Catecholate/Salicylate Heteropodands: Demonstration of a Catecholate to Salicylate Coordination Change[1]

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While iron release from enterobactin-mediated iron transport occurs primarily via an esterase that destroys the siderophore, other catechol siderophores that are not susceptible to hydrolysis act as bacterial growth factors. Elucidating the structures of protonated ferric enterobactin may reveal the pathway by which synthetic analogues fulfill bacterial iron requirements. In order to more completely model this potential delivery pathway for ferric iron, as well as to understand the pH dependent structural dynamics of ferric enterobactin, two ligands, (2-hydroxybenzoyl-2-aminoethyl)-bis(2,3-dihydroxybenzoyl-2-aminoethyl)amine (TRENCAMSAM) and (2-hydroxy-3-methoxybenzoyl-2-aminoethyl)-bis(2,3-dihydroxybenzoyl-2-aminoethyl)amine (TRENCAM(3M)SAM), have been synthesized as models for monoprotonated enterobactin. The coordination chemistry of these ligands with Fe^{3+} and Al^{3+} has been investigated. Fe[TRENCAMSAM]$^{2-}$ crystallizes in the triclinic space group $P\bar{1}$: $Z = 1$, $a = 11.3307(6)$ Å, $b = 12.5479(7)$ Å, $c = 15.5153(8)$ Å, $\alpha = 94.513(1)°$, $\beta = 105.867(1)°$, $\gamma = 94.332(1)°$. The structure is a two-metal two-ligand dimer supported by μ-oxo bridges from two catecholate moieties. Al[TRENCAMSAM]$^{2-}$ crystallizes in the triclinic space group $P\bar{1}$: $Z = 2$, $a = 9.1404(2)$ Å, $b = 13.3570(1)$ Å, $c = 15.5950(1)$ Å, $\alpha = 95.711(1)°$, $\beta = 104.760(1)°$, $\gamma = 92.603(1)°$. The complex is a monomer with a five-coordinate, square-pyramidal aluminum cation. Al[TRENCAM(3M)SAM]$^{2-}$ crystallizes in the monoclinic space group $C2/m$: $Z = 8$, $a = 34.244(2)$ Å, $b = 11.6206(6)$ Å, $c = 21.9890(12)$ Å, $\beta = 101.478(1)°$. The complex is also a monomer, but with a highly distorted five-coordinate, square-pyramidal aluminum cation coordination sphere. At high pH these complexes do not display a salicylate mode of binding; however, at low pH Al[TRENCAMSAM]$^{2-}$ converts to protonated Al[H_3TRENCAMSAM]$^{+}$, which is a six-coordinate, tris-salicylate complex. Al[H_3TRENCAMSAM]$^{+}$ crystallizes in the triclinic space group $P\bar{1}$: $Z = 2$, $a = 11.5475(4)$ Å, $b = 12.1681(4)$ Å, $c = 12.5094(4)$ Å, $\alpha = 109.142(1)°$, $\beta = 104.327(1)°$, $\gamma = 103.636(1)°$. This is the first catecholamide enterobactin analogue that has been structurally characterized in both a catecholate and salicylate mode of coordination.

Introduction

The tris-catecholate siderophore enterobactin has been the subject of intense scrutiny for nearly 30 years.[2−8] The solid state and solution properties of enterobactin and its metal complexes have been thoroughly investigated in order to elucidate the origin of the remarkable affinity of enterobactin for ferric ion ($\beta_{110} \sim 10^{49}$).[9] Enterobactin has inspired the synthesis of numerous tris-catecholate analogues which employ a variety of triamine scaffolds.[10−14] The biological behavior of enterobactin and enterobactin analogues has been investigated in order to determine the recognition and transport of these metal complexes by bacteria.[15−17] The release of iron by enterobactin is performed by an esterase which hydrolyzes the trilactone scaffold, effectively destroying the siderophore and facilitating iron release.[18,19] However, the mechanism by which siderophore analogues (which are not susceptible to enterobactin esterase) release iron (∼5% as efficiently as enterobactin) is not known.[15,20]

We have suggested a mechanism for iron release from catechol siderophore analogues based on the protonation behavior of ferric enterobactin and other tris-catecholamide

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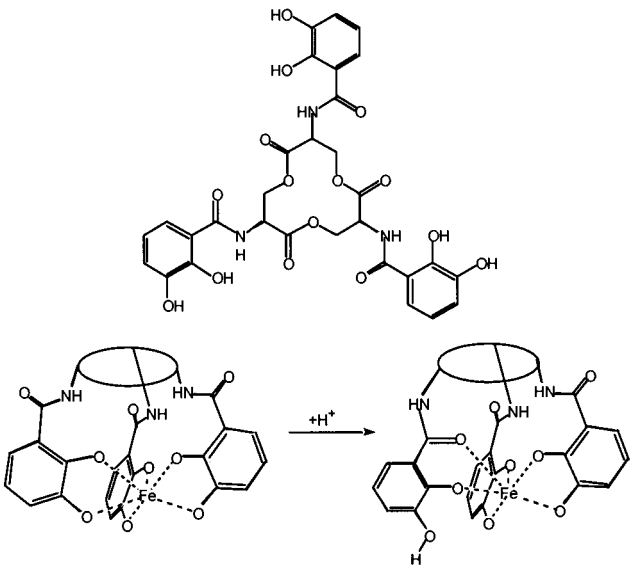

Figure 1. Enterobactin (top) and the proposed transformation in coordination for Fe[Henterobactin]$^{2-}$: the tris-catecholate ferric enterobactin complex (left) becomes protonated and converts to a monosalicylate bis-catecholate conformation (right).

podands.[21−24] Ferric enterobactin undergoes three discrete protonations with a reduction in pH, finally forming the neutral, purple complex Fe[H_3enterobactin]^0 which precipitates from solution.[21,25] We proposed that protonation of the 3-hydroxy oxygen results in a switch from a catecholate to a salicylate mode of bonding, as diagrammed in Figure 1.[26,27] Upon the third protonation, the complex achieves a tris-salicylate mode of coordination, the purple complex Fe[H_3enterobactin]^0.

Similar protonation behavior is observed with enterobactin analogues such as MECAM.[21] Iron release from analogues could be achieved by adopting a tris-salicylate mode of coordination (perhaps in the acidic periplasm) followed by complex dissociation with the aid of a biological reductant. We have reported a series of structurally characterized tris-salicylate complexes that confirm that such a binding mode is achieved in Fe[H_3-enterobactin]^0 and its synthetic analogues.[28] Other related salicylate systems have also been reported recently.[28] However, the complete pH dependent structural dynamics of ferric enterobactin and enterobactin analogues are still not known.

