Selectivity of Potentially Hexadentate Amine Phenols for Ga^{3+} and In^{3+} in Aqueous Solution[†,‡]

Ernest Wong, P. Caravan,[1a] Shuang Liu,[1b] Steven J. Rettig, and Chris Orvig*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada

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A new series of linear N_4O_2 amine phenols (H_2**badd**, H_2**Brbadd**, and H_2**Clbadd**) based on *N*,*N*′-bis(3-aminopropyl)-ethylenediamine (tnentn) were prepared and characterized by spectroscopic techniques. Monocationic hexadentate metal complexes with the tnentn-based amine phenols were obtained from the reactions of Ga^{3+} and In^{3+} with the linear amine phenol in the presence of a weak base (acetate). The molecular structure of [Ga(**Brbadd**)]ClO_4 has been determined by X-ray crystallography; crystals of [Ga(**Brbadd**)][ClO_4] ($C_{22}H_{30}Br_2ClGaN_4O_6$) are orthorhombic: $a = 12.462(1)$ Å, $b = 21.835(2)$ Å, $c = 9.961(2)$ Å, $Z = 4$, space group $P2_12_12_1$. The structure was solved by the Patterson method and was refined by full-matrix least-squares procedures to $R = 0.031$ ($R_w = 0.029$) for 1924 reflections with $I \geq 3\sigma(I)$. The Ga^{3+} ion is coordinated in a distorted octahedral geometry by an N_4O_2 donor atom set. The four nitrogen atoms of the tetraamine backbone form the equatorial plane of the octahedron, and the two phenolate oxygen atoms are coordinated trans to each other. Water-soluble 1,10-bis-(2-hydroxy-5-sulfonylbenzyl)-1,4,7,10-tetraazadecane (H_6**Sbad**$^{2+}$), 1,12-bis(2-hydroxybenzyl-5-sulfonylbenzyl)-1,5,8,12-tetraazadodecane (H_6**Sbadd**$^{2+}$), and *N*,*N*′-bis-(2-hydroxy-5-sulfonylbenzyl)-*N*,*N*′-bis(2-methylpyridyl)-ethylenediamine (H_6**Sbbpen**$^{2+}$) were also prepared and characterized; potentiometric titrations of these three ligands, in the absence and presence of Ga^{3+} and In^{3+}, were performed to determine deprotonation constants of the ligands and the thermodynamic stabilities of Ga and In amine phenol complexes. The formation constants of the Ga^{3+} and In^{3+} complexes with **Sbad**$^{4-}$ (Ga^{3+}, log $\beta = 28.33(8)$; In^{3+}, log $\beta = 24.54(2)$), **Sbadd**$^{4-}$ (Ga^{3+}, log $\beta = 28.27(5)$; In^{3+}, log $\beta = 24.56$ (5)), and **Sbbpen**$^{4-}$ (Ga^{3+}, log $\beta = 35.33(8)$; In^{3+}, log $\beta = 34.85(5)$) were obtained. All six of the Ga and In hexadentate amine phenol complexes were found to be very stable in aqueous solution. With the exception of [In(**Sbadd**)]$^-$, all the complexes were calculated to be thermodynamically stable with respect to demetalation by transferrin at physiological pH. The linear amine phenols showed a selectivity for Ga^{3+} over In^{3+}, while the **Sbbpen**$^{4-}$ derivative was indiscriminate in binding the Ga^{3+} and In^{3+} ions.

Introduction

Considerable current interest in the design of multidentate chelating ligands to form kinetically inert and/or thermodynamically stable complexes with the Ga^{3+} and In^{3+} ions stems from the potential application of ^{67}Ga, ^{68}Ga, and ^{111}In complexes as diagnostic radiopharmaceuticals.[2] In order for Ga and In complexes to be considered as potential radiopharmaceuticals, they must be kinetically inert toward demetalation and/or thermodynamically stable toward hydrolysis at physiological pH. In addition, the metal complex must also be stable with respect to demetalation by the blood serum protein transferrin. The large binding constants of Ga^{3+} and In^{3+} with the bilobal two-sited transferrin (Ga^{3+}, log $K_1 = 19.75$, log $K_2 = 18.80$; In^{3+}, log $K_1 = 18.30$, log $K_2 = 16.44$),[3] coupled with the high concentration of vacant transferrin binding sites in human blood ($\sim$50 μM), make transferrin a powerful scavenger of these metal ions. Hence, in the design of a potential radiopharmaceutical, competition with transferrin for trivalent metal ions is of utmost importance.

In recent years, we actively examined the coordination chemistry of Ga^{3+} and In^{3+} with a series of potentially hexadentate[4−6] and heptadentate[7] amine phenol ligands, all of

* To whom correspondence should be addressed. Tel: 604-822-4449. Fax: 604-822-2847. Internet: ORVIG@CHEM.UBC.CA.

† Abbreviations employed (see also Chart 1): trien = triethylenetetramine; tnentn = *N*,*N*′-bis(3-aminopropyl)ethylenediamine; H_2**bad** = 1,10-bis(2-hydroxybenzyl)-1,4,7,10-tetraazadecane; H_2**Clbad** = 1,10-bis(2-hydroxy-5-chlorobenzyl)-1,4,7,10-tetraazadecane; H_2**Brbad** = 1,10-bis(2-hydroxy-5-bromobenzyl)-1,4,7,10-tetraazadecane; H_6**Sbad**$^{2+}$ = 1,10-bis(2-hydroxy-5-sulfonylbenzyl)-1,4,7,10-tetraazadecane; H_2**badd** = 1,12-bis(2-hydroxybenzyl)-1,5,8,12-tetraazadodecane; H_2**Clbadd** = 1,12-bis(2-hydroxy-5-chlorobenzyl)-1,5,8,12-tetraazadodecane; H_2**Brbadd** = 1,12-bis(2-hydroxy-5-bromobenzyl)-1,5,8,12-tetraazadodecane; H_6**Sbadd**$^{2+}$ = 1,12-bis(2-hydroxy-5-sulfonylbenzyl)-1,5,8,12-tetraazadodecane; H_2**bbpen** = *N*,*N*′-bis(2-hydroxybenzyl)-*N*,*N*′-bis(2-methylpyridyl)ethylenediamine; H_2**Clbbpen** = *N*,*N*′-bis(2-hydroxy-5-chlorobenzyl)-*N*,*N*′-bis(2-methylpyridyl)ethylenediamine; H_2**Brbbpen** = *N*,*N*′-bis(2-hydroxy-5-bromobenzyl)-*N*,*N*′-bis(2-methylpyridyl)ethylenediamine; H_6**Sbbpen**$^{2+}$ = *N*,*N*′-bis(2-hydroxy-5-sulfonylbenzyl)-*N*,*N*′-bis(2-methylpyridyl)ethylenediamine; H_6**TRNS** = tris(((2-hydroxy-5-sulfonylbenzyl)amino)ethyl)amine; Tf = transferrin; HBED = *N*,*N*′-bis(2-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic acid; SHBED = *N*,*N*′-bis(2-hydroxy-5-sulfonylbenzyl)ethylenediamine-*N*,*N*′-diacetic acid; EHPG = 1,2-ethylenebis(*o*-hydroxyphenylglycine); PLED = *N*,*N*′-dipyridoxylethylenediamine-*N*,*N*′-diacetic acid; penten = *N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)ethylenediamine; NTA = nitrilotriacetic acid; DTPA = diethylenetrinitrilopentaacetic acid; EDTA = ethylenedinitrilotetraacetic acid.

‡ "H_2" in H_2**Xbad**, H_2**Xbadd**, and H_2**Xbbpen** refers to the two hydroxyl H atoms which are deprotonated prior to coordination to a metal. "H_6" in H_6**Sbad**$^{2+}$ and H_6**Sbadd**$^{2+}$ refers to the six H atoms on the protonated ammonium and phenolate moieties. "H_6" in H_6**Sbbpen**$^{2+}$ refers to the six H atoms on the protonated ammonium, pyridyl, and phenolate moieties.

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(1) (a) NSERC of Canada Postgraduate Scholar, 1992−1996. (b) NSERC of Canada Postdoctoral Fellow, 1991−1993. Present address: Du Pont Merck Pharmaceutical Co., Radiopharmaceutical Division, 331 Treble Cove Road, N. Billerica, MA 01862.

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Chart 1

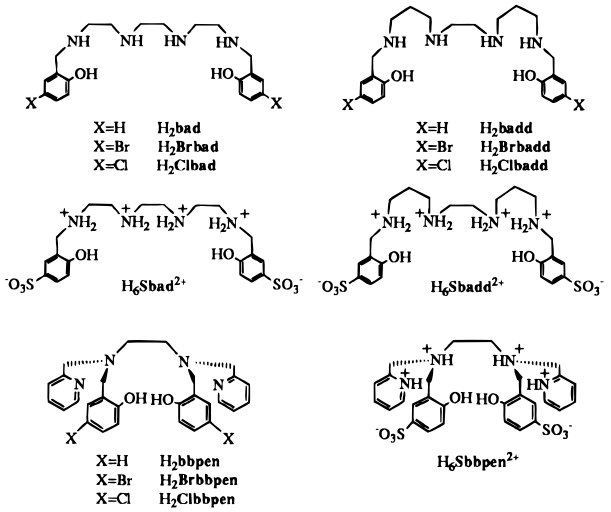
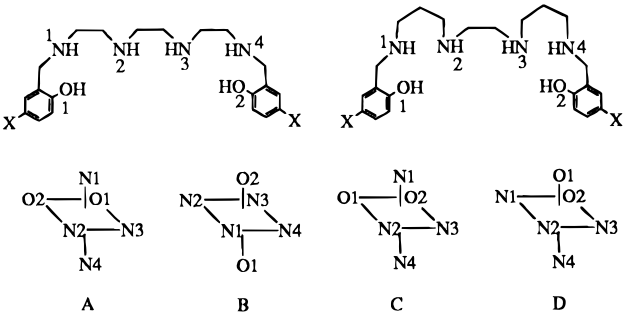


Chart 2



which possess amine nitrogen and phenolate oxygen donor atoms. Ga and In complexes with modified hexadentate amine phenol ligands that possess pyridyl nitrogen donor atoms have also been reported.[8] In these synthetic studies, it was observed that the modes of coordination and the qualitative stabilities of the metal complexes were closely related to the flexibility of the ligand, the size of the coordinated metal ion, and the type and spatial organization of the donor atoms.[4−8]

In the coordination of the linear trien-based amine phenols (H_2**Xbad**, Chart 1) to Ga^{3+} and In^{3+}, there are four possible ways in which the linear amine phenol can span the octahedral coordination sites around the metal ion (Chart 2), but only configuration A was observed.[6] For the H_2**Xbad** amine phenols, configuration A represents the least sterically demanding configuration. It was observed qualitatively that there was a difference between the stability of the Ga and In complexes; the H_2**Xbad** amine phenols seemed more suited for Ga^{3+} than for In^{3+}. We wished to determine how a lengthening of the linear amine phenol would affect the mode of coordination and the relative stabilities of the metal complexes. To quantify the stability of all these metal complexes, stability constants (log β) are reported.

