the sequence (with charges omitted)

$$Cr(OH_2)_3(nic)_3 \xrightarrow{k_{32}} Cr(OH_2)_4(nic)_2 \xrightarrow{k_{21}} Cr(OH_2)_5nic$$

with $k_{32} = 1.44 \times 10^{-4}$ s^{-1} and $k_{21} = 3.45 \times 10^{-6}$ s^{-1}. (An alternate interpretation[29] in which $k_{21} > k_{32}$ does not seem reasonable.) With these values for the two rate constants, the maximum relative concentration of bis species, which occurs at ~440 min, is ~0.91.[30]

The rate of aquation of the dimer $Cr_2(nic)OH^{4+}$ in perchloric acid was determined at 60.0 °C in an experiment with [Cr(III)] = 1.54×10^{-3} mol L^{-1} and [H$^+$] = 0.05 mol L^{-1}. Observations were made at $t = 0$ and from t values from 23 h to 11 days; during this time, the species is aquated completely to hexaaquachromium(III) ion with a decrease in light absorption at 570 nm of ~18%. For comparison a solution of hydrolytic dimer with charge 4+, described by Thompson et al.,[19] was treated similarly. Plots of log $(A_t - A_\infty)$ vs. time for both species were approximately linear over the course of the study (87% completion), suggesting that one of the steps in the aquation mechanism is slower than the others. From these data the empirical rate constants for aquation of the nicotinato dimer and hydrolytic dimer are 2.7×10^{-6} and 6×10^{-5} s^{-1}, respectively.

Thus, the empirical rate constant for aquation of $Cr_2(nic)OH^{4+}$ is appreciably smaller than that for the production of $Cr(OH_2)_6^{3+}$ either from $Cr(nic)^{2+}$ or from the hydrolytic dimer. For $Cr_2(nic)OH^{4+}$ with the structure already proposed, it is reasonable to assume that breaking of the hydroxo bridge occurs rapidly on the time scale for breaking the nicotinate bridge. (The rate constant for the conversion of hydrolytic dimer to aquachromium(III) ion is approximately 20-fold greater than that for aquation of $Cr_2(nic)OH^{4+}$.) Thus, the spectral changes occurring during the observation period are due to the reactions

$$Cr_2(OH_2)_{10}nic^{5+} + H_2O \xrightarrow{k_1} Cr(OH_2)_6^{3+} + Cr(OH_2)_5nic^{2+}$$

$$Cr(OH_2)_5nic^{2+} + H_3O^+ \xrightarrow{k_2} Cr(OH_2)_6^{3+} + Hnic$$

The independently determined values of k_2 for this temperature can be extrapolated at this acidity; k_2([H$^+$] = 0.050 mol L^{-1}, 60 °C) = 1.3×10^{-5} s^{-1}. If this value is used, the value of k_1 can be derived from the spectral data. In this data treatment, the value of the absorbance due to $Cr(OH_2)_5nic^{2+}$, the reactant in this k_2 step, must be assumed. Rather than use the value determined under different conditions, we assumed various values between the initial value and that due to hexaaquachromium(III). It was found that the value of k_2 was not particularly sensitive to the assumed value for this parameter. The derived value of k_2 changes by ~6% if the assumed value for the light absorption due to $Cr(OH_2)_5nic^{2+}$ is changed by ~5%. (As already mentioned, the total change of light absorption was only ~18%.) For the assumption that light absorption due to equal amounts of $Cr(OH_2)_5nic^{2+}$ and $Cr(OH_2)_6^{3+}$ was midway between that for no aquation ($Cr_2(OH_2)_{10}nic^{5+}$) and 100% aquation ($Cr(OH_2)_6^{3+}$), the derived value of k_1 is 2.8×10^{-6} s^{-1}. (With $k_1 = 2.8 \times 10^{-6}$ s^{-1} and $k_2 = 1.3 \times 10^{-5}$ s^{-1}, one can calculate that during the aquation the maximum relative concentration of $Cr(OH_2)_5nic^{2+}$ is only 7%. Thus, it is reasonable that the value of k_1 derived by considering the sequence of two reactions is very close to that obtained simply as $k = -\Delta[\ln (A - A_\infty)]/\Delta t$.)

Conclusion

It is clear from this work that there are several inert oxygen-bonded (nicotinato)chromium(III) species. The ion-exchange procedures employed in the present study provide the basis for the preparation of solutions of relatively pure species. The role of each of these in glucose tolerance can be tested.