In this report we present two new ligands, (2-hydroxybenzoyl-2-aminoethyl)-bis(2,3-dihydroxybenzoyl-2-aminoethyl)-amine (TRENCAMSAM) and (2-hydroxy-3-methoxybenzoyl-2-aminoethyl)-bis(2,3-dihydroxybenzoyl-2-aminoethyl)amine (TRENCAM(3M)SAM), which were designed to model monoprotonated enterobactin. The coordination chemistry of these ligands with Fe^{3+} and Al^{3+} has been characterized both in solution and in the solid state. In addition, Al[TRENCAMSAM] was shown (by ^{1}H NMR and X-ray diffraction) to switch from a catecholate to a salicylate mode of bonding with a lowering of pH. This demonstrates structurally for the first time a transformation from a catecholate to a salicylate mode of binding in accordance with the proposed iron release mechanism from enterobactin analogues. This unusual transformation and the general coordination chemistry of these interesting new heteropodands are described.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tris-(2-aminoethyl)amine was distilled under vacuum over CaH_2. Flash silica gel chromatography was performed using Merck silica gel 40−70 mesh. Microanalyses were performed by the Microanalytical Services Laboratory, College of Chemistry, University of California, Berkeley. Mass spectra were recorded at the Mass Spectrometry Laboratory, College of Chemistry, University of California, Berkeley. ^{1}H and ^{13}C NMR spectra were recorded on an AMX 300 or AMX 400 Bruker superconducting Fourier transform spectrometer or a DRX 500 Bruker superconducting digital spectrometer. Infrared spectra were measured using a Nicolet Magna IR 550 Fourier transform spectrometer. UV/visible spectra were measured using a Hewlett-Packard 8452A kept at constant temperature in a jacketed cell with a Neslab RTE-111 water bath. 2-Benzoxy-3-methoxybenzoic acid, 2,3-dimethoxybenzoylmercaptothiazoline, and 2,3-dibenzoxybenzoylmercaptothiazoline were synthesized according to previously described methods.[28,37]

2-Benzyoxybenzoic Acid (1). Salicylic acid (0.08 mol), benzyl chloride (0.23 mol), and K_2CO_3 (0.16 mol) were mixed in 100 mL of dry DMF. The flask was fitted with a reflux condenser and heated to 75 °C for 18 h. The dark reaction mixture was filtered and the fitrate evaporated to dryness to obtain a dark amber liquid. The viscous liquid was dissolved in CH_2Cl_2 and purified by flash silica column chromatography using CH_2Cl_2 to give the benzyl ester intermediate as an amber liquid after evaporation of solvent. The liquid was dissolved with 6.0 g of KOH in 50 mL of MeOH and 10 mL of water. Hydrolysis was complete in 5 h, and the solution was evaporated to dryness to afford a white residue. The residue was dissolved in water and acidified with 6 N HCl to produce an insoluble liquid. The viscous liquid was extracted with CH_2Cl_2, which was dried with Mg_2SO_4, filtered, and evaporated to dryness to afford a colorless liquid that crystallized upon standing. Yield: 80%. IR (film from CH_2Cl_2): ν 1225, 1730, 3419 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 4.69 (s, 2H, C*H*$_2$), 7.14 (t, $J = 8.8$ Hz, 1H, Ar*H*), 7.37 (m, 7H, Ar*H*), 8.21 (d, $J = 6.1$ Hz, 1H, Ar*H*). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 71.5, 113.0, 121.7, 127.1, 128.1, 128.8, 132.9, 133.1, 134.7, 140.7, 157.3, 166.2. Anal. Calcd (found) for $C_{14}H_{12}N_2O_3 \cdot 0.20\ H_2O$: C, 72.53 (72.73); H, 5.39 (5.59).

2-Benzoxy(succinimidyl)benzoic Acid (2). 2-Benzoxybenzoic acid (**1**) (0.03 mol) and *N*-hydroxysuccinimide (0.03 mol) were dissolved in 150 mL of dry THF. After stirring under N_2(g) for 30 min, 1,3-dicyclohexylcarbodiimide (0.03 mol) was added to the reaction mixture. After stirring for 5 h, the solution was filtered and the filtrate evaporated

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to dryness to give a white solid. The solid was dissolved in a minimum amount of CH_2Cl_2 and diluted with an equal amount of Et_2O. Upon cooling to 4 °C, white crystals precipitated, which were collected by filtration. Yield: 67%. IR (film from $CDCl_3$): ν 1207, 1737, 1772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.90 (br s, 4H, CH_2), 5.23 (s, 2H, CH_2), 7.04 (t, J = 7.4 Hz, 2H, ArH), 7.37 (m, 3H, ArH), 7.52 (m, 3H, ArH), 8.08 (d, J = 6.3 Hz, 1H, ArH). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 25.5, 70.2, 113.6, 114.3, 120.4, 126.7, 127.7, 128.4, 132.5, 135.7, 136.0, 159.3, 160.1, 169.4. Anal. Calcd (Found) for $C_{18}H_{15}N_1O_5$: C, 66.46 (66.51); H, 4.65 (4.91); N, 4.31 (4.43).

Bis(2,3-dimethoxybenzoyl-2-aminoethyl)-2-aminoethylamine (3). TREN (4.0 mmol) was dissolved in 150 mL of dry CH_2Cl_2. Dropwise (18 h), a solution of 2,3-dimethoxybenzoylmercaptothiazoline (9.0 mmol) in 100 mL of dry CH_2Cl_2 was added from a pressure-equalized addition funnel. The reaction mixture was loaded directly onto a silica column and eluted with a 0−20% MeOH/CH_2Cl_2 gradient. The solvent was evaporated to give the product as an amber liquid. Yield: 74%. IR (film from $CDCl_3$): ν 1476, 1652, 3374 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.69 (t, J = 5.9 Hz, 2H, CH_2), 2.80 (m, 6H, CH_2), 3.58 (q, J = 5.8 Hz, 4H, CH_2), 3.87 (s, 6H, CH_3), 6.98 (d, J = 6.5 Hz, 2H, ArH), 7.09 (t, J = 8.0 Hz, 2H, ArH), 7.58 (d, J = 6.2 Hz, 2H, ArH), 8.22 (br t, 2H, NH). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 38.0, 49.8, 51.9, 54.0, 55.9, 61.3, 115.2, 121.9, 124.1, 126.7, 147.2, 152.4, 166.1.

(2-Benzoxybenzoyl-2-aminoethyl)-bis(2,3-dimethoxybenzoyl-2-aminoethyl)amine (4). 3 (3.0 mmol) was dissolved in 20 mL of dry CH_2Cl_2. **2** (3.1 mmol) was added as a solution in 20 mL of dry CH_2Cl_2. After 2 h, the reaction mixture was loaded on a silica column and eluted with a 0−10% MeOH/CH_2Cl_2 gradient. The solvent was evaporated to give the product as a white, foamy solid. Yield: 46%. IR (film from CH_2Cl_2): ν 1522, 1653, 2934, 3386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.58 (s br, 4H, CH_2), 2.76 (s br, 2H, CH_2), 2.92 (s br, 2H, CH_2), 3.34 (s br, 4H, CH_2), 3.63 (s br, 6H, CH_3), 3.66 (s br, 6H, CH_3), 6.77 (d, J = 8.1 Hz, 2H, ArH), 6.84 (t, J = 7.9 Hz, 2H, ArH), 7.23 (d, J = 7.7 Hz, 2H, ArH), 8.10 (s br, 2H, NH). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 33.5, 37.0, 37.2, 52.5, 55.5, 60.7, 70.7, 112.3, 114.7, 120.8, 121.4, 121.9, 123.7, 126.4, 127.4, 128.2, 128.4, 131.5, 132.1, 135.4, 147.0, 152.1, 156.3, 164.8, 165.0. (+)-FABMS: m/z 685 [M^+ + H]. Anal. Calcd (found) for $C_{38}H_{44}N_4O_8 \cdot 2.5H_2O$: C, 62.54 (62.56); H, 6.77 (6.41); N, 7.68 (7.38).

