, dried, filtered, and evaporated until white crystals formed: yield 0.55 g (73%); mp 103 °C. ^{1}H NMR ($CDCl_3$): δ 8.3 (br s, 2 H), 7.2 (s, 6 H), 3.9 (s, 6 H), 3.25 (m, 4 H), 1.1 (t, 6 H). Anal. Calcd (found) for $C_{14}H_{20}N_2O_4$: C, 59.98 (59.87); H, 7.19 (7.24); N, 9.99 (10.03).

Deprotection (2). To 0.2 g (0.7 mmol, 1 equiv) of the amide **9** in 10 mL of CH_2Cl_2 was added 0.965 mL (10 mmol, 7 equiv) of neat BBr_3. The mixture was stirred at room temperature for 3 h. The solvent from the resultant yellow slurry was evaporated. The yellow residue was taken up in hot MeOH and the solvent evaporated. This process was repeated 15 times. Upon condensation of the methanol solution on the last evaporation, white crystals formed: yield 0.085 g (48%); mp 215 °C. EIMS: parent ion at *m/e* 252. ^{1}H NMR (DMSO-d_6): δ 8.3 (s, 2 H), 7.3 (s, 2 H), 3.4 (m, 4 H), 1.2 (t, 6 H). Anal. Calcd (found) for $C_{12}H_{16}N_2O_4 \cdot H_2O$: C, 53.31 (53.12); H, 6.73 (6.80); N, 10.37 (10.21).

Compounds Prepared via Route II, Scheme I. 2,3-Dihydroxy-*N*,*N*′-dipropylterephthalamide (PTA, 3). To 30 mL (0.4 mol, 83 equiv) of propylamine was added 1 g (4.4 mmol, 1 equiv) of **10**. The solution was refluxed for 2 days. The excess amine was removed by evaporation and then extraction with 3 × 100 mL of 0.5 M HCl from a 150-mL ethyl acetate solution. Crystallization was achieved in hot ethyl acetate: yield 1.03 g (84%); mp 194 °C. ^{1}H NMR (DMSO-d_6): δ 8.8 (s, 2 H), 7.3 (s, 2 H), 3.3 (m, 4 H), 1.5 (q, 4 H), 0.9 (t, 6 H). Anal. Calcd (found) for $C_{14}H_{20}N_2O_4$: C, 59.97 (59.74); H, 7.21 (7.10); N, 9.99 (9.96).

2,3-Dihydroxy-*N*,*N*′-dibutylterephthalamide (BTA, 4). To 30 mL (0.3 mol, 69 equiv) of *n*-butylamine was added 1.0 g (4.4 mmol, 1 equiv) of dimethyl 2,3-dihydroxyterephthalate (**10**). The mixture was refluxed for $1^1/_2$ days. The solvent of the light yellow reaction mixture was evaporated, and the solids were redissolved in ethyl acetate and extracted with 3 × 100 mL of 0.5 M HCl. The organic layer was dried with sodium sulfate, the solvent was evaporated, and the product was recrystallized from ethyl acetate: yield 1.36 g (87%); mp 130 °C. ^{1}H NMR (DMSO-d_6): δ 8.8 (t, 2 H), 7.3 (s, 2 H), 3.3 (q, 4 H), 1.5 (m, 4 H), 1.3 (m, 4 H), 0.9 (t, 6 H). Anal. Calcd (found) for $C_{16}H_{24}N_2O_4$: C, 62.30 (62.28); H, 7.86 (7.83); N, 9.09 (9.05).

2,3-Dihydroxy-*N*,*N*′-didecylterephthalamide (DTA, 5). To 60 mL (0.3 mol, 68 equiv) of decylamine was added 1 g (4.4 mmol, 1 equiv) of **10**. The solution was refluxed for 2 days. Partitioning of the excess amine precluded extraction of the organic layer as a useful purification route. The amine was separated by swirling the reaction mixture and Bio-Rad AG50W-X8 100–200 mesh cationic exchange resin (H^+ form) together in a beaker. The resin was rinsed with THF to remove all product from the beads, and the resulting filtrate was evaporated. Crystals were obtained from ethyl acetate as pure white rods: yield 0.8 g (45%); mp 118 °C. ^{1}H NMR (DMSO-d_6): δ 7.3 (s, 2 H), 6.8 (t, 2 H), 3.4 (q, 4 H), 1.6 (m, 8 H), 1.3 (m, 24 H), 0.8 (t, 6 H). Anal. Calcd (found) for $C_{28}H_{48}N_2O_4$: C, 70.53 (70.3); H, 10.17 (10.1); N, 5.88 (5.7).

