

Effect of Pyridyl Donors in the Chelation of Aluminum(III), Gallium(III), and Indium(III)

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A new preparation of *N,N'*-bis(2-pyridylmethyl)ethylenediamine-*N,N'*-diacetic acid (H₂bped) is reported, and its properties of complexation with Al(III), Ga(III), In(III), and Co(III) are investigated. The molecular structure of the cobalt(III) complex [Co(bped)]PF₆·CH₃CN·H₂O (C₂₀H₂₅CoF₆N₅O₅P) has been solved by X-ray methods; the complex crystallizes in the triclinic space group *P* $\bar{1}$, with *a* = 10.611(2) Å, *b* = 12.720(2) Å, *c* = 9.868(1) Å, α = 102.70(1)°, β = 93.60(1)°, γ = 106.96(1)°, and *Z* = 2. The structure was solved by direct methods and was refined by full-matrix least-squares procedures to *R* = 0.041 (*R*_w = 0.038) for 4312 reflections with *I* > 3σ(*I*). The Co(III) ion is coordinated in a distorted octahedral geometry with an N₄O₂ donor atom set. The carboxylato oxygen atoms are coordinated *trans*, while the pyridyl nitrogen atoms are coordinated *cis*. The largest distortion from octahedral geometry is the N_{pyridyl}–Co–N_{pyridyl} angle of 107°. Complex formation constants have been measured at 25 °C (μ = 0.16 M (NaCl)). log *K*([M(bped)]⁺) (log *K*([M(bped)(OH)]²⁺)): M = Al, 10.85 (6.37); M = Ga, 19.89 (15.62); M = In, 22.6 (15.44). A protonated complex was also detected, [Ga(Hbped)]²⁺, log *K* = 21.79. The order of stability is In(III) > Ga(III) > Al(III) for the binary species, [M(bped)]⁺. The solution structures of the complexes have been probed in multinuclear NMR (¹H, ¹³C, ²⁷Al) studies, and these solution structures are compared with the solid state structure of the cobalt(III) complex. The complexes [In(bped)]⁺ and [In(bped)(OH)] are proposed to contain 7-coordinate In(III) with water and hydroxide completing the respective coordination spheres. The gallium complexes are proposed to be 6-coordinate: the [Ga(Hbped)]²⁺ complex contains a nondeprotonated carboxylic acid group which is not coordinated, and [Ga(bped)(OH)] contains a coordinated hydroxide which displaces a carboxylato donor. The [Al(bped)(OH)] complex may be 5-coordinate on the basis of its downfield ²⁷Al NMR chemical shift, 54 ppm.

Introduction

The ethylenediamine unit represents an ideal fragment with which to construct a multidentate ligand—the diamino moiety allows facile functionalization to incorporate other donor atoms, and the close proximity of the donor atoms maximizes the number of five- and six-membered chelate rings.¹ A number of these ligands have been prepared offering a variety of donor atom sets^{2–13} (Chart 1). This contribution focuses on the chemistry of the group 13 metal ions Al(III), Ga(III), and In(III) with these types of multidentate ligands.

The aqueous chemistry of aluminum(III) is dominated by the oxophilicity of the ion; there is little known about the affinity of Al(III) for hexadentate ligands containing donors other than anionic oxygen, outside of edta and its derivatives. The reason for this is twofold: first, substitution kinetics with Al(III) are sluggish and long equilibration times (hours) are required to obtain reliable complex formation constants; second, the affinity of Al(III) toward the neutral nitrogen donor is known to be low.¹⁴ By anchoring a ligand via strong oxygen–aluminum bonds and exploiting the chelate effect, one can force neutral nitrogen donors to coordinate^{15–17} and aluminum complex formation constants may be determined in order to gauge the effect of neutral nitrogen donor coordination.¹⁸

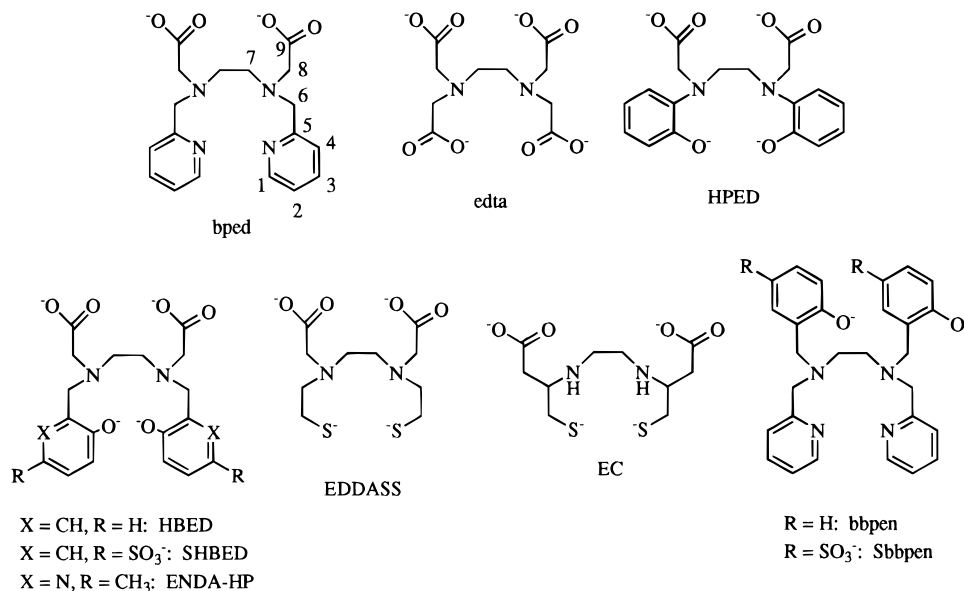
The aqueous chemistry of Ga(III) and In(III) is much richer than that of Al(III) owing to a higher affinity of these two ions for softer donor types, such as neutral nitrogen or anionic sulfur, and to the use of ⁶⁷Ga, ⁶⁸Ga, and ¹¹¹In in nuclear medicine.¹⁹ Faster ligand exchange kinetics compared to the case of Al³⁺ allows for easy determination of complex formation constants by automated potentiometric procedures. Ga(III) or In(III) chelates of many multidentate ligands have been investigated; to be useful in nuclear medicine, the complexes must be kinetically and/or thermodynamically stable with respect to hydrolysis and demetalation by the serum protein transferrin.^{20,21}

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Chart 1



A remarkable reversal of stability occurs when two of the carboxylate groups on edta are substituted by two 2-oxidobenzyl groups to give HBED (Chart 1). The affinity of In(III) for edta is 4 orders of magnitude higher than that of Ga(III) ($\log K_{ML} = 24.9$ (In), 21.0 (Ga)),²² while [Ga(HBED)]⁻ is almost 10 orders of magnitude more stable than [In(HBED)]⁻ ($\log K_{ML} = 27.8$ (In), 38.5 (Ga)).⁶ Further replacement of the remaining two carboxylate groups by pyridylmethyl moieties to give Sbb₂en (the sulfonate groups are added for aqueous solubility) almost completely mutes any selectivity for Ga(III) or In(III) ($\log K_{ML} = 34.9$ (In), 35.3 (Ga)).⁴ Three factors involved in this comparison are the donor atom type, the size of the metal chelate ring formed upon coordination, and the overall coordination number of the metal ion. The first two are obvious; the effect of the third is less so. Hancock has argued that ligands containing five-membered chelate rings coordinate with less strain to larger metal ions.²³ For hexadentate ligands such as edta which contain five five-membered chelate rings, larger metal ions such as In(III) may adopt a coordination number of 7 (by coordinating a water molecule); the longer M—O and M—N bond lengths in a 7-coordinate complex impart less strain in the ligand.²⁴ Smaller ions such as Al(III) or Ga(III), which cannot adopt a higher coordination number of 7, may alleviate some ligand strain by having one of the donor atoms replaced by solvent. In this case, a direct comparison of ligands coordinating to Al(III), Ga(III), and In(III) becomes more complex.

In an effort to understand the factors governing metal ion selectivity among group 13 metal complexes, the ligand *N,N'*-bis(2-pyridylmethyl)ethylenediamine-*N,N'*-diacetic acid (H₂bped)⁷ has been prepared in improved yield. Its deprotonation constants have been determined and assigned, and the formation constants for complexation of this ligand with Al(III), Ga(III), and In(III) have been measured. In addition, the Co(III) complex has been prepared and its structure determined by X-ray crystallography. The Co(III) complex is used as an aid in the determination of the solution structures of the group 13 metal chelates.

Experimental Section

Materials. Ethylenediamine-*N,N'*-diacetic acid, 2-(chloromethyl)pyridine hydrochloride, gallium(III) nitrate nonahydrate, indium(III) nitrate pentahydrate, cobalt(II) chloride, sodium perchlorate, sodium hexafluorophosphate, sodium deuterioxide (NaOD, 40%), deuterium chloride (DCl, 12 M), and the aluminum, gallium, and indium atomic absorption standards were obtained from Aldrich. Cetyltrimethylammonium bromide and sodium acetate were obtained from BDH, and aluminum trichloride hexahydrate was from Anachemia. Deuterium oxide (D₂O) was purchased from Isotec. All were used without further purification.