(2-Hydroxybenzoyl-2-aminoethyl)-bis(2,3-dihydroxybenzoyl-2-aminoethyl)amine (TRENCAMSAM) (5). 4 (1.3 mmol) was dissolved in 30 mL of dry CH_2Cl_2. The solution was degassed three times under an argon atmosphere. The solution was cooled in a liquid nitrogen bath, and BBr_3 (50.0 mmol) was added to the frozen solution via syringe. The turbid, yellow solution was stirred for 2 days. The reaction mixture was evaporated to dryness to give a pale yellow solid, which was slowly quenched with 20 mL of MeOH. The resulting yellow solution was dissolved in 100 mL of boiling water, and boiled for 2 h. The hot solution was filtered, and the colorless filtrate was cooled to 4 °C. A white solid precipitated from the solution overnight. The product was collected by filtration and dried in a vacuum oven. Yield: 43%. IR (KBr pellet): ν 1328, 1644, 2754 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ 3.50 (s br, 6H, CH_2), 3.71 (s br, 6H, CH_2), 6.70 (t, J = 7.9 Hz, 2H, ArH), 6.92 (m, 4H, ArH), 7.24 (d, J = 7.2 Hz, 2H, ArH), 7.40 (t br, 1H, ArH), 7.79 (d, J = 6.3 Hz, 1H, ArH). ^{13}C NMR (500 MHz, DMSO-d_6, 25 °C): δ 34.2, 51.8, 52.0, 115.6, 115.9, 117.7, 118.2, 118.6, 119.2, 119.5, 128.9, 134.3, 146.6, 149.6, 159.8, 169.6, 170.6. (+)-FABMS: m/z 539 [M^+ + H]. Anal. Calcd (found) for $C_{27}H_{31}N_4O_8Br_1 \cdot 1.5H_2O$: C, 50.16 (50.08); H, 5.30 (5.15); N, 8.67 (8.57).

Al[TRENCAMSAM] (6). 5 (0.09 mmol) was dissolved in 9 mL of MeOH. To the solution was added anhydrous $AlCl_3$ (0.07 mmol). The mixture was diluted with 4.7 mL of 0.0997 N KOH in MeOH. The solution was stirred for 4 h and then evaporated to dryness to give a white residue. The material was recrystallized with either a DMF or MeOH solution of the complex diffused with Et_2O. IR (KBr pellet): ν 1472, 1541, 1642 cm^{-1}. ^1H NMR (300 MHz, MeOD, 25 °C): δ 2.51 (br s, 2H, CH_2), 2.67 (s, 2H, CH_2), 2.82 (br s, 2H, CH_2), 3.42 (br m, 6H, CH_2), 6.28 (t, J = 7.6 Hz, 2H, CAM), 6.39 (t, 1H, SAM), 6.60 (d, 2H, J = 6.0 Hz, CAM), 6.83 (s, 2H, SAM), 6.90 (d, 2H, J = 6.8 Hz, CAM), 7.57 (d, 2H, J = 8.6 Hz, SAM). ^{13}C NMR (400 MHz, D_2O, 25 °C): δ 37.0, 40.1, 50.9, 56.4, 114.1, 114.7, 116.1, 118.8, 120.8, 123.5, 129.3, 133.0, 153.6, 155.6, 159.8, 161.4, 169.5, 169.6. (+)-FABMS: m/z 600 [M^+ + 2H + K], 638 [M^+ + H + 2K], 677 [M^+ + 3K].

Fe[TRENCAMSAM] (7). 5 (0.09 mmol) was dissolved in 9 mL of MeOH. To the solution was added anhydrous $FeCl_3$ (0.07 mmol). The solution became dark purple-red. The mixture was diluted with 4.7 mL of 0.0997 N KOH in MeOH and gave a deep red solution. The mixture was stirred for 4 h and then evaporated to dryness to give a red residue. The material was recrystallized with either a DMF or MeOH solution of the complex diffused with Et_2O. IR (KBr pellet): ν 1223, 1642, 3061 cm^{-1}. (+)-FABMS: m/z 613 [M^+ + 2H + Na], 636 [M^+ + H + 2Na], 658 [M^+ + 3Na].

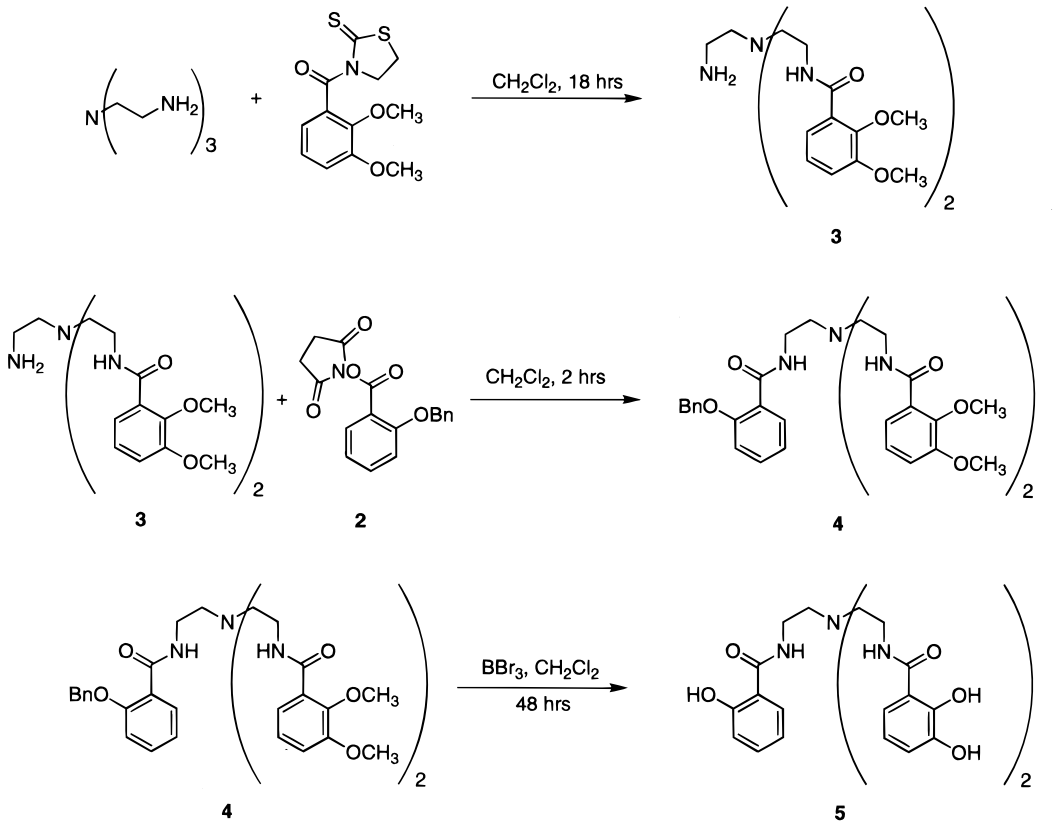
Bis(2,3-dibenzoxybenzoyl-2-aminoethyl)-2-aminoethylamine (8). TREN (3.7 mmol) was dissolved in 75 mL of dry CH_2Cl_2. Dropwise (18 h), a solution of 2,3-dibenzoxybenzoylmercaptothiazoline (7.8 mmol) in 100 mL of dry CH_2Cl_2 was added from a pressure-equalized addition funnel. The reaction mixture was loaded directly onto a silica column and eluted with a 0−20% MeOH/CH_2Cl_2 gradient. The solvent was evaporated to give the product as an amber oil. Yield: 59%. IR (film from $CDCl_3$): ν 1575, 1653, 3389 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 2.37 (br t, 4H, CH_2), 2.47 (br t, 2H, CH_2), 3.23 (br q, 6H, CH_2), 5.08 (s, 4H, CH_2), 5.16 (s, 6H, CH_2), 7.11 (m, 4H, ArH), 7.35 (m, 20H, ArH), 7.59 (m, 2H, ArH), 7.95 (br t, 2H, NH). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 37.6, 39.5, 53.1, 56.7, 71.2, 76.2, 116.9, 123.0, 124.3, 124.4, 127.6, 127.7, 127.8, 128.2, 128.6, 128.7, 136.5, 136.6, 146.7, 151.7, 165.4.