Coordination of Ga^{3+} and In^{3+} with modified hexadentate amine phenols which possess pyridyl pendant arms (H_2**Xbbpen**, Chart 1) yielded robust complexes which were resistant to demetalation in both acidic and basic conditions.[8] Solid state structures of both the Ga and In complexes revealed no significant differences between the bond lengths and bond angles in the two complexes, suggesting that the Ga and In complexes might have comparable stability. The Ga and In **bbpen** complexes appeared to be more stable than the corresponding complexes with tripodal and linear amine phenol ligands, so a quantitative comparison of the binding constants of these amine phenol complexes was desired.

To expand our understanding of the coordination chemistry of Ga and In linear amine phenol complexes, we present the coordination chemistry of Ga^{3+} and In^{3+} with a new series of linear amine phenols (H_2**Xbadd**, Chart 1) based on tnentn. It is expected that H_2**Xbadd** amine phenols may coordinate to metal ions via an N_4O_2 donor atom set but also may coordinate in a mode different from that observed in the trien-based amine phenol (**bad**) complexes. In addition, we also present the stability constants of the Ga and In complexes with sulfonated **bbpen** (H_6**Sbbpen**$^{2+}$), sulfonated trien-based (H_6**Sbad**$^{2+}$), and sulfonated tnentn-based (H_6**Sbadd**$^{2+}$) amine phenols. Variable-pH ^{1}H NMR and UV spectral data were used to assign the observed deprotonation constants (pK_a's) of the sulfonated amine phenols and to verify qualitatively the observed stability constants of the corresponding Ga and In complexes. By comparing stability constants and pM values (−log [uncomplexed M^{3+}] at a particular pH), it is possible to rank the relative stability of the various amine phenol complexes and also the selectivity of the various amine phenols for Ga^{3+} and In^{3+} metal ions. Prior to *in vivo* experiments, the ability of the amine phenols to compete with transferrin for Ga^{3+} and In^{3+} ions can also be elucidated from a comparison of pM values at physiological pH.

Experimental Section

Materials. *N*,*N*′-Bis(3-aminopropyl)ethylenediamine, salicylaldehyde, 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde, and potassium borohydride were obtained from Aldrich. Hydrated Ga and In salts were obtained from Alfa. Sulfonated salicylaldehyde was prepared according to the method reported in the literature.[9] All chemicals were used without further purification. Water was purified, deionized (Barnstead D8904 and D8902 cartridges, respectively), and distilled (Corning MP-1 Megapure still).

Instrumentation. NMR spectra were recorded on Bruker AC-200E (^{1}H, ^{13}C, ^{1}H-^{1}H COSY NMR) and Varian XL 300 (^{1}H, VT NMR) spectrometers and are reported as δ in ppm from TMS. Variable-temperature ^{1}H NMR spectra of the metal complexes were recorded from 20 to 120 °C in DMSO-d_6. Mass spectra (Cs^+ LSIMS) were obtained on a Kratos Concept II H32Q instrument with 3-nitrobenzyl alcohol or thioglycerol as the matrix. C, H, N analyses were performed by Mr. Peter Borda of UBC.

1,12-Bis(2-hydroxybenzyl)-1,5,8,12-tetraazadodecane (H_2badd). To a hot solution of *N*,*N*′-bis(3-aminopropyl)ethylenediamine (2 g, 11.5 mmol) in ethanol (200 mL) was added a hot solution of salicylaldehyde (2.8 g, 23 mmol) in ethanol (200 mL). While the solution was still hot, KBH_4 (1.36 g, 25 mmol) was added in small quantities over 10 min. The solution was heated at approximately 50 °C and stirred for an additional 2 h. The solvent was removed under reduced pressure, leaving a white residue. NH_4OAc (3 g) in 50 mL of water was added to the white residue to form an aqueous mixture, which was then extracted with chloroform (3 × 100 mL). The organic fractions were combined, washed with distilled water (3 × 100 mL), and then dried over anhydrous $MgSO_4$. The solution was filtered and the chloroform removed on a rotary evaporator to give a yellow oil. The oil was dried *in vacuo* at 60 °C for 24 h, yielding 4.43 g (87%). Elemental analysis of the yellow oil was not possible. H_2**badd** was soluble in polar solvents such as methanol, chloroform, and acetone. H_2**badd** was also water soluble at low pH in millimolar concentration. LSIMS: *m*/*z* =

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387 ([M + 1]$^+$, [$C_{22}H_{35}N_4O_2$]$^+$), 281 ([$C_{15}H_{29}N_4O$]$^+$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.63 (t, 4 backbone methylene H), 2.72 (m, 12 backbone methylene H), 3.97 (s, 4 benzylic H), 6.80 (dd, 2 aromatic H), 6.97 (dd, 2 aromatic H), 7.14 (td, 4 aromatic H). ^{13}C NMR (200 MHz, $CDCl_3$): 29.7, 47.3, 48.0, 49.4, 52.7, 116.3, 118.9, 122.6, 128.3, 128.6, 158.3.

1,12-Bis(2-hydroxy-5-chlorobenzyl)-1,5,8,12-tetraazadodecane (H_2Clbadd). The preparation of H_2**Clbadd** was similar to that of H_2**badd** and employed *N*,*N*′-bis(3-aminopropyl)ethylenediamine (2 g, 11.5 mmol), 5-chlorosalicylaldehyde (3.60 g, 23 mmol), and KBH_4 (1.36 g, 25 mmol), yielding 4.3 g (82%). Elemental analysis of the resulting oil was not possible. H_2**Clbadd** was soluble in polar solvents such as methanol, chloroform, and acetone and was also water soluble at low pH in millimolar concentration. LSIMS: *m/z* = 455 ([M + 1]$^+$ [$C_{22}H_{33}Cl_2N_4O_2$]$^+$), 315 ([$C_{15}H_{28}ClN_4O$]$^+$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.60 (t, 4 backbone methylene H), 2.60 (m, 12 backbone methylene H), 3.85 (s, 4 benzylic H), 6.67 (dd, 2 aromatic H), 6.90 (dd, 2 aromatic H), 7.05 (td, 2 aromatic H). ^{13}C NMR (200 MHz, $CDCl_3$): 29.3, 47.2, 49.2, 50.0, 52.1, 117.5, 123.2, 124,1, 128.0, 128.2, 157.0.

1,12-Bis(2-hydroxy-5-bromobenzyl)-1,5,8,12-tetraazadodecane (H_2Brbadd). The preparation of H_2**Brbadd** was similar to that of H_2**badd** and employed *N*,*N*′-bis(3-aminopropyl)ethylenediamine (2 g, 11.5 mmol), 5-bromosalicylaldehyde (4.62 g, 23 mmol), and KBH_4 (1.36 g, 25 mmol), yielding 5.25 g (84%). Elemental analysis of the resulting oil was not possible. H_2**Brbadd** was soluble in polar solvents such as methanol, chloroform, and acetone and was also water soluble at low pH in millimolar concentration. LSIMS: *m/z* = 545 ([M + 1]$^+$ [$C_{22}H_{33}Br_2N_4O_2$]$^+$), 359 ([$C_{15}H_{28}BrN_4O$]$^+$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.65 (t, 4 backbone methylene H), 2.67 (m, 12 backbone methylene H), 3.92 (s, 4 benzylic H), 6.65 (dd, 2 aromatic H), 7.07 (dd, 2 aromatic H), 7.20 (td, 2 aromatic H). ^{13}C NMR (200 MHz, $CDCl_3$): 29.4, 47.4, 48.1, 49.3, 52.2, 110.5, 118.1, 124.6, 130.9, 131.3, 157.6.