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Contribution from the Lash Miller Chemical Laboratories, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Biological Analogues. Synthetic Iron(III)-Specific Chelators Based on the Natural Siderophores

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Two synthetic analogues of the the naturally occurring iron(III)-specific siderophores, one with catechol groups and the other with hydroxamic acid groups, have been prepared. Both are sexidentate chelates consisting of three catechol and three hydroxamic acid groups attached to a triamine "platform" via amide linkages. Both ligands are specific for iron(III) and form very stable iron(III) complexes; the stability constant for the iron(III) tris(hydroxamate) complex was determined to be about 28.

Hemochromatosis[1,2] refers to a group of disorders that result from a progressive increase in deposition of iron in the parenchymal and reticuloendothelial cells of the liver, pancreas, heart, and pituitary and that lead, successively, to tissue damage, functional insufficiency of the organs, and eventually death. Idiopathic hemochromatosis is an inherited autosomal recessive trait that manifests itself after the breakdown of the regulatory mechanism for iron absorption. The gene frequency for certain ethnic groups can be high, possibly of the order of 1 in 40 of the population, but the inherent propensity for the disorder appears to be triggered by environmental factors.[3] There are epidemiological associations with alcoholism, and excessive iron intake over a long time, particularly in combination with alcohol (viz. Bantu siderosis).[4] The life expectancy of untreated patients is about 4 years after the disease has become clinically manifest. Idiopathic hemochromatosis is now treated by phlebotomy in combination with chelation therapy.

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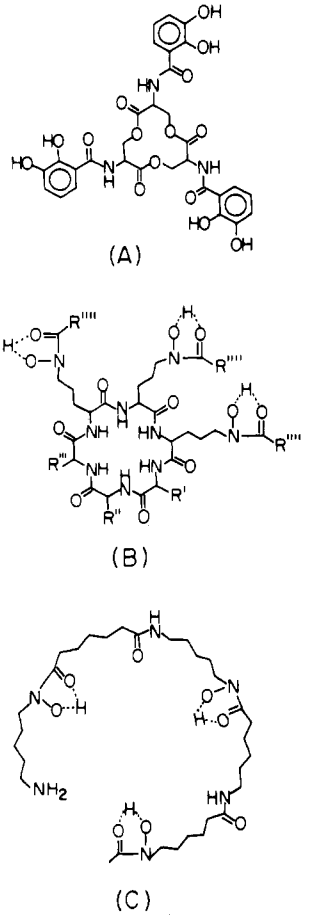

Figure 1. Structural formulas of three siderophores: (A) enterobactin (enterochelin); (B) ferrichrome family; (C) desferrioxamine B.

Not surprisingly, particular attention has focused on the strong iron(III)-specific chelators produced by microorganisms, the siderophores,[5] to mobilize the tissue-deposited iron. The siderophores, in the main, employ catecholate and hydroxamate ligands for chelation to iron(III). Three examples are shown in Figure 1, including desferrioxamine B, one of the chelators currently used in therapy. This chelator is administered subcutaneously and causes acute discomfort. Accordingly, various attempts have been made at developing more effective siderophore analogues.[6-8,14,17]

This paper describes the synthesis of two sexidentate siderophore analogues, one a catechol and the other a hydroxamic acid ligand. The two target molecules are shown in Figure 2. Although the catechol analogue has been synthesized before,[9,10] we describe here a different method that, arguably, has some advantages over the previous strategies.

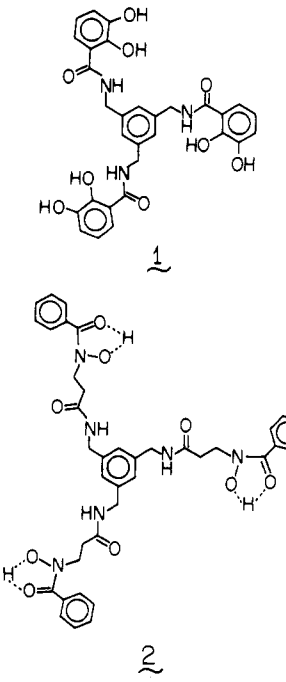

Figure 2. Structural formulas of the two siderophore analogues, **1** and **2**.

