Table I. Comparison of ^{13}C NMR Chemical Shifts[a] of Trihalomethyl Cations[b] and the Corresponding Trihalomethanes[c]

trihalomethyl cation	$\delta^{13}C$	trihalomethane	$\delta^{13}C$	$\Delta\delta^{13}C$
$^+CCl_3$	236.3	$HCCl_3$	77.7	158.6
$^+CBr_3$	207	$HCBr_3$	+12.3	194.7
$^+CI_3$	95	HCI_3	-139.7	234.7

[a] Chemical shifts in ppm from external tetramethylsilane signal. [b] In SbF_5/SO_2ClF solution at -80 °C. [c] Data taken from ref 9.

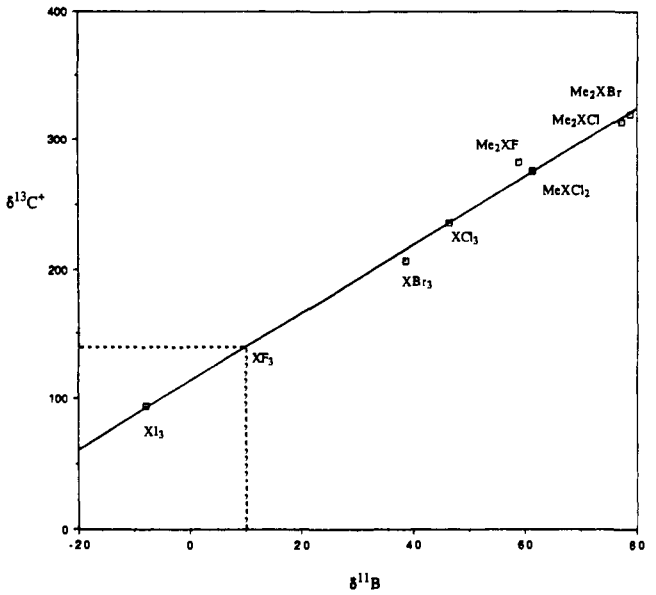

Figure 1. A plot of ^{13}C NMR chemical shifts of halomethyl cations vs ^{11}B NMR chemical shifts of isoelectronic isostructural haloboranes.

then reacts with benzene to give benzotrifluoride. Benzotrifluoride on subsequent reaction with benzene and aluminum trichloride gives triphenylmethyl chloride.

In the gas phase the CF_3^+ ion is stable and is an abundant species, specially in the mass spectra[11] of organofluorine compounds. However, in solution the great strength of the C-F bond in CF_4 (ca. 140 kcal/mol) leads to rapid quenching of CF_3^+ to CF_4 even in low nucleophilicity fluorinated superacid media.

We have compared the ^{13}C NMR chemical shifts of the trihalomethyl cations to those of the respective trihalomethanes and found a consistent trend (see Table I). The $\Delta\delta^{13}C$ chemical shift differences[12] are 158.6, 194.7, and 234.7 for the trichloro-, tribromo-, and triiodomethyl derivatives, respectively. This trend is in agreement with the positive charge stabilization (increased back-bonding) order of Cl > Br > I. The ^{13}C shifts of trihalomethyl cations correlate well with the electronegativities of the halogen atoms.[14]

The ^{13}C NMR chemical shifts of the trihalomethyl cations and related reported methyl substituted mono- and dihalocarbenium ions[3] also correlate well with the ^{11}B NMR chemical shifts of the corresponding isostructural, isoelectronic boron halides[13] (see Figure 1). An excellent linear relationship is obtained with a correlation coefficient of unity.[15] From this plot, with the known ^{11}B NMR chemical shift of BF_3 (10.4 ppm) we can estimate the corresponding ^{13}C NMR shift of the yet unknown trifluoromethyl cation as to be 140 ppm which is only 31.2 ppm more deshielded than trifluoromethane at $\delta^{13}C$ 118.8. This indicates substantial stabilization of the trifluoromethyl cation by fluorine back-bonding. Experimental verification, however, must await preparation of the still elusive CF_3^+ ion under long-lived conditions.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

