A Novel Salicylate-Based Macrobicycle with a "Split Personality"

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Two new ligands (the tripodal TRENIAM and macrobicyclic TRENSAM) which use 2-hydroxyisophthalic acid as a salicylato-type of binding group have been prepared, and their coordination chemistry has been investigated. The structures of several metal complexes have been determined in both solution and the solid state. The ferric and gallium complexes of TRENIAM are isostructural and crystallize in the triclinic space group $P\bar{1}$, with $Z = 4$. For Fe[TRENIAM]: $a = 12.0203(4)$ Å, $b = 12.6996(4)$ Å, $c = 24.6435(8)$ Å, $\alpha = 83.146(1)°$, $\beta = 88.531(1)°$, $\gamma = 85.282(1)°$. For Ga[TRENIAM]: $a = 11.9780(2)$ Å, $b = 12.6417(3)$ Å, $c = 24.5404(6)$ Å, $\alpha = 83.324(1)°$, $\beta = 88.488(1)°$, $\gamma = 85.038(1)°$. The metal cations are bound by three phenolic oxygens and three carbonyl oxygens in a ligand structure analogous to that of salicylamide. The ferric and gallium complexes of macrobicyclic TRENSAM are essentially isosteric and crystallize in the monoclinic space group $P2_1/n$, with $Z = 4$. For Fe[macrobicyclic TRENSAM]$^+$: $a = 10.7156(2)$ Å, $b = 23.10490(10)$ Å, $c = 19.8373(3)$ Å, $\beta = 98.829(1)°$. For Ga[macrobicyclic TRENSAM]$^+$: $a = 11.1144(2)$ Å, $b = 22.8382(4)$ Å, $c = 19.4525(4)$ Å, $\beta = 99.247(1)°$. The metal complexes of macrobicyclic TRENSAM impose an unusual conformational distortion on the macrobicycle, breaking the C_2 symmetry axis of the parent ligand. This results in a macrocyclic complex with two acyclic analogues, TRENSAM and TRENIAM, giving the cryptate a "split personality" with structural features of both acyclic ligands. ^{1}H NMR shows that the metal complexes of macrobicyclic TRENSAM are kinetically inert and retain an asymmetric structure in solution. Cyclic voltammetry experiments show that the ferrous complexes are strongly stabilized by the macrocyclic structure.

Introduction

Siderophores[1,2] as well as synthetic metal chelators[3,4] have been proposed to bind metals in a salicylate fashion.[5−8] This mode of binding has been proposed as part of an iron delivery pathway for siderophore analogues that act as bacterial growth factors.[5,9,10] Recently, we reported a series of tris(salicylamide) podands as models for protonated ferric enterobactin and similar tris(catecholate) ferric complexes.[7]

2-Hydroxyisophthalic acid is a salicylic acid derivative that has several advantages for use as a strong in vivo metal chelator (Figure 1). The hydroxy proton of this chelator has a pK_a of 6.22,[11] which ensures deprotonation of the ligand at physiological pH. The isophthalamide forms a hydrogen bond upon metal binding (similar to that found in catecholamide ligands)[12−15] that greatly stabilizes the resulting metal complexes (vide infra).

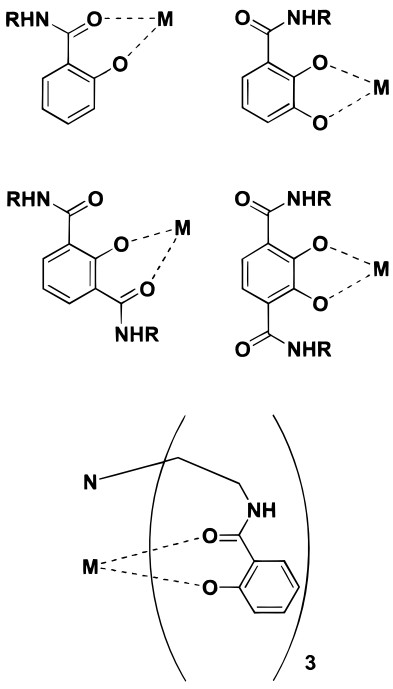

Figure 1. Salicylamide (top left) and catecholamide (top right) chelators. Analogous ligands that can be used for macrocyclic synthesis are 2-hydroxyisophthalamide (middle left) and 2,3-dihydroxyterephthalamide (middle right). Also shown is the chemical structure of the previously reported M[TRENSAM]$^+$ compounds (bottom).[7]

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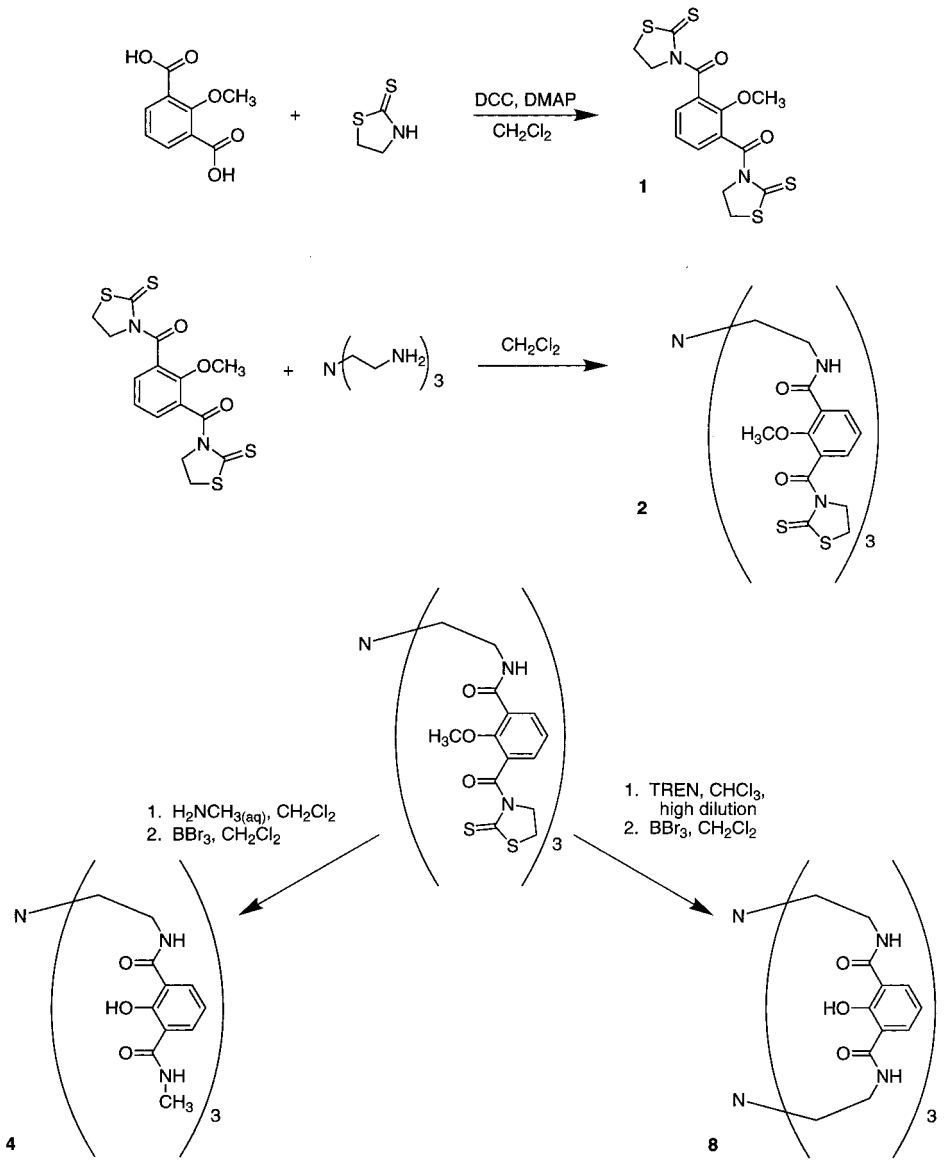
Scheme 1