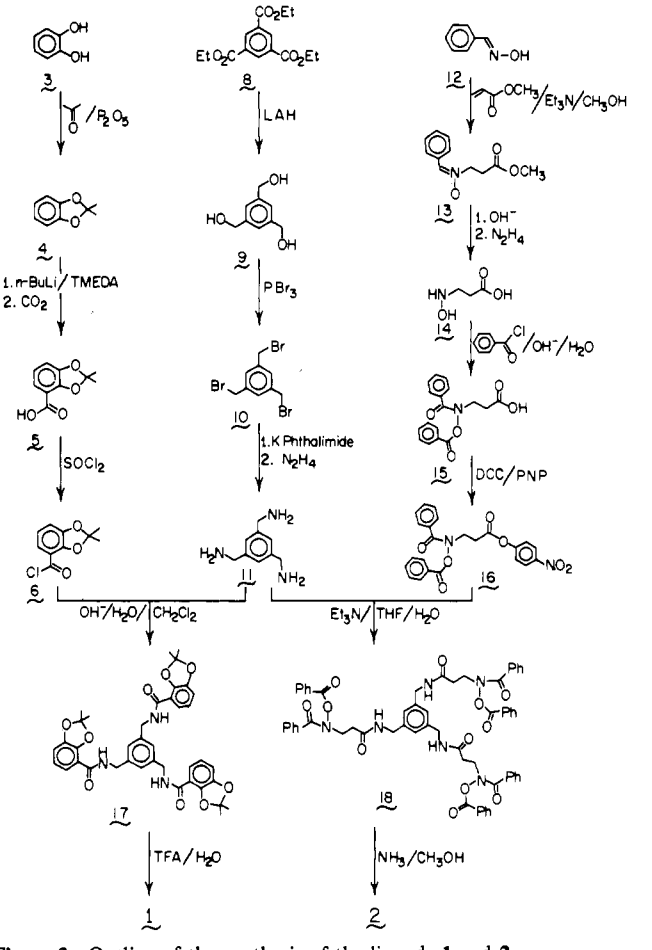

Figure 3. Outline of the synthesis of the ligands **1** and **2**.

Synthesis

The synthesis of the siderophore analogues is outlined in Figure 3. One of the obvious, direct methods of synthesizing the triamine

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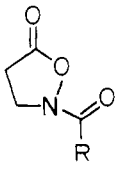
platform **11**, by (BH_3) reduction of the corresponding triamide (which is readily obtained from the commercially available tris(acid chloride)), proved unsatisfactory. The triamide is an extremely insoluble solid that is difficult to manipulate and that is very slowly reduced by BH_3 in THF to give, after acidification, the trihydrochloride salt of **11** as a sticky solid that proved difficult to purify. This method was employed in the previous synthesis.[9] By contrast, the *N*-methyl triamide is easy to handle, and we found that it is readily reduced with $BH_3{\cdot}S(CH_3)_2$ in THF to give a good yield of the trihydrochloride salt as a stable crystalline solid.[11] This tri-*N*-methyl analogue of **11**, however, proved unsatisfactory as a platform because of the decreased rate of amide bond formation in certain cases over that observed for the primary triamine platform. We therefore chose the classical conventional route to **11** (Figure 3), which, without difficulty, gave the desired triamine platform in satisfactory yield.

The activated and protected catecholate arm **6** was obtained from catechol by the conventional means outlined in Figure 3. Reaction **4** → **5** proved troublesome, giving erratic and generally low yields. Coupling of **6** with platform **11** was most expeditiously accomplished under Schotten–Baumann conditions using a water–methylene chloride dispersion. The product, **17**, is a readily crystallizable solid. Deprotection of the catecholate acetonide was accomplished at 25 °C in trifluoroacetic acid–water solution; the ratio of the solvents was adjusted so that the enterobactin analogue **1** precipitated from solution as the reaction progressed.

The synthesis of the hydroxamic acid arm began with the (Michael) addition of (*E*)-benzaldoxime (**12**) to methyl acrylate to give the nitrone **13**. Base hydrolysis to remove the ester group, followed by the hydrazine induced removal of the benzylimine group, gave 3-(hydroxyamino)propionic acid (**14**). Reaction of **14** with benzoyl chloride under Schotten–Baumann conditions gave the protected hydroxamate **15**, the carboxylate group of which was activated with DCC to give the *p*-nitrophenyl ester **16** as a highly crystalline solid. Platform **11** and hydroxamate arm **16** were coupled in THF–H_2O in the presence of triethylamine to give **18**. Deprotection of **18** with methanolic ammonia at 25 °C gave the desired product **2** as a crystalline solid.

The synthesis of the hydroxamate arm does not appear to be a general strategy; it seems to be specific for benzoyl or other aromatic acyl derivatives. Thus, for example, attempts at preparing **15** with acetyl rather than benzoyl groups failed by the procedures given here. We had attempted to use the nitrone, **13**, as a protecting group, but the corresponding acid of **13** could not be activated for amide formation without causing Beckmann rearrangement (to the benzamide) at the nitrone functionality. Similarly, we were unable to prepare the general system **19**, an active ester that could potentially provide a direct, simple, general method of coupling of the arms to platform **11** to give a variety of derivatives.