Results and Discussion

Synthesis. The two routes used in the synthesis of these compounds are shown in Scheme I. Route I is the more general and has been used extensively in the synthesis of catechoylamides. Here route I was employed in the preparation of 2,3-dihydroxy-*N*,*N*′-dimethylterephthalamide (MTA, **1**) and 2,3-dihydroxy-*N*,*N*′-diethylterephthalamide (ETA, **2**). These compounds are derivatives of gaseous amines, thus precluding the use of route II, which requires a liquid amine to serve as both nucleophile and solvent. Route I proceeds in three steps from the known compound 2,3-dihydroxyterephthalic acid (**6**). In the first step, reaction with $SOCl_2$ produces the acid chloride, which was used without purification. The methyl-protected ligands **8** and **9** were then made by reaction of **7** with aqueous solutions of methylamine or ethylamine under biphasic Schotten–Bauman conditions. Aqueous extraction of the organic phase to remove excess amine followed by evaporation and crystallization gave the desired products in 73–94% yield. Deprotection was afforded by reaction with BBr_3 in CH_2Cl_2 in 48–75% yield.

Route II proceeds in one step from the previously synthesized diester **10** in 45–87% yield. The reaction is accomplished simply by refluxing **10** in neat amine. The excess amine was removed by evaporation and extraction and the product purified by crystallization. The ligands 2,3-dihydroxy-*N*,*N*′-dipropylterephthalamide (PTA, **3**), 2,3-dihydroxy-*N*,*N*′-dibutylterephthalamide (BTA, **4**), and 2,3-dihydroxy-*N*,*N*′-didecylterephthalamide (DTA, **5**) were synthesized by this one-step procedure.

Table I. λ_{max} and ε for the 2,3-Dihydroxyterephthalamide Ligands

ligand	protonation state	λ_{max}, nm	ε, M^{-1} cm^{-1}
MTA (**1**)	L^{2-}	384	4800
	HL^-	360	4000
	H_2L	335	2700
ETA (**2**)	L^{2-}	384	4700
	HL^-	360	3800
	H_2L	332	2600
PTA (**3**)	L^{2-}	381	4700
	HL^-	360	3800
	H_2L	330	2500
BTA (**4**)	L^{2-}	385	4600
	HL^-	360	3860

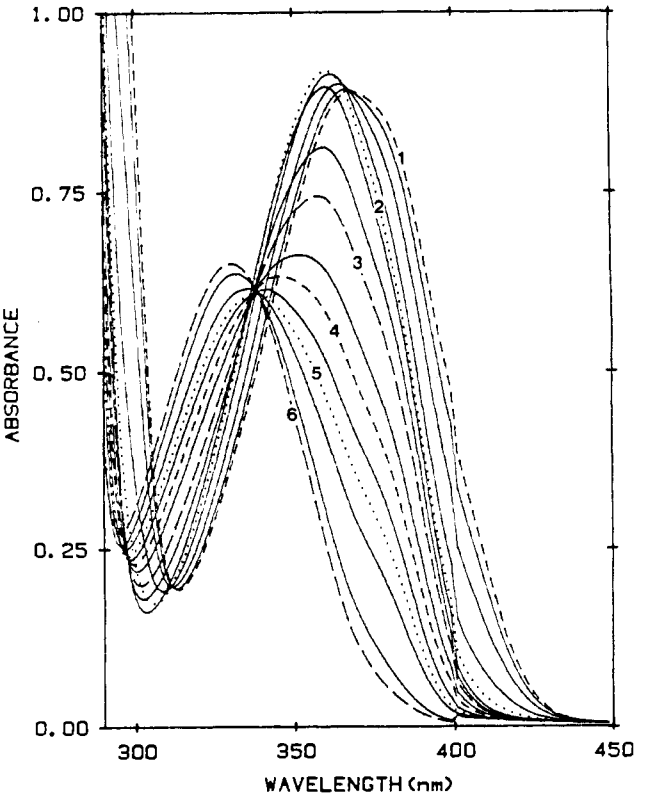


Figure 3. Family of spectra generated by spectrophotometric titration of MTA (**1**): (1) p[H^+] 11.057; (2) p[H^+] 9.700; (3) p[H^+] 6.302; (4) p[H^+] 5.663; (5) p[H^+] 4.965; (6) p[H^+] 2.971.