1,10-Bis(2-hydroxy-5-sulfonylbenzyl)-1,4,7,10-tetraazadecane Dichloride ([H_6Sbad]Cl_2). To a hot solution of triethylenetetramine (2 g, 14 mmol) in methanol (500 mL) was added a hot solution of sodium salicylaldehyde-5-sulfonate (7.66 g, 34 mmol) in methanol (1 L). While the solution was still hot, $NaBH_4$ (1.32 g, 35 mmol) was added in small quantities over 10 min. The solution was heated at approximately 50 °C and stirred for an additional 2 h. The solvent was removed under reduced pressure, leaving a pinkish white residue. The residue was dissolved in a minimum amount of distilled deionized water. The pH of the solution was approximately 10. The solution was loaded onto a Rexyn 101 (H) cationic exchange column (active group RSO_3^-; ionic form H^+; mesh size 16−50) and eluted with deionized distilled water. The eluant was acidified with 1 mL of concentrated HCl. The solvent was then removed under reduced pressure at 100 °C, leaving a pink residue which was dried *in vacuo* at 100 °C for 2 days. Characterization of the residue revealed it to be the hydrochloride salt of the desired sulfonated amine phenol. The yield was 3.76 g (43%). The compound was extremely hygroscopic and was, therefore, stored in a dry nitrogen environment. ^{1}H NMR and UV spectra of H_6**Sbad**$^{2+}$ were pH dependent. Anal. Calcd (found) for [$C_{20}H_{32}N_4O_8S_2$]Cl_2·$2H_2O$: C, 38.38 (38.18); H, 5.78 (6.00); N, 8.93 (9.00). LSIMS: *m/z* = 519 ([$C_{20}H_{31}N_4O_8S_2$]$^+$), 1037 ({2[$C_{20}H_{30}N_4O_8S_2$] + 1}). UV (λ_{max}, nm (ϵ, cm^{-1} M^{-1})): at pH 2.1, 274 (6400), 232 (23 900); at pH 10.0, 288 (7600), 256 (24 500). ^{1}H NMR (300 MHz, D_2O): at pH 2.0, 3.54 (m, 12 backbone methylene H), 4.34 (s, 4 benzylic H), 7.05 (dd, 2 aromatic H), 7.80 (m, 4 aromatic H); at pH 12.2, 2.66 (s, 4 backbone methylene H), 2.75 (m, 8 backbone methylene H), 3.69 (s, 4 benzylic H), 6.6 (dd, 2 aromatic H), 7.48 (m, 4 aromatic H).

1,12-Bis(2-hydroxy-5-sulfonylbenzyl)-1,5,8,12-tetraazadodecane Dichloride ([H_6Sbadd]Cl_2). The preparation of H_6**Sbadd**$^{2+}$ was similar to that of H_6**Sbad**$^{2+}$ and employed *N*,*N*′-bis(3-aminopropyl)-ethylenediamine (2.00 g, 11.5 mmol), sodium salicylaldehyde-5-sulfonate (6.40 g, 28.7 mmol), and $NaBH_4$ (1.08 g, 23.0 mmol). The yield was 3.91 (42%). The compound was also found to be very hygroscopic and was, therefore, stored in a dry nitrogen environment. ^{1}H NMR and UV spectra of H_6**Sbadd**$^{2+}$ were pH dependent. Anal. Calcd (found) for [$C_{22}H_{36}N_4O_8S_2$]Cl_2·$2H_2O$: C, 40.31 (40.18); H, 6.15 (6.43); N, 8.55 (8.24). LSIMS: *m/z* = 547 ([$C_{22}H_{35}N_4O_8S_2$]$^+$), 1093 ({2[$C_{22}H_{34}N_4O_8S_2$] + 1}). UV (λ_{max}, nm (ϵ, cm^{-1} M^{-1})): at pH 2.0, 280 (3100), 232 (22 100); at pH 11.0, 290 (4900), 256 (26 400). ^{1}H NMR (300 MHz, D_2O): at pH 2.0, 2.12 (m, 4 backbone methylene H), 3.20 (m, 8 backbone methylene H), 3.42 (m, 4 backbone methylene H), 4.28 (s, 4 benzylic H), 7.03 (dd, 2 aromatic H), 7.74 (m, 4 aromatic H); at pH 12.0, 1.67 (m, 4 backbone methylene H), 2.57 (m, 8 backbone methylene H), 2.65 (m, 4 backbone methylene H), 3.7 (s, 4 benzylic H), 6.56 (dd, 2 aromatic H), 7.46 (m, 4 aromatic H).

***N*,*N*′-Bis(2-hydroxy-5-sulfonylbenzyl)-*N*,*N*′-bis(2-methylpyridyl)-ethylenediamine Dichloride ([H_6Sbbpen]Cl_2).** H_2**bbpen** was prepared as previously reported[8] and was dissolved (5.00 g, 11.0 mmol) in 35 mL of concentrated H_2SO_4. The solution was heated at 70 °C for 7 h, allowed to cool to room temperature, and cooled in an ice bath, whereupon acetone (1 L) was carefully added and a white precipitate formed. This white precipitate was collected by vacuum filtration and washed with cold acetone, after which it was dissolved in a minimum amount of concentrated HCl and the acid solution was loaded onto an Amberlite IRA 402 anionic exchange column (ionic form Cl^-; mesh size 20−50) and eluted with distilled deionized water. The eluant was collected and the volume reduced to 2 mL. The pH was raised to 10 using concentrated NH_3. The basic solution was then loaded onto a Rexyn 101 (H) cationic exchange column (active group RSO_3^-; ionic form H^+; mesh size 16−50) and eluted with distilled deionized water. The solvent was removed under reduced pressure at 100 °C to yield a pink residue. This residue was dried for 3 days at 100 °C under vacuo. Characterization of the residue revealed it to be a hydrochloride salt of the desired product. The yield was 4.18 g (55%). The compound was hygroscopic and was stored in a dry nitrogen environment. ^{1}H NMR and UV spectra of H_6**Sbbpen**$^{2+}$ were pH dependent. Anal. Calcd (found) for [$C_{28}H_{32}N_4O_8S_2$]Cl_2·$2.5H_2O$: C, 45.90 (45.83); H, 5.09 (4.94); N, 7.65 (7.58). LSIMS: *m/z* = 615 ([$C_{28}H_{31}N_4O_8S_2$]$^+$). UV (λ_{max}, nm (ϵ, cm^{-1} M^{-1})): at pH 2.4, 280 (7100), 262 (12 200), 232 (24 400); at pH 12.3, 294 (8500), 255 (31 000). ^{1}H NMR (300 MHz, D_2O): at pH 2.2, 3.53 (s, 4 backbone ethylene H), 4.14 (m, 4 benzylic H), 4.39 (m, 4 pyridyl methylene H), 6.69 (d, 2 hydroxybenzyl H), 7.46 (dd, 2 hydroxybenzyl H), 7.59 (d, 2 hydroxybenzyl H), 7.63 (m, 4 pyridyl H), 8.09 (td, 2 pyridyl H), 8.48 (d, 2 pyridyl H); at pH 12.4, 2.68 (s, 4 backbone ethylene H), 3.63 (m, 4 benzylic H), 3.66 (m, 4 pyridyl methylene H), 6.60 (d, 2 hydroxybenzyl H), 7.26 (d, 2 pyridyl H), 7.32 (d, 2 pyridyl H), 7.40 (dd, 2 hydroxybenzyl H), 7.62 (d, 2 hydroxybenzyl H), 7.72 (d, 2 pyridyl H), 8.35 (td, 2 pyridyl H).

Synthesis of Metal Complexes. Because many of the syntheses were similar, detailed procedures are given only for representative examples. It was not possible to obtain analytically pure products of [In(**badd**)]$^+$ owing to interference and contamination from precipitation of indium hydroxide.

N.B. Perchlorate salts of metal complexes are potentially explosive and should be handled with care.

[Ga(Brbadd)][ClO_4]. To a solution of $Ga(ClO_4)_3$·$6H_2O$ (405 mg, 0.85 mmol) and H_2**Brbadd** (719 mg, 1.4 mmol) in methanol (15 mL) was added NaOAc (245 mg, 3.0 mmol) in methanol (5 mL). The mixture was immediately filtered, and the filtrate was left at room temperature. Slow evaporation of the solvent yielded a beige precipitate, which was collected by filtration and washed with cold methanol followed by diethyl ether. The precipitate was dried *in vacuo* at 80 °C to yield 441 mg (74%). Recrystallization of the precipitate from methanol afforded crystals suitable for X-ray crystallographic analysis. Similar procedures were used to prepare [Ga(**badd**)][ClO_4] and [Ga(**Clbadd**)][ClO_4] in yields of 298 mg (67%) and 389 mg (78%), respectively.

[Ga(**badd**)][ClO_4]: Anal. Calcd (found) for [$GaC_{22}H_{32}N_4O_2$]-[ClO_4]·$0.5H_2O$: C, 46.96 (47.05); H, 5.91 (5.81); N, 10.14 (9.96). LSIMS: *m/z* = 453 (ML^+, [$GaC_{22}H_{32}N_4O_2$]$^+$). ^{1}H NMR (300 MHz, DMSO-d_6): 1.60 (d), 1.80 (q), 2.62 (t), 2.74 (d), 2.84 (d), 2.92 (m), 3.32 (m), 3.64 (m), 4.00 (q), 4.38 (m) (20 benzylic and backbone methylene H); 6.66 (d), 6.80 (t), 7.04 (d), 7.16 (t) (8 aromatic H).

[Ga(**Clbadd**)][ClO_4]: Anal. Calcd (found) for [$GaC_{22}H_{30}Cl_2N_4O_2$]-[ClO_4]: C, 42.44 (42.34); H, 4.86 (4.90); N, 9.00 (8.97). LSIMS: *m/z* = 523 (ML^+, [$GaC_{22}H_{30}Cl_2N_4O_2$]$^+$). ^{1}H NMR (300 MHz, DMSO-d_6): 1.60 (d), 1.84 (q), 2.60 (t), 2.74 (d), 2.86 (d), 2.94 (m), 3.30 (m),

Table 1. Crystallographic Data for [Ga(**Brbadd**)]ClO_4

compound	[Ga(**Brbadd**)][ClO_4]
formula	$C_{22}H_{30}Br_2ClGaN_4O_6$
fw	711.48
crystal system	orthorhombic
space group	$P2_12_12_1$
a, Å	12.462(1)
b, Å	21.835(2)
c, Å	9.961(2)
V, Å^3	2710.6(5)
Z	4
ρ_{calc}, g/cm^3	1.743
T, °C	21
λ, Å	1.541 78
μ(Cu *K*), cm^{-1}	61.79
transm factors	0.85−1.00
$R(F)^a$	0.031
$R_w(F)^a$	0.029

^{a} $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w(F) = (\sum w(|F_o| - |F_c|)^2/\sum wF_o^2)^{1/2}$.

3.62 (m), 3.66 (d), 4.00 (q), 4.48 (m) (20 benzylic and backbone methylene H); 6.68 (d), 7.14 (t), 7.18 (d) (6 aromatic H).

