Ferric Ion Sequestering Agents. 1. Hexadentate O-Bonding *N,N′,N″*-Tris(2,3-dihydroxybenzoyl) Derivatives of 1,5,9-Triazacyclotridecane and 1,3,5-Triaminomethylbenzene

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Abstract: Two new types of sequestering agents for ferric ion have been prepared. Both are tris(2,3-dihydroxybenzoyl) (DHB) derivatives of triamines and are patterned after the microbial iron chelating agent enterobactin. Compound **10**, 1,5,9-*N,N′,N″*-tris(2,3-dihydroxybenzoyl)cyclotriazatridecane, was prepared from spermidine (**5**) and 2,3-dioxomethylenebenzoyl chloride. It consists of a flexible cyclic ring with three appended DHB groups. The second ligand type is based on the planar mesitylene group; 1,3,5-*N,N′,N″*-tris(2,3-dihydroxybenzoyl)triaminomethylbenzene (**15**) was prepared from trimesoyl chloride (**11**) and 2,3-dimethoxybenzoyl chloride (**1**). The model mono-DHB ligand, *N,N*-dimethyl-2,3-dihydroxybenzamide (**3**), was prepared from dimethylamine and the previously unreported 2,3-dioxosulfinylbenzoyl chloride (**4**). Compound **4** was not a useful synthon in the preparation of **10** or **15**. Preliminary pH-titration and optical spectroscopic data indicate that compound **15** (= H_6L) complexes Fe^{3+} more effectively than either **10** or **3** to give a tris(catecholate) complex, FeL^{3-}, which is fully formed at pH 8 and which removes Fe^{3+} from its human transferrin complex as effectively as does enterobactin.

Our approach to the design and synthesis of new sequestering agents for ferric ion has focused initially on catechol-containing analogues of enterobactin, a siderophore (microbial iron transport compound) whose formation constant ($\log K_f = 52$),[2] redox properties,[3] and mode of coordination[4-6] we have described previously. The enormous stability of the Fe^{3+}–enterobactin complex is the key factor in its role as the iron transport agent of enteric and other bacteria.[7] Recently the biosynthesis of another series of catechol-containing siderophores has been discovered.[8] The compounds are conjugates of the 2,3-dihydroxybenzoyl group (DHB) with spermidine (**1**). These products,[9] like enterobactin,[10] are capable of removing iron from the human iron transport protein, transferrin.

There is a critical need for new iron sequestering agents in the treatment of acute iron poisoning cases (the fifth or sixth most common household poison[11]) and chronic iron poisoning accompanying the transfusion therapy for the genetic disease Cooley's anemia (for which a major program is underway[12]). This has led us to a biomimetic approach to the synthesis of new hexadentate chelating agents based on the siderophores, which has begun with the preparation of tris(DHB) amides. These tricatechols are geometrically capable of encapsulating the ferric ion in an octahedral cavity analogous to that of enterobactin. Properties desired of these compounds are sufficient water solubility, good hydrolytic stability (in contrast to enterobactin, which is subject to facile ester hydrolysis), and good to moderate stability toward oxidation. We have recently prepared the tetra-DHB amides of several cyclic tetraamines via acylation with 2,3-dioxomethylenebenzoyl chloride followed by removal of the methylene O-protecting group with BCl_3.[13] A carbocyclic analogue of enterobactin has been prepared by using the acid-labile acetonide protecting group.[14] Prior to these results, the synthesis of DHB amides had been limited to biosynthesis[8] or DCC-mediated condensations of amino acids with DHB acid.[15] The lack of general synthetic routes to DHB amides has led us to the development of such procedures, which we report here. These include the use of 2,3-dioxomethylenebenzoyl chloride (**1a**), 2,3-dimethoxybenzoyl chloride (**1**), and 2,3-dioxosulfinylbenzoyl chloride (**4**). The latter compound was previously reported as "2,3-dihydroxybenzoyl chloride" in the synthesis of enterobactin by Corey et al.[16] In our hands it was not a useful synthon in the preparation of either of the target compounds **10** or **15** but was used in the preparation of the enterobactin model compound *N,N*-dimethyl-2,3-dihydroxybenzamide (**3** in Figure 1). The unsubstituted catechol sulfite (catechol and $SOCl_2$) is reported to be thermally and hydrolytically unstable.[17]