Instrumentation. ¹H NMR (200 and 300 MHz) and ¹³C NMR (50.3 and 75.5 MHz) spectra were referenced to TMS and recorded on Bruker AC-200E and Varian XL300 spectrometers, respectively. ²⁷Al NMR spectra were recorded at 78.2 MHz on the Varian XL300 spectrometer and are referenced to 0.1 M AlCl₃ in 1 M HCl. ¹H NOE difference spectra were recorded on a Bruker WH-400 spectrometer. The ¹H-detected heteronuclear multiple-quantum coherence (HMQC) and ¹H-detected multiple-bond heteronuclear multiple-quantum coherence (HMBC) experiments were run on a Bruker AMX-500 spectrometer. Mass spectra were obtained with a Kratos Concept II H32Q (Cs⁺, LSIMS) instrument. UV-vis spectra were recorded on a Shimadzu UV-2100. Infrared spectra were obtained as KBr disks in the range 4000–400 cm⁻¹ on a Galaxy Series FTIR 5000 spectrophotometer and were referenced to polystyrene. Analyses of C, H, and N were performed by Peter Borda in this department. The relationship $pD = pH + 0.40$ ²⁵ was used to relate the acid concentration of the NMR samples (pD) to the potentiometric results (pH).

***N,N'*-Bis(2-pyridylmethyl)ethylenediamine-*N,N'*-diacetic Acid Di-hydrochloride (H₂bped·2HCl).** To a yellow suspension of 2-(chloromethyl)pyridine hydrochloride (16.40 g, 0.1 mol), ethylenediamine-*N,N'*-diacetic acid (8.81 g, 0.05 mol), and hexadecyltrimethylammonium bromide (1.80 g, 0.005 mol) in water (400 mL) were added sodium hydroxide pellets until a pH of 12 was obtained. Addition of base gave a red-orange solution. The solution was stirred at room temperature under nitrogen for 36 h. During this time, the solution was maintained at pH 11 by occasional (over 4 h) addition of sodium hydroxide pellets. Upon completion of the reaction, the mixture was passed down a Rexyn 101 cation exchange column (H⁺ form) and eluted with deionized distilled water until the eluate was no longer acidic. The solvent was removed from the eluate under reduced pressure to give an orange solid. Hot ethanol (200 mL) was added and any insoluble material filtered off. The orange ethanol solution was acidified with 6 M HCl, and the solvent was removed under reduced pressure. The resultant solid was taken up in a minimum amount of

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hot ethanol (300 mL), and acetone was added to precipitate a white powder. The powder was collected by vacuum filtration, washed with cold ethanol (2×10 mL), and dried *in vacuo* at 60 °C for 24 h. If excess acid is used, the compound may be obtained as the trihydrochloride salt. Yield: 16.45 g (76%). Anal. Calc (found) for $C_{18}H_{22}N_4O_4 \cdot 2HCl$: C, 50.12 (49.94); H, 5.61 (5.66); N, 12.99 (12.67). MS (+LSIMS): m/z 359 ($[M + 1]^+$, $[C_{18}H_{23}N_4O_4]^+$). IR (cm^{-1} , KBr disk): 3500–2500 (b, s, ν_{O-H} , ν_{N-H}), 1728 (s, $\nu_{C=O}$), 1632 (m, δ_{N-H}), 1612, 1548, 1521, 1463 (ms, $\nu_{C=C}$, $\nu_{C=N}$), 1409 (m), 1388 (m), 1227 (b, s), 1161 (s), 765 (m). UV (λ_{max} , nm (ϵ , $M^{-1} cm^{-1}$): pH = 2, 259 (10 900); pH = 10, 261 (7400).

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

[Co(bped)]PF₆. To a solution of $H_2bped \cdot 2HCl$ (210 mg, 0.49 mmol) in 20 mL of methanol was added 65 mg of $CoCl_2$ (0.50 mmol) to yield a mauve suspension. Sodium acetate (170 mg, 2.07 mmol) was then added, whereupon the suspension became a red-brown solution. Air was bubbled through the solution overnight and the color changed to a cherry red. A solution of tetra-*n*-propylammonium hexafluorophosphate (180 mg, 0.54 mmol) in 10 mL of methanol was added to the red solution, and a red precipitate formed after allowing the solution to stand overnight at room temperature. The precipitate was recrystallized from acetonitrile and dried *in vacuo* to yield 103 mg (38%). Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of a solution of $[Co(bped)]PF_6$ in acetonitrile. Anal. Calc (found) after extensive drying for $[CoC_{18}H_{20}N_4O_4]PF_6 \cdot 0.5CH_3CN$: C, 39.29 (39.16); H, 3.73 (3.78); N, 10.85 (10.79). MS (+LSIMS): m/z 415 ($[M + 1]^+$, $[CoC_{18}H_{20}N_4O_4]^+$). IR (cm^{-1} , KBr disk): 1675 (b, s, $\nu_{C=O}$), 1614, 1467 (m, $\nu_{C=C}$, $\nu_{C=N}$), 1443 (m), 1351 (m), 1303 (s), 1065 (m), 928 (m), 842 (vs, ν_{P-F}), 763 (m), 558 (s, ν_{P-F}).

The group 13 complexes were all prepared by a similar procedure; it is given in detail only for the Al complex.

[Al(bped)]PF₆. To a solution of $H_2bped \cdot 2HCl$ (142 mg, 0.33 mmol) in 50 mL of methanol was added 82 mg of $AlCl_3 \cdot 6H_2O$ (0.33 mmol). Sodium acetate (110 mg, 1.32 mmol) was then added to the colorless solution. The solution was refluxed for 30 min and allowed to cool to room temperature; sodium hexafluorophosphate (55 mg, 0.33 mmol) was added, and the resulting solution was filtered into a 50 mL beaker. After standing overnight at room temperature, a white powder formed. The powder was collected on a frit, washed with methanol (1×5 mL) and then acetone (2×5 mL), and dried overnight *in vacuo* at 65 °C to yield 92 mg (53%). MS (+LSIMS): m/z 383 ($[M + 1]^+$, $[AlC_{18}H_{20}N_4O_4]^+$). IR (cm^{-1} , KBr disk): 1690 (s, $\nu_{C=O}$), 1650, 1618 (s, $\nu_{C=C}$, $\nu_{C=N}$), 1475 (m), 1442 (m), 1391 (m), 1308 (m), 1161 (m), 937 (s), 844 (vs, ν_{P-F}), 780 (m), 558 (s, ν_{P-F}).

[Ga(bped)]PF₆. Anal. Calc (found) for $[GaC_{18}H_{20}N_4O_4]PF_6$: C, 37.86 (38.26); H, 3.53 (3.49); N, 9.81 (9.50). MS (+LSIMS): m/z 425 ($[M + 1]^+$, $[GaC_{18}H_{20}N_4O_4]^+$). IR (cm^{-1} , KBr disk): 1681 (s, $\nu_{C=O}$), 1643, 1616 (s, $\nu_{C=C}$, $\nu_{C=N}$), 1468 (m), 1441 (m), 1345 (m), 1306 (m), 1035 (m), 921 (s), 842 (vs, ν_{P-F}), 777 (m), 558 (s, ν_{P-F}).

[In(bped)]PF₆. Anal. Calc (found) for $[InC_{18}H_{20}N_4O_4]PF_6 \cdot H_2O$: C, 34.09 (34.47); H, 3.50 (3.40); N, 8.83 (8.44). MS (+LSIMS): m/z 471 ($[M + 1]^+$, $[InC_{18}H_{20}N_4O_4]^+$). IR (cm^{-1} , KBr disk): 1631 (s, $\nu_{C=O}$), 1609, 1561 (s, $\nu_{C=C}$, $\nu_{C=N}$), 1492 (m), 1430 (m), 1382 (m), 1318 (m), 1027 (m), 844 (vs, ν_{P-F}), 770 (m), 558 (s, ν_{P-F}).

X-ray Crystallographic Analysis of $[Co(bped)]PF_6 \cdot CH_3CN \cdot H_2O$. 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 $2\theta = 30.3$ – 33.8° . The intensities of three standard reflections, measured every 200 reflections throughout the data collections, showed only minor random fluctuations. The data were processed and corrected for Lorentz and polarization effects and for absorption (empirical; based on azimuthal scans).