[Ga(**Brbadd**)][ClO_4]: Anal. Calcd (found) for [$GaC_{22}H_{30}Br_2N_4O_2$][ClO_4]: C, 37.14 (37.48); H, 4.25 (4.16); N, 7.87 (7.76). LSIMS: *m/z* = 611 (ML^+, [$GaC_{22}H_{30}Br_2N_4O_2]^+$). ^{1}H NMR (300 MHz, DMSO-d_6): 1.60 (d), 1.84 (q), 2.58 (t), 2.72 (d), 2.84 (d), 2.92 (m), 3.30 (m), 3.62 (m), 3.96 (d), 4.52 (q) (20 benzylic and backbone methylene H); 6.62 (d), 7.22 (t), 7.26 (d) (6 aromatic H).

[In(Brbadd)][ClO_4]. To a solution of $In(ClO_4)_3{\cdot}8H_2O$ (503 mg, 0.90 mmol) and H_2**Brbadd** (651 mg, 1.5 mmol) in methanol (15 mL) was added NaOAc (245 mg, 3.0 mmol) in methanol (5 mL). The mixture was immediately filtered, and the filtrate was left to stand at room temperature. Slow evaporation of the solvent yielded a white precipitate, which was collected by filtration and washed with cold methanol, followed by diethyl ether. The precipitate was dried *in vacuo* at 80 °C to yield 444 mg (77%). [In(**Clbadd**)][ClO_4] was prepared via a similar procedure to yield 458 mg (76.2%). Attempts to prepare analytically pure [In(**badd**)][ClO_4] were unsuccessful.

[In(**Brbadd**)][ClO_4]: Anal. Calcd (found) for [$InC_{22}H_{30}Br_2N_4O_2$][ClO_4]: C, 34.93 (35.06); H, 4.00 (4.36); N, 7.41 (7.19). LSIMS: *m/z* = 657 (ML^+, [$InC_{22}H_{30}Br_2N_4O_2]^+$). ^{1}H NMR (300 MHz, DMSO-d_6): 1.75 (d), 1.82 (q), 2.05 (m), 2.55 (m), 2.80 (m), 3.00 (m), 3.52 (m), 3.76 (d), 4.20 (m), 4.45 (m) (20 benzylic and backbone methylene H); 6.78 (d), 7.20 (t), 7.25 (d) (6 aromatic H).

[In(**Clbadd**)][ClO_4]: Anal. Calcd (found) for [$InC_{22}H_{30}Cl_2N_4O_2$][ClO_4]·1.5H_2O: C, 38.04 (37.94); H, 4.79 (4.66); N, 8.06 (7.98). LSIMS: *m/z* = 567 (ML^+, [$InC_{22}H_{30}Cl_2N_4O_2]^+$). ^{1}H NMR (300 MHz, DMSO-d_6): 1.76 (d), 1.82 (q), 2.52 (t), 2.68 (d), 2.86 (d), 2.92 (m), 3.04 (m), 3.50 (m), 3.72 (d), 4.18 (q), 4.48 (m) (20 benzylic and backbone methylene H); 6.72 (d), 7.10 (t), 7.18 (d) (6 aromatic H).

X-ray Crystallographic Analysis of [Ga(Brbadd)][ClO_4]. Crystallographic data appear in Table 1. The final unit-cell parameters were obtained by least-squares calculations on the setting angles for 25 reflections with 2θ = 42.8−53.8°. The intensities of three standard reflections, measured every 200 reflections throughout the data collection, decreased uniformly by 5.1%. The data were processed and corrected for Lorentz and polarization effects, decay, and absorption (empirical, based on azimuthal scans for three reflections).[10]

The structure was solved by the Patterson method. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were fixed in idealized positions (N−H/C−H = 0.98 Å, B_H = 1.2$B_{\text{bonded atom}}$). A correction for secondary extinction (Zachariasen type II, isotropic) was applied, the final value of the extinction coefficient being 1.00(6) × 10^{-5}. Neutral-atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from ref 11. A parallel refinement of the mirror-image structure gave significantly higher residuals, the *R* and R_w factor ratios both being 1.12. Selected bond lengths and selected angles appear in Tables 2 and 3, respectively. Complete tables of crystallographic data, final atomic coordinates and equivalent isotropic thermal parameters, bond distances, bond angles, and anisotropic thermal parameters are included as Suppoting Information (see paragraph at end of paper). Structure factors are available from the authors upon request.

Table 2. Selected Bond Distances (Å) for the [Ga(**Brbadd**)]$^+$ Cation in [Ga(**Brbad**)]ClO_4

Ga−O1	1.934(4)	N3−C6	1.459(9)
Ga−O2	1.913(4)	N3−C5	1.484(10)
Ga−N1	2.101(6)	N4−C8	1.480(9)
Ga−N2	2.087(6)	N4−C16	1.513(8)
Ga−N3	2.093(6)	C1−C2	1.52(1)
Ga−N4	2.146(6)	C2−C3	1.50(1)
Br1−C14	1.918(8)	C4−C5	1.50(1)
Br2−C21	1.900(7)	C6−C7	1.52(1)
O1−C11	1.327(8)	C7−C8	1.51(1)
O2−C18	1.345(7)	C5−C6	1.367(13)
N1−C1	1.487(7)	C9−C10	1.505(8)
N1−C9	1.499(8)	C10−C11	1.406(9)
N2−C3	1.484(9)	C16−C17	1.495(10)
N2−C4	1.46(1)	C17−C18	1.394(9)
C12−C13	1.39(1)	C14−C15	1.384(8)

Table 3. Selected Bond Angles (deg) for the [Ga(**Brbadd**)]$^+$ Cation in [Ga(**Brbad**)]ClO_4

O1−Ga−O2	177.6(2)	Ga−O2−C18	124.6(4)
O1−Ga−N1	91.4(2)	Ga−N1−C1	114.9(5)
O1−Ga−N2	89.9(2)	Ga−N1−C9	113.4(4)
O1−Ga−N3	88.1(2)	C1−N1−C9	109.9(5)
O1−Ga−N4	87.9(2)	Ga−N2−C3	116.7(5)
O2−Ga−N1	90.5(2)	Ga−N2−C4	108.1(5)
O2−Ga−N2	91.5(2)	C3−N2−C4	110.9(7)
O2−Ga−N3	90.2(2)	Ga−N3−C5	106.6(5)
O2−Ga−N4	90.6(2)	Ga−N3−C6	118.8(5)
N1−Ga−N2	89.9(3)	C5−N3−C6	111.1(7)
N1−Ga−N3	172.6(2)	Ga−N4−C8	118.5(5)
N1−Ga−N4	93.9(2)	Ga−N4−C16	111.9(4)
N2−Ga−N3	82.8(3)	C8−N4−C16	111.5(5)
N2−Ga−N4	175.7(3)	N1−C1−C2	113.1(6)
N3−Ga−N4	93.4(2)	C1−C2−C3	114.7(7
Ga−O1−C11	122.0(4)	N2−C3−C2	113.8(7)
N2−C4−C5	109.6(7)	N1−C9−C10	113.8(5)
N3−C5−C4	107.2(7)	C9−C10−C11	117.7(7)
N3−C6−C7	111.9(7)	O1−C11−C10	121.6(6)
C6−C7−C8	114.9(7)	N4−C16−C17	112.3(6)
N4−C8−C7	116.9(7)	C16−C17−C18	119.6(6)
O2−C18−C17	120.9(7)		

Potentiometric Equilibrium Measurements. Potentiometric equilibrium measurements of H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ in the absence and presence of Ga^{3+} and In^{3+} metal ions were performed by methods described in detail previously.[12,13] Stock solutions of NaCl, NaOH, and HCl were prepared and standardized as previously described.[12] The temperature was maintained at 25.0 ± 0.1 °C throughout all titrations. Ga^{3+} and In^{3+} solutions were prepared from appropriate dilution of atomic absorption standard solutions (Aldrich). The ionic strengths of all solutions were maintained at 0.16 M NaCl. The amounts of excess acid present in the metal ion solutions were accurately determined as described previously.[13] Solutions of H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ were degassed with Ar prior to use. Due to the extremely hygroscopic nature of the sulfonated compounds, the exact ligand concentration of each solution was calculated from the mass of the analytically pure ligand sample and was checked potentiometrically using the Gran extrapolation method.[14] The accuracy of the determined ligand concentration was also verified by plotting

(10) *teXsan*: *Crystal Structure Analysis Package*; Molecular Structure Corp.: The Woodlands, TX, 1985 and 1992.

(11) (a) *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 99−102. (b) *International Tables for Crystallography*; Kluwer Academic Publishers: Boston, MA, 1992; Vol. C, pp 200−206.

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Table 4. Deprotonation Constants (pK_a's) of Various Amines and Amine Phenols (25 °C, 0.16 M NaCl Unless Otherwise Noted)

compound	pK_{a_1}	pK_{a_2}	pK_{a_3}	pK_{a_4}	pK_{a_5}	pK_{a_6}
H_6**Sbad**$^{2+}$	10.35(9)	9.77(5)	8.16(4)	7.19(4)	5.65(6)	2.71(9)
H_6**Sbadd**$^{2+}$	10.88(8)	10.49(7)	8.59(5)	7.35(6)	5.83(6)	1.95(8)
H_6**Sbbpen**$^{2+}$	11.33(4)	10.64(7)	9.09(7)	6.87(3)	4.70(3)	2.17(8)
Trien[a]	9.68	9.09	6.58	3.28		
Tnentn[b]	10.66	9.96	8.54	5.84		
HBED[c]	12.64	11.03	8.34	4.40	2.24	
SHBED[d]	12.91	10.42	7.90	4.29	1.96	1.2
H_6**TRNS**[e]	11.2	10.6	9.59	8.07	7.29	6.17

[a] Reference 23; $\mu = 0.1$ (KNO_3). [b] Reference 24; $\mu = 0.5$ M (KNO_3). [c] Reference 25; $\mu = 0.10$ M (KCl). [d] Reference 26; $\mu = 0.10$ M (KCl). [e] Reference 13; $\mu = 0.16$ M (NaCl).

observed UV absorbance at 232 nm versus concentration at pH 2−3. In all cases, the rigorous linearity indicated conclusively that the concentration obtained from the Gran extrapolation method was correct.