19

Iron(III) Complexes

When the tris(catechol) ligand **1** is allowed to react with iron(III) in solutions maintained at pH values greater than 8.5, the violet tris(catecholate) complex is fully formed. Similarly, the tris(hydroxamic acid) ligand **2** gives the fully formed tea-colored iron(III) tris(hydroxamate) complex under the same conditions. The latter complex, however, is insoluble in all common solvents except for DMF and Me_2SO, and hence we resorted to the use of solvent mixtures for subsequent work on this complex. We chose 3:1 DMF–water mixtures buffered with borax at pH 8.5. For this mixed-solvent buffer, the solution electronic absorption spectra of the complex $[Fe(\mathbf{2}')]^0$ and of $[Fe(\mathbf{1}')]^{3-}$ in 98% water–methanol at pH 8.5, where **2**′ and **1**′ refer to the fully deprotonated ligands **2** and **1**, respectively, are shown in Figures 4 and5. The spectrum of $[Fe(\mathbf{1}')]^{3-}$ is identical with the one described previously,[9] and that of $[Fe(\mathbf{2}')]^0$ is very similar to those observed for the naturally occurring iron(III) tris(hydroxamate) complexes.[12]

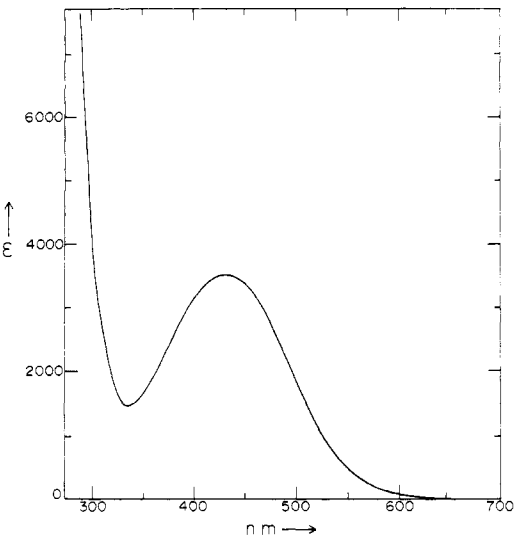


Figure 4. Visible absorption spectrum of [Fe(**2**′)] in 3:1 DMF–water solution at pH 8.5.

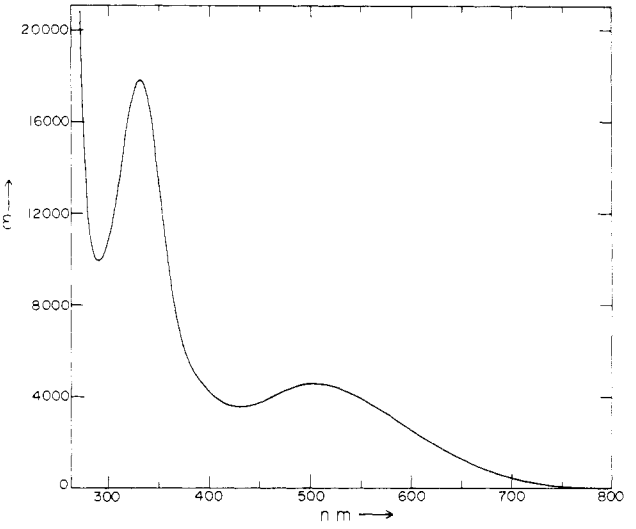


Figure 5. Visible absorption spectrum of $[Fe(\mathbf{1}')]^{3-}$ in 98% water–methanol solution at pH 8.5.

The $(Ph_4As)_3[Fe(\mathbf{1}')]$ salt and the neutral [Fe(**2**′)] compound could be isolated as deep violet and brick red powders, respectively. In neither case could we obtain crystals suitable for X-ray analysis.

The stability constant of $[Fe(\mathbf{1}')]^{3-}$ has been determined in water solution; a value of about 46 was reported.[13] As expected, the catechol ligand **1** forms much stronger complexes with iron(III) than does the hydroxamic acid ligand **2**. Thus we find that, in our 3:1 DMF–water pH 8.5 buffer, ligand **1** fully displaces the hydroxamate ligand from [Fe(**2**′)] after 10 h at 25 °C when equimolar amounts of **1** and [Fe(**2**′)] are used at 2.5×10^{-4} M concentrations. In order to obtain an estimate of the stability constant of [Fe(**2**′)], we determined the competitive equilibrium constant with EDTA:[14]