The general synthetic route to the spermidine derivatives is outlined in Figure 2. The addition of three tosyl groups to spermidine (**5**) gave the linear sulfonamide (**6**). This was then treated with sodium hydride in dimethylformamide (DMF) to give the terminal dianion in situ, which was cyclized to compound **7** by the addition of 1,3-ditosylpropane in DMF. Removal of the tosyl groups in concentrated sulfuric acid gave compound **8**, which was characterized as the trihydrochloride salt. Addition of 3 equiv of 2,3-dioxomethylenebenzoyl chloride to the free amine **4** gave **9** and deprotection of the catechol oxygen with BCl_3 in CH_2Cl_2 gave the hexadentate macrocycle **10**. Molecular models (CPK[18]) indicated that **10** can readily form an octahedral cavity composed of catechol oxygen atoms suitable for complexation of ferric iron. Ligand **10** is water soluble (~1 mg/mL, at neutral pH) and shows no evidence of hydrolysis or decomposition. A similar compound, 1,5,10-*N,N′,N″*-tris(2,3-dihydroxybenzoyl)triazadecane, is too water insoluble to be of use for our purposes or to be evaluated by the procedures described for **10** and **15** (vide infra).

An alternative structural type was approached by the synthesis of the benzene-based ligand **15** (shown schematically in Figure 3) in which we sought the absence of the ring conformational effects of ligands such as **10**, a recent carbocyclic analogue of enterobactin,[14] or enterobactin itself. In this procedure trimesoyl chloride (**11**) was treated with cold, concentrated ammonium hydroxide to provide the amide **12**. This was then reduced to the triamine, which was isolated as the trihydrochloride salt **13**. The addition of 3 equiv of 2,3-dimethoxybenzoyl chloride to the free amine of **13** gave **14**—from which the methyl O-protecting groups were removed with BBr_3 in CH_2Cl_2 to give the hexadentate ligand **15**.

Experimental Section

Melting points were taken on a Buchi apparatus in open capillaries and are uncorrected. ^1H NMR spectra were recorded on a Varian T-60 instrument using Me_4Si as internal standard. Infrared spectra were recorded on a Perkin-Elmer 283 instrument. Visible spectra were recorded on a Cary 118 spectrophotometer. Evaporations were ac-

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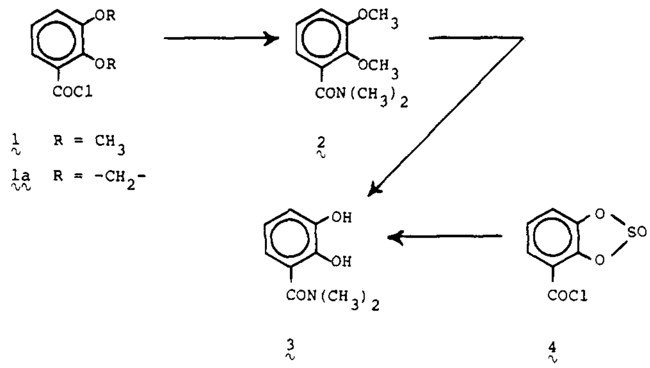

Figure 1. Synthesis of model compound 3.

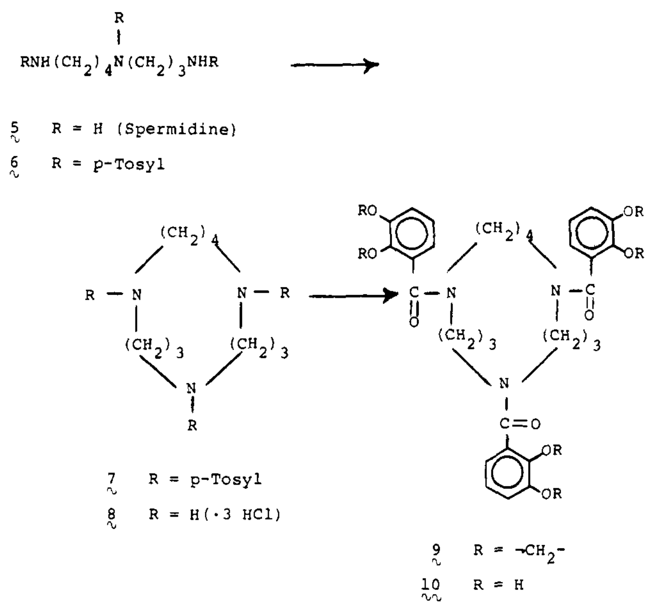

Figure 2. Synthesis of title compound 10.