(2-Benzoxy-3-methoxybenzoyl-2-aminoethyl)-bis(2,3-dibenzoxybenzoyl-2-aminoethyl)amine (9). 2-Benzoxy-3-methoxybenzoic acid (2.2 mmol) was dissolved in 25 mL of thionyl chloride and 0.1 mL of DMF. The mixture was stirred under a nitrogen atmosphere overnight. The solution was evaporated to dryness and coevaporated with 2 × 30 mL of $CHCl_3$, to give an amber oil. The oil was dissolved in 10 mL of dry THF and was mixed with **8** (0.9 mmol) and TEA (1 mL) dissolved in 45 mL of dry THF under nitrogen gas. After 1.5 h, the solution was filtered and evaporated to dryness to obtain a brown liquid. The thick liquid was purified on a silica column eluted with a 0−5% MeOH/CH_2Cl_2 gradient. The solvent was evaporated to give the product as a pale brown liquid. Yield: 80%. IR (film from $CDCl_3$): ν 1472, 1653, 2941 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.27 (br t, 6H, CH_2), 3.10 (br q, 6H, CH_2), 3.80 (s, 3H, CH_3), 4.96 (s, 4H, CH_2), 5.03 (s, 2H, CH_2), 5.04 (s, 4H, CH_2), 7.04 (m, 4H, ArH), 7.29 (m, 28H, ArH), 7.56 (m, 2H, ArH), 7.70 (br t, 3H, NH). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 25.6, 37.3, 52.6, 53.7, 56.0, 71.1, 76.2, 113.0, 115.1, 116.8, 119.2, 122.5, 122.9, 124.3, 124.9, 127.6, 127.9, 128.2, 128.3, 128.6, 128.9, 136.5, 136.6, 136.8, 146.3, 146.7, 151.7, 152.6, 165.3. (+)-FABMS: m/z 1019 [M^+ + H]. Anal. Calcd (found) for $C_{63}H_{62}N_4O_9 \cdot 1.5H_2O$: C, 72.33 (72.11); H, 6.26 (6.02); N, 5.36 (5.00).

(2-Hydroxy-3-methoxybenzoyl-2-aminoethyl)-bis(2,3-dihydroxybenzoyl-2-aminoethyl)amine (TRENCAM(3M)SAM) (10). 9 (1.8 mmol) was dissolved in 40 mL of 1:1 glacial acetic acid/concentrated HCl and stirred for 24 h. The solution was evaporated to dryness and coevaporated with 4 × 50 mL of MeOH to obtain a beige foam. Yield: 92%. IR (film from $CDCl_3$): ν 1458, 1587, 1646 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ 3.51 (br s, 6H, CH_2), 3.77 (br s, 9H, CH_2/CH_3), 6.70 (t, J = 7.9 Hz, 2H, ArH), 6.81 (br t, 1H, ArH), 6.93 (d, J = 7.8 Hz, 2H, ArH), 7.10 (br d, 1H, ArH), 7.31 (d, J = 8.2 Hz, 2H, ArH), 7.50 (br d, 1H, ArH), 9.08 (br t, 3H, NH). ^{13}C NMR (400 MHz, DMSO-d_6, 25 °C): δ 25.8, 33.8, 34.2, 51.9, 56.3, 115.3, 115.5, 116.1, 118.2, 118.4, 118.6, 119.6, 129.0, 146.6, 148.8, 149.8, 151.0, 170.4, 170.6. (+)-FABMS: m/z 569 [M^+ + H]. Anal. Calcd (found) for $C_{28}H_{33}N_4O_9Cl_1 \cdot 0.25MeOH$: C, 55.35 (55.54); H, 5.59 (5.69); N, 9.14 (8.83).

Al[TRENCAM(3M)SAM] (11). 10 (0.19 mmol) was dissolved in 5.0 mL of MeOH. To the solution was added anhydrous $AlCl_3$ (0.15 mmol) in 2.0 mL of MeOH. The mixture was diluted with 9.0 mL of 0.0994 N KOH in MeOH. The solution was refluxed for 3 h and then evaporated to dryness. The product was recrystallized from a DMF solution of the complex diffused with Et_2O. IR (KBr pellet): ν 1470, 1589, 2941 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 25 °C): δ 3.41 (br s, 12H, CH_2), 3.74 (br s, 3H, CH_3), 6.31 (br m, 5H, ArH), 6.66 (br m, 2H, ArH), 7.30 (br m, 2H, ArH). ^{13}C NMR (400 MHz, DMSO-d_6, 25

Scheme 1



°C): δ 35.4, 37.8, 56.3, 56.6, 56.8, 111.9, 113.9, 114.3, 114.7, 117.5, 119.7, 122.5, 126.9, 128.5, 153.4, 156.6, 157.5, 167.0, 167.6.

Fe[TRENCAM(3M)SAM] (12). 10 (0.07 mmol) was dissolved in 20 mL of MeOH. To the solution was added anhydrous $FeCl_3$ (0.07 mmol) in 2.0 mL of MeOH. The mixture was diluted with 4.0 mL of 0.0994 N KOH in MeOH to give a deep purple solution. The reaction mixture was heated to reflux overnight. The cooled mixture was diluted with Et_2O (40 mL) and the resulting purple precipitate collected by filtration. IR (KBr pellet): ν 1457, 1585, 2939 cm^{-1}. (−)-FABMS *m*/*z*: 620 [M^- + H].