$$[Fe(\mathbf{2}')] + EDTA^{4-} \rightleftharpoons [Fe(EDTA)]^- + \mathbf{2}'$$

Using the 3:1 DMF–water pH 8.5 buffer, we measured the decrease in the optical density of the spectrum of [Fe(**2**′)] (Figure 4) for 1:1 and 2:1 Na_2EDTA:[Fe(**2**′)] ratios. Equilibration was complete after about 5 h at 25 °C. For both of these ratios the effective stability constant, pK_{eff}, of [Fe(**2**′)] was found to be 24.3, assuming that the stability constant of $[Fe(EDTA)]^-$ and the

proton dissociation constants of EDTA are the same for our solvent mixture as they are in water.[15] Similarly, we assumed that the proton dissociation constants of **2** would be similar to those observed for other polyhydroxamic acids in water and that we could use these values for our solvent system. Because of the aqueous insolubility of **2**, we were unable to determine its proton dissociation constants, but for other hydroxamic acids these constants are in the range[14] of 8–10. The proton interference term,[16] α_L, for **2** is dominated by the values of its highest dissociation constant at pH 8.5; the other two constants contribute insignificantly to the complexation constant. The highest acid dissociation constants of polyhydroxamic acids vary between 9.5 and 10. Using 9.5 as the highest constant for **2**, we find a stability constant for [Fe(**2**′)] of 27.3, and using a value of 10 gives a stability constant of 28.8 for the complex.

The stability constants found for [Fe(**2**′)] are within the range expected for a sexidentate hydroxamate complex of iron(III) despite the assumptions we have made. Thus the biological hydroxamic acid siderophores for iron(III) complexes have stability constants in the range[14] of 29–32.5, that of iron(III) tris(acetylhyroxamate) being[17] 28.3.

Discussion

Although the hydroxamic acid analogue **2** is specific for iron(III) and forms very stable iron(III) complexes, its value as a drug appears to be limited by the water insolubility of both ligand and its iron(III) complex. Presumably these problems could be circumvented by, for example, attaching sulfonic acid groups to the benzyl rings.

The main purpose of this paper, however, is to provide a reasonably simple methodology for the synthesis of sexidentate hydroxamic acid ligands analogous to **2**. The approach outlined here appears to be less complicated than a recently described strategy reported[8] for a similar hydroxamic acid ligand.

Experimental Section

A. Platform 11. (1) 1,3,5-Tris(bromomethyl)benzene (10). To 1,3,5-tris(hydroxymethyl)benzene (**9**) (10.0 g, 0.06 mol; prepared by a LAH reduction of triethyl-1,3,5-benzenetricarboxylate (**8**) using the method of Safar[19]) cooled in an ice bath under N_2 was slowly added PBr_3 (52.8 g, 0.195 mol). The resultant stirred mixture was slowly allowed to come to room temperature and was then heated at 115 °C for 1 h. After cooling to room temperature, the orange solution was quenched with ice water and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with cold saturated aqueous $NaHCO_3$ and water and then were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was crystallized from hot hexane, yielding **10** (17.4 g, 82%; mp 92–93 °C) as a white solid. ^1H NMR ($CDCl_3$): δ 4.5 (s, 6 H), 7.4 (s, 3 H). Anal. Calcd for $C_9H_9Br_3$: C, 30.3; H, 2.5; Br, 67.2. Found: C, 30.5; H, 2.6; Br, 66.7.

(2) 1,3,5-Tris(aminomethyl)benzene (11). Freshly crystallized **10** (25.0 g, 0.07 mol) in dry DMF (60 mL) was added over 20 min to a stirred suspension of potassium phthalimide (40.9 g, 0.221 mol) in dry DMF (200 mL) maintained at 120 °C under N_2. After 20 min at 120 °C, the reaction was cooled slightly, water (150 mL) was added, and then this mixture was poured into vigorously stirred water (3 L). The mixture was filtered, and the precipitate, after being washed with water and Et_2O, was air-dried, yielding 1,3,5-tris(phthalimidomethyl)benzene (36.4 g, 94%). Anal. Calcd for $C_{33}H_{21}N_3O_6$: C, 71.4; H, 3.8; N, 7.6; O, 17.3. Found: C, 71.2; H, 3.8; N, 7.6; O, 17.6. A solution of hydrazine hydrate (85%, 12.2 g 0.22 mol) in EtOH (95%, 20 mL) was added to a suspension of 1,3,5-tris(phthalimidomethyl)benzene (36.4 g, 0.065 mol) in EtOH (95%, 750 mL), and the mixture was refluxed for 12 h. The reaction was cooled slightly and was then carefully acidified (pH ~3) with HCl (12 M). When it had come to room temperature, the mixture was filtered and the precipitate was washed well with 95% EtOH. The combined filtrates were evaporated to dryness under reduced pressure, and the white residue was slurried with water and filtered out. The aqueous filtrate was evaporated to dryness under reduced pressure, and the residue was crystallized from H_2O–EtOH–acetone to yield long white needles of **11** as the trihydrochloride (16.4 g, 91%; mp >300 °C). ^1H NMR (D_2O): δ 4.4 (s, 6 H), 7.6 (s, 3 H). Anal. Calcd for $C_9H_{18}Cl_3N_3$: C, 39.4; H, 6.6; Cl, 38.7; N, 15.3. Found: C, 39.1; H, 6.7; Cl, 38.6; N, 15.1.