The structure analysis was initiated in the centrosymmetric space group $P\bar{1}$ on the basis of the E statistics. The structure was solved by direct methods²⁶ and expanded using Fourier techniques.²⁷ All six fluorine atoms of the hexafluorophosphate anion were modeled as (1:1) 2-fold disordered. All non-hydrogen atoms were refined with

Table 1. Crystallographic Data for $[Co(bped)]PF_6 \cdot CH_3CN \cdot H_2O$

empirical formula	$C_{20}H_{25}CoF_6N_5O_5P$
fw	619.35
crystal system	triclinic
space group	$P\bar{1}$
a , Å	10.611(2)
b , Å	12.720(2)
c , Å	9.868(1)
α , deg	102.70(1)
β , deg	93.60(1)
γ , deg	106.96(1)
V , Å ³	1231.4(3)
Z	2
ρ_{calc} , $g \cdot cm^{-3}$	1.670
T , °C	21
λ , Å	0.710 69
μ (Mo K α), cm^{-1}	8.50
transm factors	0.95–1.00
$R(F)^a$	0.041
$R_w(F)^a$	0.038

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

Table 2. Selected Bond Lengths (Å) and Angles (deg) for the $[Co(bped)]^+$ Cation in $[Co(bped)]PF_6 \cdot CH_3CN \cdot H_2O$

Co–O(1)	1.878(2)	Co–O(3)	1.888(2)
Co–N(1)	1.937(2)	Co–N(2)	1.941(2)
Co–N(3)	1.960(2)	Co–N(4)	1.958(2)
O(1)–Co–O(3)	178.53(8)	O(1)–Co–N(1)	87.36(9)
O(1)–Co–N(2)	92.51(8)	O(1)–Co–N(3)	92.34(8)
O(1)–Co–N(4)	86.40(8)	O(3)–Co–N(1)	94.10(9)
O(3)–Co–N(2)	87.39(9)	O(3)–Co–N(3)	87.99(8)
O(3)–Co–N(4)	92.14(8)	N(1)–Co–N(2)	88.87(9)
N(1)–Co–N(3)	82.14(9)	N(1)–Co–N(4)	169.12(9)
N(2)–Co–N(3)	169.58(9)	N(2)–Co–N(4)	82.51(9)
N(3)–Co–N(4)	107.01(9)		

anisotropic thermal parameters. Carbon-bound hydrogen atoms were fixed in idealized positions ($C-H = 0.98$ Å, $B_H = 1.2B_{bonded\ atom}$), and water H atoms were placed in difference map positions and were not refined. The acetonitrile H atoms were modeled as (1:1) 2-fold disordered on the basis of difference map peaks. A correction for secondary extinction (Zachariasen type II, isotropic) was applied, the final value of the extinction coefficient being $9.0(6) \times 10^{-7}$. Neutral-atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms (included in F_{calc})²⁸ were taken from refs 29–31. All calculations were performed using the *teXsan*³² crystallographic package. Selected bond lengths and bond angles appear in Table 2. Complete tables of crystallographic data, final atom coordinates and equivalent isotropic thermal parameters, anisotropic thermal parameters, bond lengths, bond angles, torsion angles, intermolecular contacts, and least-squares planes are included in the Supporting Information.

Potentiometric Equilibrium Measurements. The equilibrium constants were determined by potentiometric methods as described previously ($-\log [H^+]$ was read directly).³³ The ionic strength was

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Table 3. ^1H NMR (300 MHz) Spectral Data^{a,b} for H_2bped^c and Its Co(III)^d and $\text{In(III)}^{e,f}$ Complexes

	H_2bped	$[\text{Co}(\text{bped})]^+$	$[\text{In}(\text{bped})]^+$	$[\text{In}(\text{bped})(\text{OH})]$
H(1)	8.59 (4.4)	8.95 (5.4)	8.73 (5.0)	8.74 (5.2)
H(2)	7.76 (4.4, 7.7)	7.84 (5.4, 7.5)	7.77 (5.0, 7.7)	7.71 (5.2, 7.4)
H(3)	8.28 (7.7, 7.8)	8.30 (7.5, 8.0)	8.22 (7.7, 7.9)	8.17 (7.4, 7.9)
H(4)	7.85 (7.8)	7.80 (8.0)	7.70 (7.9)	7.65 (7.9)
H(6 _a) (Pro R)	4.43	4.73 (−15.0)	4.03 (−16.9)	4.04 (−16.0)
H(6 _b) (Pro S)		4.37 (−15.0)	4.45 (−16.9)	4.30 (−16.0)
H(7 _a) (Pro R)	3.34	3.94 (−9.4)	3.05 (−10.2)	2.97 (−10.7)
H(7 _b) (Pro S)		3.56 (−9.4)	3.18 (−10.2)	3.04 (−10.7)
H(8 _a) (Pro R)	3.67	4.00 (−17.9)	3.32 (−16.8)	3.23 (−16.8)
H(8 _b) (Pro S)		3.55 (−17.9)	3.45 (−16.8)	3.34 (−16.8)

^a For labeling, see Chart 1. ^b Numbers in parentheses refer to coupling in Hz (H(1) = $^3J_{12}$; H(2) = $^3J_{12}$, $^3J_{23}$; H(3) = $^3J_{23}$, $^3J_{34}$; H(4) = $^3J_{34}$; H(6) = $^2J_{ab}$; H(7) = $^2J_{ab}$; H(8) = $^2J_{ab}$). ^c H_2bped at pD = 2.3. ^d $[\text{Co}(\text{bped})]\text{PF}_6$ in $\text{DMSO}-d_6$. ^e $[\text{In}(\text{bped})]\text{Cl}$ at pD = 3.2. ^f $[\text{In}(\text{bped})(\text{OH})]$ at pD = 9.7.

fixed at 0.16 M NaCl, and the solutions were maintained at 25 ± 0.5 °C. Ar, which had been passed through 10% NaOH, was bubbled through the solutions to exclude CO_2 .

H_2bped was checked for purity by NMR and elemental analysis before titration. Titrations were also employed to verify the molecular weight obtained by elemental analysis. Metal ion solutions were prepared by dilution of the appropriate atomic absorption (AA) standards. The exact amount of acid present in the AA standards was determined by titration of an equimolar solution of metal standard and $\text{Na}_2\text{H}_2\text{edta}$. The amount of acid present was determined by Gran's method,³⁴ and this is equal to the amount of acid in the AA standard plus the 2 equiv of acid liberated from the complexed edta. Alternatively, hydrated metal salts (chlorides or nitrates) were dissolved in deionized distilled water and the exact metal ion concentration was determined by passing an aliquot down a Rexyn 101 cation exchange column (H^+ form). The liberated acid was determined by titration with sodium hydroxide (1 equiv of M^{3+} displaces 3 equiv of H^+).

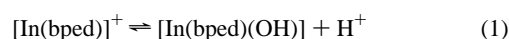
The ratio of ligand to metal used was in the range 1:1 < L:M < 1.5:1. Concentrations were in the range 1.0–2.5 mM. Six titrations (three titrations from two batches of ligand) defined the H_2bped system, while five titrations were performed to determine the $\text{Ga(III)}-\text{H}_2\text{bped}$ equilibria, each titration consisting of about one hundred data points. The ligand solutions were titrated over the range $2 < \text{pH} < 10$, while the metal–ligand solutions were titrated over the range $2-10.5$ (Complexation was usually rapid (1–3 min per point to give a stable pH reading) in the Ga(III) and In(III) studies; however, caution was taken to ensure that no trace hydrolysis or precipitation was occurring by monitoring up to 30 min for pH drift).

The $[\text{In}(\text{bped})]^+$ complex was completely formed by pH 2. Potentiometric titrations as described above gave no evidence for a $[\text{In}(\text{Hbped})]^{2+}$ species but did allow determination of a $[\text{In}(\text{bped})(\text{OH})]$ species. The UV spectrum of the binary species $[\text{In}(\text{bped})]^+$ remained unchanged until below pH 1, suggesting a lower limit of $\log K_{\text{ML}} = 20.5$. On the basis of this evidence, the tris(aminophenolato) ligand TAPS^{6-} was chosen for a ligand–ligand competition study. TAPS^{6-} forms complexes with In(III) of sufficient stability ($\log K_{\text{HML}} = 31.93$, $\log K_{\text{ML}} = 27.56$)¹⁸ that ligand exchange should take place above pH 6. A series of 49 solutions was prepared, 2 mM each in H_2bped , $\text{H}_6\text{-TAPS}$, and In(III) , and varying amounts of NaOH were added to each solution. The solutions were equilibrated for 2 days, and the pH of each solution was recorded.

For the Al(III) stability constant studies, equilibration was too slow for the automated titration procedure and a batch method was employed instead. Here, a series of 24 (0.16 M NaCl) CO_2 -free solutions were prepared with a 1.1:1 L:M ratio and varying amounts of NaOH were added. These solutions were equilibrated for 2 days at 25 °C until the pH reading of each stabilized.

The data were refined using the program BEST.³⁵ The hydrolysis constants used were taken from Baes and Mesmer,³⁶ and in the case of In(III) , formation constants for complexation with chloride were also included in the model. Although Ga(III) was completely complexed

at pH 2, the complex was unstable to hydrolysis to $[\text{Ga}(\text{OH})_4]^-$ at pH >9.5. The $[\text{Ga}(\text{OH})_4]^-$ formation constant was used to obtain the absolute $[\text{Ga}(\text{bped})]^+$ stability constant.³⁷ The relative stability constant for eq 1 could be determined by direct titration. The stability constant



$$K_{\text{MLOH}} = \frac{[\text{In}(\text{bped})(\text{OH})][\text{H}^+]}{[\text{In}(\text{bped})]^+}$$

for equilibrium, eq 2 was determined by competition with the ligand



$$K_{\text{ML}} = \frac{[\text{In}(\text{bped})]^+}{[\text{In}^{3+}][\text{bped}^{2-}]}$$

TAPS^{6-} (charges omitted for simplicity) as shown in eq 3. The



calculation involved keeping fixed the stability constants of $[\text{In}(\text{HTAPS})]^{2-}$ and $[\text{In}(\text{TAPS})]^{3-}$, the deprotonation constants of $\text{H}_6\text{-TAPS}$ and H_2bped , and the relative stability constant (K_{MLOH}), while iteratively varying the constant (K_{ML}) from eq 2 until the observed pH agreed with the calculated.