The 2-hydroxyisophthalamide ligand contains two carbonyl functional groups that can be derivatized with a variety of amines. The symmetric orientation of these carbonyl groups also allows for the synthesis of macrocyclic ligands, analogous to those investigated with the catechol derivative 2,3-dihydroxyterephthalic acid (Figure 1).[13,16−19] Despite these advantageous features, only a few coordination complexes have been reported using 2-hydroxyisophthalic acid or amide derivatives with this chelator as a ligand.[20,21] Herein we report novel tripodal (TRENIAM) and macrobicyclic ligands (macrobicyclic TRENSAM) based on this new salicylamide-type chelator (Scheme 1). Metal complexes with both ligands have been synthesized and their spectroscopic, electrochemical, and solid-state structural properties examined. In addition, the solution structures of the macrocyclic complexes have been probed by variable-temperature ^{1}H NMR spectroscopy.

Experimental Section

General Procedures. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed using Merck 40−70 mesh silica gel. 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 a Bruker AMX

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300 or AMX 400 superconducting Fourier transform spectrometer or on a Bruker DRX 500 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 8453 instrument kept at constant temperature in a jacketed cell with a Neslab RTE-111 water bath. ^{1}H NMR data provided for M[TRENIAM] and M[macrobicyclic TRENSAM]$^+$ refer to the gallium complexes.

2-Methoxyisophthalic Bis(2-mercaptothiazolide) (1). 2-Methoxyisophthalic acid (0.02 mol), 2-mercaptothiazoline (0.04 mol), and 4-(dimethylamino)pyridine (20 mg) were dissolved in 150 mL of CH_2Cl_2 under a nitrogen atmosphere. 1,3-Dicyclohexylcarbodiimide (0.04 mol) was added to the reaction mixture, which gradually became yellow. After 5 h of stirring, the reaction mixture was filtered and the filtrate evaporated to dryness to afford a yellow oil. Recrystallization from hot ethyl acetate gave a bright yellow microcrystalline solid. Yield: 55%. IR (film from $CDCl_3$): ν 1229, 1684, 2955 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 3.42 (t, J = 7.3 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 4.60 (t, J = 7.3 Hz, 2H, CH_2), 7.13 (t, J = 7.7 Hz, 1H, Ar *H*), 7.43 (d, J = 7.6 Hz, 2H, Ar *H*). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 29.2, 55.6, 62.9, 123.1, 128.1, 131.9, 154.7, 167.1, 200.8. Anal. Calcd (found) for $C_{15}H_{14}N_2O_3S_4$·0.25H_2O: C, 44.70 (44.75); H, 3.63 (3.53); N, 6.95 (6.82).

Me$_3$(TRENIAM)(2-mercaptothiazolide)$_3$ (2). Tris(2-aminoethyl)-amine (TREN) (1.7 mmol) dissolved in 100 mL of CH_2Cl_2 was added dropwise to **1** (15.1 mmol) dissolved in 600 mL of CH_2Cl_2. The reaction mixture was evaporated to dryness to give a yellow oil. The oil was purified by flash silica column chromatography with 0−4% MeOH/CH_2Cl_2. The solvent was evaporated to give the product as a yellow foam. Yield: 70%. IR (film from $CDCl_3$): ν 1635, 2939, 3386 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 2.83 (s, 6H, CH_2), 3.42 (br t, 6H, CH_2), 3.84 (s, 9H, CH_3), 4.63 (br t, 6H, CH_2), 7.18 (t, J = 7.7 Hz, 3H, Ar *H*), 7.39 (d, J = 5.7 Hz, 3H, Ar *H*), 7.73 (br t, 3H, N*H*), 8.01 (d, J = 6.0 Hz, 3H, Ar *H*). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 29.2, 38.2, 53.6, 55.7, 63.2, 124.4, 127.1, 129.1, 132.2, 134.1, 155.6, 165.0, 167.3, 201.4. Anal. Calcd (found) for $C_{42}H_{45}N_7O_9S_6$: C, 51.26 (51.26); H, 4.61 (4.71); N, 9.96 (10.09).