B. Catecholate Arm. 2,2-Dimethyl-1,3-benzodioxole-4-carbonyl Chloride (6). Catechol was converted to 2,2-dimethyl-1,3-benzodioxole (**4**) by the method of Slooff,[20] and **4** was then carbonylated according to the method described by Corey,[21] yielding **5**. A solution of **5** (8.92 g, 0.046 mol) in dry CH_2Cl_2 (100 mL) under N_2 was cooled to 0 °C. Triethylamine (7.68 mL, 0.055 mol) and 1 drop of dry DMF were added, followed at 0 °C by the slow addition $SOCl_2$ (5.0 mL, 0.069 mol). The yellow solution was kept at 0 °C for 3 h and then at room temperature for 1 h. After the volatiles were removed under reduced pressure, the residue was triturated with hot hexane. The hexane was removed under reduced pressure and the residue crystallized from hexane to yield **6**[21] ((7.62 g, 78%).

C. Hydroxamic Acid Arm. (1) *O*-Benzoyl-*N*-benzoyl-*N*-(2-carboxyethyl)hydroxylamine (15). A solution of 3-(hydroxyamino)-propionic acid (**14**) (5.0 g, 0.0475 mol; prepared from the Michael adduct **13** of (*E*)-benzaldoxime[22] and methyl acrylate by the method of Bellasio[23]) and NaOH (1.9 g, 0.0475 mol) in water (15 mL) under N_2 was ice-cooled and was vigorously stirred while benzyl chloride (11.05 mL, 0.095 mol) in dry Et_2O (30 mL) was added over 10 min. After 15 min NaOH (1.9 g, 0.0475 mol) in water (15 mL) was added dropwise and after an additional 10 min more NaOH (1.9 g, 0.0475 mol) in water (15 mL) was added dropwise to the vigorously stirred reaction. The mixture was then stirred 10 min with ice-cooling and 0.5 h at room temperature. Ethyl acetate (200 mL) was added, and the layers were separated. The organic layer was washed with cold saturated aqueous $NaHCO_3$ (40 mL); the combined aqueous layers were acidified (pH 3) with HCl (1 M), and the mixxture was then extracted with ethyl acetate. The organic extracts were washed with brine and were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was crystallized from Et_2O–hexane, yielding **15** (8.5 g, 62%; mp 84.0–85.5 °C) as a white crystalline solid. ^1H NMR ($CDCl_3$): δ 2.5–2.9 (m, 2 H), 4.0–4.4 (m, 2 H), 7.0–7.9 (m, 10 H), 10.9 (s, 1 H). Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.2; H, 4.9; N, 4.9. Found: C, 65.3; H, 4.7; H, 4.4.

(2) *O*-Benzoyl-*N*-benzoyl-*N*-(2-((*p*-nitrophenoxy)carbonyl)ethyl)-hydroxylamine (16). *N*,*N*′-Dicyclohexylcarbodiimide (6.21 g, 0.0301 mol) was added to a solution of *p*-nitrophenol (4.77 g, 0.0343 mol) and **15** (9.0 g, 0.0287 mol) in ethyl acetate (10 mL) under N_2. After for 2.5 h of stirring, the mixture was filtered and the precipitate was washed with a little ethyl acetate. The combined filtrates were evaporated to dryness under reduced pressure, and the residue was crystallized from hot EtOH (95%) to give **16** (10.7 g, 86%; mp 96.5–97.5 °C) as white needles. ^1H NMR ($CDCl_3$): δ 2.9–3.3 (m, 2 H), 4.2–4.6 (m, 2 H), 7.0–8.2 (m, 14 H). Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.6; H, 4.2; N, 6.5. Found: C, 63.7; H, 4.2; N, 6.3.