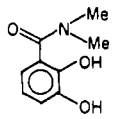
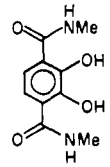
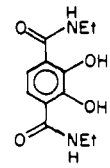
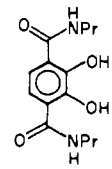
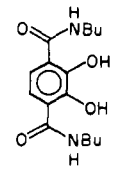
Note Added in Proof. Two German patents (in French) describe the preparation of some 2,3-dihydroxyterephthalamides and their organic derivatives: *Chem. Abstr.* **1978**, *78*, 159279e; **1975**, *75*, 5913h.

Ligand Equilibria. The protonation behavior of the *N*-methyl, *N*-ethyl, and *N*-propyl amide derivatives was studied by spectrophotometric methods. The methyl compound shows a $\pi \rightarrow \pi^*$ transition for the doubly deprotonated ligand at 384 nm (ε = 4800 M^{-1} cm^{-1}), which shifts to 360 nm (ε = 4000) for the singly protonated species, and moves again to 335 nm (ε = 2700) for the fully protonated compound. The ethyl and propyl compounds show similar behavior (Table I). The family of spectra (e.g. Figure 3) produced by titrations were analyzed by means of a three-component model composed of two consecutive one-proton steps:

$$L^{2-} \overset{H^+}{\rightleftharpoons} LH^- \overset{H^+}{\rightleftharpoons} LH_2 \qquad (1)$$

Refinement resulted in *R* factors ≤1.5%.[14] The resulting protonation constants are tabulated in Table II, and the corresponding species distributions are shown in Figure 4.

Table II. Protonation and Formation Constants for the 2,3-Dihydroxyterephthalamides[a]

					
	1	2	3	4	
log K_{110}	17.8	16.4 (1)	16.3 (1)	16.0[b]	
log K_{120}	13.9	14.5 (1)	14.4 (1)	15.2 (1)	
log K_{130}	8.5	10.9 (1)	11.5 (1)	11.9 (1)	
log β_{130}	40.2	41.8	42.2 (1)	43.1 (1)	
pM	15.0	21.1	21.6	22.7	
log K_{011}	12.1[b]	11.1 (1)	11.1 (1)	11.0 (1)	11.0 (1)
log K_{012}	8.42	6.1 (1)	6.0 (1)	6.0 (1)	

[a] pM = −log [Fe] at pH 7.4; $[L]_T = 10^{-5}$ M; $[Fe]_T = 10^{-6}$ M. [b] Estimate.

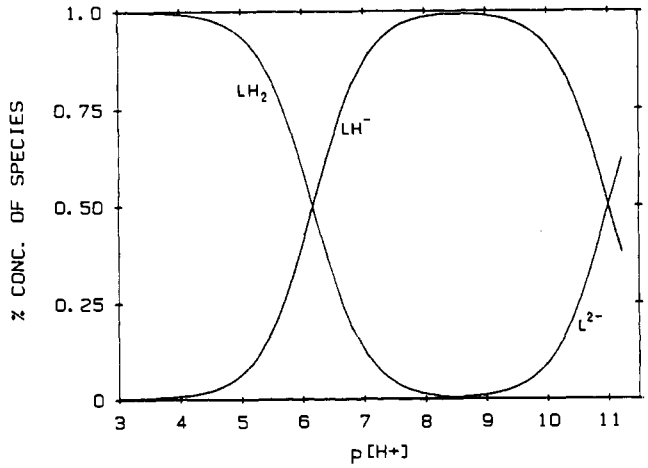


Figure 4. Species distribution of the MTA ligand.