Me$_3$TRENIAM (3). **2** (1.6 mmol) was dissolved in 10 mL of CH_2Cl_2. To this solution was added ∼1 mL of aqueous methylamine (40 wt %), followed by vigorous shaking of the biphasic mixture. Within 1 min, all the yellow thiazolide color disappeared. The mixture was evaporated to dryness and the remaining residue purified by flash silica column chromatography (0−10% MeOH in CH_2Cl_2 gradient). Removal of solvent and oven-drying gave a white foam. Yield: 80%. IR (film from CH_2Cl_2): ν 1540, 1652, 3293 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 2.74 (br t, 6H, CH_2), 2.98 (d, J = 6.2 Hz, 9H, CH_3), 3.55 (br q, 6H, CH_2), 3.76 (s, 9H, CH_3), 7.03 (t, J = 7.0 Hz, 3H, Ar *H*), 7.39 (br d, 3H, N*H*), 7.61 (d, J = 5.8 Hz, 3H, Ar *H*), 7.76 (br t, 3H, N*H*), 7.86 (d, J = 5.8 Hz, 3H, Ar *H*). ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ 26.8, 38.2, 53.9, 63.3, 124.8, 127.5, 128.3, 133.4, 134.0, 155.7, 165.7, 165.9. Anal. Calcd (found) for $C_{36}H_{45}N_7O_9$·2H_2O: C, 57.21 (56.91); H, 6.53 (6.52); N, 12.97 (13.28).

H$_3$TRENIAM·HBr (4). **3** (1.5 mmol) was dissolved in 40 mL of dry, degassed CH_2Cl_2. The solution was cooled in an ice bath, and BBr_3 (48.0 mmol) was added via syringe under a nitrogen atmosphere. The pale yellow slurry was stirred for ∼48 h, after which the reaction was slowly quenched with MeOH. The mixture was diluted with water (total volume ∼100 mL) and boiled until all the yellow color was gone. The resulting colorless solution was boiled to a volume of ∼50 mL and then cooled, giving a white solid. The product was collected by filtration and oven-dried. Yield: 77%. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ 2.81 (br s, 9H, CH_3), 3.53 (br m, 6H, CH_2), 3.74 (br m, 6H, CH_2), 6.88 (br t, 3H, Ar *H*), 7.88 (br d, 6H, Ar *H*), 8.69 (br t, 3H, N*H*), 8.84 (br d, 3H, N*H*). ^{13}C NMR (400 MHz, DMSO-d_6, 25 °C): δ 26.6, 34.8, 52.8, 116.8, 118.5, 119.7, 132.2, 134.5, 160.2, 167.2, 169.3. (+)-FABMS: m/z 678 [M$^+$ + H]. Anal. Calcd (found) for $C_{33}H_{40}N_7O_9$-Br·2H_2O: C, 49.88 (49.50); H, 5.58 (5.56); N, 12.34 (12.55).

M[TRENIAM] (M = Fe^{3+}, Ga^{3+}) (5, 6). The same procedure was followed for the synthesis of both metal complexes. **4** was dissolved in 5 mL of MeOH, followed by addition of 1 molar equiv of the appropriate metal salt (e.g., $FeCl_3$·6H_2O). An excess of pyridine was then added to the mixture, and the solution was stirred for 2 h. Evaporation of the solution gave solids which could be recrystallized from hot water/MeOH (1:1 v/v). Yield: ∼55%. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ 2.48 (br s, 9H, CH_3), 3.38 (br s, 12H, CH_2), 6.70 (t, J = 7.7 Hz, 3H, Ar *H*), 7.71 (d, J = 8.0 Hz, 3H, Ar *H*), 8.11 (d, J = 7.7 Hz, 3H, Ar *H*), 9.43 (br s, 3H, N*H*), 10.18 (br s, 3H, N*H*).

Me$_3$(macrobicyclic TRENSAM) (7). **2** (7.0 mmol) dissolved in 400 mL of $CHCl_3$ and TREN (6.9 mmol) dissolved in 400 mL of $CHCl_3$ were added, using laboratory pumps, to a 5 L round-bottom flask filled with 2800 mL of $CHCl_3$ and fitted with a mechanical overhead stirrer. During the addition, the mixture was heated to ∼40 °C under a nitrogen atmosphere. After 24 h, the reaction mixture was purified on a silica column, eluted with a 0−10% MeOH/CH_2Cl_2 gradient. The solvent was evaporated to give the product as a colorless glass. Yield: 46%. IR (film from $CDCl_3$): ν 1522, 1652, 2939 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 3.45 (s, 24H, CH_2), 3.47 (s, 9H, CH_3), 7.15 (t, J = 7.7 Hz, 3H, Ar *H*), 7.54 (br t, 6H, N*H*), 7.80 (d, J = 7.7 Hz, 6H, Ar *H*). ^{13}C NMR (500 MHz, $CDCl_3$, 25 °C): δ 39.4, 56.2, 62.5, 124.2, 128.2, 133.1, 155.7, 166.1. (+)-FABMS: m/z 773 [M$^+$ + H]. Anal. Calcd (found) for $C_{39}H_{48}N_8O_9$·2MeOH: C, 58.84 (58.68); H, 6.74 (6.73); N, 13.39 (13.19).

H$_3$(macrobicyclic TRENSAM)·2HBr (8). **7** (0.3 mmol) was dissolved in 30 mL of dry, degassed CH_2Cl_2. To the cooled solution was added BBr_3 (42.3 mmol) via syringe under a nitrogen atmosphere. After ∼36 h of stirring, the solution was evaporated to dryness, giving a pale orange solid. The solid was slowly quenched with MeOH and added to 100 mL of boiling water. The solution was boiled for 3.5 h and then allowed to cool, precipitating a white solid. The solid was collected by filtration and oven-dried. Yield: 80%. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ 3.67 (s, 24H, CH_2), 6.97 (t, J = 7.9 Hz, 3H, Ar *H*), 8.00 (d, J = 7.8 Hz, 6H, Ar *H*), 9.10 (br s, 6H, N*H*). ^{13}C NMR (500 MHz, DMSO-d_6, 25 °C): δ 36.2, 57.1, 117.6, 118.9, 134.1, 159.6, 169.0. (+)-FABMS: m/z 731 [M$^+$ + H]. Anal. Calcd (found) for $C_{36}H_{44}N_8O_9Br_2$·3H_2O: C, 45.68 (45.81); H, 5.32 (5.47); N, 11.84 (11.66).