(11) Murdoch, H. D.; Weiss, E. *Helv. Chim. Acta* **1962**, *45*, 1927.
(12) Schleyer, P. v. R.; Lenoir, D.; Mison, P.; Liang, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 683.
(13) Nuclear Magnetic Resonance Spectroscopy of Boron Compounds. Nöth, H.; Wrackmeyer, B. A volume of *NMR Basic Principles and Progress*; Diehl, P., Fluck, E., Kosefeld, R., Eds.; Springer-Verlag: New York, 1978.
(14) Correlation with Pauling's electronegativities of the halogens were excellent (r^2 = 1). From this correlation the ^{13}C NMR shift of $^+CF_3$ is estimated to be ≈150 ppm.
(15) The equation from the plot is $\delta^{13}C$ = 112.4272 + 2.6504 $\delta^{11}B$, r^2 = 1.

Anatoxin-a(s), a Potent Anticholinesterase from *Anabaena flos-aquae*

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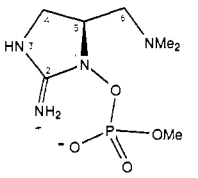
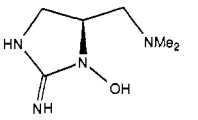
Anatoxin-a(s) is a neurotoxic alkaloid associated with the blue-green alga *Anabaena flos-aquae*.[1] It potent toxicity (LD_{50} 20-40 μg/kg mice) is attributed to exceptional anticholinesterase activity.[2] We report here the isolation of anatoxin-a(s) from a cultured strain NRC 525-17 and a field-collected bloom implicated in animal poisonings[3] and the determination of its structure as **1**.



1



2

Freeze-dried alga was extracted with 0.05 N AcOH/EtOH. The filtered extract was partitioned between water and CH_2Cl_2, the aqueous layer was washed with *n*-BuOH and evaporated in vacuo, and the residue was extracted successively with small portions of 0.05 N AcOH/MeOH and 0.05 N AcOH/EtOH to give a toxic concentrate. Gel filtration on Toyopearl HW40F (Supelco)[4] followed by HPLC on CN and ODS columns gave pure anatoxin-a(s) as a colorless solid in 0.05% yield. Toxin isolation was followed by assaying fractions for anticholinesterase activity.[5] Anatoxin-a(s) decomposed rapidly in basic solution but was

(1) Mahmood, N. A.; Carmichael, W. W. *Toxicon* **1986**, *24*, 425.
(2) (a) Mahmood, N. A.; Carmichael, W. W. *Toxicon* **1987**, *25*, 1221. (b) Cook, W. O.; Beasley, V. R.; Dahlem, A. M.; Dellinger, J. A.; Harlin, K. S.; Carmichael, W. W. *Toxicon* **1988**, *26*, 750.
(3) Mahmood, N. A.; Carmichael, W. W.; Pfahler, D. *Am. J. Vet. Res.* **1988**, *49*, 500.
(4) Harada, K.; Kimura, Y.; Suzuki, M.; Dahlam, A. M.; Beasley, V. R.; Carmichael, W. W. Abstracts, Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, 1988; p 288.
(5) Ellman, G. L.; Courtney, K. D.; Andres, V., Jr.; Featherstone, R. M. *Biochem. Pharm.* **1961**, *7*, 88. A modification of the assay described in this paper was used to observe the enzyme inhibitory activity. Solutions of samples to be tested were first spotted on filter paper or a TLC plate and sprayed with a mixture of acetylthiocholine (5 mg/mL) and 5,5'-dithiobis(2-nitrobenzoic acid) (5 mg/mL) in ethanol. After drying in a stream of air, a solution of electric eel acetylcholinesterase (EC 3.1.1.7, 0.5 units/mL) was next applied to the paper or plate. Active samples showed a white zone on a dense yellow background.