Results

H_2bped . N,N' -Bis(2-pyridylmethyl)ethylenediamine- N,N' -diacetic acid was prepared previously by Lacoste *et al.*⁷ as the monosodium salt. The previous method involved attaching a nitrile function to each of the secondary aliphatic amines of N,N' -bis(2-pyridylmethyl)ethylenediamine and then hydrolyzing the nitrile groups to carboxylic acids. The product was obtained in a relatively low yield (22%) and was characterized only by elemental analysis and alkimetric titration. The preparation described in this paper is a one-pot method, which gives a much higher yield (76%). H_2bped has been fully characterized by a variety of spectral methods. The ^1H NMR spectrum shows seven resonances with the correct integral ratios (Table 3). There are nine resonances observed in the ^{13}C NMR spectrum (Table 4). The NMR chemical shifts were assigned on the basis of HMQC, HMBC, and COSY experiments. Positive LSIMS clearly showed the parent monocation at m/z 359. The infrared spectrum showed a broad absorption at $3500-2500 \text{ cm}^{-1}$, indicative of extensive hydrogen bonding in the solid. Bands consistent with carboxylate and pyridyl functions were also observed. The UV spectrum was typical of a substituted pyridine and exhibited a hyperchromic effect with decreasing pH.³⁸

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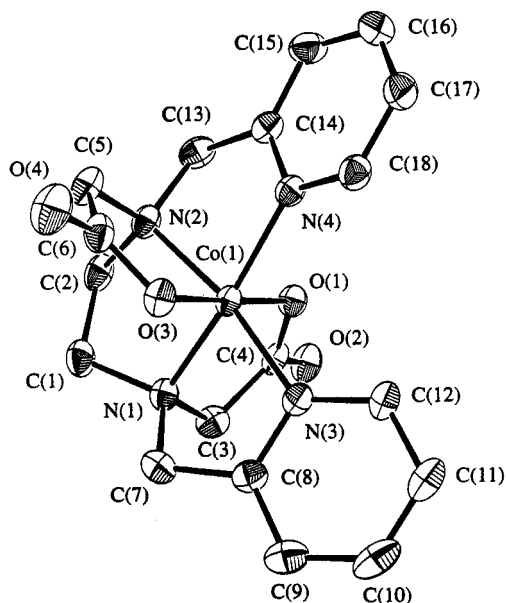
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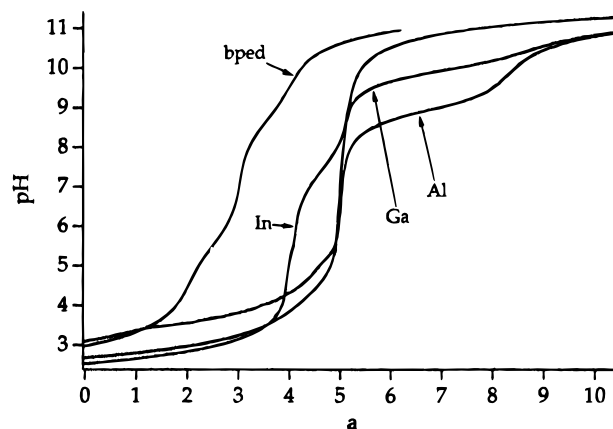
Table 4. ^{13}C NMR (75.5 MHz) Spectral Data^a for H_2bped^b and Its Co(III) ,^c In(III) ,^{d,f} and Ga(III) ^g Complexes

	H_2L	CoL^+	InL^+	InL(OH)	$[\text{InL}]\text{PF}_6$	$[\text{GaL}]\text{PF}_6$
C(1)	147.52	152.65	151.00	151.29	148.30 (148.40)	148.13
C(2)	129.65	126.68	128.83	128.43	125.45 (125.90)	125.65
C(3)	146.53	141.15	145.52	144.84	141.81	140.22
C(4)	128.91	124.75	128.23	128.02	125.36 (125.27)	124.84
C(5)	152.94	162.77	155.23	155.19	153.45 (153.77)	154.03
C(6)	58.90	64.96	61.05	60.86	57.76 (57.90)	63.26
C(7)	50.03	63.04	51.78	51.74	49.76 (49.66)	55.72
C(8)	57.40	63.27	58.48	58.60	57.26 (57.01)	59.65
C(9)	175.18	178.52	178.57	178.95	170.47 (170.24)	170.41

^a For labeling, see Chart 1. ^b $\text{L}^{2-} = \text{bped}^{2-}$, H_2L at $\text{pD} = 2.3$. ^c $[\text{CoL}]\text{PF}_6$ in $\text{DMSO-}d_6$. ^d $[\text{InL}]\text{Cl}$ at $\text{pD} = 3.2$. ^e $[\text{InL(OH)}]$ at $\text{pD} = 9.7$. ^f $[\text{InL}]\text{PF}_6$ in $\text{DMSO-}d_6$; numbers in parentheses refer to the minor species. ^g $[\text{GaL}]\text{PF}_6$ in $\text{DMF-}d_7$ at 120°C .

**Figure 1.** ORTEP representation of the molecular structure of the $[\text{Co}(\text{bped})]^+$ cation (33% probability thermal ellipsoids).

Metal Complexes. The group 13 complexes of bped^{2-} were all prepared in a similar manner. These cations, $[\text{M}(\text{bped})]^+$, were isolated as either the hexafluorophosphate or perchlorate salts from methanol or ethanol. The Co(III) complex was prepared by the aerial oxidation of the Co(II) complex, followed by precipitation with hexafluorophosphate or perchlorate. All of the metal complexes gave acceptable elemental analyses, with the exception of the Al(III) complex which was also found to be quite hygroscopic. Positive LSIMS mass spectral studies showed strong parent ion peaks for $[\text{M}(\text{bped})]^+$ with the expected isotopic pattern. The infrared spectra were similar for all four $[\text{M}(\text{bped})]^+\text{X}$ complexes with strong bands typical of noncoordinated hexafluorophosphate ($842, 558\text{ cm}^{-1}$)³⁹ or perchlorate (1092 cm^{-1}).⁴⁰ The carboxylate asymmetric stretch undergoes a considerable bathochromic shift upon coordination from 1728 cm^{-1} ($\text{H}_2\text{bped}\cdot 2\text{HCl}$) to 1690 cm^{-1} ($[\text{Al}(\text{bped})]^+$) to 1631 cm^{-1} ($[\text{In}(\text{bped})]^+$). The ^1H and ^{13}C NMR spectra of the Co(III) and In(III) complexes display 2-fold symmetry showing only 10 of a possible 20 ^1H resonances (Table 3) and 9 out of a possible 18 ^{13}C resonances (Table 4). In addition, the methylene hydrogen atoms on carbons 6 and 8 and the ethylene hydrogen atoms on C(7) are inequivalent, indicating rigid solution structures. The ^1H and ^{13}C NMR spectra of the

**Figure 2.** Titration curves (pH vs a ; $a = \text{mol of OH}^-/\text{mol bped}$) for $\text{H}_2\text{bped}\cdot 2\text{HCl}$ in the presence and absence of equimolar (2 mM) Al(III) , Ga(III) , and In(III) .

Ga(III) and Al(III) complexes were complicated by fluxional processes and/or more than one isomer being present.

Crystals of $[\text{Co}(\text{bped})]\text{PF}_6$ suitable for X-ray crystallographic analysis were grown by slow evaporation of an acetonitrile solution at room temperature. The complex crystallized with one water molecule and an acetonitrile solvate. An ORTEP diagram of the $[\text{Co}(\text{bped})]^+$ cation is shown in Figure 1, and the bond lengths and angles in the Co(III) coordination sphere are listed in Table 2. The Co(III) ion is hexacoordinated via two neutral pyridyl nitrogen atoms, two neutral tertiary aliphatic amino nitrogen atoms, and two anionic carboxylate oxygen atoms in a distorted octahedral coordination geometry. The carboxylate moieties coordinate in a *trans* fashion with the O(1)-Co-O(3) angle being $178.53(8)^\circ$. The largest deviation from octahedral geometry occurs among the N-Co-N angles. The angle defined by the two pyridyl nitrogen atoms and the cobalt atom, N(3)-Co-N(4) , is opened to 107° , while the angles defining the aliphatic amine-pyridyl chelate rings, N(1)-Co-N(3) and N(2)-Co-N(4) , are compressed to about 82° . The Co-N and Co-O distances are comparable to those found in other chelating aminopyridyl and amino carboxylate cobalt(III) complexes.⁴¹⁻⁴⁷

Potentiometric Titrations. The titration of $\text{H}_2\text{bped}\cdot 2\text{HCl}$ (Figure 2) is indicative of two fairly strongly acidic sites and two weakly acidic sites. The pK_a 's determined (at the 3σ level) are listed in Table 5 along with those reported by Lacoste *et al.*⁷ Variable-pH ^1H NMR and UV spectroscopy of the ligand allows assignment of the deprotonation scheme (Figure S1, Supporting Information). The first deprotonation occurs at a pyridyl nitrogen. The assignment of the second deprotonation is more ambiguous. The largest degree of chemical shift change about $\text{pH } 3.11$ occurs at the methylene hydrogens of the acetate group (H(8)). The third deprotonation takes place at a second pyridyl nitrogen, while the final deprotonation occurs at an aliphatic ammonium.