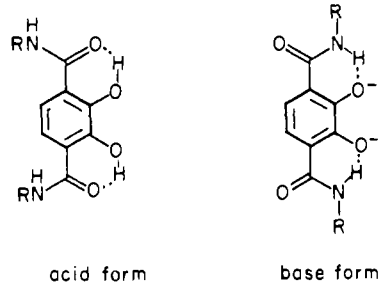


Figure 5. Proposed acid and base forms of the 2,3-dihydroxyterephthalamide ligand.

The ligand protonation constants are dramatically lower for the terephthalamides as compared to the benzamide catechol derivatives. This is expected from the more extended π network available to the anionic charge produced upon deprotonation. In addition, the deprotonated form of the terephthalamides may be stabilized by hydrogen bonding to the amide hydrogen, forming the stable six-membered rings seen in Figure 5. Recent X-ray studies have shown the presence of these hydrogen-bonded forms in a ferric complex of a tris(terephthalamide) ligand.[9]

There are no significant differences between the protonation constants of the terephthalamide series. The H_2L form of BTA (**4**) precipitates at about 10 μM concentration, making the detection of the second protonation constant inaccessible by the spectrophotometric method.

Ferric Complex Equilibria. The ferric complexes of the *N*-methyl, *N*-ethyl, and *N*-propyl amide derivatives were also studied by spectrophotometric methods. The tris methyl complex shows $\pi^* \rightarrow$ d ligand-to-metal charge-transfer bands at 446 nm (ϵ = 5700) and 510 nm (ϵ = 5400) from pH 12 to about pH 7. From pH 7 to pH 5 there is a buffer region, and from pH 5 to pH 4.4 the bis complex shows a LMCT band at 577 nm (ϵ = 4300). From pH 4.4 to pH 3.4 there is another buffer region, and then from pH 3.4 the monomeric complex shows LMCT bands at 410 nm (ϵ = 2000) and 691 nm (ϵ = 2000). The monomeric complex slowly disappears as the solution is titrated below pH 3.4. The *N*-ethyl and *N*-propyl amide derivatives show similar behavior (Table III). The family of spectra generated by titration (e.g. Figure 6) were fit with a nine-component model. Three of these components were identified in the visible spectra during factor-

Table III. λ_{max} and ϵ for the Ferric Complexes of the 2,3-Dihydroxyterephthalamide Ligands

complex	λ_{max}, nm	ϵ, M^{-1} cm^{-1}	λ_{max}, nm	ϵ, M^{-1} cm^{-1}
$[Fe(MTA)_3]^{3-}$	446	5700	510	5400
$[Fe(MTA)_2]^-$	577	4300		
$[Fe(MTA)]^+$	410	2000	691	2000
$[Fe(ETA)_3]^{3-}$	448	5790	509	5100
$[Fe(ETA)_2]^-$	577	3400		
$[Fe(ETA)]^+$	411	2000	689	2000
$[Fe(PTA)_3]^{3-}$	448	5800	511	5000
$[Fe(PTA)_2]^-$	577	3200		
$[Fe(PTA)]^+$	404	2000	669	2000