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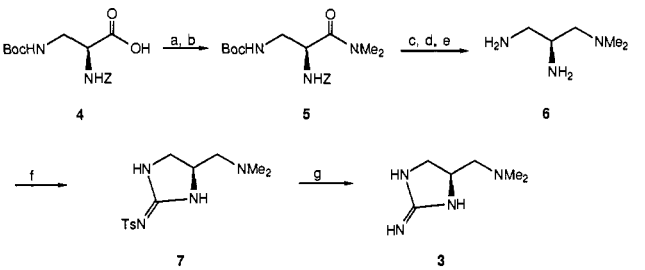
Scheme I[a]



[a] Reagents and conditions: (a) *N*-hydroxysuccinimide (1.2 equiv), DCC (1.2 equiv), dioxane, 0 °C 10 min → room temperature 15 h; (b) Me_2NH (2 equiv) in ether, room temperature 10 min; (c) CF_3CO_2H, room temperature 1 h; (d) 10% Pd–C, H_2, MeOH; (e) excess BH_3/Me_2S, THF, reflux 15 h; (f) *S,S*-dimethyl-*N*-tosyliminodithiocarbonimidate (1 equiv), EtOH, reflux 15 h; (g) 48% HBr, reflux 4 h.

relatively stable in neutral or acidic (pH 3–5) media.[6] Anatoxin-a(s) from cultured and field-collected *A. flos-aquae* exhibited identical chemical and spectral properties, including optical (CD in H_2O: $[\theta]_{207}$ −3300, $[\theta]_{232}$ +3900).

Mass spectral analysis of anatoxin-a(s) [positive FABMS (*m/z* 253.1067, MH^+), negative FABMS (*m/z* 251, $M-H^-$), FDMS (*m/z* 253, MH^+)] indicated the molecular formula $C_7H_{17}N_4O_4P$. The ^1H and ^{13}C NMR spectra[7,8] revealed the presence of dimethylamino and P-OMe (J_{H-P} 11.0 Hz; J_{C-P} 6.7 Hz) groups, a 1,2,3-trisubstituted propane unit, and an sp^2 carbon that was fully substituted by heteroatoms (δ_C 163.7). The methoxyl protons and carbon were the only ones showing distinct coupling to phosphorus. Only one signal was seen in the ^{31}P NMR spectrum and its chemical shift (δ 6.16) agreed well for either a phosphate ester or phosphoramide.[9] The J_{gem} (−10.1 Hz) and $^1J_{H,C}$ values for the protons in one of the methylenes of the propane unit suggested that this CH_2 was in a five-membered ring, along with the adjacent CH.

More information was obtained from NMR analysis of anatoxin-a(s) that had been uniformly enriched to 50% ^{13}C and 90+% ^{15}N[10,11] (See also Supplementary Material). The following conclusions could be made: (1) The sp^2 carbon at 163.7 ppm was connected to three nitrogens of a guanidine group and that two of these nitrogens were attached to the CH and CH_2 in the five-membered ring. (2) The NMe_2 group was connected to the side-chain CH_2 on the resulting imidazoline.[12] (3) No nitrogens were connected to the phosphorus; a methyl phosphate group was therefore present in the toxin. (4) The methyl phosphate group was attached to one of the nitrogens ($^2J_{P-N}$ 4 Hz); the toxin was therefore zwitterionic.

Anatoxin-a(s) slowly decomposed during storage at −20 °C into a mixture of **2**, **3** (sometimes), and monomethyl phosphate, separable by Toyopearl HW40F chromatography. Compound **2** (FABMS, MH^+ *m/z* 159.1245; CD in H_2O, $[\theta]_{235}$ +2400), which differed from compound **3** by an oxygen, could be converted into **3** (FABMS, MH^+ *m/z* 143.1298; CD in H_2O, $[\theta]_{198}$ +11 000) by catalytic hydrogenation (Pd–C/MeOH). Hydrolytic removal of the monomethyl phosphate group caused a diamagnetic shift of the H-5 signal from 4.71 ppm in **1** to 4.48 ppm in **2**; the methylene ^1H chemical shifts, however, were essentially identical for the two compounds. Although the ^1H chemical shifts for **3** were similar to those for **2**, except for one of the H-6 signals which was shifted upfield appreciably (−0.37 ppm), the ^{13}C chemical shifts were significantly different, i.e., upfield for C-5 (−7.8 ppm) and C-2 (−1.9 ppm) and downfield for C-4 (+2.7 ppm) and C-6 (+2.4 ppm).[13,14] These chemical shift differences were consistent with placements of the hydroxyl group on N-1 in **2**[15] and the methyl phosphate group on N-1 in **1**. Anatoxin-a(s) therefore had to have structure **1**.