The deprotonation constants (pK_a's) of H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ were determined potentiometrically from a total of 12, 8, and 11 titrations, respectively. For each compound, several different solutions were prepared using products obtained from two or more separate syntheses. Titrations of solutions of varying concentrations were repeated on different days to ensure reproducibility.

Potentiometric titrations of H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ in the presence of Ga^{3+} and In^{3+} metal ions were performed with the ratio of metal to ligand ranging from 1:1.2 to 1:2. Amine phenol solutions of differing concentrations prepared from different synthetic batches were used in the titrations of each metal-ligand system. Concentrations of the ligand and the metal ion used in each titration ranged from 0.5 to 3 mM. A minimum of seven titrations were performed for each metal−amine phenol system. Potentiometric titrations of H_6**Sbadd**$^{2+}$ in the presence of each metal ion were performed in two steps in order to prevent the hydrolysis of the metal ion prior to complexation. The first step involved the addition of base until a pH of 3 was attained, and these data were used to check the excess acid concentration. This was followed by a rapid addition of base to a pH of 4.5; the solution was then allowed to equilibrate for 30 min and titrated to completion.

The deprotonation constants (pK_a's) for H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ and the stability constants of the corresponding Ga and In complexes were calculated from the titration data using the program BEST.[15] For all Ga and In amine phenol systems, the computations allowed for the presence of $M(OH)^{2+}$, $M(OH)_2^+$, $M(OH)_3$, and $M(OH)_4^-$; in addition, for In^{3+}, $InCl^{2+}$, $InCl_2^+$, $InCl_3$, and $In(OH)Cl^+$ were also included.[16] The possibilities of protonated and ternary hydrolysis metal complexes were investigated, but no evidence was found for the presence of such species. The pK_a's of H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ are listed in Table 4, and the stability constants of all the Ga and In complexes are listed in Table 5. Values of pM at physiological pH are also listed in Table 5; the pM values were calculated with [M] = 1 μM, [L] = 10 μM, pH 7.4.

To verify the observed pK_a's and stability constants, variable-pH ^{1}H NMR and UV spectroscopic studies were conducted. Variable-pH ^{1}H NMR spectra of the ligands and of the metal complexes were collected in D_2O, the pD values being measured by a Fisher Accumet 950 pH meter equipped with an Accumet Ag/AgCl combination microelectrode. pD was converted to pH by adding 0.40.[17] ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer from pH 2 to 12. Variable-pH UV spectra (400−200 nm) of the ligands and the metal complexes were recorded on a Shimadzu UV-2100 UV/visible recording spectrophotometer from pH 2 to 12. The concentrations of the ligands and metal ions in the UV studies were $\sim 10^{-5}$ M.

Results and Discussion

Tnentn-Based Linear Amine Phenols (H_2Xbadd). The H_2**Xbadd** (X = H, Cl, Br) compounds were prepared similarly to H_2**Xbad** (X = H, Cl, Br).[6] This involved the *in situ* borohydride reduction of the Schiff base condensation products of tnentn with appropriately substituted salicylaldehydes. The products of these *in situ* reductions were oils that were determined by NMR and mass spectrometry to be the desired N_4O_2 linear amine phenols. For the H_2**Xbad** amine phenols, refluxing the oily product in acetone produced a more tractable acetone adduct, which contained two imidazolidine rings.[6] Similar treatment of H_2**Xbadd** amine phenols with acetone did not produce acetone adducts because six-membered 1,3-piperazine rings are much less stable than five-membered imidazolidine rings. Unlike their Schiff base analogs, the amine phenols were completely stable toward hydrolysis.

Table 5. log β and pM Values (pH 7.4) for Ga and In Complexes with H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, H_6**Sbbpen**$^{2+}$, HBED, EHPG, PLED, NTA, DTPA, EDTA, and Transferrin

	log β		pM	
ligand	Ga^{3+}	In^{3+}	Ga^{3+}	In^{3+}
H_6**Sbad**$^{2+}$	28.33(8)	24.54(2)	22.9	19.2
H_6**Sbadd**$^{2+}$	28.27(5)	24.56(5)	21.1	17.4
H_6**Sbbpen**$^{2+}$	35.33(8)	34.85(5)	27.4	26.9
HBED	38.51[a]	27.76[a]	29.6[f]	18.9[f]
SHBED	37.47[h]	29.37[h]	29.4[f]	21.2[f]
rac-EHPG	33.89[b]	26.68[b]	25.3[f]	18.1[f]
PLED	32.02[c]	26.25[c]	26.7[f]	20.9[f]
EDTA	20.3[g]	24.9[g]	19.9[e]	23.1[e]
Tf (1st binding site)	19.75[d]	18.80[d]	20.9[e]	18.7[d]
Tf (2nd binding site)	18.30[d]	16.44[d]		

[a] Reference 25. [b] Reference 28. [c] Reference 27. [d] Reference 3. [e] Reference 2c. [f] Recalculated for [M] = 1 μM and [L] = 10 μM. [g] Reference 36. [h] Reference 26.

^{1}H NMR spectral data for H_2**Xbadd** showed them to be symmetrical about the central ethylene moieties of the tetraamine backbone−only one set of aromatic ^{1}H NMR resonances was observed for the two chemically equivalent hydroxybenzyl groups, and only one singlet was observed for the four benzylic hydrogen atoms. ^{13}C NMR spectra of the H_2**Xbadd** amine phenols showed 11 ^{13}C resonances. Mass spectral data were consistent with NMR spectral data in confirming the formulation of N_4O_2 linear amine phenols, parent peaks being easily assignable in every case.

Ga and In Complexes of Tnentn-Based Linear Amine Phenols. Monocationic Ga complexes with tnentn-based amine phenols were easily prepared from reactions of H_2**badd**, H_2**Clbadd**, or H_2**Brbadd** with hydrated gallium perchlorate in the presence of a slight excess of sodium acetate; however, it was much more difficult to isolate the analogous In complexes in analytically pure form due to the formation of In hydroxide. The Ga complexes were stable under neutral, weakly acidic, and basic conditions; the In complexes were not stable under weakly acidic conditions. Precipitation of In hydroxide often occurred when the [In(**Xbadd**)]$^+$ complexes were left in methanol for several days at room temperature and pH 5−6; this was not observed for the [In(**Xbad**)]$^+$ complexes. The Ga and In complexes were soluble in DMSO and slightly soluble in alcohols. All metal complexes were characterized by spectroscopic techniques (NMR, LSIMS) and elemental analyses. All data were consistent with the proposed formulation of monocationic hexacoordinated complexes.

^{1}H and ^{13}C NMR spectra of the Ga and In **Xbadd** complexes were recorded in DMSO-d_6 and showed similar features. Only one set of ^{1}H NMR resonance signals in the aromatic region of the spectra proved that the two hydroxybenzyl groups of the **badd** amine phenols remained chemically equivalent upon coordination. This was in contrast with the Ga and In **bad** amine phenol complexes, which had two chemically inequivalent hydroxybenzyl groups.[6] Upon coordination of **badd** amine

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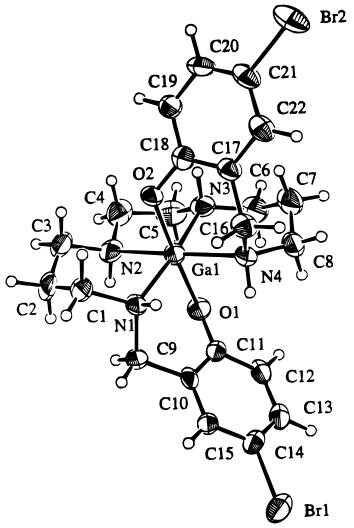

Figure 1. ORTEP drawing of the [Ga(**Brbadd**)]$^+$ cation in [Ga(**Brbadd**)]ClO_4 showing the crystallographic numbering. 33% probablity thermal ellipsoids are shown for the non-hydrogen atoms.

phenols to Ga^{3+} and In^{3+}, the ^1H NMR signals of the benzylic and the aliphatic H atoms became a complex series of overlapping resonances; however, the degree of complexity of these resonances in the **badd** complexes was significantly less than that observed in the NMR spectra of the **bad** complexes. ^1H NMR spectral data showed clearly a 2-fold symmetry in the **badd** amine phenol complexes that was absent in the complexes of the **bad** amine phenols, indicating that the coordination configuration of metal complexes with the longer chain **badd** linear amine phenols was different from the configuration of complexes with the shorter chain **bad** amine phenols. ^{13}C NMR spectra supported this assignment—only 11 out of a possible 22 ^{13}C resonance signals were observed. ^{13}C NMR spectra of the **bad** complexes showed 20 ^{13}C resonance signals, corresponding to the 20 inequivalent carbon atoms of the amine phenol.[6]

Variable-temperature ^1H NMR experiments were performed on [Ga(**Brbadd**)]$^+$ and [In(**Clbadd**)]$^+$, both as ClO_4^- salts. For [Ga(**Brbadd**)]$^+$, no significant change was observed in the ^1H NMR spectra as the temperature was raised from room temperature to 120 °C; some minor shifts and broadening of the ^1H NMR resonance signals were observed at elevated temperature, consistent with increased thermal vibrations of the coordinated ligand. Similar behavior was observed in the variable-temperature ^1H NMR study of [In(**Clbadd**)]$^+$, except for decomposition at 120 °C as indicated by the presence of free amine phenol.