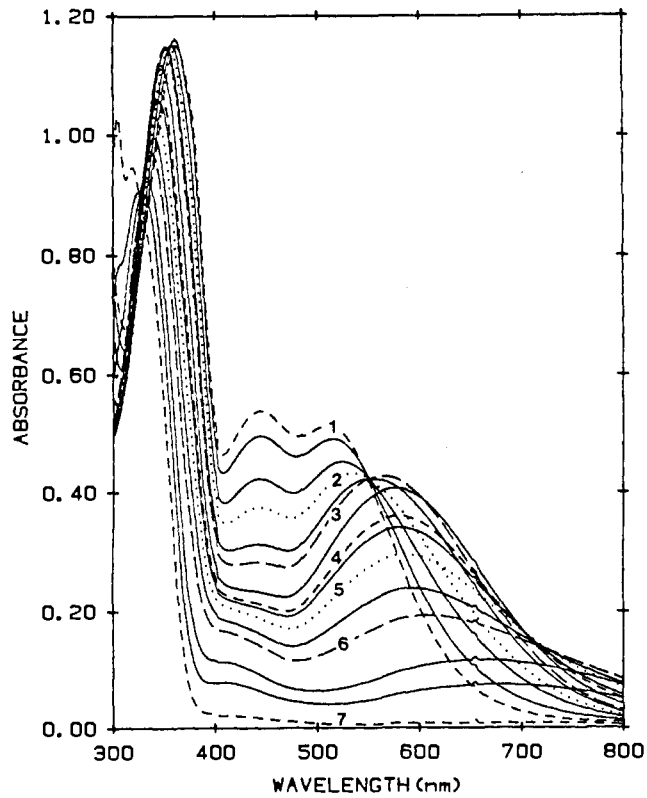


Figure 6. Family of spectra generated by spectrophotometric titration of $Fe(MTA)_n$: (1) p[H^+] 8.160; (2) p[H^+] 5.856; (3) p[H^+] 5.316; (4) p[H^+] 4.193; (5) p[H^+] 3.946; (6) p[H^+] 3.610; (7) p[H^+] 2.228.

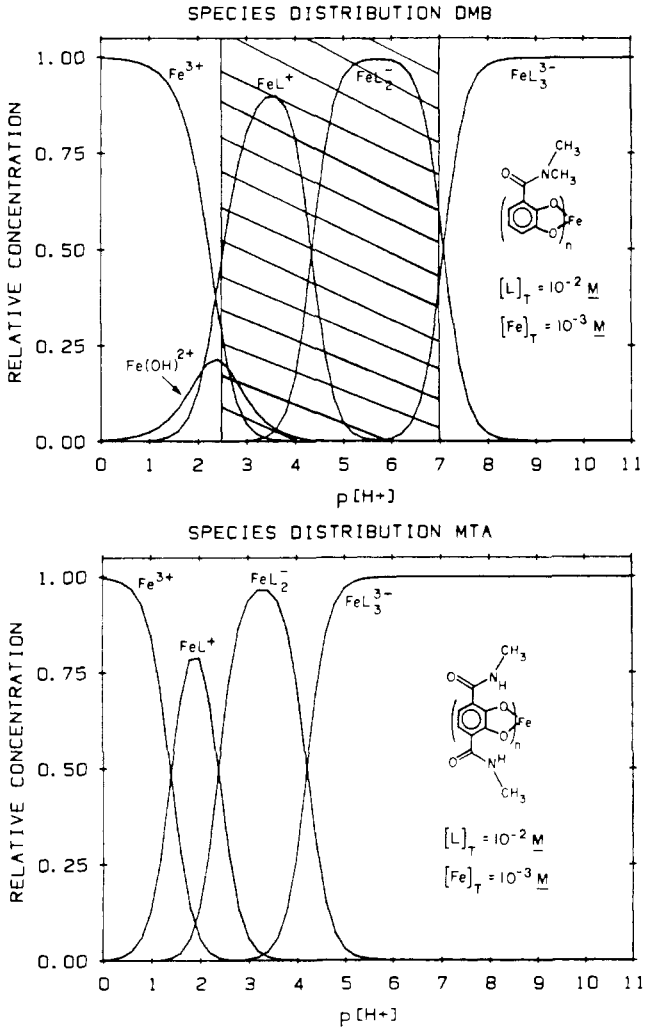


Figure 7. Species distributions for the ferric complexes of DMB and MTA. The cross-hatched region in the upper diagram shows where precipitation of $Fe(OH)_3$ is expected.

analysis componentization. These were assigned to ML, ML_2, and ML_3, related to each other by a series of two proton steps:

$$ML_3^{3-} \underset{-H_2L}{\overset{+2H^+}{\rightleftharpoons}} ML_2^{-} \underset{-H_2L}{\overset{+2H^+}{\rightleftharpoons}} ML^{+} \underset{-H_2L}{\overset{+2H^+}{\rightleftharpoons}} M^{3+} \qquad (2)$$

The other six components (assigned negligible visible absorbances in the region studied) were Fe^{3+}, L^{2-}, LH^{-}, LH_2, $Fe(OH)^{2+}$, and $Fe(OH)_2^{+}$. The final R factors were all $\leq 1.8\%$. The resulting stability constants are tabulated in Table II, and the corresponding species distribution curves are shown in Figure 7.