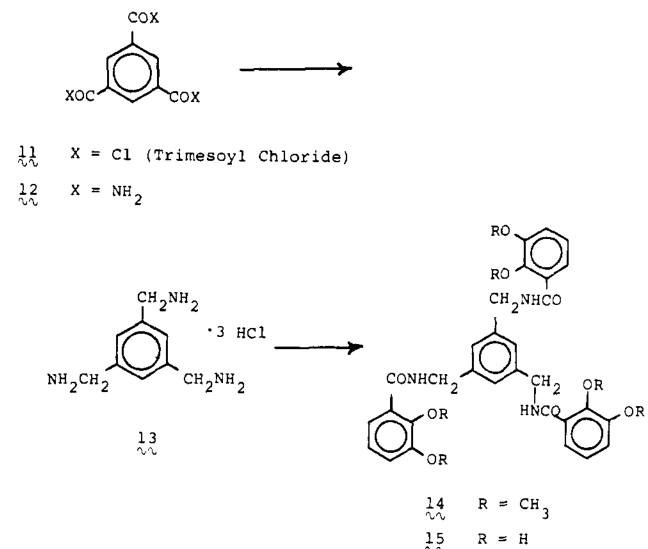

Figure 3. Synthesis of title compound 15.

complished in vacuo with a Buchi Rotovapor-RE at ≤55 °C. Thin layer chromatography (TLC) was performed on precoated 60 F-254 silica gel sheets which were developed in tetrahydrofuran (93 mL) /C_6H_{12} (7 mL)/H_2O, then visualized with UV, iodine, or Fe^{3+}/ H_2O/EtOH spray. Column chromatography was performed using 60-200 mesh silica gel in a 35 × 2.5 cm o.d. column and fractions monitored by TLC. Microanalyses and mass spectra (*m/e*, 70 eV) were performed by Analytical Services, Chemistry Department, University of California, Berkeley, except for compounds **10** and **15**, which were analyzed, and molecular weights determined, by Galbraith Laboratories, Inc., Knoxville, Tenn. Spermidine (**5**) and trimesoyl chloride (**11**) were purchased from Ames Laboratories, Inc., Milford, Conn., and Aldrich Chemical Co., Milwaukee, Wis., respectively. The 2,3-dimethoxybenzoyl chloride and 2,3-dioxomethylenebenzoyl chloride[19] used in this work were prepared from the corresponding acids (2,3-dihydroxybenzoic acid was obtained from Pfaltz and Bauer, Inc., Stamford, Conn.) by treatment with excess $SOCl_2$ followed by coevaporation with benzene or CCl_4 to remove $SOCl_2$. The crude acid chlorides were used without further purification.

2,3-Dihydroxy-*N,N*-dimethylbenzamide (3). Method A. Treatment of 6.0 g (30 mmol) of **1** in benzene solution with excess $(CH_3)_2NH$ (added via gas cylinder and diffusion tube) gave reaction products which were partitioned between benzene and saturated aqueous NaCl. The $MgSO_4$-dried benzene solution was evaporated to yield **2,3-dimethoxy-*N,N*-dimethylbenzamide (2)**, 5.9 g (92%), as a crude, yellow oil: TLC R_f 0.58; ^{1}H NMR (CCl_4) δ 2.80 (s, 3 H, >NCH_3), 3.03 (s, 3 H, >NCH_3), 3.77 (s, 3 H, -OCH_3), 3.83 (s, 3 H, -OCH_3), 6.5-7.1 (m, 3 H, aromatic).