X-ray Structure of [Ga(Brbadd)]ClO_4. Crystals of [Ga(**Brbadd**)]ClO_4 suitable for X-ray crystallographic analysis were grown from a methanol solution by slow evaporation of the solvent at room temperature. An ORTEP drawing of the cation [Ga(**Brbadd**)]$^+$ is illustrated in Figure 1, while selected bond lengths and bond angles are listed in Tables 2 and 3, respectively. The Ga^{3+} ion is hexacoordinated via four neutral amine nitrogen atoms and two anionic phenolate oxygen atoms (an N_4O_2 donor atom set) in a distorted octahedral coordination geometry.

Linear N_4O_2 amine phenols can span the octahedral positions around a metal ion in four possible configurations (Chart 2). By crystallography and NMR spectroscopy, it was shown that Ga and In complexes with **bad** amine phenols assumed configuration A;[6] however, crystallographic analysis of [Ga(**Brbadd**)]ClO_4 showed the **Brbadd**$^{2-}$ ligand coordinated to Ga^{3+} according to configuration B, the two phenolate oxygen atoms coordinated trans to one other. The four nitrogen atoms of the amine backbone formed a distorted equatorial plane with the phenolate oxygen atoms located above and below the plane of the amine nitrogen atoms. The NMR spectral data were consistent with the solid state structure of [Ga(**Brbadd**)]ClO_4.

The difference in the coordination modes of **Xbad**$^{2-}$ and **Xbadd**$^{2-}$ has a parallel in metal complexes involving similar hexadentate ligands with trien or tnentn amine backbones. Ni(II),[18] Fe(III),[19] and Mn(IV)[20] complexes with trien ligand backbones all assume configuration A. Related Mn(IV)[20] and Ga(III)[21] complexes with tnentn backbones assume configuration B. For both trien-based and tnentn-based amine phenols, only one coordination configuration was observed for Ga and In complexes. The difference in coordination configuration between the **bad** and **badd** amine phenol complexes can be attributed to the increased length of the tetraamine backbone in the latter and the change in the number of five- and six-membered chelate rings. Barring any major interference from electronic factors, ligands will coordinate via a configuration involving the least steric strain. Configuration A represents the least sterically demanding configuration available for coordination of the **bad** amine phenol to a metal center. As the length of the amine backbone is increased by substituting trien with tnentn, configuration B becomes the preferred configuration for coordination of the linear hexadentate ligand to the metal ion. It would be interesting to see what would be the least sterically demanding configuration for complexes with linear amine phenols based on *N*,*N*′-bis(2-aminoethyl)-1,3-propanediamine (2,3,2-tet) and *N*,*N*′-bis(3-aminopropyl)1,3-propanediamine (3,3,3-tet); 3,3,3-tet-based amine phenols would only have six-membered chelate rings when coordinated to a metal center.

Coordination of Ga^{3+} to **Brbadd**$^{2-}$ results in the formation of one five-membered and four six-membered chelate rings. The cis angles N(1)−Ga−N(2), N(2)−Ga−N(3), N(3)−Ga−N(4), and N(1)−Ga−N(4) are 89.9(3), 82.8(3), 93.4(2), and 93.9(2)°, respectively. The N(2)−Ga−N(3) angle is much less than the other three cis angles due to the restriction of the five-membered chelate ring. The trans angles average 175°, and the cis angles O−Ga−N are close to 90°, ranging from 88.9 to 91°. The degree of distortion in the octahedral geometry of [Ga(**Brbadd**)]$^+$ is much less than the distortion observed in the octahedral geometry of [Ga(**Brbad**)]$^+$, suggesting that **Brbadd**$^{2-}$ is more suited to its coordination configuration (configuration B) than is **Brbad**$^{2-}$ (configuration A).

The Ga−O1 and Ga−O2 bond lengths are 1.934 and 1.913, respectively, while the four Ga−N bonds average 2.107 Å. Ga−N(2) and Ga−N(3) are shorter than Ga−N(1) and Ga−N(4), most likely due to the restriction of the five-membered chelate ring N2, C4, C5, N3, Ga. The other two Ga−N bonds are involved in six-membered chelate rings. The observed Ga−O and Ga−N bond lengths are comparable to those of other Ga and In amine phenol[4−8] and Schiff base complexes.[21,22]

H_6Sbad^{2+}, H_6Sbadd^{2+}, and H_6Sbbpen^{2+}. Preparations of H_6**Sbad**$^{2+}$ and H_6**Sbadd**$^{2+}$ involved the Schiff base condensation and subsequent *in situ* reduction of sulfonated salicylaldehyde and the tetraamine in the presence of $NaBH_4$. Inorganic impurities such as NaCl were removed by ion exchange

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chromatography. The synthesis of H_6**Sbbpen**$^{2+}$, on the other hand, involved the direct sulfonation of the unsubstituted H_2**bbpen** with concentrated H_2SO_4. H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ were all prepared as dihydrochloride salts, the purity of which was checked by ^{1}H NMR, mass spectrometry, and elemental analyses. All the sulfonated compounds were stored in a dry nitrogen environment because they are extremely hygroscopic.

Deprotonation constants (pK_a's) of H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$ and H_6**Sbbpen**$^{2+}$ are listed in Table 4. The deprotonation constants of trien,[23] tnentn,[24] HBED,[25] SHBED,[26] and H_6**TRNS**[13] are also listed in Table 4 for comparison. The observed pK_a's are comparable to the pK_a's of compounds with similar ionizable moieties. For each sulfonated compound, six pK_a's were determined by potentiometric titrations. Although there were eight potentially ionizable groups on each sulfonated compound, the two sulfonic acid moieties on the hydroxybenzyl groups have pK_a's $\ll 1$. ^{1}H NMR resonance signals are sensitive to the deprotonation of the various groups; hence variable-pH ^{1}H NMR studies were used to verify and assign observed pK_a's to the six ionizable groups on each amine phenol. Variable-pH UV studies were also used to verify the observed pK_a's since the $\pi \rightarrow \pi^*$ transition of the aromatic ring is sensitive to the deprotonation of the two phenol moieties (the same obtains for the two pyridyl moieties in H_6**Sbbpen**$^{2+}$).

The six observed pK_a's of H_6**Sbad**$^{2+}$ and H_6**Sbadd**$^{2+}$ corresponded to the deprotonation of two phenols and four protonated ammonium moieties. The four ammonium moieties were of two discrete types, outer and inner. The two sets of linear amine phenols followed the same order of deprotonation. The two highest pK_a's were assigned to the deprotonation of the two outer ammonium moieties, while the two lowest pK_a's were assigned to the deprotonation of the two inner ammonium moieties. The deprotonation of the two phenols accounted for the two intermediate pK_a's.

The assignment of the two intermediate pK_a's in H_6**Sbad**$^{2+}$ (7.19 and 8.16) to the two phenols was verified by a plot of chemical shift change ($\Delta\delta$) versus pH for the ^{1}H NMR resonance α to the hydroxyl moiety (Figure 2, top). As the pH was raised from 5.5 to 9.5, deprotonation of the two phenols was noted by a downfield shift of the aromatic ^{1}H resonance signals. The deprotonation of the phenols from pH 5.5 to 9.5 was also observed in the variable-pH UV spectra of H_6**Sbad**$^{2+}$ (Figure 3), where a significant change in the UV spectrum was observed between pHs 6 and 9, corresponding to the deprotonation of the phenols. The ^{1}H NMR resonance of the four benzylic hydrogen atoms was also sensitive to the deprotonation of the two phenols, a plot of $\Delta\delta$ for the benzylic ^{1}H NMR resonance versus pH (Figure 2, top) showing a drop in $\Delta\delta$ between pHs 5 and 9. The deprotonation of the outer ammonium groups was also observed in the plot of $\Delta\delta$ for the benzylic ^{1}H resonance versus pH (Figure 2, top). At pH > 9, a much sharper drop in $\Delta\delta$ was observed with increase in pH. This sharper drop in $\Delta\delta$ resulted from the deprotonation of the outer ammonium moieties—the benzylic H are sensitive to changes in the chemical environment around these outer ammonium moieties. Therefore, the two highest pK_a's (9.77 and 10.35) were assigned to the two outer ammonium moieties. The large decrease in $\Delta\delta$ for the benzylic H between pHs 9 and 12 could not be attributed to the deprotonation of the inner

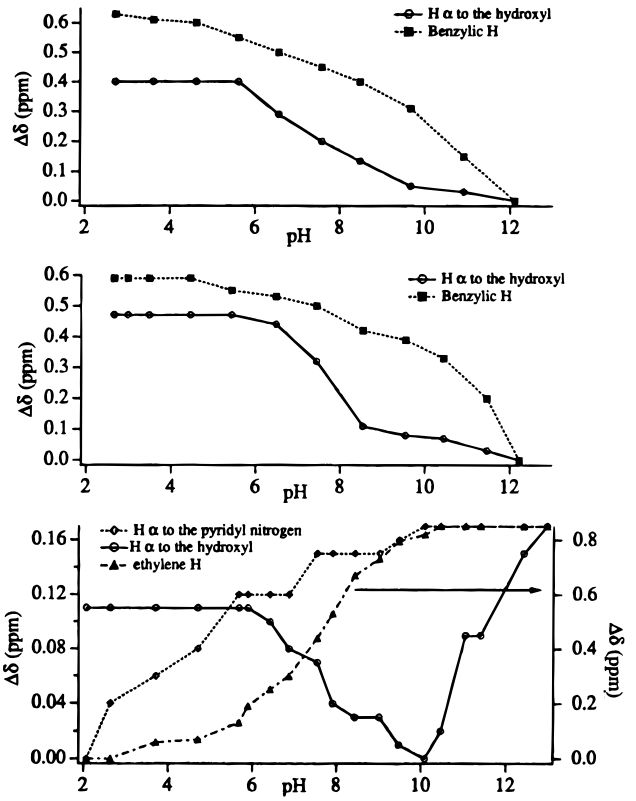

Figure 2. Plot of chemical shift change ($\Delta\delta$ in ppm) versus pH for selected ^{1}H NMR resonances in H_6**Sbad**$^{2+}$ (top), H_6**Sbadd**$^{2+}$ (middle), and H_6**Sbbpen**$^{2+}$ (bottom).