Structure Solution and Refinement. All X-ray structure data sets were collected, solved, and refined as previously described.[28,38,39]

Fe[TRENCAMSAM]$^{2-}$ (6). Crystals of Fe[TRENCAMSAM] were grown from a solution of the complex in DMF diffused with diethyl ether. Fe[TRENCAMSAM] crystallized as dark red, opaque blocks. Two sodium counterions and four DMF molecules (three were highly disordered) were found in the asymmetric unit. The solution revealed the complex to be a μ-oxo-bridged 2:2 metal:ligand dimer.

Al[TRENCAMSAM]$^{2-}$ (5). Crystals of Al[TRENCAMSAM] were grown from a solution of the complex in DMF diffused with diethyl ether. Al[TRENCAMSAM] crystallized as slightly pink, transparent blocks. Two potassium counterions and two molecules of DMF were found in the asymmetric unit.

Al[TRENCAM(3M)SAM]$^{2-}$ (11). Crystals of Al[TRENCAM(3M)SAM]$^{2-}$ grew as transparent plates from a solution of the complex in DMF and MeOH diffused with diethyl ether. Two potassium counterions, three molecules of DMF, and a partial occupancy methanol molecule (75%) were found in the asymmetric unit. Two of the DMF molecules were disordered.

Al[H_3TRENCAMSAM]$^+$ (5 + 3H^+). Crystals of Al[H_3TRENCAMSAM]$^+$ grew as slightly beige prisms from a solution of D_2O at pH ~6. The protonated catechol oxygens were disordered, so that the salicylate ring could not be determined absolutely. One aromatic ring has a full occupancy 3-hydroxy oxygen (O33) while the other two rings share a near 50:50 partial occupancy disorder of the meta oxygen (O13 and O23). In addition, the counterion in this crystal was found to be a roughly 50:50 split between a chloride and bromide anion in overlapping positions in the unit cell. The protons on the full occupancy protonated oxygen (O33) and the TREN backbone (N1) were found, and their positions were not calculated. Four and one-half molecules of water (D_2O) were found in the asymmetric unit.

NMR Titrations. In 10 mL of D_2O (Aldrich) was dissolved ~100 mg of the pure Al[TRENCAMSAM]K_2 complex. The pD was then adjusted to ~11 using NaOD (~5% diluted from Aldrich, 30 wt %). The pD was reduced using DCl (~4% diluted from Aldrich, 20 wt %), and 0.5 mL aliquots were taken down to pD 2.7 for a total of 14 samples. Apparent pH values were measured using a microelectrode (Microelectrodes MI-412 combination electrode filled with 3 M KCl), which was calibrated by a two-point calibration with standardized buffer solutions at pH 10 and 4. The corrected p[D] values were calculated according to the equation $p[D] = p[H]_{meas} + 0.4$.[40] Spectra were measured on a DRX 500 Bruker superconducting digital spectrometer at 25 °C.

Results and Discussion

Syntheses. TRENCAMSAM was synthesized by the method shown in Scheme 1. Two equivalents of 2,3-dimethoxybenzoylmercaptothiazoline were slowly added to 1 equiv of tris(2-aminoethyl)amine (TREN). The resulting compound, with one free primary amine, was mixed with the NHS-activated ester of 2-benzoxybenzoic acid. The protected heteropodand was then deprotected using BBr_3 to afford the free ligand. TRENCAM(3M)SAM was synthesized in an analogous fashion shown in Scheme 2. Two equivalents of 2,3-dibenzoxybenzoylmercaptothiazoline were combined with 1 equiv of TREN. The intermediate was combined with 2-benzoxy-3-methoxybenzoyl chloride

(38) *SHELXTL, Crystal Structure Analysis Determination Package*; Siemens Industrial Automation, Inc.: Madison, 1994.
(39) *SMART, Area-Detector Software Package*; Siemens Industrial Automation, Inc.: Madison, 1994.
(40) Perrin, D. D.; Dempsey, B. *Buffers for pH and Metal Ion Control*; Chapman and Hall: London, 1974.

Scheme 2

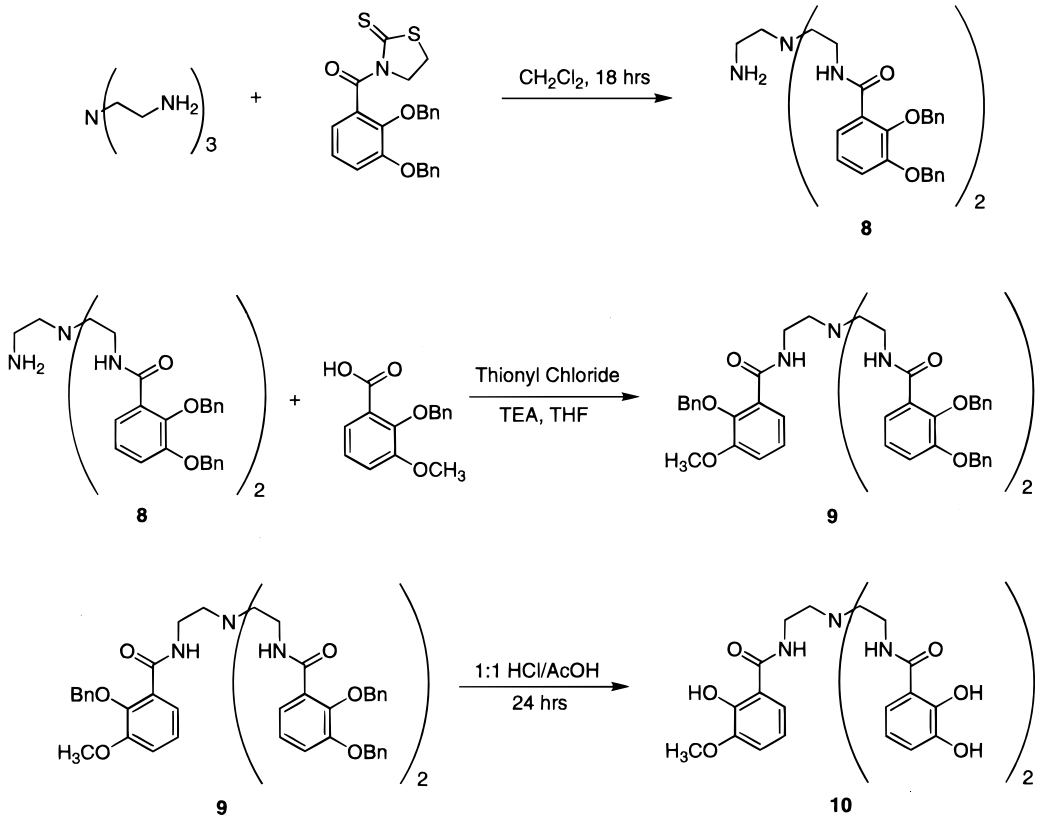


Table 1. UV−Visible Spectroscopic Data for Relevant Catecholate/Salicylate Fe^{3+} Complexes

compound	LMCT (nm)	ϵ ($\times 10^3$ M^{-1} cm^{-1})	$\pi-\pi^*$ (nm)	ϵ ($\times 10^3$ M^{-1} cm^{-1})
$Fe[TRENCAMSAM]^{2-}$ [c]	488	5.5(4)	324	14.6(3)
$Fe[TRENCAM(3M)SAM]^{2-}$ [c]	516	4.7(1)	326	15.5(3)
$Fe[HMMECAM]^{2-}$ [a,d]	514	3.8	n/a	n/a
$Fe[HEMECAM]^{2-}$ [b,d]	514	3.7	n/a	n/a
$Fe[HMECAM]^{2-}$ [e]	n/a	n/a	332	13.4
$Fe[Henterobactin]^{2-}$ [e]	514	4.6	332	14.7