Compound **2**, 5.8 g (28 mmol), in 25 mL of CH_2Cl_2 was added dropwise to 5 mL (53 mmol) of BBr_3 in 25 mL of CH_2Cl_2, then stirred overnight under argon and hydrolyzed by addition of 20 mL of H_2O (dropwise). Addition of MeOH followed by evaporation of volatile material gave an oil which crystallized upon trituration with acetone/Et_2O. This material was fractionally sublimed (discarding the early fractions) at 115 °C, 15 μm, to obtain **3**, 2.8 g (55%): mp 183-185 °C; TLC R_f 0.64; ^{1}H NMR (Me_2SO) δ 2.91 (s, 6 H, $N(CH_3)_2$), 6.4-6.9 (m, 3 H, aromatic), 7.63 (s, 2 H, -$C_6H_3(OH)_2$); mass spectrum *m/e* (rel intensity) 181 (M, 81), 136 (M − $NH(CH_3)_2$, 100). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.29; H, 6.06; N, 7.60.

Method B. A benzene solution of 3.5 g (16 mmol) of 2,3-dioxosulfinylbenzoyl chloride (**4**) was treated with excess $(CH_3)_2NH$ gas at ambient temperature, then allowed to stand for ~8 h. The reaction mixture was filtered to remove NEt_3·HCl and the benzene solution evaporated to a residue. Trituration with H_2O gave 1.8 g of solid. A $CHCl_3$ extract of the H_2O layer was evaporated to give an additional 0.6 g. The combined solids were sublimed to obtain **3**, 2.3 g (79%), mp 182-185 °C. A mixture melting point with **3** produced by method A proved the two identical.

2,3-Dioxosulfinylbenzoyl Chloride (4). Heating 15.2 g (100 mmol) of 2,3-dihydroxybenzoic acid in 50 mL of $SOCl_2$ under reflux for 3 h gave a solution which was coevaporated with benzene to dryness. Sublimation at 100 °C, <1 mmHg, gave **4**, 20.3 g (93%): mp 84-86 °C; mass spectrum *m/e* (rel intensity) 218 (M, 51), 183 (M − Cl, 77), 135 (M − Cl − SO, 71), 107 (M − Cl − SO − CO, 85). Anal. Calcd for $C_7H_3ClO_4S$: Cl, 16.25; S, 14.64. Found: Cl, 16.33; S, 14.64.

1,5,9-*N,N',N''*-Tris(*p*-toluenesulfonyl)triazacyclotridecane (7). According to the general tosylation procedure of Koyama and Yoshino,[20] an Et_2O (250 mL) solution of *p*-tosyl chloride (59.1 g, 310 mmol) was added dropwise (2 h) to a vigorously stirred H_2O (100 mL) solution of spermidine (**5**, 14.5 g, 100 mmol) and NaOH (12.4 g, 310 mmol). The water bath cooled reaction was allowed to stir for an additional 3 h before workup. The Et_2O layer was discarded and the product partitioned between H_2O and CH_2Cl_2. The $MgSO_4$-dried CH_2Cl_2 solution was concentrated, then eluted from a silica gel column with mixtures of CCl_4 and $CHCl_3$ to obtain 1,5,10-*N,N',N''*-tris(*p*-toluenesulfonyl)triazadecane (**6**, 51.2 g, 84%) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.2-1.8 (broad m, 6 H, >NCH_2CH_2-), 2.43 (s, 9 H, -$C_6H_4CH_3$), 2.5-3.3 (broad m, 8 H, >NCH_2-), 5.1-5.7 (broad m, 2 H, >NH), 7.22 and 7.70 (AB quartet, 12 H, J_{AB} = 8 Hz, C_6H_4-); IR (neat, NaCl) 3280 s (>N-H) cm^{-1}. This material was satisfactory for use in the next step.

To an ambient temperature DMF (100 mL) solution of **6** (51.0 g, 84 mmol) was added, in 1-g portions, NaH (50% in oil, 8.5 g, 177 mmol) over a 2-h period. After the vigorous evolution of H_2 ceased the linear disodium derivative was cyclized by the procedure of Richman and Atkins.[21] A DMF (500 mL) solution of 1,3-ditosylpropane[22] (32.0 g, 84 mmol) was added dropwise (2 h) to the vigorously stirred reaction mixture heated at 95 °C by an oil bath. An additional 24 h at 95 °C was allowed for reaction completion. The cyclic product solution was slowly poured into 3.5 L of H_2O vigorously stirred. The resulting crude white solid was collected by filtration, washed well with H_2O, and dried overnight in vacuo at 50 °C. Recrystallization from a minimum amount of boiling $CHCl_3$ was achieved by addition of MeOH to turbidity. Upon cooling, crystalline **7** (41.7 g, 76%) was obtained, mp 213–214 °C. IR (KBr) showed the complete absence of a peak at 3280 cm^{-1} (>N–H), but had all the following major peaks in common with **2**: 2940 and 2870 (–C–H), 1600, 1335, and 1155 ($-SO_2N<$), 1020, 810, 650, 545 cm^{-1}. Anal. Calcd for $C_{31}H_{41}N_3O_6S_3$: C, 57.47; H, 6.38; N, 6.49; S, 14.85. Found: C, 57.56; H, 6.31; N, 6.41; S, 14.8.