D. Ligand 1. Freshly recrystallized **11**·3HCl (2.98 g, 0.011 mol) in water (100 mL) under N_2 was neutralized with NaOH (1.32 g, 0.033 mol); CH_2Cl (100 mL) was then added, and the vigorously stirred mixture was ice-cooled. Solutions of Et_3N (5.03 mL, 0.036 mol) in CH_2Cl_2 (50 mL) and freshly prepared **6** (7.62 g, 0.036 mol) in CH_2Cl_2 (50 mL) were simultaneously added dropwise to the ice-cooled, vigorously stirred mixture. The reaction was slowly allowed to come to room temperature. After 18 h the layers were separated and CH_2Cl_2 was removed under reduced pressure. The oily residue was dissolved in benzene, the mixture was washed with water, saturated aqueous $NaHCO_3$, water, a pH 4 buffer, and water and was then dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded an oily residue from which was crystallized (benzene–hexane) **17** (7.0 g, 83%; mp 82–83 °C) as white needles. These needles contain a molecule of benzene solvate, which was removed at 30 °C under high vacuum. ^1H NMR ($CDCl_3$): δ 1.7 (s, 18 H), 4.6 (br d, J = 6 Hz, 6 H), 6.8–7.4 (m, 15 H). Anal. Calcd for $C_{39}H_{39}N_3O_9$: C, 67.5; H, 5.8; N, 6.1; O, 20.8. Found: C, 67.5; H, 5.6; N, 6.4; O, 21.1. A solution of trifluoroacetic acid and water (4:1, 15 mL) was added to (desolvated) **17** (1.4 g, 0.002 mol) at room temperature under N_2, and the mixture was swirled to effect dissolution. On standing, the light yellow solution deposited an off-white solid. After 24 h the mixture was filtered and the precipitate was washed with water and air-dried. The crude product was recrystallized from ethyl acetate–Et_2O–hexane to yield **1** (0.9 g, 79%; mp 123–125 °C (lit.[9] mp ~130 °C)) as white needles. ^1H NMR (Me_2SO-d_6): δ 4.5 (br d, J = 6 Hz, 6 H), 6.4–7.4 (m, 12 H), 9.1–9.5 (m, 6 H), 12.0–13.00 (br s, 3 H). Anal. Calcd for $C_{30}H_{27}N_3O_9$: C, 62.9; H, 4.8; N, 7.3. Found: C, 62.5; H, 5.2;

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N, 7.4.

E. Ligand 2. Triethylamine (2.0 mL, 0.0143 mol) was added to a stirred solution of **11**·3HCl (1.3 g, 0.0047 mol) in water (10 mL) under N_2, and after 5 min **16** (6.3 g, 0.0145 mol) in THF (80 mL) was added all at once. There was an immediate formation of a bright yellow two-phase mixture. After 1 h the cloudy mixture was partially cleared by the addition of water (2 mL) and THF (20 mL), and after an additional 5 h more Et_3N (2.0 mL, 0.0143 mol) was added. The mixture was stirred for a total of 20 h, and then the THF was removed under reduced pressure. The residue was extracted with ethyl acetate (2 × 75 mL), and the combined organic layers were washed with water (5 × 120 mL) and brine (4 × 100 mL) and were dried over Na_2SO_4. After the extract was passed through a short column of Florisil, ethyl acetate was removed under reduced pressure, yielding **16** (6.0 g) as a light green foam. This was then dissolved in methanolic ammonia (65 g, 8%, w/w) and the mixture was allowed to stand at room temperature for 1.5 h. The bright yellow, slightly cloudy solution was filtered through Celite, and the solvent was removed under reduced pressure, yielding a bright yellow oil, which was taken up in hot EtOH (25 mL). Upon standing (10 h at room temperature, 2 days at 4 °C, and 1 day at −20 °C), a yellow solid was deposited, which was recrystallized twice from hot EtOH, yielding **2** (1.76 g, 50%; mp 162–165 °C) as an off-white solid. ^{1}H NMR Me_2SO-d_6): δ 2.4–2.8 (m, 6 H), 3.7–4.1 (m, 6 H), 4.2 (d, J = 5 Hz, 6 H), 7.0 (s, 3 H), 7.2–7.7 (m, 15 H), 8.4 (br t, J = 5 Hz, 3 H), 9.8 (br s, 3 H). Anal. Calcd for $C_{39}H_{42}N_6O_9$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.2; H, 5.8; N, 11.3.

F. Iron(III) Complexes. A solution of $Fe(NH_4)(SO_4)_2$·$12H_2O$ (0.015 57 g, 3.23 × 10^{-5} mol) in water (2 mL) was treated with **1** (0.018 57 g, 3.23 × 10^{-5} mol) in MeOH (2 mL). The purple milky solution was made up to 100 mL with a pH 8.50 borax buffer, producing a clear violet solution that displayed absorptions (Varian 2300 spectrophotometer) at λ_{max} = 498 nm (ϵ = 4697 M^{-1} cm^{-1}) and λ_{max} = 328 nm (ϵ = 17 900 M^{-1} cm^{-1}). The spectrum showed no change over several weeks.