To elucidate the absolute configuration at C-5, *R*- and *S*-**3** were prepared from D- and L-asparagine, respectively (Scheme I). N^2-(Benzyloxycarbonyl)-N^3-(*tert*-butoxycarbonyl)-L-2,3-diaminopropionic acid (**4**),[16] for example, was converted to dimethylamide **5** via the *N*-hydroxysuccinimide ester.[17] After removal of the amino-protecting groups (trifluoroacetic acid; H_2/Pd–C), the resulting diamine was reduced with BH_3–Me_2S complex[18] to give the triamine **6**, which was then treated with *S,S'*-dimethyl-*N*-tosyliminodithiocarbonimidate[19] to furnish the tosylguanidine **7**. Removal of the *N*-tosyl group was accomplished by refluxing **7** in 48% HBr.[20] Synthetic **3** showed identical chromatographic properties and ^1H and ^{13}C NMR spectra with the degradation product. The CD spectrum of **3** derived from anatoxin-a(s) was identical with that of synthetic **3** from L-Asn ($[\theta]_{198}$ +13 000), which meant that C-5 was *S*.

Anatoxin-a(s) is a unique phosphate ester of a cyclic *N*-hydroxyguanidine. The structure and reactivity is reminiscent of an ester of *N*-hydrosuccinimide or 1-hydroxybenzotriazole. Cholinesterase inactivation may proceed by nucleophilic attack of Ser at the esteratic site of the enzyme on the phosphate group of **1** with concomitant elimination of **2**.[21]

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(6) Air evaporation of a methanolic solution of the toxin results in significant hydrolysis to **2**.

(7) All NMR spectra have been determined in D_2O with 5 μL of acetic acid-d_4 added per 0.5 mL of D_2O, unless otherwise noted.

(8) **1**: ^1H NMR δ 3.00 (s, NMe_2), 3.47 (dd, J = 2.9 and −13.9 Hz, H-6), 3.51 (dd, J = 9.7 and −10.1 Hz, H-4), 3.75 (dd, J = 9.3 and −13.9 Hz, H-6), 3.79 (d, $^3J_{H-P}$ = 11.0 Hz, P–OMe), 4.01 (dd, J = 9.4 and −10.1 Hz, H-4), 4.71 (m, H-5); exchangeable proton signals seen in acidic 80% H_2O/20% D_2O, δ 8.21 and 7.72 (two v br s, NH_2 on C-2), 7.44 (br s, H-3); ^{13}C NMR δ 43.9 (v br, NMe_2), 45.3 (C-4), 56.1 (d, $^2J_{C-P}$ = 6.7 Hz, P–OMe), 58.7 (C-6), 60.3 (C-5), 163.7 (C-2).

(9) (a) Tebby, J. C.; In Phosphorus-*31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G.; Quin, L. D.; Eds.; VCH Publishers: Florida, 1987; p 1. (b) Gorenstein, D. G. *Prog. NMR Spectrosc.* **1983**, *16*, 1.

(10) The labeled toxin was isolated from *A. flos-aquae* NRC 525-17 that had been grown in culture on $NaH^{13}CO_3$ (99 atom %) and $Na^{15}NO_3$ (99 atom %) by using the procedure described in the following: Moore, R. E.; Bornemann, V.; Niemczura, W. P.; Gregson, J. M.; Chen. J.-L.; Norton, T. R.; Patterson, G. M. L.; Helms, G. L. *J. Am. Chem. Soc.* **1989**, *111*, 6128.