1,5,9-Triazacyclotridecane (8) Trihydrochloride. Compound **7** (6.5 g, 10 mmol) was dissolved in concentrated H_2SO_4 (20 mL) and heated at 90–100 °C for 48 h according to the general literature method.[21] The product-H_2SO_4 solution was poured onto excess ice, and NaOH pellets were added to achieve pH ~10. Products were partitioned between CH_2Cl_2 and H_2O, then filtered to remove solid Na_2SO_4. The CH_2Cl_2 layer was separated, and both the H_2O layer and Na_2SO_4 cake were washed well with CH_2Cl_2. The combined CH_2Cl_2 washes were dried over $MgSO_4$, then evaporated to leave cyclic amine **8** (1.9 g, ~100%): TLC, R_f 0.0, indicated complete absence of any UV-detectable material; *m/e* (70 eV) (rel intensity) 185 (M, 7.9). This material was used in the synthesis of **9**.

Treatment of **8** with 1 N HCl in MeOH and addition of several volumes of Et_2O gave tan solid **8**·3HCl, mp 279–280 °C dec. Anal. Calcd for $C_{10}H_{26}N_3Cl_3\cdot{}^1/_2CH_3OH$: C, 40.59; H, 9.08; N, 13.52; Cl, 34.22. Found: C, 40.89; H, 8.77; N, 13.74; Cl, 34.30.

1,5,9-*N,N′,N″*-Tris(2,3-dihydroxybenzoyl)triazacyclotridecane (10). According to the general literature procedure of Weitl et al.,[13] **8** (1.6 g, 8.65 mmol) in dimethylacetamide (25 mL) solution was added to 2,3-dioxomethylenebenzoyl chloride[19] (26 mmol) followed by NEt_3 (2.6 g, 26 mmol). This reaction mixture was stirred for 4 h at 55–60 °C in a closed system. Evaporation in vacuo at 60 °C gave a residue which was partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 layer was washed well with dilute aqueous NaOH, then aqueous HCl, dried over $MgSO_4$, concentrated, and eluted from a silica gel column with 2% EtOH in $CHCl_3$. This gave the trisdioxomethylenebenzoyl intermediate **9** (2.7 g, 50%): ^1H NMR ($CDCl_3$) δ 1.5–2.4 (broad m, 8 H, $>NCH_2CH_2-$), 3.1–3.9 (broad m, 12 H, $>NCH_2-$), 6.07 (s, 6 H, $-OCH_2O-$) 6.88 (s, 9 H, $-C_6H_3-$). This was used directly in the synthesis of **10**.

A CH_2Cl_2 (40 mL) solution of **9** (2.7 g, 4.3 mmol) in an addition funnel, under argon atmosphere, was added dropwise (20 min) to a vigorously stirred, ice bath cooled, 1 M BCl_3/CH_2Cl_2 solution (40 mL). The ice bath was allowed to warm to room temperature (~12 h). The boron compounds were hydrolyzed by the dropwise addition of 20 mL of H_2O. After an additional 2 h, the reaction mixture was evaporated to a residue, coevaporated several times with MeOH to volatilize the borates, and precipitated from MeOH with copious Et_2O. This gave pure **10** (1.5 g, 60%): mp ≈130–135 °C; ^1H NMR (Me_2SO) shows complete absence of a $-OCH_2O-$ moiety at δ 6.07; TLC R_f 0.57, both UV and $FeCl_3/H_2O/EtOH$ spray visualized. Anal. Calcd for $C_{31}H_{35}N_3O_9$: C, 62.72; H, 5.94; N, 7.08; O, 24.26. Found: C, 62.58; H, 5.97; N, 6.96; O, 24.04. Mol wt: calcd, 594; found, 619 (MeOH).