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Table 5. Deprotonation Constants of H₂bped·2HCl (Charges Omitted for Simplicity) at 25 °C

	$\mu =$ 0.16 M (NaCl) ^a	$\mu =$ 0.10 M (KNO ₃) ^b
[H ₃ L][H]/[H ₄ L] (pK _a 1)	<2	2.34
[H ₂ L][H]/[H ₃ L] (pK _a 2)	3.11(2)	3.02
[HL][H]/[H ₂ L] (pK _a 3)	5.53(3)	5.63
[L][H]/[HL] (pK _a 4)	8.67(8)	8.84

^a This work. ^b Reference 7.**Table 6.** Logarithms of the Formation Constants for Al(III), Ga(III), and In(III) with bped²⁻ and edta⁴⁻

	Al(III)	Ga(III)	In(III)
bped ²⁻ ^a			
[HML]/[ML][H]		1.90(2)	
[ML]/[M][L]	10.85(10)	19.89(10)	22.6(1)
[ML(OH)][H]/[M][L]	6.37(8)	15.62(3)	15.44(3)
[ML]/[ML(OH)][H]	4.48(8)	4.27(3)	7.16(3)
edta ⁴⁻ ^b			
[HML]/[ML][H]	2.5	1.8	1.5
[ML]/[M][L]	16.5	21.0	24.9
[ML(OH)][H]/[M][L]	10.67	15.42	16.41
[ML]/[ML(OH)][H]	5.83	5.58	8.49

^a This Work. ^b Reference 22.

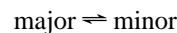
Titration curves for H₂bped in the presence of Al(III), Ga(III), and In(III) are shown in Figure 2. The 1:1 curves with Al(III) and Ga(III) both display an inflection at (mol of OH⁻/mol of bped²⁻) = 5, indicative of the formation of a [M(bped)(OH)] species. The 1:1 titration curve with In(III) shows an inflection at *a* = 4, a second buffer region between pH 7 and 8, and another inflection at *a* = 5, suggesting a [In(bped)]⁺ species being converted to [In(bped)(OH)] above pH 7. The formation constants of the group 13 metal–bped complexes are shown in Table 6, along with those of edta⁴⁻ for comparison.

Solution NMR Studies. The ¹H and ¹³C NMR spectra of [Co(bped)]⁺ (Tables 3 and 4, respectively) were assigned on the basis of HMQC, HMBC, and ¹H NOE difference experiments. The HMQC and HMBC experiments established the connectivity in the molecule. The individual hydrogen atoms of each AB pattern for the two methylene resonances, H(6) and H(8), and those of the AA'BB' (δ_A = δ_{A'}; δ_B = δ_{B'}) spin system, H(7), were assigned on the basis of ¹H NOE difference spectra. There were NOE enhancements between H(4) and H(6_b), H(6_a) and H(7_a), and H(6_b) and H(8_b). Using the coordination geometry from the crystal structure and these NOE correlations, the individual a and b hydrogen atoms were assigned.

The complex [In(bped)]⁺ could be prepared *in situ* by mixing appropriate amounts of ligand, metal, and hydroxide, and it displayed ¹H and ¹³C NMR resonance in D₂O identical with those of the isolated and redissolved complex. The ¹H NMR spectrum of the latter, as a Cl⁻ salt, is shown in Figure 3. The assignments were again made on the basis of HMQC, HMBC, and NOE difference spectra. There were NOE enhancements between H(4) and H(6_b), H(6_a) and H(8_b), H(6_b) and H(7_b), and H(7_a) and H(8_a). Preparation of the [In(bped)(OD)] complex by reaction of a 1:1 mixture of In(III)–H₂bped·2HCl with 5 equiv of sodium deuteroxide in D₂O gave ¹H and ¹³C NMR spectra very similar to those of [In(bped)]⁺ (Tables 3 and 4, respectively). The chemical shifts change slightly, but the 2-fold symmetry is preserved, and the methylene hydrogen atoms on carbons 6–8 remain inequivalent.

If [In(bped)]PF₆ is dissolved in DMSO-*d*₆, two species are observed in the ¹H NMR spectrum in a 4.7:1 ratio at 20 °C. The assignment of the spectrum is marred by overlapping resonances between 3 and 3.5 ppm. Both species have 2-fold

symmetry as evinced by a single set of pyridyl resonances per species and by one set of H(6) resonances which are split in an AB pattern. The ¹³C NMR spectrum is consistent with this symmetry as nine major and nine minor resonances are observed (Table 4); the tentative assignment of the resonances is based on a comparison between the spectra of the In(III) complex in D₂O and the Co(III) complex in DMSO-*d*₆. The resonances for H(1) and H(6a) are sufficiently separated for each species that the species ratio can be calculated as a function of temperature. For the equilibrium



the thermodynamic parameters are Δ*H* = +7.9 ± 0.9 kJ·mol⁻¹ and Δ*S* = +14 ± 3 J·K⁻¹·mol⁻¹, which indicates that the minor isomer is favored at elevated temperatures for entropic reasons.

The ¹H NMR spectrum of solid [Ga(bped)]PF₆ dissolved in D₂O, DMSO-*d*₆, or DMF-*d*₇ is described by a series of broad overlapping resonances. Heating a DMF-*d*₇ solution to 120 °C caused the spectra to simplify, consistent with fluxionality. No individual isomers (or resonances) could be assigned at any temperature because of overlap and line broadening. There was no evidence for dissociation at high temperature. The ¹³C NMR spectrum at -14 °C displayed a multitude of resonances: 12 peaks were observed between 50 and 65 ppm, the chemical shift region for C(6)–C(8); at least three carboxylate, C(9), resonances were observed clustered about 171 ppm. Heating to 120 °C gave rise to a much simpler spectrum of only nine ¹³C resonances (Table 4); however, these resonances are broadened to about 35 Hz.

A series of equimolar solutions of H₄bped·2HCl and Ga(NO₃)₃ were prepared and 0–6 molar equiv of sodium hydroxide were added. The solutions were evaporated to dryness, the residues were taken up in D₂O, the solutions were evaporated again, and the residues were dissolved in D₂O to give ca. 60 mM metal–ligand solutions. The ¹H NMR spectra were recorded, and some of these spectra are shown in Figure 4. The spectra of solutions containing up to 3 equiv of base (pD = 1.8) indicated three distinct pyridyl environments. The 0–2-equiv-base spectra (pD = 0.9–1.5) contained two sharp singlets at 3.36 and 3.37 ppm. At 4 equiv of base (pD = 3.1), all of the resonances had broadened excessively. At 5 equiv of base (pD = 6.6), the resonances remained broadened, but had shifted, and there was now a new sharp resonance at 3.39 ppm. Adding a sixth equivalent of base (pD = 10.2) resulted in the same spectrum as at pD = 6.6; however, some free ligand resonances were now observed.