As can be seen clearly in Figure 7, these bidentate ligands demonstrate a much greater efficacy as chelating agents at pH 7.4 than do the dihydroxybenzamides. Under comparable conditions ($[L]_T = 10^{-2}$ M, $[M]_T = 10^{-3}$ M), MTA, the least powerful of the three ligands studied, remains as the FeL_3^{3-} complex until below pH 5, while, in contrast, the FeL_3^{3-} complex of DMB (**15**), begins to disassociate below pH 8. In fact, DMB is effectively demetalated below pH 7 due to precipitation of $Fe(OH)_3$, while the pH must be lowered below 1.5 to achieve greater than 50% demetalation of MTA. These results are a direct consequence of the lower ligand protonation constants coupled with a novel increase in the overall stability constant, β_{130},[14] for the terephthalamide ligands (vide infra).

For any weak acid ligand, as protonation constants decrease, the concentration of the free-ligand species necessary for metal binding at pH 7.4 increases, producing a more effective sequestering agent at lower pH. Normally, the decrease in protonation constant is accompanied by a decrease in metal–ligand binding constant. This effect is seen here in the lower K_{110}'s for the terephthalamides versus DMB.

In addition, there is normally a steady decrease in the stepwise formation constants as ligands are bound sequentially, such that $K_{110} > K_{120} > K_{130}$. The two major contributions to this are (1) the decrease in the metal ion acidity that occurs as ligands complex the ion sequentially and (2) the accumulation of charge on the complex as negatively charged ligands are brought together in the complex. However, notice that, although the K_{110} values are decreased relative to that for DMB, the K_{120} and K_{130} values are higher for the terephthalamide ligands. For the DMB complex (Table II) the average difference in log K for the sequential formation constants is 4.6, while for the *N,N'*-dimethylterephthalate ligand it is only 2.8. These correspond to free energy differences in sequential catechol ligand binding of 6.2 and 3.8 kcal/mol, respectively. In other words, while the first ligand group of the terephthalate ligands binds more weakly than that of the benzamide ligands, there is less of a decrease in stepwise formation constants for the subsequent ligands. We explain this by noting that in the terephthalamide ligands the increased π network can to some degree delocalize this charge relatively more than can the benzamides, resulting in a smaller decrease in each sequential stepwise formation constant. Thus, the equilibrium constant for the reaction

$$ML_2^{-} + L^{2-} \rightleftharpoons ML_3^{3-} \qquad (3)$$

is greater for L = **1**–**3** than for L = DMB (**15**). This novel result of increased ligand acidity coupled with an increased formation constant is reflected in the higher pM values of the terephthalamides. [The pM is a direct thermodynamic measurement of a ligand's ability to bind the metal at a given pH.] The pM values for the terephthalamides are the highest yet known for any bidentate ligand, up to 8 orders of magnitude higher than that of DMB.

Within the terephthalamide series the K_{130}'s increase as the ligands become more lipophilic. We ascribe this trend as due to the desolvation energy of the ligands. For the two equilibria

$$L^{2-} + ML_2^{-} \overset{K_{eq}}{\rightleftharpoons} ML_3^{3-} \qquad (4)$$

$$L'^{2-} + ML'_2{}^{-} \overset{K_{eq}}{\rightleftharpoons} ML'_3{}^{3-} \qquad (5)$$

where L and L' have the same protonation constants and both ML_3^{3-} and $ML'_3{}^{3-}$ are very soluble species, the equilibrium constant is larger for the least hydrophilic L and L' since that system has more desolvation energy to gain by forming the complex.

We ascribe the trend of K_{110} *decreasing* with increasing ligand lipophilicity as due to the desolvation energy of the complex. For the two equilibria

$$M^{3+} + L^{2-} \overset{K_{eq}}{\rightleftharpoons} ML^{+} \qquad (6)$$

$$M^{3+} + L'^{2-} \overset{K_{eq}}{\rightleftharpoons} ML'^{+} \qquad (7)$$

where again L and L' have the same protonation constants but now the complexed species ML^+ is less soluble than the reactants, K_{eq} will be larger for the system with the most hydrophilic L and L' because that system will form a relatively more soluble ML^+ complex, gaining more desolvation energy by complexation than the other system.

The butyl derivative again behaves very differently from the methyl, ethyl, and propyl cases. As acid was added to a high-pH solution of the ferric complex, a precipitate immediately developed; thus, we were unable to ascertain the equilibrium constants for the ferric complex of BTA.