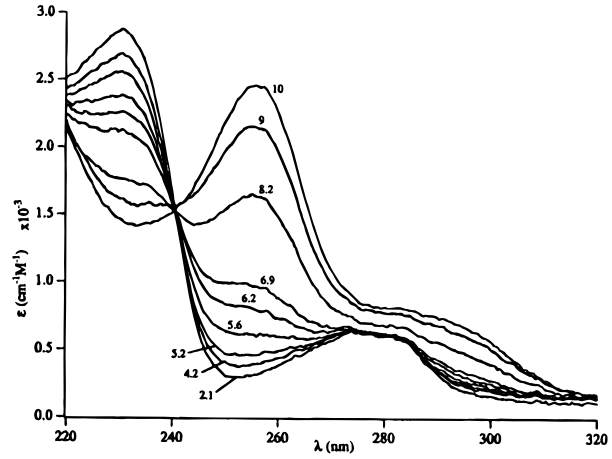

Figure 3. Variable-pH (pH 2−10) UV spectra (220−320 nm) of H_6**Sbad**$^{2+}$.

ammonium moieties because the benzylic H atoms were not sensitive enough (too far away) to significantly detect this deprotonation; however, the benzylic H atoms were sensitive (close) enough to detect the deprotonation of the phenols between pHs 5 and 9.

For H_6**Sbadd**$^{2+}$, the assignment of the six pK_a's paralleled the assignments for H_6**Sbad**$^{2+}$. Plots of $\Delta\delta$ versus pH (Figure 2, middle) were again used to verify and assign the six observed pK_a's in H_6**Sbadd**$^{2+}$. Variable-pH UV spectral data were consistent with the variable-pH ^{1}H NMR data in the assignment of the pK_a's which were on average higher than those of H_6**Sbad**$^{2+}$, consistent with the parent tetraamines, tnentn and trien.

In general, the basicity of amines is comparable with that of phenols; however, the pK_a's of the two phenols were higher than those of the two inner ammoniums but were lower than

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the pK_a's of the two outer ammoniums. This is neither uncommon nor surprising. The high pK_a's of the two outer ammonium moieties can be attributed to strong ion−hydrogen bonds present between the negatively charged oxygen atoms of the phenolate groups and the hydrogen atoms on the protonated outer ammonium moieties. This phenomenon has been observed previously in other amine phenols[13] and in ligands with hydroxybenzyl groups attached to amine nitrogen atoms.[27] H-bonding also acounts for the significant difference between the pK_a's of the two inner ammoniums. After the deprotonation of one inner ammonium, an H-bond will be established between the deprotonated amine nitrogen atom and the hydrogen atom on the other protonated inner ammonium. Overall, the pK_a's of H_6**SBadd**$^{2+}$ were higher than the pK_a's of H_6**Sbad**$^{2+}$, reflecting the overall higher basicity of tnentn compared to trien.

The six pK_a's determined from the potentiometric titrations of H_6**Sbbpen**$^{2+}$ were assigned, in increasing order, to the deprotonation of two pyridinium moieties, two ammonium moieties, and two phenol moieties. A plot of $\Delta\delta$ vs pH for the H atom α to the pyridinium nitrogen atom (Figure 2, bottom) showed a large increase in $\Delta\delta$ from pH 2−6, consistent with the deprotonation of the pyridinium moieties. The two lowest pK_a's were therefore assigned to the deprotonation of the two pyridinium moieties. From pH 6 to 10, increases in $\Delta\delta$ of the ethylene H resonance signified the deprotonation of the two ammonium moieties (Figure 2, bottom) and confirmed the assignment of the two intermediate pK_a's to these ammonium groups. The two highest pK_a's were assigned to the deprotonation of the two phenols and were verified between pH 10 and 13 by an increase in the $\Delta\delta$ of the aromatic H atom α to the hydroxyl groups (Figure 2, bottom). Variable-pH UV spectral data were consistent with the NMR data in the assignment of the last two pK_a's to the deprotonation of the two phenols. From Figure 2 (bottom), a decrease in $\Delta\delta$ for the ^{1}H NMR resonance α to the hydroxyl moieties was observed in the pH range corresponding to the deprotonation of the ammonium moieties. The H atoms on the hydroxybenzyl groups were also sensitive to the deprotonation of the ammonium nitrogen atoms.

The order of deprotonation for the ammonium and phenol moieties in H_6**Sbbpen**$^{2+}$ was opposite to that in the linear amine phenols. The two intermediate pK_a's were assigned to the deprotonation of the two ammonium nitrogen atoms, and the two highest pK_a's were assigned to the deprotonation of the two phenols. The difference in the order of deprotonation for the ammonium and phenol moieties can be attributed to the nature of the H-bonds present in H_6**Sbbpen**$^{2+}$ versus those in the linear amine phenols. Figure 2 shows the H atoms on the hydroxybenzyl groups to be sensitive to the deprotonation of the ammonium moieties. This suggested that H-bonding similar to that observed in the linear amine phenols was also present in H_6**Sbbpen**$^{2+}$. As the ammoniums were deprotonated to amines, H-bonds were established between the amine nitrogen atoms and the H atoms of the hydroxyl groups, with the H atom affiliated more with the phenolate oxygen atom than with the amine nitrogen atom. In the linear amine phenols, the opposite was found, with the H atom affiliated more with the ammonium nitrogen atom than with the phenolate oxygen atom. Hence, the assignments of the pK_a's for the ammonium and phenol moieties in H_6**Sbbpen**$^{2+}$ and the linear amine phenols were opposite.

Ga and In Complexes of H_6Sbad^{2+}, H_6Sbadd^{2+}, and H_6Sbbpen^{2+}. The formation of the Ga and In complexes with H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ in aqueous isotonic saline was studied by potentiometric titrations, and stability constants were determined from these titrations. ^{1}H NMR spectra of the Ga and In complexes with H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ showed the aqueous solution structures of these complexes to be consistent with both the solid state and solution structures of the metal complexes with the analogous nonsulfonated amine phenol ligands.[6,8] Stability constants and pM values of Ga and In complexes with H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$ are expected to be slightly different from those of complexes with analogous nonsulfonated amine phenols; however, the observed trends and differences between metal complexes with sulfonated amine phenols will also be valid for complexes with nonsulfonated amine phenol ligands. The effects of SO_3 groups on the stability constants and pM values of metal complexes are demonstrated in the stability constants and pM values of Ga and In complexes with HBED and SHBED ligands (Table 5).[25,26]

Potentiometric titrations were performed with ratios of metal to ligand varying from 1:1.2 to 1:2. In all cases, only 1:1 metal:ligand complexes were observed. Figure 4 shows the titration curves for 1:1.2 solutions of Ga^{3+} and In^{3+} with H_6**Sbad**$^{2+}$, H_6**Sbadd**$^{2+}$, and H_6**Sbbpen**$^{2+}$. In all cases, an inflection was observed at $a = 6$ (a = moles of OH^- added/moles of amine phenol), indicating the formation of hexacoordinated 1:1 metal:ligand complexes of the three amine phenols; **Sbbpen**$^{4-}$ showed complexation occurring at the lowest pH, indicating that the Ga and In **Sbbpen**$^{4-}$ complexes were the most stable of the three types of amine phenol complexes considered in this study. Titrations of H_6**Sbadd**$^{2+}$ in the presence of Ga^{3+} and In^{3+} could not be performed in one continuous experiment because of hydrolysis of the metal ion prior to complexation; complexation began at pH ∼5, but hydrolysis occurred at pH 3−4. To circumvent this problem, the titrations of H_6**Sbadd**$^{2+}$ in the presence of metal ions were carried out in two steps. Figure 4 (middle) illustrates the two-step titration of Ga^{3+} or In^{3+} with H_6**Sbadd**$^{2+}$.

The log β and pM values (at pH 7.4) of Ga and In complexes with **Sbad**$^{4-}$, **Sbadd**$^{4-}$, and **Sbbpen**$^{4-}$ are summarized in Table 5. Values for the Ga and In complexes with HBED,[25] SHBED,[26] PLED,[27] and *rac*-EHPG[28] are also listed in Table 5 for comparison, as are the binding constants of Ga^{3+} and In^{3+} with transferrin.[3] To verify qualitatively the stability constant, variable-pH UV spectral data were compared with the calculated metal complex speciations. For instance, the speciation diagram of the Ga/**Sbad** system predicted that complexation should begin at pH 3 and hydrolysis to $[Ga(OH)_4]^-$ should begin at pH 9. This was borne out by a comparison of the variable-pH UV spectra of H_6**Sbad**$^{2+}$ with and without Ga^{3+}. The magnitude of the binding constant was confirmed for the other Ga and In complexes in an analogous manner.