A similar series of experiments were performed with aluminum. At pD = 2.8 (3 equiv of base), hydrogen resonances corresponding to free ligand and metal complex were observed; the ²⁷Al NMR spectrum showed a broad peak (*W*_{1/2} = 2600 Hz) at 40 ppm and a sharp peak at 0 ppm. At 4 equiv of base (pD = 3.5), the ¹H NMR spectrum showed a series of broad resonances, while the peak at 40 ppm in the ²⁷Al NMR spectrum remained. At slightly less than 5 equiv of base (pD = 4.6), the hydrogen atom resonances became sharper and two distinct pyridyl environments could be distinguished; however, the peaks between 3 and 4.5 ppm could not be assigned; a ¹³C NMR spectrum at this pD contained only 18 resonances. Formation of the hydroxo complex also resulted in a shift downfield of the ²⁷Al NMR resonance to 46 ppm (*W*_{1/2} = 2800 Hz). Further addition of hydroxide (pD = 8.9) increased the resolution of the ¹H spectrum; metal complex peaks corresponding to those at pD = 4.6 and also free-ligand hydrogen resonances were observed. The broad peak in the ²⁷Al spectrum moved further

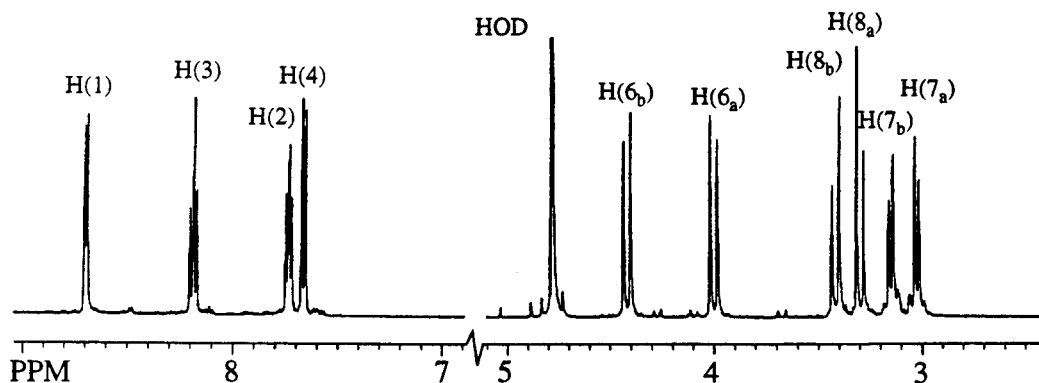


Figure 3. ^1H NMR spectrum (500 MHz) of $[\text{In}(\text{bped})]\text{Cl}$ in D_2O at $\text{pD} = 3.2$.

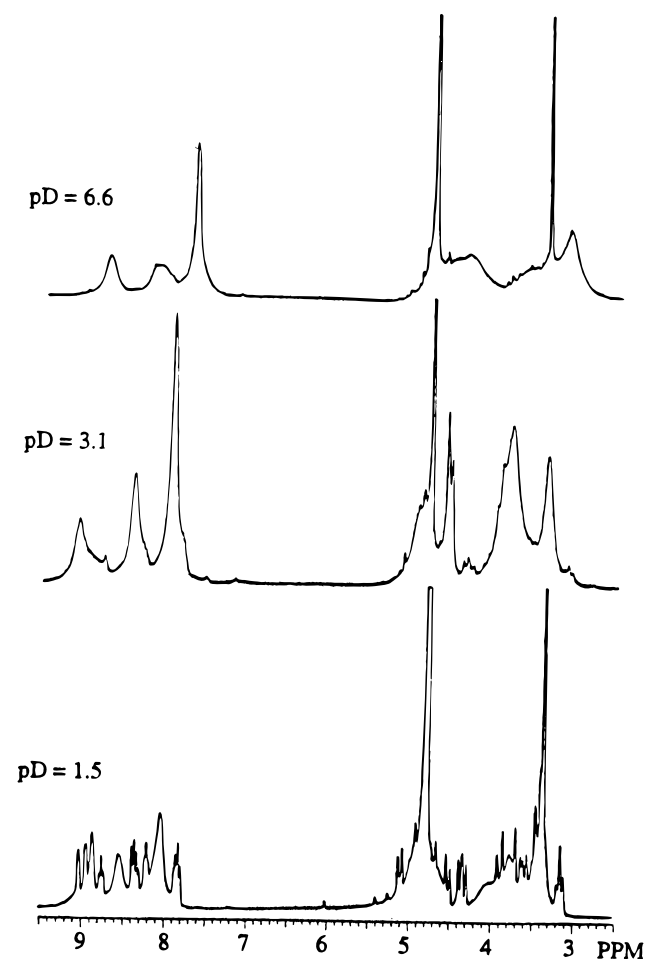


Figure 4. ^1H NMR spectra (300 MHz) of equimolar (~ 70 mM) mixtures of $\text{Ga}(\text{III})\text{-H}_2\text{bped}\cdot 2\text{HCl}$: bottom, 2 equiv of base ($\text{pD} = 1.5$); middle, 4 equiv of base ($\text{pD} = 3.1$); top, 5 equiv of base ($\text{pD} = 6.6$).

downfield to 54 ppm, and there was also a sharp peak at 80 ppm corresponding to $[\text{Al}(\text{OH})_4]^-$.⁴⁸

Discussion

The synthesis of H_2bped has been improved from that of the previously reported method.⁷ The agreement among the deprotonation constants is reasonable except for those of the first deprotonation (Table 5). Lacoste *et al.*⁷ assigned the deprotonation steps by comparing the basicities of the various donors. The variable-pH ^1H NMR and UV spectroscopic titrations of H_2bped (Figure S1) indicate clearly that the first and third

Table 7. Binary Metal–Ligand Formation Constants and Calculated pM Values ($\text{pH} = 7.4$) for $\text{Al}(\text{III})$, $\text{Ga}(\text{III})$, and $\text{In}(\text{III})$ Complexes of Ethylenediamine-Based Hexadentate Ligands

ligand	$\log K_{\text{AlL}}$ (pAl)	$\log K_{\text{GaL}}$ (pGa)	$\log K_{\text{InL}}$ (pIn)
bped	10.85 (13.4)	19.89 (22.7)	22.6 (22.7)
edta ^a	16.5 (16.3)	21.0 (21.0)	24.9 (23.1)
ENDA-HP ^b		29.2 (21.8)	28.0 (20.6)
Sbbpen ^c		35.3 (27.4)	34.9 (26.9)
HBED ^d		38.5 (29.6)	27.8 (18.9)
SHBED ^e		37.5 (29.4)	29.4 (21.2)
HPED ^f	25.8 (18.8)	32.0 (25.0)	26.3 (19.3)
EDDASS ^g		35.6 (30.0)	37.0 (31.3)
EC ^h		31.5 (25.6)	33.0 (27.1)

^a Reference 2. ^b Reference 9. ^c Reference 4. ^d Reference 6. ^e Reference 12. ^f Reference 13. ^g Reference 10. ^h Reference 8.

deprotonations occur at the pyridinium moieties, while the final pK_a corresponds to a tertiary ammonium deprotonation. The second deprotonation is assigned to a carboxylic acid. The high acidity of one of the tertiary ammonium nitrogen atoms in this molecule is to be expected because of Coulombic repulsion from the second tertiary ammonium group and the presence of the pyridyl and carboxylate groups over which the positive charge can be delocalized.

The stability constants determined for bped^{2-} with the group 13 metal ions (Table 6) follow the trend expected for this ligand, on the basis of a comparison of ligands with similar donor atoms. 2,2'-Bipyridine has a slightly higher affinity for $\text{In}(\text{III})$ than for $\text{Ga}(\text{III})$,²² while amino carboxylates such as nitrilotriacetate bind in the order $\text{In}(\text{III}) > \text{Ga}(\text{III}) > \text{Al}(\text{III})$.²² Martell and co-workers have shown⁶ that replacing two of the carboxylate donors in edta by two 2-oxidobenzyl moieties reverses the selectivity of $\text{In}(\text{III})$ over $\text{Ga}(\text{III})$ by 14 orders of magnitude (Table 7), whereas Wong *et al.*⁴ have shown that replacing the remaining two carboxylate groups by pyridylmethyl units gives a ligand with approximately equal affinity for gallium and indium ions (Table 7). By replacement of 2-oxidobenzyl groups of HBED with 2-pyridylmethyl moieties to give bped, it was expected that bped would be selective for $\text{In}(\text{III})$. This is indeed the case, but the selectivity is not as great as expected.

Figure 5 shows the speciation of $\text{Al}(\text{III})$, $\text{Ga}(\text{III})$, and $\text{In}(\text{III})$ with bped^{2-} at a ligand to metal millimolar ratio of 2:2, the same conditions used for the titrations. Both $\text{Ga}(\text{III})$ and $\text{In}(\text{III})$ are completely complexed at $\text{pH} = 2$, whereas $\text{Al}(\text{III})$ begins to be complexed at $\text{pH} \approx 3$. The striking feature of the speciation diagrams is the high stability of the monohydroxo species of $\text{Ga}(\text{III})$ and $\text{Al}(\text{III})$. It is known that larger metal ions bind to smaller chelate rings with less ligand strain than do smaller metal ions.^{23,49,50} Furthermore, Hancock has pointed

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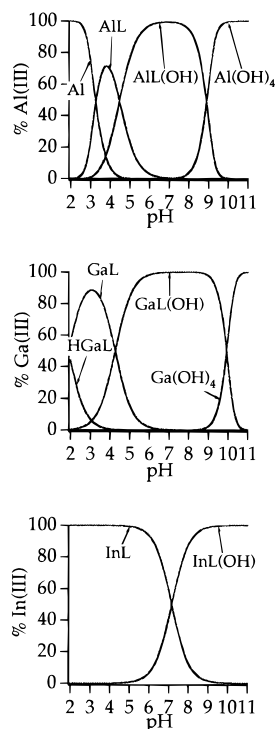
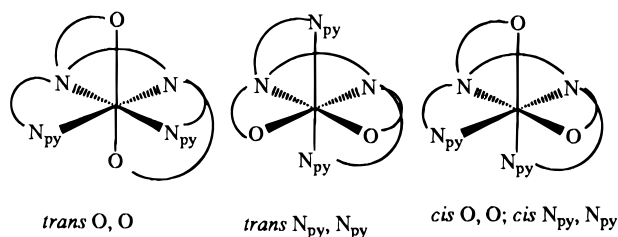


Figure 5. Speciation diagrams (% M(III) vs pH) calculated for equimolar (2 mM) Al(III)–H₂bped·2HCl (top), Ga(III)–H₂bped·2HCl (middle), and In(III)–H₂bped·2HCl (bottom).