(11) **1** uniformly enriched with ^{13}C to 50+% and ^{15}N to 90+%: ^1H NMR signals for NMe_2 and H-6 ($^1J_{H-C}$ = 144 Hz), OMe ($^1J_{C-H}$ = 148 Hz), H-4 and H-5 ($^1J_{H-C}$ = 151 Hz); ^{13}C NMR δ 43.9 (v br → doublet at 43.8 ppm in MeOH-d_3 or two doublets at 42.0 and 45.7 ppm in D_2O/CF_3CO_2H, J_{C-N} = 4.1 Hz, NMe_2), 45.3 (dd, J_{C4-C5} = 33.5 Hz, J_{C4-N1} = 8.7 Hz, J_{C4-N3} = 0, C-4), 56.1 (d, $^2J_{C-P}$ = 6.7 Hz, P–OMe), 58.7 (br d, J_{C5-C6} = 40.5 Hz, J_{C6-N7} = 2–3 Hz, C-6), 60.3 (br t, J_{C5-N1} = 0 Hz, C-5), 163.7 (td, J_{C2-N} = 23.5, 23.5, and 11.5 Hz, C-2); ^{15}N NMR (acidic 4:1 H_2O/D_2O) δ 350.6 (NMe_2), 306.9 and 306.7 (br, NH_2 on C-2 and N-4), 300.2 (N-1); ^{31}P NMR (acidic 4:1 H_2O/D_2O) δ 6.15 (d, $^2J_{P-N1}$ = 4 Hz).

(12) Also supported by FAB MS–MS and high-resolution data. Fragmentation of MH^+, for example, leads to *m/z* 58 ($Me_2N^+{=}CH_2$) as the base peak.

(13) **2**: ^1H NMR δ 3.00 (s, NMe_2), 3.46 (dd, J = 8.0 and −10.0 Hz, H-4), 3.47 (dd, J = 4.5 and −13.9 Hz, H-6), 3.75 (dd, J = 6.8 and −13.9 Hz, H-6), 3.93 (dd, J = 8.5 and −10.0 Hz, H-4), 4.48 (dddd, H-5); ^{13}C NMR δ 44.7 (q, NMe_2), 44.9 (t, C-4), 58.7 (t, C-6), 58.8 (d, C-5), 162.5 (s, C-2).

(14) **3**: ^1H NMR δ 2.96 (s, NMe_2), 3.38 (dd, J = 4.8 and −13.4 Hz, H-6), 3.48 (dd, J = 8.1 and −13.4 Hz, H-6), 3.50 (dd, J = 5.4 and −10.1 Hz, H-4), 3.98 (dd, J = 9.7 and −10.1 Hz, H-4), 4.55 (dddd, H-5); ^{13}C NMR δ 44.3 (q, NMe_2), 47.6 (t, C-4), 51.0 (d, C-5), 61.1 (t, C-6), 160.6 (s, C-2).

(15) When the hydroxyl group is removed from a *N*-hydroxyguanidine, the signals for the carbons α to the relevant nitrogen shift upfield, whereas the ones for the β-carbons shift downfield, e.g., neosaxitoxin and saxitoxin (Shimizu, Y.; Hsu, C.; Fallon, W. E.; Ohima, Y. *J. Am. Chem. Soc.* **1978**, *100*, 6791) and δ-*N*-hydroxyarginine and arginine (Seto, H.; Koyama, M.; Ogino, H.; Tsuruoka, T. *Tetrahedron Lett.* **1983**, *24*, 1805).

(16) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266.

(17) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839.

(18) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 441.

(19) (a) Tsuji, S.; Kusumoto, S.; Shiba, T. *Chem. Lett.* **1975**, 1281. (b) Todricks, J. V.; Rapoport, H. *J. Org. Chem.* **1971**, *36*, 46.