1,3,5-Tricarboxamidobenzene (12). Trimesoyl chloride (**11**, 5.3 g, 20 mmol) was added dropwise via syringe to a vigorously stirred, ice bath cooled, concentrated NH_4OH (30 mL) solution. The addition rate was controlled to keep the solution <30 °C. Stirring was continued for an additional 15 min before addition of H_2O (200 mL), followed by concentrated HCl (20 mL). The resulting mixture was filtered, giving a white, solid product which was washed well with 0.5 N NH_4OH, then H_2O, then MeOH before oven drying at 100 °C to obtain **12** (3.8 g, 93%), mp >325 °C. Anal. Calcd for $C_9H_9N_3O_3\cdot{}^1/_4H_2O$: C, 51.06; H, 4.52; N, 19.84. Found: C, 51.38; H, 4.42; N, 19.61.

1,3,5-*N,N′,N″*-Tris(2,3-dimethoxybenzoyl)triaminomethylbenzene (14). To solid **12** (2.1 g, 10 mmol) under argon was added 1 M BH_3/THF (75 mL) solution via syringe and septum. The resulting slurry was heated at reflux for ~70 h under slightly positive argon pressure, then concentrated HCl (7 mL) was cautiously added and the mixture heated to reflux for 2.5 h to hydrolyze all boron compounds. The resulting mixture was evaporated to residue, triturated with H_2O, and filtered to remove solid. The clear filtrate was evaporated to dryness and coevaporated several times with MeOH to volatilize the borates. To a MeOH solution of this product was added EtOH, then Et_2O to give fluffy, white, hygroscopic solid 1,3,5-triaminomethylbenzene trihydrochloride (**13**, 1.4 g, 52%), which was used directly in the next reaction: mp >300 °C; ^1H NMR (D_2O-DSS) δ 4.43 (s, 6 H, $-CH_3NH_3^+$), 7.75 (s, 3 H, $-C_6H_3-$).

The following reactants were combined in a stoppered 100-mL round-bottom flask and stirred at 60 °C for 20 h: 2,3-dimethoxybenzoyl chloride (**1**, 11 mmol), dimethylacetamide (35 mL), **13** (1.0 g, 3.6 mmol), NEt_3 (2.2 g, 22 mmol). The product mixture was filtered to remove $NEt_3\cdot HCl$ (2.5 g, ~84%) and evaporated to a residue. The latter was partitioned between $CHCl_3$ and dilute aqueous NaOH. The $CHCl_3$ layer was washed with aqueous HCl, concentrated, and eluted from a silica gel column with 5% EtOH in $CHCl_3$. Appropriate fractions were combined and evaporated to obtain oil which crystallized when neat or from EtOH solution. This gave **14** (2.0 g, 83%): mp 143–144 °C; TLC R_f 0.63; *m/e* (70 eV) (rel intensity) 657 (M, 14), 492 (M − $(CH_3O)_2C_6H_3CO$, 16), 165 [$(CH_3O)_2C_6H_3CO$, 100]; ^1H NMR ($CDCl_3$) δ 3.83 (s, 9 H, $-OCH_3$), 3.86 (s, 9 H, $-OCH_3$), 4.70 (d, 6 H, J = 3 Hz, $-CH_2NH-$), 7.33 (s, 3 H, Ar*H*- central ring), 7.0–7.8 (complex m, H_3 system, 9 H, Ar*H*- exterior rings), 8.40 (broad t, 3 H, J = 3 Hz, $-CH_2NH-$). Anal. Calcd for $C_{36}H_{39}N_3O_9$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 5.93; N, 6.39.