[a] MMECAM = 1,3,5-tris(2,3-dihydrobenzamidomethyl)-2,4,6-trimethylbenzene. [b] EMECAM = 1,3,5-tris(2,3-dihydrobenzamidomethyl)-2,4,6-triethylbenzene. [c] This work. [d] Reference 29. [e] Reference 9.

to give the protected ligand after purification by flash silica column chromatography. The benzyl ether protecting groups were selectively removed under strongly acidic conditions, leaving the desired 3-methoxy group intact.

Metal complexes of both ligands were prepared under similar conditions. The ligand was dissolved in a minimum amount (~10 mL) of MeOH to which was added the anhydrous metal chloride salt. Five equivalents of base (0.1 M KOH in MeOH) were then added, and the reaction mixture was either stirred or heated to reflux for a minimum of 3 h. The solution was then evaporated to dryness, and the complexes were purified by recrystallization.

UV−Visible Spectroscopy. The spectroscopic properties of the ferric complexes of TRENCAMSAM and TRENCAM(3M)-SAM were investigated for comparison with $Fe[Henterobactin]^{2-}$ and analogues such as $Fe[HMECAM]^{2-}$ (Table 1).[9,29] In aqueous solution, $Fe[TRENCAMSAM]^{2-}$ shows a strong absorption in the UV due to $\pi-\pi^*$ transitions at 324 nm (ϵ = 14600) and displays a deep red color due to ligand-to-metal charge-transfer bands (LMCT) at 488 nm (ϵ = 5500). Both of these values are significantly different from those reported for $Fe[Henterobactin]^{2-}$ and related complexes (Table 1).[29] As we have described previously,[28] the 3-methoxysalicylate derivatives are better spectroscopic models for protonated ferric enterobactin species than the simple salicylate species. Indeed, aqueous solutions of $Fe[TRENCAM(3M)SAM]^{2-}$ display a UV absorption at 326 nm (ϵ = 15500) and a LMCT band at 516 nm (ϵ = 4700) giving rise to a deep purple color. Table 1 summarizes the absorption spectra for monoprotonated ferric enterobactin and a number of analogues. All of these complexes have a visible absorption maximum at 514 nm, nearly identical to that of $Fe[TRENCAM(3M)SAM]^{2-}$.

X-ray Structures. Single crystals of $Fe[TRENCAMSAM]^{2-}$ were obtained by diffusion of ether into a DMF solution of the complex (Table 2). $Fe[TRENCAMSAM]^{2-}$ crystallizes as a 2:2 metal/ligand dimer (Figure 2). The dimer is supported by two η^2-μ-oxo bridges provided by the 3-hydroxy functionality of one catecholamide from each ligand. This results in a core of two ferric ions and two bridging oxygens at the center of the structure (Figure 2). A number of oxo-bridged dimers with similar core structures have been synthesized as model compounds for small molecule activation in metalloproteins.[30,31] The structure shows that the salicylate ring does not participate in a salicylate-chelate mode of binding, rather the salicylate arm of the ligand behaves as a simple monodentate phenolic-type donor. The dimeric structure of the $Fe[TRENCAMSAM]^{2-}$ complex

Table 2. Crystal Data for Fe[TRENCAMSAM]$^{2-}$, Al[TRENCAMSAM]$^{2-}$, Al[TRENCAM(3M)SAM]$^{2-}$, and H_3^+[TRENCAMSAM]Al

	Fe[TRENCAMSAM]	Al[TRENCAMSAM]	Al[TRENCAM(3M)SAM]	Al[H_3TRENCAMSAM]
empirical formula	$Fe_2C_{78}H_{106}N_{16}O_{24}Na_4$	$AlC_{33}H_{39}N_6O_{10}K_2$	$AlC_{37.75}H_{51}N_7O_{12.75}K_2$	$AlC_{27}H_{37}N_4O_{12.5}Cl_{0.5}Br_{0.5}$
cryst syst	triclinic	triclinic	monoclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$C2/c$	$P\bar{1}$
unit cell dimens				
a, Å	11.3307(6)	9.1404(2)	34.244(2)	11.5475(4)
α, deg	94.513(1)	95.711(1)	90	109.142(1)
b, Å	12.5479(7)	13.3570(1)	11.6206(6)	12.1681(4)
β, deg	105.867(1)	104.760(1)	101.478(1)	104.327(1)
c, Å	15.5153(8)	15.5950(1)	21.9890(12)	12.5094(4)
γ, deg	94.332(1)	92.603(1)	90	103.636(1)
vol, Å^3; *Z*	2104.4(2); 1	1827.04(4); 2	8575.2(8); 8	1509.38(9); 2
cryst size, mm	0.10 × 0.15 × 0.30	0.10 × 0.20 × 0.30	0.05 × 0.25 × 0.40	0.10 × 0.15 × 0.30
reflns collected	8886	7602	17285	7209
indep reflns	5922 [*R*(int) = 0.0340]	5100 [*R*(int) = 0.0255]	6126 [*R*(int) = 0.0360]	5034 [*R*(int) = 0.0232]
data/restraints/params	5921/0/572	5098/0/469	6125/0/573	5033/0/463
goodness-of-fit on F^2	1.175	1.083	1.077	1.167
final *R* indices	R1 = 0.0778	R1 = 0.0454	R1 = 0.0679	R1 = 0.0450
[$I > 2\sigma(I)$]	wR2 = 0.1707	wR2 = 0.1043	wR2 = 0.1601	wR2 = 0.1079
R indices (all data)	R1 = 0.0954	R1 = 0.0555	R1 = 0.0921	R1 = 0.0552
	wR2 = 0.1873	wR2 = 0.1155	wR2 = 0.1821	wR2 = 0.1208
largest diff peak/hole, e Å^{-3}	0.749/−0.852	0.798/−0.321	1.142/−0.435	0.467/−0.340