M[macrobicyclic TRENSAM]$^+$·HX (M = Fe^{3+}, Al^{3+}, Ga^{3+}; X = Cl$^-$, Br$^-$, ClO$_4^-$) (9, 10, 11). The same procedure was followed for the synthesis of all metal complexes. **8** was dissolved in a 1:5 DMF/MeOH mixture, followed by addition of 1 molar equiv of the anhydrous metal chloride salt. Excess pyridine was then added and the solution refluxed for at least 3 h. The solution was then evaporated to dryness and the remaining solid suspended in water. The solid was isolated by filtration and washed with water. Yield: ∼60%. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ 2.35 (m, 6H, CH_2), 2.56 (t, J = 12.0 Hz, 6H, CH_2), 3.49 (m, 6H, CH_2), 3.90 (m, 3H, CH_2), 4.27 (m, 3H, CH_2), 6.82 (t, J = 7.7 Hz, 3H, Ar *H*), 7.82 (dd, J = 6.2 Hz, 3H, Ar *H*), 8.11 (br s, 1H, (CH$_2$)$_3$N$^+$*H*), 8.27 (dd, J = 5.0 Hz, 3H, Ar *H*), 9.96 (m, 3H, N*H*), 10.31 (br s, 3H, N*H*).

Structure Solution and Refinement. All X-ray structure data sets were collected, solved, and refined as previously described.[7,22−24]

Fe[TRENIAM] (5). Orange-red crystals (thin plates) of **5** were grown from a MeOH solution diffused with Et_2O. Two solvent molecules, one MeOH (disordered) and one Et_2O, were found in the asymmetric unit.

Ga[TRENIAM] (6). Colorless crystals (thin plates) of **6** were grown from a MeOH solution diffused with Et_2O. Two solvent molecules, one MeOH (disordered) and one Et_2O, were also found in the asymmetric unit.

Fe[macrobicyclic TRENSAM]$^+$·HBr (9). Orange-red crystals of **9** were grown from a DMF solution diffused with acetone. Two ordered DMF molecules and one disordered solvent molecule were found in the asymmetric unit. The hydrogen on the TREN scaffold was found during the refinement.

Ga[macrobicyclic TRENSAM]$^+$·HClO$_4$ (11). *Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive.*

(22) *SHELXTL: Crystal Structure Analysis Determination Package*; Siemens Industrial Automation, Inc.: Madison, WI, 1994.
(23) *SMART: Area-Detector Software Package*; Siemens Industrial Automation, Inc.: Madison, WI, 1994.
(24) *SAINT: SAX Area-Detector Integration Program*, version 4.024; Siemens Industrial Automation, Inc.: Madison, WI, 1994.

Only small amounts of these materials should be prepared, and they should be handled with great caution. Colorless crystals of **11** were grown from a MeOH/DMF mixture diffused with THF. Three solvent molecules, two DMF molecules and one THF, were also found in the asymmetric unit. The hydrogen on the TREN scaffold was found during the refinement.

Electrochemical Measurements. All measurements were obtained using a BAS 100A electrochemical analyzer controlled with an IBM personal computer. Solutions were prepared by dissolving 1.0−10.0 mM metal complex in degassed anhydrous DMSO (Aldrich, anhydrous, 99.8%) containing 0.1 M *n*-$Bu_4N(PF_6)$ (Fluka, electrochemical grade). The auxiliary and reference electrodes were a platinum wire and a freshly prepared silver reference electrode (0.01 M $AgNO_3$ in 0.1 M *n*-$Bu_4N(PF_6)$ in DMSO/Ag(s)), respectively. A platinum electrode was used for the working electrode. Cyclic voltammetry experiments were performed at various sweep rates (10−100 mV/s), with multiple cycles, starting at high and low potentials for all samples to evaluate the reversiblity of the redox reactions. Data for all complexes are reported at ambient temperature (25 °C) with a sweep rate of 100 mV/s.

Samples were calibrated relative to the Cp_2Fe^+/Cp_2Fe couple for which $E_{1/2} = +0.170$ V ($\Delta E_p = 0.086$ V, 100 mV/s) was measured under the experimental conditions described. Corrected potentials are reported relative to the normal hydrogen electrode (NHE) in water and were estimated with the aid of the literature[25] using the equation $E_{NHE(aq)} = E_{Ag(DMSO)} + 0.357$ V.[26]

Variable-Temperature NMR. Variable-temperature ^1H NMR experiments were performed on a Bruker DRX 500 digital spectrometer operating at 500 MHz. The temperature was controlled by a B-VT3000 temperature control unit. The sample temperature was allowed to equilibrate for at least 2 min after the desired probe temperature was reached. Errors in the measured temperatures were typically ±0.1 °C. Calibration of the measured temperature was determined by peak difference analysis of a pure MeOH sample. Spectra for Al[macrobicyclic TRENSAM]$^+$ were recorded in MeOD (Aldrich, 99.8%) from 255 to 350 K in 5 K increments. Spectra for Ga[macrobicyclic TRENSAM]$^+$ were recorded in MeOD from 240 to 300 K (Aldrich, 99.8%) and in DMSO-d_6 (Cambridge Isotope Laboratories, 99.9%) from 298 to 363 K in 10 K increments. All chemical shifts were referenced to the respective solvent peak.

Results and Discussion

Syntheses. The synthesis of the tripodal ligand TRENIAM (**4**) proceeded according to Scheme 1. 2-Methoxyisophthalic acid was activated with 2 equiv of 2-mercaptothiazoline to give the doubly activated ester as a yellow, crystalline solid (**1**). TREN was combined with a large excess of **1** (>10 equiv) to provide the triply activated intermediate **2** as a yellow foam. The yellow foam **2** was triturated with aqueous methylamine until all the yellow color had vanished. Purification by flash silica chromatography gave the protected ligand **3**. The methyl protecting groups were removed using BBr_3 to give the ligand (**4**) as the hydrobromide salt. The macrobicycle macrobicyclic TRENSAM (**8**) was synthesized under high-dilution conditions[13] by reaction of the intermediate **2** with 1 equiv of TREN (Scheme 1). This provided the protected ligand as a colorless foam (**7**), which was deprotected using BBr_3. The metal complexes of the acyclic TRENIAM were synthesized by addition of a metal salt to a methanol solution of the ligand, followed by the addition of excess pyridine as base. Metal complexes of macrobicyclic TRENSAM were synthesized by addition of a metal salt to a DMF/MeOH (1:5) solution of the ligand. An excess of pyridine was added as base, and the solution was refluxed for several hours. Complexes of both ligands can be purified by recrystallization from various solvent systems as exemplified by the isolation of X-ray-quality crystals.