(20) Snyder, H. R.; Heckert, R. *J. Am. Chem. Soc.* **1952**, *74*, 2006.

(21) Hucho, F. *Neurochemistry*; VCH Publishers: Weinheim, FRG, 1986.

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Supplementary Material Available: ^{1}H, ^{13}C, and ^{31}P NMR spectra of **1**, **2**, and **3**, ^{1}H, ^{13}C, ^{15}N, and ^{31}P NMR spectra of 50% ^{13}C and 90+% ^{15}N enriched **1**, and experimental details for the synthesis of *R*- and *S*-**3** from D- and L-Asn (16 pages). Ordering information is given on any current masthead page.

A New Macrobicyclic (Cryptand) Siderophore Containing Three Endocyclic Hydroxamate Donor Groups

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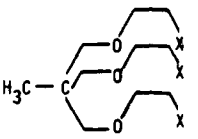
The natural hydroxamate siderophores contain bidentate hydroxamate donor groups in acyclic, exocyclic, and endocyclic arrangements.[1] Of these, the sexadentate endocyclic ligands, such as desferriferrioxamine E, have the highest affinities for iron(III), because of the involvement of the macrocyclic rings in coordination of the metal ion. The only synthetic endocyclic hydroxamate ligand previously reported is a diamino bishydroxamate macrocycle containing pendant carboxylate donors.[2] Up to the present time, no synthetic or natural endocyclic trishydroxamate cryptand has been reported, although the potential of such ligands for effective binding of trivalent metal ions has been pointed out.[3]

The orientation of oxygen donor groups in the hydroxamates places stringent demands on the polyatomic chains which link them together in a manner that places three pairs of oxygen donors symmetrically around a six-coordinate (octahedral) metal ion. Molecular models indicate that eight or more connecting atoms are needed to accomplish this effectively. It is the purpose of this paper to report the synthesis and properties of the first trishydroxamate cryptand. In this case the ligand has nine and 11 atoms between the bidentate hydroxamate units.

Cyanoethylation at 25–35 °C in *p*-dioxane of the 1,1,1-tris(hydroxymethyl)ethane gives the tricyano ether **1** in 83% yield. Hydrolysis of **1** with hydrogen chloride gas in methanol leads to the tricarboxylic acid trimethyl ester **2** (yield = 64%) (Calcd for $C_{17}H_{30}O_9$: C, 53.97; H, 7.94. Found: C, 53.63; H, 7.93. FAB MS $(M + H)^+ = 379$). Treatment of **2** with lithium aluminum hydride affords the triol **5** in 83% yield (Calcd for $C_{14}H_{30}O_6$: C, 57.12; H, 10.27. Found: C, 57.24; H, 10.20. FAB MS $(M + H)^+ = 295$). The tosylate **6**, prepared from tosyl chloride and **5**, was treated with *O*-benzylhydroxylamine in 1,2-dimethoxyethane to give the tris(*O*-benzylhydroxylamine) **7** (Calcd for $C_{35}H_{51}N_3O_6$: C, 68.96; H, 8.37; N, 6.90. Found: C, 68.68; H, 8.45; N, 6.69. FAB MS $(M + H)^+ = 610$, yield = 37%). The triacid chloride **4** was obtained by allowing **3**, which was prepared from its methyl ester, to react with oxalyl chloride in benzene, yield >95%. High dilution acylation of **7** with **4** in benzene gives the protected macrobicyclic trishydroxamate **8** (Calcd for $C_{49}H_{69}N_3O_{12}\cdot 4H_2O$: C, 61.06; N, 4.36; H, 8.00. Found: C, 60.95; N, 4.18; H, 7.10. FAB MS $(M + H)^+ = 893$) in 30% yield. The