1,3,5-*N,N′,N″*-Tris(2,3-dihydroxybenzoyl)triaminomethylbenzene (15). A CH_2Cl_2 (25 mL) solution of **14** (2.2 g, 3.3 mmol) was added (via argon-flushed addition funnel) dropwise (15 min) to a vigorously stirred CH_2Cl_2 (25 mL) solution of BBr_3 (3.1 mL, 33 mmol). The reaction vessel was immersed in an ice bath. After the solution was stirred overnight at room temperature, under argon, H_2O (25 mL) was added dropwise to hydrolyze boron compounds. After stirring for an additional 2 h, the crude product was collected by filtration, washed well with H_2O, dissolved in MeOH, and evaporated to dryness several times. The solid was triturated with EtOAc and filtered to clarify, and several volumes of Et_2O followed by low-boiling petroleum ether were added to precipitate white, deliquescent solid **15** (58%): mp ~130–135 °C; *TLC* R_f 0.70, visualized with $FeCl_3$-H_2O-EtOH spray; ^1H NMR (Me_2SO-D_2O) δ 4.53 (s, 6 H, $-CH_2NH-$), 6.7–7.6 (complex m, 9 H, Ar*H* external rings), 7.30 (s, 3 H, Ar*H* central ring); *m/e* (70 eV) (rel intensity) 573 (M, 1), 437 [M − $(HO)_2C_6H_3CO$, 20], 136 [$(HO)_2C_6H_3CO$, 100]. Anal. Calcd for $C_{30}H_{27}N_3O_9\cdot{}^1/_2H_2O$: C, 61.85; H, 4.84; N, 7.21; O, 26.09. Found: C, 61.74; H, 4.88; N, 7.17; O, 26.12. Mol wt: calcd, 574; found, 568 (MeOH).

Discussion and Summary

A biomimetic approach to the synthesis of Fe(III) sequestering agents has resulted in the preparation of the first members (**10, 15**) of two new ligand designs. Unlike enterobactin, which has exocyclic amide bonds, macrocycle **10** is an endocyclic triamide. This feature may result in additional conformational demands upon the ring system during formation of the encapsulated hexadentate O-bonded Fe(III) complex, causing lowered thermodynamic stability of **10** relative to the exocyclic amide ligands. However, the planar mesitylene platform in **15** allows each 2,3-DHB amide moiety to chelate independently of the other and eliminates ring conformation considerations altogether.

Our initial titration data indicate that ligand **15** chelates Fe(III) more effectively than does **10**, since the red six-coordinate complex of **15** is fully formed at pH 8, compared to pH 10 for ligand **10**. The visible spectrum of the iron complex, FeL (λ_{max} 492 nm, ϵ 4700, for L = **15**) indicates that coordination takes place through the six phenolic oxygens. The visible spectrum of the Fe^{3+} complex of **15** is unchanged upon raising the pH as high as 11.0 and shows no indication of decomposition or hydrolysis when allowed to stand at this pH for several days. Thus ligand **15** is an exceptionally good sequestering agent for ferric ion in neutral and basic aqueous solutions.[23] Other considerations such as in vivo evaluation are yet to be determined. *However, we have shown with in vitro tests that* ***15*** *removes* Fe^{3+} *from its transferrin complex as effectively as does enterobactin itself.*[24]

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Communications to the Editor

Attachment of Organic Groups to Heteropoly Oxometalate Anions

Sir:

The large polyoxoanions of vanadium, molybdenum, and tungsten[1] have for many years attracted attention as catalysts, electron microscope "stains", analytical reagents, etc. Recently we have sought to develop the chemistry of possible organic derivatives of such polyanions[2] with a view to their potential use as selective labeling and imaging agents for biological systems. We report here a direct derivatization of heteropoly anions under mild aqueous conditions that leads to the first examples of organoheteropoly complexes that are stable at biological pH and are reducible to intensely colored heteropoly blues. Independent work by Knoth has lead to similar complexes.[3]