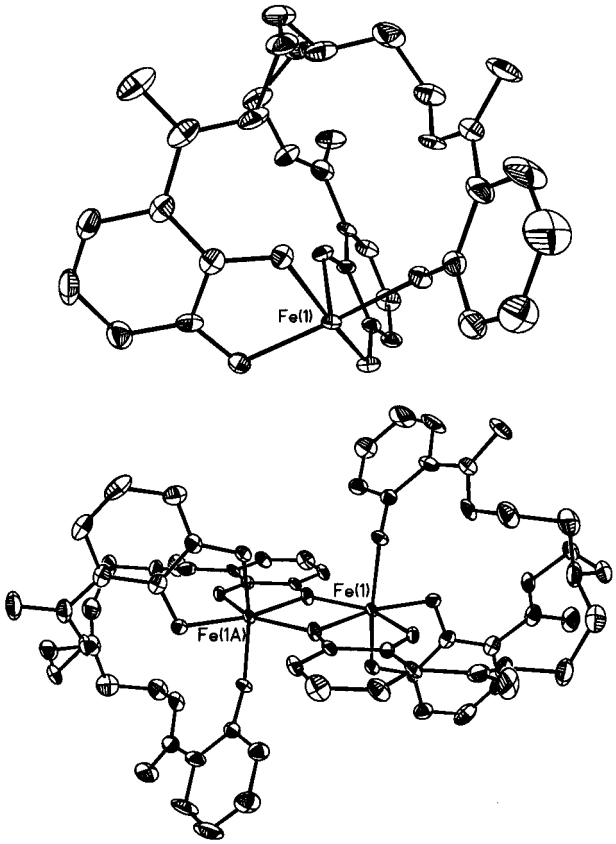


Figure 2. Structural diagrams (ORTEP) of one-half (top) and the complete (bottom) iron dimer Fe[TRENCAMSAM]$^{2-}$ showing the Fe_2O_2 core structure. The solvent molecules, counterions, and hydrogen atoms are omitted for clarity (50% probability ellipsoids).

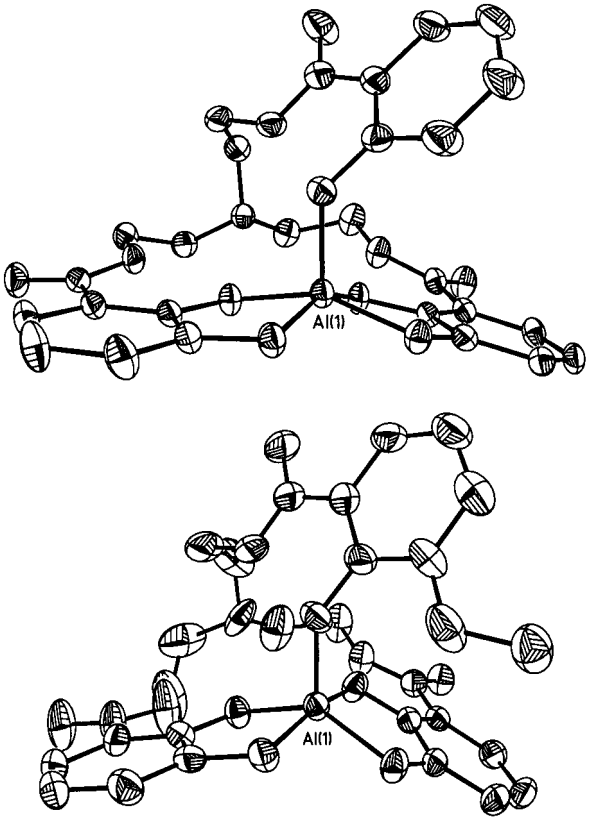


Figure 3. Structural diagrams (ORTEP) for Al[TRENCAMSAM]$^{2-}$ (top) and Al[TRENCAM(3M)SAM]$^{2-}$ (bottom) showing the square-pyramidal coordination geometries. Solvent, counterions, and hydrogen atoms are omitted for clarity (50% probability ellipsoids).

may not be maintained in solution (particularly at low concentrations), more likely forming a monomeric, six-coordinate solvated phenolate complex.

Crystals of both Al[TRENCAMSAM]$^{2-}$ and Al[TRENCAM(3M)SAM]$^{2-}$ were obtained by diffusion of ether into a DMF solution of the complex (Table 2). Both ligands form monomeric five-coordinate complexes with Al^{3+}. The aluminum ions have square-pyramidal coordination geometries, where the salicylate (TRENCAMSAM) and 3-methoxysalicylate (TRENCAM(3M)SAM) donors occupy the apical site of the pyramid (Figure 3). Both complexes adopt a scorpionate conformation with the catecholamide "pincers" holding the cation poised for the salicylate "sting."[32,33] All of the 2-hydroxy donors are stabilized by a hydrogen bond with the adjacent amide protons (as typically observed for catecholamide podands).[5,34−36] Al[TRENCAMSAM]$^{2-}$ has a nearly ideal square-pyramidal geometry about the Al^{3+} cation. The salicylate oxygen is held about 0.05 Å closer to the metal center (1.79 Å) than the catecholate oxygens (1.84 Å). Also the catecholate oxygens bind the potassium cations on the opposite face of the square plane from the aluminum ion. One of the potassium ions is bound by

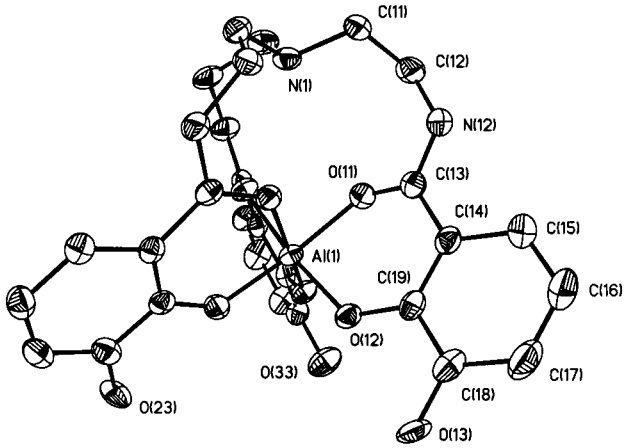


Figure 4. Structural diagram (ORTEP) of Al[H_3TRENCAMSAM]$^+$ viewed perpendicular to the approximate 3-fold axis. This structure is obtained upon protonation of the Al[TRENCAMSAM]$^{2-}$ complex. Oxygen atoms O13 and O23 are part of a 50:50 occupancy disorder (the ligand has two catecholate rings and one salicylate ring). The solvent molecules, counterions, and hydrogen atoms are omitted for clarity (50% probability ellipsoids).

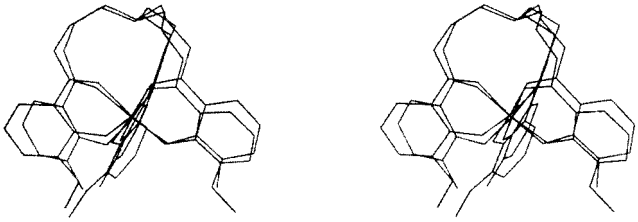


Figure 5. Stereoscopic view of an overlay of Al[TREN(3M)SAM]$^+$ and Al[H_3TRENCAMSAM]$^+$. The rms deviation for 41 atom pairs is 1.98 Å.

the 2-hydroxyl oxygens while the other is coordinated by the 3-hydroxyl oxygens of the catecholamides. Al[TRENCAM-(3M)SAM]$^{2-}$ has a highly distorted geometry, although the bond distances around the metal center are roughly the same as those found in Al[TRENCAMSAM]$^{2-}$ (1.78 Å for the salicylate oxygen and 1.84 Å for the catecholate oxygens). An overlay of the metal core (six atom pairs) of these Al^{3+} complexes results in a root-mean-squared (rms) deviation of 1.82 Å, demonstrating the severely distorted geometry in Al[TRENCAM(3M)SAM]$^{2-}$.