The gallium linear amine phenol complexes (those of **Sbad**$^{4-}$ and **Sbadd**$^{4-}$) were 3 orders of magnitude more stable than the corresponding indium analogs. This selectivity for gallium is expected on the basis of the information available for ligands containing only aliphatic amine and phenolate donor atoms—hydroxybenzyl[29] and hydroxypyridyl[30] derivatives of triazacyclononane, the hexadentate Schiff base saltames,[31] and the tripodal N_3O_3 amine phenols based on the amines tap and tame.[32] This is not surprising given that Hancock and Martell have shown that the affinity of amines for gallium and indium

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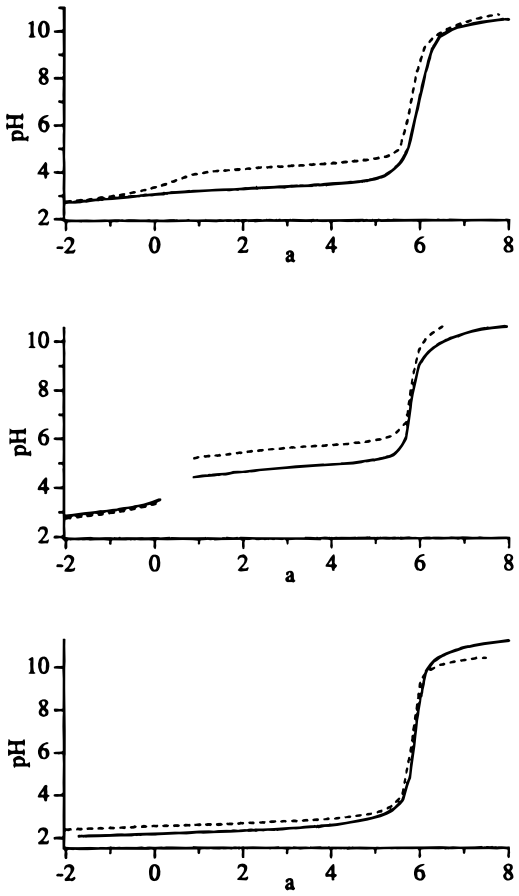

Figure 4. Experimental Ga (—) and In (- - -) titration curves for H_6**Sbad**$^{2+}$ (top), H_6**Sbadd**$^{2+}$ (middle—see text), and H_6**Sbbpen**$^{2+}$ (bottom) at ligand:metal = 1.2:1.

is of the same order of magnitude,[33] and Martell and co-workers have demonstrated that the 2-oxybenzyl group favors complexation with gallium over indium.[34] The selectivity of **Sbad**$^{4-}$ and **Sbadd**$^{4-}$ for gallium is much less than in the cited examples.[29−32] One obvious difference is that the prior literature on gallium and indium amine phenol complexes involved ligands with N_3O_3 donor sets, not the N_4O_2 donor set in **Sbad**$^{4-}$ and **Sbadd**$^{4-}$. Substituting an amine for a phenolate, and hence "softening" the donor set, has muted the selectivity for gallium over indium. The **Sbbpen**$^{4-}$ ligand provides an even better example of this effect (*vide infra*).

It has been shown that complex stability is intimately related to the size of the metal ion and the size of the chelate ring.[33,35] Stability generally decreases as the chelate ring size changes from 5 to 6; however, this destabilization is generally greater for larger metal ions.[35] Coordination of **Xbad** ligands to Ga^{3+} or In^{3+} produced complexes with three five- and two six-membered chelate rings, while **Xbadd** complexes contained one five- and four six-membered rings. On the basis of the above criteria, **Xbadd** complexes should be less stable than **Xbad** complexes, but **Xbadd** ligands, with the greater number of six-membered rings, should have a greater selectivity for gallium. However, the stability constants and the pM values for Ga and In complexes with **Sbad**$^{4-}$ and **Sbadd**$^{4-}$ ligands did not show any indication of this effect. The stability constants of metal complexes with **Sbad**$^{4-}$ and **Sbadd**$^{4-}$ were of equal magnitude, and the differences in pM values (Ga−In) for **Sbad**$^{4-}$ and **Sbadd**$^{4-}$ are approximately the same. This is not to say that the relationships between complex stability and the size of metal ion and between complex stability and the size of the chelate ring are not valid for linear amine phenol complexes. The difference in the basicity of **Sbad**$^{4-}$ and **Sbadd**$^{4-}$ plus the difference in coordination geometry between the **Sbad**$^{4-}$ and **Sbadd**$^{4-}$ complexes may be masking the effect of chelate ring size on the stability of the metal complexes.

Attempts to isolate analytically pure Al complexes with both the **Xbad** and **Xbadd** linear amine phenols were unsuccessful, as the Al linear amine phenol complexes were not particularly stable. Although no attempt was made to determine the stability constants of the Al complexes, they should be much lower than the stability constants of the Ga and In complexes. This is actually corroborated by the pM values of the Al and Ga complexes with the Schiff base analog of H_2**bad**.[31] The Ga Schiff base complex pM value was ∼9 units higher than that for the corresponding Al complex. The linear amine phenols are not well suited to complexation of the Al^{3+} ion because of its small size, relative hardness, and lower affinity for nitrogen donor atoms.

The stability constants and pM values of [Ga(**Sbbpen**)]$^-$ and [In(**Sbbpen**)]$^-$ were significantly higher than the stability constants and pM values of the linear amine phenol complexes; the **bbpen** amine phenols have a much greater affinity for Ga^{3+} and In^{3+} than the linear amine phenols. It is intuitive that the **bbpen** amine phenols have a higher affinity for Ga^{3+} and In^{3+} than the linear amine phenols because of the preorganization of the **bbpen** donor atoms to form a 3-dimensional clamp. The donor atoms are arranged such that they could coordinate to a metal ion simultaneously, not in a linear sequential arrangement. If a metal ion were of appropriate size, the **bbpen** amine phenol could clamp and coordinate to that metal ion simultaneously with all 6 of its donor atoms, which are prearranged into positions ideal for coordination. This is in contrast with the donor atoms of the linear amine phenols, which would sequentially position themselves for coordination to the metal ion as the ligand wrapped around the metal center. Examples of this are the divalent metal complexes of penten and *N*,*N*′-dimethyl-3,6,9,12-tetraazatetradecane-1,14-diamine, in which the stability constants of penten metal complexes[36] were 3−6 orders of magnitude higher than those of corresponding linear polyamine metal complexes.[37] The preorganization of the **bbpen** donor atoms appears to be well suited for coordination to metal ions whose ionic radii are similar to those of Ga^{3+} and In^{3+}. Complexes of Mn^{3+} (0.645 Å),[38] V^{3+} (0.64 Å),[38] and Ru^{3+} (0.82 Å)[38] with **bbpen** have been reported.[39−41]

The stability constants and pM values of [Ga(**Sbbpen**)]$^-$ and [In(**Sbbpen**)]$^-$ are very similar to each other. **Sbbpen** does not discriminate between Ga^{3+} and In^{3+}, in stark contrast to ligands such as HBED,[25] SHBED,[26] PLED,[27] and EHPG,[28] which exhibit a significant selectivity for Ga^{3+} over In^{3+}, approximately 7−10 orders of magnitude (Table 5). SHBED, HBED, PLED, and EHPG are sterically similar to **bbpen** in

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that they all have four pendant arms attached to an ethylenediamine backbone and coordination of these ligands to a metal center results in the formation of three five-membered and two six-membered chelate rings; however, they differ in the donor atoms used for coordination. Both **bbpen** and HBED type ligands have two amine and two aromatic hydroxyl moieties, but the **bbpen** amine phenols also have two pyridyl moieties while HBED type ligands have two carboxyl moieties. Upon replacement of the two hard carboxylate oxygen atoms in HBED type ligands with two softer pyridyl nitrogen atoms in the **bbpen** amine phenols, the set of donor atoms becomes softer and more suitable for coordination to the slightly softer In^{3+} ion. Multidentate amino polycarboxylate ligands (NTA, EDTA, and DTPA) have a selectivity for In^{3+} over Ga^{3+}, while amino polyphenolate ligands (amine phenols and HBED) show a selectivity for Ga^{3+} over In^{3+}. The relatively harder donor atom set of amino polyphenolate ligands are more suited for the harder Ga^{3+} ion, while the softer In^{3+} prefers the softer donor atom set of amino polycarboxylate ligands. The hardness of the **bbpen** donor atom set lies between those of the amino polycarboxylate and the amino polyphenolate ligands. Hence, **bbpen** amine phenols show no selectivity for one metal over another and bind equally well to both Ga^{3+} and In^{3+} ions. The difference in selectivity of **bbpen**, amino polycarboxylate, and amino polyphenolate ligands follows from, and nicely complements, the work of Motekaitis *et al.*[34]

In order to compare the abilities of chelating ligands of differing denticities to compete with each other or with the iron transport protein transferrin for metal ions at physiological pH, pM values were calculated from observed stability constants; as a pM value increases, so does the affinity of the ligand for the metal ion. From the observed stability constants of these metal complexes, it was not surprising to discover that **Sbbpen**$^{4-}$ also had the highest pM values for both Ga^{3+} and In^{3+}. The **bbpen** amine phenols should be quite capable of competing with transferrin for Ga^{3+} and In^{3+}. For **Sbad**$^{4-}$, the pM values of the Ga and In complexes were respectively $\sim$2 and $\sim$0.5 units greater than the pM values for the binding of Ga^{3+} and In^{3+} to transferrin. In solutions where the concentrations of transferrin and amine phenols are approximately equal, the amine phenol should be thermodynamically capable of competing with transferrin for these trivalent metal ions though the competion for In^{3+} may be more fierce than the competion for Ga^{3+}. For **Sbadd**$^{4-}$, the pM value of the Ga complex was similar to the pM value for the binding of Ga^{3+} to transferrin, while the pM value of the In complex was lower than the pM value for transferrin. It is doubtful whether **Xbadd** amine phenols would be able to compete with transferrin *in vivo* for Ga^{3+} and In^{3+}; however, Ga and In complexes with linear amine phenols may still have potential as diagnostic radiopharmaceuticals if the *in vivo* demetalation of the complexes is kinetically slow enough to carry out the imaging procedure. Ga complexes with Schiff base analogs of the linear amine phenol have been considered as myocardial imaging agents and have been shown to have excellent myocardial uptake.[21,42,43] The lipophilicities of these complexes were altered by placing substituent groups on the aromatic rings and on the amine backbone. These complexes showed significant myocardial uptake and good myocardial retention at 2 h postinjection. We expect Ga complexes with linear amine phenols to also exhibit excellent myocardial uptake and retention. We are optimistic about the potential of Ga and In **bbpen** complexes as diagnostic radiopharmaceuticals; biodistribution studies of [^{67}Ga(**bbpen**)]$^{+}$ are presently underway.

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Supporting Information Available: Complete tables of crystallographic data, final atomic coordinates, hydrogen atom parameters, anisotropic thermal parameters, bond lengths, and bond angles for [Ga(**Brbadd**)]ClO_4 and variable-pH UV spectra of H_6**Sbadd**$^{2+}$ and H_6**Sbbpen**$^{2+}$ (17 pages). Ordering information is given on any current masthead page.

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