Conclusions

The 2,3-dihydroxyterephthalamide ligands form surprisingly stable complexes for such relatively simple bidentate ligands. Their greater acidity relative to the 2,3-dihydroxybenzamide unit (found in enterobactin and other naturally occurring ferric ion chelating agents) was anticipated. However, the novel charge delocalization of these ligands slows the usual decrease in stepwise formation constants and strongly promotes the formation of the fully formed FeL_3 complex. This results in the highest pM ever seen in a

bidentate ligand (22.7 vs 15 for DMB or 20.0 for mimosine[19]), making these ligands the most effective bidentate iron(III)-chelating agents extant. These binding subunits are excellent iron chelators, even before incorporation into a macrocyclic or macrobicyclic structure.

(19) Stunzi, H.; Perrin, D. D.; Teitei, T.; Harris, R. L. N. *Aust. J. Chem.* **1979**, *32*, 21–30. Stunzi, H.; Harris, R. L. N.; Perrin, D. D.; Teitei, T. *Aust. J. Chem.* **1980**, *33*, 2207–2220.

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Supplementary Material Available: Figures S1–S4, showing sample Y_{obs} and Y_{calc} for MTA ligand titration (Y is a linear combination of the absorbance data), calculated extinction coefficient spectra for the MTA ligand, sample Y_{obs} and Y_{calc} for titration of ferric complexes of MTA, and calculated extinction coefficient spectra for ferric complexes of the MTA ligand (4 pages). Ordering information is given on any current masthead page.

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Effects of Anions on Redox Reactions. 2. Chromium(II) Reduction of $[Co(sep)]^{3+}$ (sep = Sepulchrate) in the Presence of Halide Ions

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Temperature-dependence studies on the Cr(II) reduction of $[Co(sep)]^{3+}$ (I = 0.5 M ($LiClO_4$)) provided the activation parameters $\Delta H^{\ddagger} = 9 \pm 2$ kcal mol^{-1} and $\Delta S^{\ddagger} = -43 \pm 5$ eu. In a chloride medium (I = 0.5 M ($LiCl + LiClO_4$)) the reaction was markedly accelerated, with $\Delta H^{\ddagger} = 11 \pm 2$ kcal mol^{-1} and $\Delta S^{\ddagger} = -28 \pm 5$ eu. The reaction was also carried out in the presence of bromide and iodide ions, showing significant rate enhancements. Analysis of experimental parameters suggests that the anion catalysis is best explained in terms of reduction of the entropic contribution to the activation energy through hydrogen-bonding interactions, originating from outer-sphere complexation of the reactants with the anions. The catalyzed rate constants for electron transfer seem to be the same for all the halides, with a value of $(2.5 \pm 0.3) \times 10^{-2}$ M^{-1} s^{-1}, whereas the ion-pairing formation constants at I = 0.5 M were estimated to be 5.5, 2.3, and 1.7 M^{-1} for Cl^-, Br^-, and I^-, respectively.

Introduction

Ever since the earliest studies on electron-transfer processes, the role of anions and specifically halides has attracted the attention of reseachers working in this field.[1-20] The original workers reported some remarkable catalytic effects, but interest in these studies faded after a fairly simple mechanism was suggested.[21] However, later investigations[22-26] in biologically interesting systems suggested that more detailed information on simple systems would be welcome. Our earlier studies[27] in this area were concerned with a comparison of the magnitudes of the catalytic effect of anions on inner-sphere and outer-sphere processes occurring in the same system. We found that inner-sphere paths in the Cr(II) reduction of $[Co(en)(ptdn)_2]^+$ (where ptdn is the abbreviation for pentane-2,4-dionato, also called acetylacetonato or acac) did not show any catalysis in the presence of chloride ions but the outer-sphere path was accelerated in the same medium. Our objective in the present work was to determine the role of the anion in the activated complex for electron transfer; specifically, we wished to determine if it functions simply to reduce the Coulombic repulsion between the cationic redox partners, as some have suggested, or if it functions by complexing to the labile reductant $[Cr(OH_2)_6]^{2+}$ to create a different reductant, $[Cr(OH_2)_5Cl]^+$, for example. In the case of Cr(II) reductions of proteins[26] such as cyt *c*, azurin, and cyt *a*, electrostatic interactions were considered to be inferior in importance to the symmetry and degree of orbital overlap between the reactants, facilitated by the anion, as the factor that determines the electron-transfer rate.