The complex Al[TRENCAMSAM] was also crystallized from a solution buffered at pH 6, producing Al[H_3TRENCAMSAM]$^+$ (Table 2). In this complex, the meta oxygens of the two catechol ligands are protonated and the ligand adopts a tris-salicylate mode of binding (Figure 4).

The third proton is on the tertiary amine nitrogen, giving the complex an overall positive charge. Protonation of the tertiary amine is consistent with previously reported complexes of tris-salicylate TREN-based ligands.[28] The complex is disordered with respect to the protonated 3-hydroxy groups, so that the salicylate arm of the ligand could not be precisely identified. The best refinement was obtained by having one full-occupancy oxygen (O33) and a roughly 50:50 occupancy between the other two possible positions (O13 and O23). The geometry of Al-[H_3TRENCAMSAM]$^+$ is very similar to that of previously reported tris-salicylate complexes such as Al[TREN(3M)-SAM]$^+$.[28] Figure 5 shows a minimized overlay of the two structures, showing that their overall geometries are essentially identical. However, the many minor deviations (41 atom pairs overlaid) between the structures results in an rms deviation of 1.98 Å.

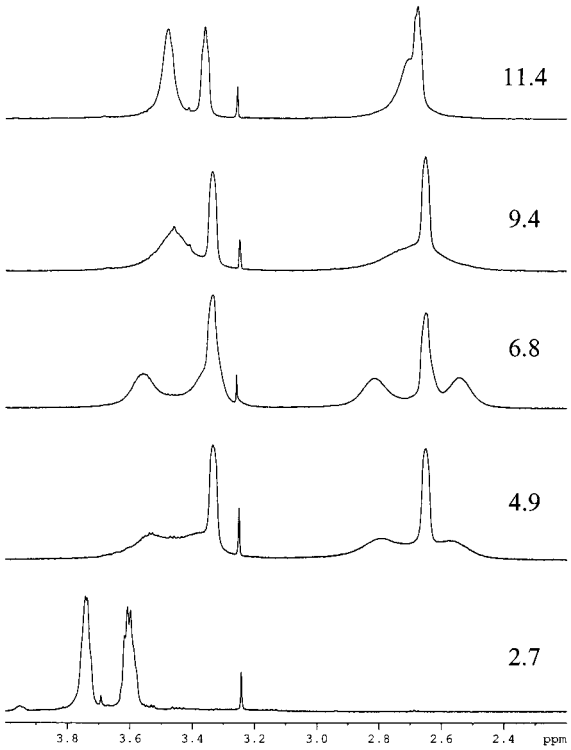


Figure 6. Representative spectra from a ^{1}H NMR titration of Al[TRENCAMSAM] in D_2O. The conversion from a catecholate to salicylate mode of binding gives rise to the broad, diastereotopic resonances of the TREN scaffold. At very low pD the complex is dissociated and the spectrum of the free ligand TRENCAMSAM is obtained. pD (top to bottom): 11.4, 9.4, 6.8, 4.9, 2.7. T = 25 °C.

Despite abundant spectroscopic evidence for transformations from catecholate to salicylate bonding in catecholamide metal complexes,[22,27] this is the first example that has been structurally characterized and clearly demonstrates that such transformations can and do occur. Fe[TRENCAMSAM]$^{2-}$ is unlikely to form a five-coordinate complex in solution like that found for Al[TRENCAMSAM]$^{2-}$. If the solution structures of Fe[TRENCAMSAM]$^{2-}$ and Al[TRENCAMSAM]$^{2-}$ are different, then the manner by which each complex rearranges from one coordination geometry to another will also be different. Indeed, the transformation for Al[TRENCAMSAM]$^{2-}$ is more involved than would be expected for an octrahedral ferric ion, as the former involves a change in both coordination number (five- to six- coordinate) and coordination geometry (square-pyramidal to octahedral). However, the reorganization of the aluminum complex is important structural evidence that catecholamide tripodal metal complexes can undergo a catecholate to salicylate coordination change that is stimulated by a lowering of pH. Therefore the ferric complex of a siderophore can be protonated to a more readily reduced salicylate species.[21−24]

^{1}H NMR Titration of Al[TRENCAMSAM]. To observe the transition from a catecholate to salicylate mode of binding, an ^{1}H NMR titration was performed on Al[TRENCAMSAM]. Starting with the catecholate complex at high pD (11.4), 14 samples were prepared down to pD 2.7. The transition was monitored by following the resonances of the methylene protons on the TREN backbone. In catecholate complexes these protons are relatively sharp and well resolved. However, NMR spectra of TREN-capped salicylate complexes show that these protons become broad and diastereotopic (sensitive to the chirality at

the metal center).[28] These effects are most probably due to both the proximity of the metal center to the cap and the protonation of the TREN bridgehead nitrogen (which contributes to peak broadening).

Figure 6 shows some representative spectra from the titration of Al[TRENCAMSAM]. At high pD the TREN methylenes appear as three sharp singlets (however, one peak is composed of two overlapping resonances), as expected for a catecholate species. However, as the pD is lowered, the methylene protons for the catecholate arms of the TREN scaffold diverge and become broadened, while the methylene protons for the salicylate arm remain as relatively sharp singlets. The catecholate methylenes diverge to four broad resonances; one pair arising from each of the two singlets, displaying diastereotopic behavior similar to that observed in TREN salicylate complexes. These diastereotopic resonances broaden further with decreasing pD. In the region of pD ~4.5−3.5 most of the complex precipitates from solution and no proton resonances are observed (this insolubility is consistent with previously synthesized tris-salicylate complexes).[28] Finally, below pD 3.5, the complex is dissociated and two sharp, shifted singlets are observed that correspond to the free ligand TRENCAMSAM. This NMR titration complements the X-ray structures of $Al[TRENCAMSAM]^{2-}$ and $Al[H_3TRENCAMSAM]^{+}$, confirming that the catecholate to salicylate transition occurs in solution.[22]

Conclusion

The ligands TRENCAMSAM and TRENCAM(3M)SAM have been synthesized and their coordination chemistry explored both in solution and in the solid state. The structure of $Fe[TRENCAMSAM]^{2-}$ is a dimer with an Fe_2O_2 core geometry. $Al[TRENCAMSAM]^{2-}$ and $Al[TRENCAM(3M)SAM]^{2-}$ are monomeric, five-coordinate complexes with the cation in a square-pyramidal coordination environment.

The pH dependent structure of Al[TRENCAMSAM] has been probed by ^1H NMR titration and two X-ray structures. The complex has been shown to change, upon the addition of three protons, from a pentadentate square-pyramidal geometry to a hexadentate octahedral geometry. This transformation occurs with a coincident reorganization from a bis-catecholate monophenolate coordination to a tris-salicylate mode of bonding.

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Supporting Information Available: Four X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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