UV/Vis Spectra. The salicylate mode of coordination in Fe[TRENSAM]$^+$ (TRENSAM = tris[(2-hydroxybenzoyl)-2-aminoethyl]amine),[7] Fe[TRENIAM], and Fe[macrobicyclic TRENSAM]$^+$ is characterized by their bright orange color. The previously reported spectrum of Fe[TRENSAM]$^+$ has $\pi \rightarrow \pi^*$ transitions in the UV region at 279 nm ($\epsilon = 13\,600$ M^{-1} cm^{-1}) and 301 nm ($\epsilon = 13\,300$ M^{-1} cm^{-1}), as well as a broad ligand-to-metal charge-transfer (LMCT) band at 455 nm ($\epsilon = 5600$ M^{-1} cm^{-1}).[7] The spectra of Fe[TRENIAM] and Fe[macrobicyclic TRENSAM]$^+$ (in MeOH) are very similar to that obtained for Fe[TRENSAM]$^+$. Fe[TRENIAM] shows bands in the UV region at 286 nm ($\epsilon = 12\,500$ M^{-1} cm^{-1}) and 332 nm ($\epsilon = 16\,900$ M^{-1} cm^{-1}) and a LMCT band at 445 nm ($\epsilon = 4200$ M^{-1} cm^{-1}). The absorption bands for Fe[macrobicyclic TRENSAM]$^+$ are present at 292 nm ($\epsilon = 13\,100$ M^{-1} cm^{-1}) and 335 nm ($\epsilon = 15\,400$ M^{-1} cm^{-1}) in the UV region, and a visible LMCT band appears at 451 nm ($\epsilon = 4\,600$ M^{-1} cm^{-1}). Because the salicylamide and isophthalamide ligands bind iron with the same type of donor atoms, the spectra of the iron complexes are expected to be comparable. The differences in the absorption spectra between the salicylamide (TRENSAM) and isophthalamide (TRENIAM, macrobicyclic TRENSAM) complexes are likely due to the differences in the structures of the aromatic rings (the additional carbonyl group in the isophthalamide chelators). The LMCT band of similar iron complexes has been shown to be sensitive to small changes in the geometry of the iron complex.[13] The visible band of Fe[macrobicyclic TRENSAM]$^+$ lies between those of the two acyclic analogues, suggesting that the metal complex possesses structural features common to both tripodal complexes.

Electrochemistry. Electrochemical experiments on the iron complexes of TRENSAM, TRENIAM, and macrobicyclic TRENSAM revealed significant differences depending on the ligand structures. The cyclic voltammograms of the three ferric complexes measured in DMSO are shown in Figure 2. For all three systems, the peak separation between the cathodic and anodic waves (ΔE) is between 70 and 101 mV and is independent of the sweep rate in the range 10−200 mV. Fe[TRENSAM]$^+$ displays a weak, pseudoreversible couple with an $E_{1/2}$ of +0.148 V (versus NHE in water; see Experimental Section for details). The very low potential couple and partial reversibility of this complex are consistent with the types of siderophore analogues this compound was designed to model.[27] The measured potential of +0.148 V is very close to the estimated reduction potential of +0.17 V for ferric enterobactin at pH 4.[5,28] In addition, the reduction potential of Fe[TRENCAM]$^{3-}$ (the catecholate analogue of TRENSAM) was previously determined to be $E_{1/2} = -1.04$ V,[17,27] giving a 1.152 V difference in potential! The change in potential from a tris(catecholate) (Fe[TRENCAM]) to a tris(salicylate) (Fe[TRENSAM]$^+$) is a result of the change in coordination environment as well as the free energy associated with the protonation of the iron−catecholate complex.[28]

The acyclic complex Fe[TRENIAM] displays a quasireversible redox couple at $E_{1/2} = -0.606$ V. Fe[macrobicyclic TRENSAM]$^+$ shows an essentially reversible redox couple at $E_{1/2} = -0.393$ V ($\Delta E_p = 0.070$ V). The couple is observed at a less negative potential than that found for the acyclic complex Fe[TRENIAM] ($E_{acyclic} - E_{cyclic} = 0.213$ V).

In contrast to Fe[TRENSAM]$^+$, the ferric complexes of TRENIAM and macrobicyclic TRENSAM show more intense electrochemical waves. The reduction potentials for both of these complexes are at substantially more negative voltage, indicating that the isophthalamide Fe^{3+} complexes are significantly more

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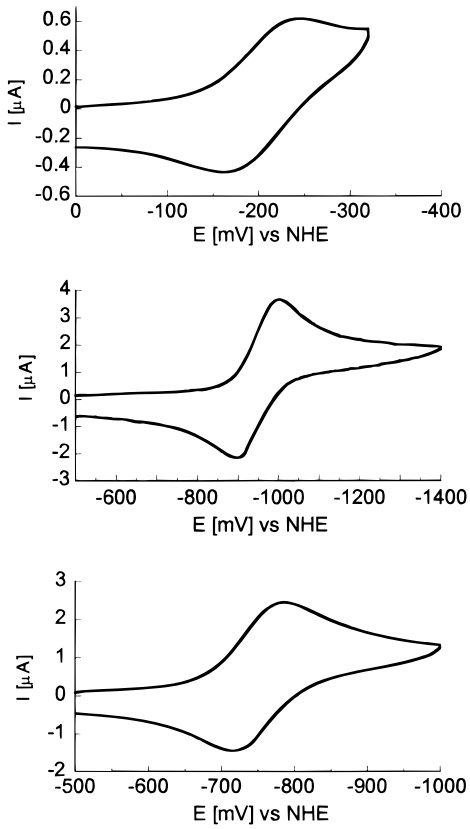

Figure 2. Cyclic voltammograms of Fe[TRENSAM]$^+$ (top), Fe[TRENIAM] (middle), and Fe[macrobicyclic TRENSAM]$^+$ (bottom) in dry DMSO (I = 0.1 M, scan rate = 100 mV/s, T = 25 °C).