Chart 2



out that a hexadentate ligand such as edta, which forms only five-membered chelate rings, often coordinates to larger metal ions with the addition of a unidentate ligand such as water.⁵¹ The increase in coordination number will result in longer metal–ligand bond lengths and will reduce the strain introduced into the ligand upon coordination. If the metal ion is too small (*e.g.*, Ga(III) or Al(III)) to accommodate seven donors, then the strain induced by coordinating all six donors in a ligand which only forms five-membered rings may be alleviated by displacement of one of the ligand donor atoms by solvent (*i.e.*, the ligand lowers its denticity). This is implied from the titration data for both edta and bped whereby Al(III) and Ga(III) both form stable monohydroxo complexes at much lower pH than does In(III).

A ligand such as bped can coordinate in an octahedral fashion to a metal ion with three possible geometries: *trans*(O,O), *trans*(N_{py},N_{py}), and *cis*(O,O) or *cis*(N_{py},N_{py}) (Chart 2). Despite the use of a variety of anions and solvents, crystalline complexes of In(III), Ga(III), and Al(III) were never isolated. The [Co(bped)]PF₆ complex was prepared as an inert structural probe of the group 13 metal complexes. Even if all three isomers of the cobalt(III) complex formed, it was hoped that the inert nature of Co(III) would allow separation of the isomers. Only one isomer formed, and this was shown to have the *trans*(O,O) configuration, both in the solid state and in solution. The ¹H

and ¹³C NMR spectra of the [Co(bped)]⁺ cation indicated 2-fold symmetry in solution. This can only be satisfied by the *trans*(O,O) or the *trans*(N_{py},N_{py}) isomer. The NOE enhancements observed in the ¹H spectrum were consistent with those expected from analysis of the crystal structure. Furthermore, a *trans*(N_{py},N_{py}) isomer should show a strong NOE correlation between H(1) and H(8); there are no NOE enhancements with H(1).

The assignment of the ¹H and ¹³C spectra in the Co(III) system was then used to aid in the estimation of the possible solution structures of [In(bped)]⁺ and [In(bped)(OH)]. Both [In(bped)]⁺ and [In(bped)(OH)] displayed 2-fold symmetry by NMR (Figure 3). The NOE enhancements were the same as those seen for the [Co(bped)]⁺ cation, although the chemical shift order was different (*i.e.*, H(6_a) was more deshielded than H(6_b) for [Co(bped)]⁺ and the reverse order was seen with [In(bped)]⁺). Again no NOE enhancement was observed with the H(1) resonance ruling out a *trans*(N_{py},N_{py}) isomer. The ¹H NMR data thus implied a solution structure for [In(bped)]⁺ similar to that of the [Co(bped)]⁺ cation in the solid state. On the basis of the potentiometric data, a 1:1 In(III):H₂bped solution was prepared and the pH was raised to above 9, where the [In(bped)(OH)] complex dominates. The 2-fold symmetry in the ¹H NMR spectrum was retained, as was the rigidity of the molecule. The hydrogen atom resonances for H(6)–H(8) all remained as AB quartets, suggesting that all six bped donor atoms remain coordinated. If hydroxide was to displace one of the donor atoms, more resonances would be expected because of the lowered symmetry, and a singlet should appear for H(6) or H(8) if a pyridyl or acetato arm becomes displaced. The only effect observed on forming [In(bped)(OH)] is a slight change in the ¹H and ¹³C NMR chemical shifts. This implies that the [In(bped)(OH)] complex contains a 7-coordinate In(III) ion.

The angle defined by the two pyridyl nitrogen atoms and the cobalt atom, N(3)–Co–N(4), spanned 107° in the crystal structure of [Co(bped)]PF₆. Shannon⁵² lists the ionic radii for Co(III) (low spin, CN = 6) and In(III) (CN = 6) as 0.545 and 0.800 Å, respectively. Substituting the larger In(III) for Co(III) should result in longer In–N and In–O bond lengths and an even more obtuse N(3)–In–N(4) angle than in the cobalt structure. Insertion of an aquo or hydroxo ligand between the two pyridyl donors of the indium complex would result in a pentagonal bipyramidal-like geometry which would still maintain a C₂ axis and hence be consistent with the NMR results. In addition, a crystal structure of Na₃[In(edta)(SO₃)] has been reported in which a 7-coordinate In(III) is bound to the six donors of edta and a monodentate sulfato ligand.⁵³

The ¹H and ¹³C NMR spectra of a solution of [In(bped)]PF₆ in DMSO-*d*₆ each indicate the presence of two species. Again, 2-fold symmetry is observed in the ¹³C NMR spectrum; the ¹H NMR spectrum reveals only one environment for the pyridyl resonances of each species and H(6) is again split into an AB quartet. The resonances for H(7) and H(8) are obscured by overlap and broadening. The ratio of minor species to major species increases with temperature ($\Delta H = +7.9 \pm 0.9 \text{ kJ}\cdot\text{mol}^{-1}$, $\Delta S = +14 \pm 3 \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$). The lack of a well-defined AB system for H(8) suggests that this process may involve the displacement of one or both of the carboxylato donors by DMSO and that this displacement increases with temperature (Scheme 1).

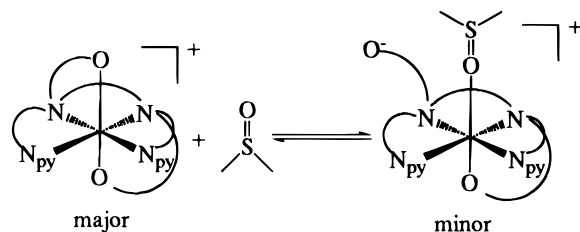
The gallium complex [Ga(bped)]PF₆ is fluxional in DMF-*d*₇, with the required number of resonances for all three isomers

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Scheme 1



being observed at $-14\text{ }^{\circ}\text{C}$. Alternately, the spectrum could represent bped coordinating with a lower denticity and the presence of solvent donors.

The variable-pH ^1H NMR spectra of the Ga–bped system are much more revealing (Figure 4). There is evidence of complexation at very low pH. In the region where the protonated complex obtains, there are two sharp singlets at 3.36 and 3.37 ppm, which, together, integrate to 2 hydrogens and are assigned to a noncoordinated carboxylic acid group. This is analogous to the crystal structure of $[\text{Ga}(\text{Hedta})(\text{H}_2\text{O})]^{54}$ where one of the carboxylate groups is protonated and noncoordinating and a water molecule occupies the sixth site of the coordination octahedron. Between 0 and 2 equiv of base, three environments are observed for the pyridyl hydrogen atoms, implying the existence of two or three isomers. At 4 equiv of base ($\text{pD} = 3.1$), the spectrum shows fluxional behavior, but the singlet corresponding to the free carboxylic acid has vanished. At $\text{pD} = 6.6$, where the hydroxo complex should dominate, the resonances have shifted but remain broad, with the exception of a sharp singlet at 3.39 ppm, again attributed to a noncoordinated carboxylate. At higher pH, the complex resonances remain the same but diminish in intensity as free-ligand resonances appear and increase in intensity.

The variable-pH ^1H and ^{27}Al NMR spectra are consistent with the potentiometric results. If less than a stoichiometric amount of base (3 equiv, $\text{pD} = 2.8$) to produce $[\text{Al}(\text{bped})]^+$ is added, both metal-complex and free-ligand resonances are observed in the ^1H NMR spectrum. At $\text{pD} = 3.5$, where $[\text{Al}(\text{bped})]^+$ should be the dominant species, the ^1H NMR spectrum is similar to that of $[\text{Ga}(\text{bped})]^+$, a series of broad resonances. At $\text{pD} = 4.6$, there should be a mixture of $[\text{Al}(\text{bped})]^+$ and $[\text{Al}(\text{bped})(\text{OH})]$. At this point, the hydrogen atom resonances have become sharper and two distinct pyridyl environments can be distinguished; however, the peaks between 3 and 4.5 ppm could not be assigned; the 18 resonances in the ^{13}C NMR spectrum suggest the presence of only one isomer, since $[\text{Al}(\text{bped})(\text{OH})]$ cannot have C_2 symmetry if a hydroxide is coordinated to the aluminum center and aluminum is 6-coordinate. A sharp singlet corresponding to the displacement of an acetato group was not observed in the ^1H NMR spectrum. It was expected that one of the pyridyl donors would be displaced by hydroxide, and this would result in a sharp singlet between 4 and 4.5 ppm corresponding to H(6), but this was not observed. A pyridyl arm may have been displaced, but the methylene hydrogen atoms remain diastereotopic. In the gallium system, rotation enabled H(8_a) and H(8_b) to have identical chemical shifts and appear as a singlet; the pyridylmethyl moiety is much larger than an acetato group and may suffer hindered rotation. Displacement of a pyridyl donor breaks one five-membered chelate ring. Alternately, a tertiary nitrogen may have been displaced, but this would result in the loss of three five-membered chelate rings; however loss of the chelate effect to coordinate stronger donors has preceded in aluminum chemistry.¹⁵ Displacement of a carboxylate is less likely, given the

affinity of Al(III) for oxygen donors and the lack of a singlet at about 3.4 ppm. Further addition of base ($\text{pD} = 8.9$) sharpens the ^1H NMR resonances of the complex, and resonances corresponding to free ligand are observed.