A solution of $Fe(NH_4)(SO_4)_2$·$12H_2O$ (0.012 05 g, 2.50 × 10^{-5} mol) in water (2 mL) was treated with **2** (0.018 47 g, 2.50 × 10^{-5} mol) in DMF (10 mL), producing a clear red solution. DMF (65 mL) and a pH 8.50 borax buffer (22 mL) were added to this solution in portions, with sufficient DMF being added before the buffer to prevent the appearance of a fluffy orange-red precipitate. The total volume was made up to 100 mL with the buffer, producing an orange-red solution that exhibited only a broad absorption at λ_{max} = 428 nm (ϵ = 3466 M^{-1} cm^{-1}). The absorption reached its maximum intensity after ~20 h and remained unchanged for at least 5 days.

Stability Constants. For the determination of the stability constant of the iron complex, the same procedure was followed except that Na_2EDTA·$2H_2O$ (1 or 2 equiv based on **2**) dissolved in a little of the buffer was added after iron and the ligand **2** had been mixed. DMF and the rest of the buffer were then added as before. The absorption spectra showed that the intensity of the absorption at 428 nm in the case of 1 equiv of added Na_2EDTA·$2H_2O$ reached a maximum value after 5 h, a showing 23.8% loss of intensity. For the 2 equiv of added Na_2EDTA·$2H_2O$ the maximum value was reached in under 5 h, showing a 35.0% loss of intensity. Both of these solutions deposited a precipitate on standing after ~36 h.

Instrumentation. The ^{1}H NMR spectra were obtained on a Varian T-60 spectrometer, and the UV spectra were run on a Varian 2300 spectrophotometer.

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Ultraviolet Resonance Raman Study of Deoxyguanosine Monophosphate and Its Complexes with *cis*-$(NH_3)Pt^{2+}$, Ni^{2+}, and H^+

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Raman spectra are reported with deep ultraviolet excitation at 240 and 218 nm for dilute (5 mM) aqueous solutions of 2′-deoxyriboguanosine 5′-monophosphate (dGMP), its N7-protonated form (pH 1.5), its 1:1 complex with aqueous Ni^{2+}, and its 1:1 and 2:1 complexes with *cis*-$(NH_3)_2Pt^{2+}$. The C=O6 stretching band at 1677 cm^{-1} in dGMP shifts up to 1702 cm^{-1} on N7 protonation and to 1686 cm^{-1} in the 2:1 Pt complex, reflecting the polarizing effect of these positive centers. In the Ni complex, however, this band shifts down to 1660 cm^{-1}, an effect attributed to intramolecular H bonding of the carbonyl oxygen atom by Ni-bound H_2O, as observed in the crystal structure. In the 1:1 Pt complex, a smaller downshift is seen, to 1670 cm^{-1}, and is suggested to be the resultant of opposing effects of polarization and intramolecular H bonding via the Pt-bound H_2O molecule; this H_2O is displaced by another guanine N7 in the 2:1 complex. Several guanine ring modes show progressive increases or decreases in frequency and/or intensity upon binding Ni, Pt, and H^+ due to polarization. Guanine modes at 682 and 855 cm^{-1} in dGMP, which are known to be sensitive to the sugar conformation, develop prominent shoulders at 666 and 864 cm^{-1} in the Ni and Pt complexes, and also in riboguanosine 5′-monophosphate (rGMP). These additional components are attributed to molecules with a C3′-endo ribose configuration, while the 682- and 855-cm^{-1} bands are associated with the C2′-endo conformation, which is dominant in dGMP. The crystal structure of the Ni complex shows a C3′-endo conformation, which allows the 5′-monophosphate linkage to accept H bonds from Ni^{2+}-bound H_2O molecules. It is suggested that this structural feature is only partially retained in solution. Prominent 666-cm^{-1} C3′-endo bands are also seen for Pt (but not Ni) complexes of 3′-dGMP and 2′-deoxyguanosine. Pt binding is suggested to stabilize the C3′-endo conformation via an electronic polarization effect.

Introduction

It has recently become possible to obtain Raman spectra with deep ultraviolet excitation by using pulsed YAG lasers and various frequency shifting devices.[1-4] This technology has made it possible to explore resonance effects in Raman spectra of simple aromatic chromophores, including aromatic side chains of proteins[5-12] and the purine and pyrimidine bases of nucleic acids.[13-16] Rich spectra of purine and pyrimidine ring modes have been reported, with the enhancement pattern varying strongly with laser excitation wavelength, as different π–π^* excited states are accessed. Variable-wavelength excitation can therefore be used to sort out and identify the different vibrational modes, whose overlap tends to obscure the band assignments in nonresonance Raman spectra

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