stable than the corresponding simple salicylamide complex. Because the donor atoms in the two types of ligands are essentially the same, the enhanced stability of the Fe^{3+} complex originates in part from the three stabilizing hydrogen bonds found in the isophthalamide compounds, which are absent in the salicylamide ligand. The lower potential of Fe[macrobicyclic TRENSAM]$^+$ relative to Fe[TRENIAM] suggests that the Fe^{2+} complex of macrobicyclic TRENSAM is more stable (relative to the Fe^{3+}) than the Fe^{2+} complex of TRENIAM. This stabilization is probably due to a macrocyclic or cryptate effect.[29,30] When the Fe^{2+} complex is formed, the resulting compound has an overall charge of −1. This charge is centered on the ligand chelates (specifically on the hydroxy oxygens), which repel each other due to the excess charge. This repulsion in the acyclic ligand greatly destabilizes the complex as the ligating arms of the podand are free to move apart from one another. However, in the macrocyclic structure, the charge repulsion is effectively suppressed by the three ligand arms being tethered together, resulting in an overall stabilization of the ferrous complex. Similar results have been obtained with acyclic and macrobicyclic iron complexes based on the catecholamide derivative 2,3-dihydroxyterephthalamide: the acyclic structures have more negative potentials than their macrocyclic counterparts.[17]

X-ray Structures. Crystals of M[TRENIAM] (M = Fe^{3+}, Ga^{3+}) were obtained by diffusion of MeOH solutions of the complex with diethyl ether. The structures of Fe[TRENIAM] and Ga[TRENIAM] represent a type of salicylate bonding different from that in previously described complexes (Table 1).[7] The ligand binds the ferric ion with three six-membered metallacycles, as in other salicylamide complexes. The chelates are made up of the 2-hydroxy and 3-carbonyl amide oxygen atoms which bind to the metal center (Figure 3). Unlike the case of previously synthesized salicylamide complexes, the carbonyl group attached to the TREN scaffold is not involved in metal binding. These three carbonyl oxygen atoms are directed outside the metal-binding cavity, and the other three carbonyl oxygen atoms (which are part of the methylamide moiety) bind to the metal center. This conformation of the carbonyl groups provides the 2-hydroxy oxygen atoms with stabilizing hydrogen bonds from the adjacent amide nitrogen of the TREN cap. These types of stabilizing hydrogen bonds are prevelant throughout catecholamide and terephthalamide coordination chemistry and contribute significantly to the stability of those complexes.[14,15,26]

The coordination environments of the metal centers are similar to those found for other salicylamide podands. As in the M[TRENSAM]$^+$ (M = Fe^{3+}, Al^{3+}) complexes, the 2-hydroxy oxygen atoms are held closer to the metal center than the carbonyl oxygens in the M[TRENIAM] complexes. However, in the latter complexes, the difference in these M−O bond distances are 0.08 Å for the iron complex and 0.06 Å for the gallium complex, significantly smaller than the differences found in the TRENSAM complexes (0.15 Å for Fe^{3+} and 0.11 Å for Al^{3+}). In addition, further examination reveals that the donor atoms in Fe[TRENIAM] are closer to the metal center than those in Fe[TRENSAM]$^+$ (0.05 Å for the carbonyl oxygen and 0.03 Å for the 2-hydroxy oxygen). This suggests that the geometries of TRENIAM ligands are better suited for metal binding, allowing for a more tightly bound and symmetric coordination sphere around the cation.

The higher symmetry of the M[TRENIAM] complexes compared to the M[TRENSAM]$^+$ complexes is evidenced by a geometric analysis of the metal coordination sphere. In the TRENSAM complexes, a twist angle (defined as the angle between the two coordinating atoms of a chelate projected onto the idealized 3-fold axis) could not be properly defined because of the large discrepancies between the individual twists of each of arm of the podand. However, the chelates of the TRENIAM complexes are very similar and display twist angles about the metal centers of 50 and 54° for the Fe^{3+} and Ga^{3+} complexes, respectively (60° is the twist angle for a perfectly octahedral metal center).[32] The theoretical twist angle for a tris-chelate can be calculated by measuring the normalized bite angle of the ligand, which is the distance between the two donor atoms divided by the metal−heteroatom bond distance.[32] Because the M−O bond lengths in the 2-hydroxyisophthalic acid chelators are not equivalent, only an approximate normalized bite angle can be calculated, which predicts twist angles of 54 and 58° for the Fe^{3+} and Ga^{3+} complexes, respectively.[32] The difference between the calculated and observed values is probably due to steric effects imposed by the TREN scaffold, which imposes a similar reduction of the twist angle in related ligand systems.[26,33,34]

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Table 1. Crystallographic Data for Fe[TRENIAM], Ga[TRENIAM], Fe[Macrobicyclic TRENSAM]$^+$, and Ga[Macrobicyclic TRENSAM]$^+$

	Fe[TRENIAM]	Ga[TRENIAM]	Fe[macrobicyclic TRENSAM]$^+$	Ga[macrobicyclic TRENSAM]$^+$
empirical formula	$FeC_{35.30}H_{41}N_7O_{10.30}$	$GaC_{35.35}H_{41}N_7O_{10.35}$	$FeC_{42}H_{54}N_{10}O_{11}Br$	$GaC_{46}H_{62}N_{10}O_{16}Cl$
fw	784.00	799.27	1010.70	1116.23
temp, K	171(2)	185(2)	157(2)	137(2)
crystal system	triclinic	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$	$P2_1/n$
a, Å	12.0203(4)	11.9780(2)	10.7156(2)	11.1144(2)
α, deg	83.146(1)	83.324(1)		
b, Å	12.6996(4)	12.6417(3)	23.10490(10)	22.8382(4)
β, deg	88.531(1)	88.488(1)	98.829(1)	99.247(1)
c, Å	24.6435(8)	24.5404(6)	19.8373(3)	19.4525(4)
γ, deg	85.282(1)	85.038(1)		
V, Å^3; *Z*	3721.9(2); 4	3676.44(14); 4	4853.18(12); 4	4873.5(2); 4
density (calcd), g cm^{-3}	1.395	1.444	1.586	1.506
crystal size, mm	0.10 × 0.15 × 0.30	0.05 × 0.15 × 0.20	0.04 × 0.20 × 0.35	0.20 × 0.20 × 0.40
no. of reflns collected	12 655	15 362	20 021	22 593
no. of indep reflns	9140 [*R*(int) = 0.0330]	10 271 [*R*(int) = 0.0484]	6927 [*R*(int) = 0.0599]	8634 [*R*(int) = 0.0343]
data/restraints/parameters	9137/0/958	10 267/0/973	6920/0/660	8634/0/67
goodness-of-fit on F^2 [a]	1.156	1.083	1.133	1.111
final R indices [$I > 2\sigma(I)$]:[b] R1, wR2	0.0568, 0.1264	0.0752, 0.1486	0.0590, 0.1278	0.0573, 0.1414
R indices (all data):[b] R1, wR2	0.0758, 0.1487	0.1319, 0.1795	0.0886, 0.1474	0.0758, 0.1551
largest diff peak/hole, e Å^{-3}	0.561/−0.469	0.797/−0.714	0.617/−0.779	0.520/−0.935

[a] GOF = $[\sum w(|F_o| - |F_c|)^2/(N_o - N_v)]^{1/2}$, where $w = 1/(\sigma^2|F_o|)$. [b] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, wR2 = $\{\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^4]\}^{1/2}$.