Certain polyanion structures undergo partial hydrolysis to yield so-called "defect" or "lacunary" structures in which one or more MO_6 octahedral units have been lost. Such defect structures act as penta- or tetradentate ligands to a broad variety of transition metal cations.[1] Defect structure polyanions derived from the α isomers[4] of 1:12 and 2:18 polytungstates, i.e., $XW_{11}O_{39}{}^{n-}$ (X = P, Si, Ge, B) and $X_2W_{17}O_{61}{}^{10-}$ (X = P, As), were treated with $RMCl_3$, RMO(OH) (RM = MeSn, *n*-BuSn, PhGe) or $PhPb(OAc)_3$ in buffered aqueous or mixed aqueous-organic solvents to yield $XW_{11}(MR)O_{39}{}^{(n-3)-}$ and $X_2W_{17}(MR)O_{61}{}^{7-}$. The conditions of pH and solvent used depended upon the charge and structure of the polyanion and the nature of R. The resulting complexes were isolated as potassium and guanidinium salts and characterized by chemical analysis,[5] vibrational, electronic, and ^{1}H NMR spectroscopy, polarography, and X-ray diffraction. The complexes are presumed to have structures in which octahedral $M(O_5R)$ occupies the "defect" caused by the loss of a WO_6 octahedron. Ultraviolet and infrared spectra of the products resemble the corresponding spectra of the "complete" anions $XW_{12}O_{40}{}^{n-}$ and $X_2W_{18}O_{62}{}^{6-}$, and are almost identical with those of the corresponding $XM^{II,III}W_{11}O_{39}(OH_2)^{p-}$ and $X_2M^{II,III}W_{17}O_{61}(OH_2)^{q-}$ anions[6] ($M^{II,III}$ = most bi- or trivalent transition or group 3b metal ions). They differ, however, clearly from those of the "defect" structures.[6] The potassium salts of $BW_{11}(Sn\text{-}n\text{-}Bu)O_{39}{}^{6-}$, $BW_{11}(GePh)O_{39}{}^{6-}$, $BW_{11}(PbPh)O_{39}{}^{6-}$, and $SiW_{11}(SnMe)O_{39}{}^{5-}$ are isomorphous with several other 12-tungstates, such as $K_5CoW_{12}O_{40}\cdot 20H_2O$ and $K_4SiW_{12}O_{40}\cdot{\sim}17H_2O$ (space group $P6_222$).[7] They are also isomorphous with the potassium salts of some $XM^{III}W_{11}O_{39}(OH_2)^{r-}$ anions (X = P, As, B).[14] As is frequently observed with hydrated salts of substituted Keggin anions, crystallographic disorder equalizes the twelve heavy metal atoms.[8] The $X_2W_{18}O_{62}{}^{6-}$ structure has six equivalent WO_6 octahedra in "polar" positions and twelve equivalent "equatorial" octahedra.[9] Two isomers (α_1,α_2-$P_2W_{17}O_{61}{}^{10-}$), corresponding to the loss of each type of WO_6 octahedron, have been prepared by Contant and Ciabrini,[10] who tentatively suggest that the α_1 isomer results from the loss of a "polar" tungsten and α_2 from loss of an equatorial tungsten. A single crystal structure analysis of the potassium salt of $P_2W_{17}(Sn\text{-}n\text{-}Bu)O_{61}{}^{7-}$ prepared from the α_2 isomer is nearing completion, and it shows clearly that the tin occupies a "polar" position in the $P_2W_{18}O_{62}{}^{10-}$ framework.[15]

The new complexes exhibit an extensive redox chemistry, as is to be expected from their structures.[11] Polarograms show a series of reversible one-, two-, and/or four-electron waves corresponding to the sequential reduction of W(VI) to form mixed-valence heteropoly blues.[12] The half-wave potentials and their dependence on pH are characteristic of each complex, and the polarograms are similar to those of the corresponding $XM^{III}W_{11}O_{39}(OH_2)^{p-}$ complexes;[14] they are readily distinguishable from those of the corresponding "complete" and "defect" structure anions.[10,13,14] The polarograms also demonstrate the hydrolytic stability of the complexes at millimolar concentrations; the common stability range of the $XW_{11}(Sn\text{-}n\text{-}Bu)O_{39}{}^{n-}$, $XW_{11}(GePh)O_{39}{}^{n-}$, and $X_2W_{17}(Sn\text{-}n\text{-}Bu)O_{61}{}^{7-}$ anions is, respectively, pH ~4 to ~6, ~4 to ~7, and ~2 to ~8. The first two series of complexes decompose to $XW_{12}{}^{m-}$ at pH 1 to ~4, the latter to $X_2W_{18}{}^{10-}$ at pH 1 to 2. Alkaline decomposition starts at pH ~6, ~7, and ~8, respectively. Extension of the chemistry of these complexes via reduction, introduction of functionalized organic groups, and the use of other polyanion structures is in progress.

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