^{27}Al chemical shifts have been used to assign the coordination number of the aluminum ion in a given complex.^{48,55} Octahedral complexes resonate between -30 and $+50$ ppm, tetrahedral complexes resonate between 60 and 120 ppm, and 5-coordinate complexes are intermediate between octahedral and tetrahedral, while aluminum alkyls resonate even further downfield, from 100 to 300 ppm. The $[\text{Al}(\text{bped})]^+$ cation resonates at 40 ppm, which is at the extreme of chemical shifts reported for octahedral Al(III) complexes. The ^{27}Al spectra complement the potentiometric results, in that both $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ and $[\text{Al}(\text{OH})_4]^-$ are observed at the extremes of the pD range measured, in accordance with the stability constants reported. The ^{27}Al chemical shifts of aluminum complexes of edta, *trans*-1,2-diaminocyclohexanetetraacetate (cdta), and 1,3-propanediaminetetracetate (pdta) all occur between 40 and 41 ppm.⁵⁶ The aluminochromes, aluminum complexes of tris(hydroxamate) cyclic peptide ligands, also resonate at 41 ppm.⁵⁷ In the Al(III) study with edta, pdta, and cdta, it was noted that formation of a hydroxo complex resulted in an upfield shift of about 3 ppm. In the Al(III)–bped system, addition of base resulted in a downfield shift to 46 ppm ($\text{pD} = 4.6$) for a mixture of $[\text{Al}(\text{bped})]^+$ and $[\text{Al}(\text{bped})(\text{OH})]$. Full conversion to $[\text{Al}(\text{bped})(\text{OH})]$ ($\text{pD} = 8.9$) results in a 54 ppm ^{27}Al chemical shift. This may suggest that $[\text{Al}(\text{bped})(\text{OH})]$ formation also brings about a lowering in the coordination number of aluminum from 6 to 5. The aluminum–glycolate (ga) system has been studied,⁵⁸ and the ^{27}Al chemical shifts of mononuclear and oligomeric octahedral aluminum glycolates were determined. In addition, at $\text{pH} > 9$, two complexes, $[\text{Al}(\text{H}_{-1}\text{ga})_2]^-$ and $[\text{Al}(\text{H}_{-1}\text{ga})(\text{OH})_2]^-$, were tentatively assigned as having tetrahedral aluminum, on the basis of chemical shifts of 60.5 and 55.5 ppm, respectively. Chemical shifts in the octahedral and tetrahedral range were also seen in the aluminum–tartrate system⁵⁹ and in the aluminum–catechol system.⁶⁰ The downfield (tetrahedral) resonances were only observed above pH 9. While the chemical shift of $[\text{Al}(\text{bped})(\text{OH})]$ lies in the range of 5-coordinate aluminum, it should be noted that the vast majority of octahedral aluminum complexes studied by ^{27}Al NMR have the Al(III) ion coordinated by only oxygen donors or by polyamino polycarboxylates; no shifts of octahedral aluminum complexes containing pyridyl donors have been reported until now. Further ^{27}Al NMR studies on octahedral Al(III) with different donors would certainly be useful.

The stability constants listed in Table 6 are lower for the bped complexes than for the edta complexes with the same metal ion, with the exception of that for $[\text{Ga}(\text{bped})(\text{OH})]$, which is slightly higher than that for $[\text{Ga}(\text{edta})(\text{OH})]$. The differences between metal–bped and metal–edta stability constants are relatively small for gallium or indium. Since the pK_a 's are different, a comparison of edta and bped was made by calculating the speciation of 1:1:1 M(III)edtabped (2 mM) system from $\text{pH} = 2$ to $\text{pH} = 10$. In Figure S2 (Supporting

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Information), the percent metal bound to bped is plotted against pH. It is seen that replacing two carboxylates of edta with 2-pyridylmethyl units of bped results in a slightly better ligand for gallium, has little effect on indium (the metal is distributed almost equally), but has a detrimental effect on aluminum.

From a comparison of the complexing properties of bped among the three metal ions studied, the order is $\text{In(III)} > \text{Ga(III)} > \text{Al(III)}$. However, the high stability of the $[\text{Ga}(\text{bped})(\text{OH})]$ complex means that gallium competes with indium at higher pH, and this is the reason for the similarity in pM values at $\text{pH} = 7$ (Table 7).

A comparison of bped with the other ligands listed in Table 7 indicates that it is not as effective at binding gallium or indium at $\text{pH} = 7.4$ as are ligands containing thiolato or phenolato donors. This is a consequence of the lower basicity of the ligand, which makes it more effective at lower pH. An interesting case is the ligand ENDA-HP,⁹ which is identical to bped, but with the addition of a methyl group in the 3-position and a hydroxy group in the 6-position of the pyridine ring. ENDA-HP can potentially coordinate through either the pyridyl nitrogen or the anionic oxygen of a deprotonated hydroxy group on the aromatic ring. It was assumed that the ligand coordinates via an N_2O_4 donor set, since two protonated complexes were formed with protonation constants in the same range as those for pyridine derivatives. Unfortunately no structural or metal complex NMR results have been presented to delineate between the various isomers possible. The pM values for Ga(III) and In(III) with ENDA-HP (Table 7) are lower than those listed for bped, while the pM value for Ga(III)–ENDA-HP is much lower than that for Ga(III)–HBED. This suggests some sort of steric interference that makes the 3-methyl-6-hydroxypyridyl moiety less effective than either the 2-pyridylmethyl or 2-hydroxido-benzyl moieties at coordinating gallium when linked to an ethylenediaminediacetic acid framework.

Of the ligands (Chart 1) listed in Table 7, all have a charge of 4– or greater, with the exception of bped^{2-} . Although the binary metal–bped complexes are cationic, they still possess high thermodynamic stability. Lacoste *et al.*⁷ found the same behavior in their study of divalent metal–bped complexes and noted that $[\text{Cu}(\text{bped})]$ was over 1000 times more stable than $[\text{Cu}(\text{edta})]^{2-}$. The ability of a 2-pyridylmethyl group to substitute for a carboxylate without loss of thermodynamic stability in Ga(III) and In(III) complexes has important ramifications in the design of multidentate chelators for these metals. Ligands with an established high affinity for Ga(III) and In(III) such as EDDASS,^{10,11} EC,^{8,51} and HBED^{6,61} can be altered by substitution of one or both of the carboxylate groups to yield

neutral and cationic complexes respectively. This substitution should not have too deleterious an effect on the new gallium complexes and may actually improve the stability of the indium complexes. The work done on Sbbpen⁴ supports this.

Conclusions

The ligand bped^{2-} coordinates to Co(III) in a distorted octahedral fashion with *trans* carboxylato groups. With Al(III), Ga(III), and In(III) ions, complexes of the type $[\text{M}(\text{bped})]^+$ and $[\text{M}(\text{bped})(\text{OH})]$ are observed in aqueous solution. The indium complexes are believed to contain 7-coordinate In(III) with a bound water or hydroxo ligand in the seventh position. The gallium complexes are likely 6-coordinate. A protonated species $[\text{Ga}(\text{Hbped})]^{2+}$ was detected, and it exists in two or three isomeric forms with a noncoordinated carboxylic acid. The $[\text{Ga}(\text{bped})(\text{OH})]$ complex has a noncoordinated carboxylate. The donor types about the $[\text{Al}(\text{bped})(\text{OH})]$ complex could not be determined, but only one isomer is present. The carboxylato donors remain coordinated to Al(III), while ²⁷Al NMR spectroscopy suggests that the complex may be 5-coordinate.

The order of stability of the binary complexes, $[\text{M}(\text{bped})]^+$, is $\text{In(III)} > \text{Ga(III)} > \text{Al(III)}$. The gallium(III) ion circumvents its inability to be 7-coordinate by forming the most stable hydroxo complex of the three and displacing a carboxylate donor. Pyridyl donors can be substituted for carboxylate donors in multidentate ligands without significant loss of thermodynamic stability in the Ga(III) or In(III) complexes.

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Supporting Information Available: Figures of the variable pH-UV and NMR titrations of H_2bped and a plot of percent M(III) bound to bped as a function of pH calculated, as well as complete tables of crystallographic data, final atomic coordinates and equivalent isotropic thermal parameters, anisotropic thermal parameters, bond lengths, bond angles, torsion angles, and intermolecular contacts (24 pages). Ordering information is given on any current masthead page.

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