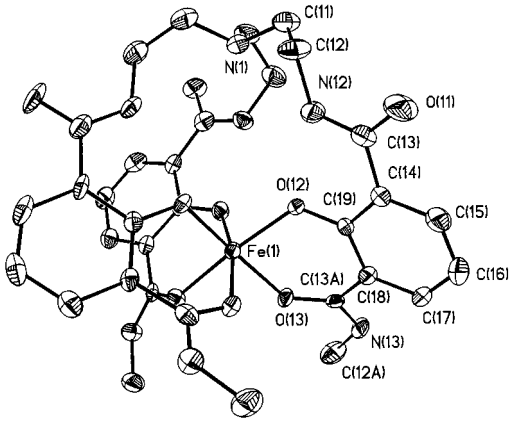

Figure 3. Structural diagram of Fe[TRENIAM] (ORTEP, 50% probability ellipsoids) with the atom-numbering scheme for one-third of the complex. Hydrogen atoms and solvent molecules have been omitted for clarity. Three salicylamide chelate rings bind the metal. The gallium complex, Ga[TRENIAM], is isostructural. The average hydrogen-bond distance between the amide hydrogens and the metal-coordinating phenolic oxygens is 1.95(2) Å. Selected distances (Å): Fe1−O12, 1.941(3); Fe1−O13, 2.011(3); Fe1−O22, 1.960(3); Fe1−O23, 2.039(3); Fe1−O32, 1.932(3); Fe1−O33, 2.017(3).

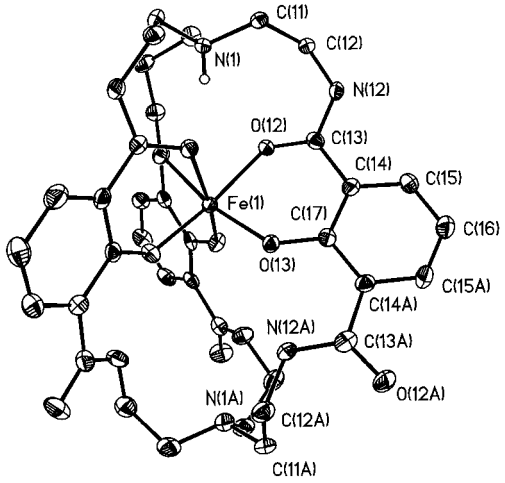

Figure 4. Structural diagram of Fe[macrobicyclic TRENSAM]$^+$ (ORTEP, 50% probability ellipsoids) with the atom-numbering scheme for the complex. Hydrogen atoms (except one), counterion, and solvent molecules have been omitted for clarity. Note that the bridgehead nitrogen of the top TREN cap is protonated (average distance to the metal-coordinating carbonyl oxygens is 2.34(5) Å) giving the complex an overall +1 charge. The gallium complex, Ga[macrobicyclic TRENSAM]$^+$, is essentially isosteric. The average hydrogen-bond distance between the amide hydrogens and the metal-coordinating phenolic oxygens is 2.00(3) Å. Selected distances (Å): Fe1−O12, 2.054(3); Fe1−O13, 1.934(3); Fe1−O22, 2.063(3); Fe1−O23, 1.924(3); Fe1−O32, 2.030(3); Fe1−O33, 1.933(3).

The crystal structures of M[macrobicyclic TRENSAM]$^+$ (M = Fe^{3+}, Ga^{3+}) demonstrate that the macrobicycles bind the metal cations in a fashion identical to that seen in M[TRENIAM] complexes. However, these macrocycles also complex the metal in the same manner as that seen in the previously reported M[TRENSAM]$^+$ (M = Fe^{3+}, Al^{3+}) complexes (Figure 4).[7] The crystal data for Fe[macrobicyclic TRENSAM]$^+$ and Ga[macrobicyclic TRENSAM]$^+$ are listed in Table 1. The binding of a metal by the macrobicyclic ligand destroys the C_2 symmetry of the free ligand, with the resulting complex possessing structural features found in both acyclic analogues. The two TREN caps of the ligand have inverted conformations relative to one another. One cap is "puckered in", pointing the amide protons to the outside of the complex (as in M[TRENSAM]$^+$), while the other is "puckered out", with the amide protons pointing to the interior of the complex. As in the M[TRENIAM] complexes, the latter cap conformation stabilizes the complex by providing the 2-hydroxy oxygens with hydrogen bonds from the adjacent amide nitrogens. The different conformations of the TREN scaffolds clearly demonstrate the effect of the amide protons on the pK_a of the TREN tertiary nitrogen. The tertiary nitrogen of the TREN cap with the "puckered in" conformation was found to be protonated, giving these complexes an overall positive charge. This is similar to the case of previously described TREN-based salicylamide podands.[7] This proton is hydrogen-bonded to the three carbonyl oxygens that bind the metal center. The "puckered out" TREN scaffold, with the amide protons pointing into the cavity of the complex, is not protonated at the bridgehead amine. These amide protons also form

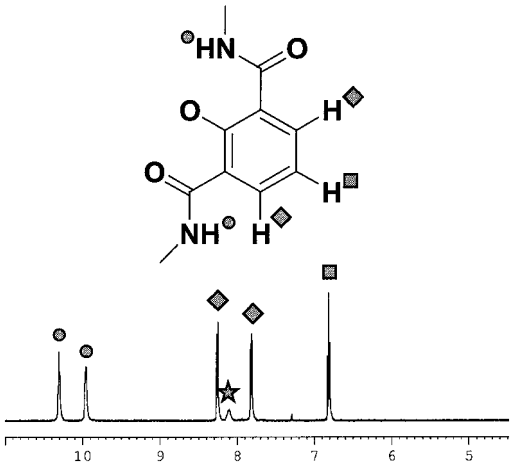

Figure 5. ^{1}H NMR spectrum (aromatic region only) of Ga[macrobicyclic TRENSAM]$^+$ in DMSO-d_6 at room temperature. The spectrum clearly demonstrates that the complex retains the same structure in solution as in the solid state. Labeling of the spectrum is shown in the figure (top): circles = amide protons; diamonds = protons ortho to the carbonyl groups; square = proton meta to the carbonyl groups. The star designates the proton bound to the TREN cap inside the macrobicycle (see text).

hydrogen bonds with the tertiary amine lone pair, dramatically reducing its basicity.