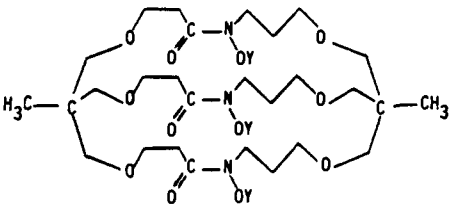


1 X = CN **5** X = CH_2OH

2 X = $COOCH_3$ **6** X = OTs

3 X = COOH **7** X = NHOBz

4 X = COCl



8 Y = Bz

9 Y = H

macrobicyclic trishydroxamate cryptand **9** was obtained from **8** by catalytic hydrogenation. This cryptand (1,13-dimethyl-3,11,15,23,26,34-hexaoxa-6,20,29-trioxo-7,19,30-tris(hydroxyaza)bicyclo[11.11.11]pentatricontane, H_3THX) was characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and FAB MS (Calcd for $C_{28}H_{51}N_3O_{12}\cdot{}^{1}/_{2}H_2O$: C, 53.27; H, 8.40; N, 6.59. Found: C, 53.16; H, 8.19; N, 6.38. FAB MS $(M + H)^+ = 622$). This cryptand is very soluble in methanol and sparingly soluble in water. Its sodium salt is very water soluble.

The 1:1 Fe(III) complex of the cryptand was prepared by combining Fe(III) chloride with a slight excess of the neutral (acid) form of the ligand to form a 2.0×10^{-4} molar solution in 2:8 v/v methanol–water and gradually increasing the pH to the desired neutral value. The absorbance spectra of the cryptate (Figure 1) compare well with those of the Fe(III) chelate of desferriferrioxamine B, DFB, reported by Anderegg et al.[4] At pH 4.0 the Fe(III) cryptate has a molar absorbance of 2700 at λ_{max} 423 nm (see Figure 1), while that of Fe^{III}-DFB is 2640 (λ_{max} 440 nm) at pH 4.[4] The absorbance shifts with pH are also similar for the cryptate and DFB complexes, with an isosbestic point at 480 nm for the cryptand and 481 for the DFB complex. The close similarity in the magnitudes of the molar absorbances of the iron(III) complexes of DFB and the cryptand provide assurance that all three bidentate donor groups of the latter are coordinated to the Fe(III) center. The observed isosbestic point indicates the conversion of one pure Fe(III) complex to another as the pH increases. It is suggested that the reaction corresponds to a monoprotonated complex $FeHTHX^+$, having two coordinated hydroxamate groups, and one protonated, non-coordinated hydroxamate group, which is converted at higher pH to the octahedral Fe(III) cryptate FeTHX, with three coordinated hydroxamate groups arranged in an octahedral fashion around the metal ion. At pH 4.4 and above there is little further increase in absorbance, and one therefore concludes the cryptate to be fully formed, with a molar absorbance of 2750 at $\lambda_{max} = 430$ nm.

Because the Ga(III) ionic radius is only slightly smaller than that of Fe(III), the new cryptand would also be expected to complex Ga(III) strongly in an octahedral fashion. The 1:1 Ga(III) complex was prepared by the reaction of molar equivalents of $Ga(OH)_4^-$ and the ligand in aqueous solution at pH 8.9. This is above the pH at which Ga(III) precipitates as $Ga(OH)_3$. The white solid which separated was characterized by elemental analysis and mass spectra (Calcd for $C_{28}H_{48}N_3O_{12}Ga\cdot 2H_2O$: C,

(1) Nielands, J. B. In *Development of Iron Chelators for Clinical Use*; Martell, A. E., Anderson, W. F., Badman, D. G., Eds.; Elsevier North Holland: New York, 1981; pp 13–31.
(2) Sun, Y.; Martell, A. E.; Motekaitis, R. J. *Inorg. Chem.* **1985**, *24*, 4343.
(3) Martell, A. E. In *Development of Iron Chelators for Clinical Use*; Martell, A. E., Anderson, W. F., Badman, D. G., Eds.; Elsevier North Holland: New York, 1981; pp 102–108.
(4) Anderegg, G.; L'Eplattenier, F.; Schwarzenbach, G. *Helv. Chim. Acta* **1963**, *46*, 1409.

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