The synthesis of (*S*)-(1,3,6,8,10,13,16,19-octaazabicyclo-[6.6.6]eicosane)cobalt(III), or $[Co(sep)]^{3+}$ (sep = sepulchrate), reported by Sargeson and co-workers in 1977[28] provided an oxidant that is ideal for our purposes since it is symmetrical, is an obligate

(1) Taube, H.; Myers, H. *J. Am. Chem. Soc.* **1954**, *76*, 2103.
(2) Zwickel, A.; Taube, H. *J. Am. Chem. Soc.* **1961**, *83*, 793.
(3) Ardon, M.; Levitan, J.; Taube, H. *J. Am. Chem. Soc.* **1962**, *84*, 872.
(4) Manning, P. V.; Jarnagen, R. C. *J. Phys. Chem.* **1963**, *67*, 2284.
(5) Dulz, G.; Sutin, N. *J. Am. Chem. Soc.* **1964**, *86*, 829.
(6) Dodel, P. H.; Taube, H. *Z. Phys. Chem. (Munich)* **1965**, *44*, 92.
(7) Doyle, J.; Sykes, A. G. *J. Chem. Soc. A* **1965**, 795.
(8) Diebler, H.; Taube, H. *Inorg. Chem.* **1965**, *4*, 1029.
(9) Baker, B. R.; Orhanovic, M.; Sutin, N. *J. Am. Chem. Soc.* **1967**, *89*, 722.
(10) Przystas, T. J.; Sutin, N. *J. Am. Chem. Soc.* **1973**, *95*, 5545.
(11) Sutin, N.; Forman, A. *J. Am. Chem. Soc.* **1971**, *93*, 5274.
(12) Ng, F. T. T.; Henry, P. M. *Can. J. Chem.* **1975**, *53*, 3319.
(13) Pasternak, R. F.; Sutin, N. *Inorg. Chem.* **1974**, *13*, 1956.
(14) Pasternak, R. F. *Inorg. Chem.* **1976**, *15*, 643.
(15) Huth, S. W.; Kimberly, K. E.; Piszkiewicz, D.; Fleischer, E. B. *J. Am. Chem. Soc.* **1976**, *98*, 8467.
(16) Adegite, A.; Egboh, H.; Ojo, J. F.; Olieh, R. *J. Chem. Soc., Dalton Trans.* **1977**, 833.
(17) Akinyugha, N.; Ige, J.; Ojo, J. F.; Olubuyide, O.; Simoyi, R. *Inorg. Chem.* **1978**, *17*, 218.
(18) Adewumi, N.; Ige, J.; Ojo, J. F.; Olubuyide, O. *Inorg. Chem.* **1979**, *18*, 1399.
(19) Dekorte, J. M.; Owens, G. D.; Margerum, D. W. *Inorg. Chem.* **1979**, *18*, 1538.
(20) McAuley, A.; Olubuyide, O.; Spencer, L.; West, P. R. *Inorg. Chem.* **1984**, *23*, 2594.
(21) Early, J. E. *Prog. Inorg. Chem.* **1970**, *13*, 243.
(22) Kowalsky, A. *J. Biol. Chem.* **1969**, *244*, 6619.
(23) (a) Sutin, N.; Yandell, J. K. *Biol. Chem.* **1972**, *247*, 6932. (b) Yandell, J. K.; Fay, D. P.; Sutin, N. *J. Am. Chem. Soc.* **1973**, *95*, 1131.
(24) Przystas, T. J.; Sutin, N. *Inorg. Chem.* **1975**, *14*, 2103.
(25) Jones, G. D.; Jones, M. G.; Wilson, M. T.; Brunori, M.; Colosimo, A.; Sarti, P. *Biochem. J.* **1983**, *209*, 175.
(26) Jones, G. D.; Wilson, M. T. *J. Inorg. Biochem.* **1984**, *21*, 147.
(27) Lewis, N. A.; Ray, A. M. *Inorg. Chem.* **1984**, *23*, 3649.
(28) Creaser, I. I.; Harrowfield, J. MacB.; Herlt, A. J.; Sargeson, A. M.; Springborg, J.; Geue, R. J.; Snow, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 3181.

0020-1669/89/1328-0133$01.50/0