Similar macrobicyclic ligands based on the 2,3-dihydroxyterephthalamide chelator have shown very small twist angles for transition metal complexes, including the first trigonal prismatic coordination geometry for Fe^{3+} (twist angle = 0°).[13,17] The twist angles of the macrobicyclic TRENSAM structures (Fe^{3+}, 51°; Ga^{3+}, 55°) are very similar to those observed in TRENIAM structures, and no distortion toward trigonal prismatic coordination is observed in the iron complex. The metal center bond distances in the macrobicyclic TRENSAM complexes demonstrate the similarities to both TRENIAM and TRENSAM type chelates. The M−O distances for the carbonyl and 2-hydroxy oxygens are different, with the latter being shorter by 0.12 and 0.10 Å in the Fe^{3+} and Ga^{3+} complexes, respectively. Comparison of the individual bond lengths for the Fe^{3+} complexes shows that the macrocyclic structure lies between the two acyclic structures. The Fe−O bond length for the carbonyl oxygen (2.05 Å) of Fe[macrobicyclic TRENSAM]$^+$ lies between those of Fe[TRENIAM] (2.02 Å) and Fe[TRENSAM]$^+$ (2.07 Å). The Fe−O distance for the 2-hydroxy oxygen (1.93 Å) also lies between those of Fe[TRENSAM]$^+$ (1.92 Å) and Fe[TRENIAM] (1.95 Å). The structures of these macrocyclic compounds clearly demonstrate their "split personalities", with structural features found in both TRENSAM and TRENIAM type complexes.

Variable-Temperature ^{1}H NMR. The ^{1}H NMR spectra of Al[macrobicyclic TRENSAM]$^+$ and Ga[macrobicyclic TRENSAM]$^+$ were examined to determine if structures of these complexes in solution were the same as those seen in the solid state. Indeed, the ^{1}H NMR spectra of Ga[macrobicyclic TRENSAM]$^+$ clearly shows the same structure as observed in the solid state (Figure 5). The C_3 symmetry of the ligand is maintained, while the C_2 symmetry is lost, which is consistent with the X-ray crystal structures. Indicative of this conformation, two amide proton resonances are observed (9.96 and 10.31 ppm) corresponding to the three amide protons pointing into the macrocyclic cavity and the other trio pointing out of the cavity in the two different TREN caps (vide supra). Two doublets are also observed for the aromatic protons ortho to the carbonyl groups (7.82 and 8.26 ppm), which for the C_2 symmetric ligand are observed as a doublet at 8.01 ppm. Also, the TREN methylene proton signals are split into six resonances, two sharp and four slightly broadened. The two sharp resonances are due to the TREN scaffold in the "puckered out" conformation and are typical for TREN-capped tris(catecholate) or tris(hydroxypyridinonate) metal complexes.[35] The other four resonances are ascribed to the "puckered in" TREN cap, as the proximity of the metal center to these methylene protons causes broadening and diastereotopic splitting. This unusual splitting has been found with all other TREN-based tris(salicylate) complexes where the triamine is in a "puckered in" conformation.[7,35] Finally, the proton bound to the bridgehead TREN amine could also be identified as a small broad resonance at 8.11 ppm. The ^{1}H NMR spectrum for Al[macrobicyclic TRENSAM]$^+$ is essentially the same as that described for the Ga^{3+} complex. These spectra demonstrate that, at room temperature in solution, these complexes retain the same structure as that found in the solid state.

Variable-temperature experiments demonstrated that the solution structure was static and was not the result of time averaging. The spectra of Al[macrobicyclic TRENSAM]$^+$ and Ga[macrobicyclic TRENSAM]$^+$ show little change from −18 to +80 °C. Only the resonances assigned to the "puckered out" TREN cap (in MeOD) showed some shifts, indicative of the less confined cap undergoing a Δ to Λ twist. However, this twist is independent of the metal center, as the resonances associated with the "puckered in" TREN cap did not show any significant shift or coalescence at temperatures as high as 350 K. Therefore, the energy barrier ($\Delta G^{\ddagger}$) for the inversion of configuration for Al[macrobicyclic TRENSAM]$^+$ is greater than 66 kJ mol^{-1}. In addition, no changes were observed in the amide, aromatic, or sharp methylene resonances. This is quite different from the case of Al[TRENSAM]$^+$, which showed coalescence of the TREN cap resonances at 320 K, with a calculated barrier for the interconversion of $\Delta G^{\ddagger} = 62$ kJ mol^{-1}.[7] The macrobicyclic ligand structure increases the rigidity of the complex relative to the acyclic TRENSAM, restricting motion about the metal center. Even in Ga[macrobicyclic TRENSAM]$^+$, the much more labile Ga^{3+} metal center is held in a dynamically inactive environment. These experiments demonstrate the high kinetic stability of the macrobicyclic complexes.

Conclusion

The synthesis of two new ligands, TRENIAM and macrobicyclic TRENSAM, have been presented. Both form metal complexes with a novel hydrogen-bond stabilized salicylate mode of binding. This hydrogen bonding is evident in the solid state structures and contributes significantly to the stability of the Fe^{3+} complex, as evidenced by cyclic voltammetry experiments. The X-ray structures of the macrobicyclic complexes show an unusual ligand conformation which has features of two different acyclic tripodal analogues. Subsequently, the complexes of this macrobicycle possess properties common to both acyclic systems, which is clearly reflected in the M−O bond lengths of the metal complexes. The retention of this unusual structure in solution is demonstrated by ^{1}H NMR spectroscopy. Unlike previously synthesized 2,3-dihydroxyterephthalamide-based macrocycles,[17] these show no tendency toward trigonal prismatic geometry with Fe^{3+}. However, the TRENSAM macrobicyclic structure exhibits a strong cryptate effect, forming a more stable Fe^{2+} complex when compared to the acyclic complexes.

(35) To be submitted for publication.

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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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