Cationic Lanthanide Complexes of *N,N′*-Bis(2-pyridylmethyl)ethylenediamine-*N,N′*-diacetic Acid (H₂bped)

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A series of monocationic lanthanide complexes containing the ligand *N,N′*-bis(2-pyridylmethyl)ethylenediamine-*N,N′*-diacetate(2−) (bped^{2-}) have been prepared and isolated as either the hexafluorophosphate or perchlorate salts. The complexes have been characterized by ^{1}H and ^{13}C NMR, +LSIMS, IR, and elemental analysis. Complex formation constants have been measured in water at 25 °C ($\mu = 0.16$ M (NaCl)). log K (Ln(bped)]$^+$) (log K([Ln(bped)(OH)])): Ln = La, 10.81 (0.06); Ln = Nd, 11.99 (1.45); Ln = Gd, 12.37 (2.10); Ln = Ho, 12.31 (3.00); Ln = Yb, 13.42 (4.43). The stability constants for [M(bped)]$^+$ increase from La(III) to Nd(III), plateau to Ho(III), and increase again to Yb(III), while the formation constants for [Ln(bped)(OH)] increase almost linearly with atomic number. The solution structures of the [Ln(bped)]$^+$ complexes have been probed by multinuclear NMR (^{1}H, ^{13}C, ^{17}O) studies, and these indicate only one isomer present in solution; this isomer has 2-fold symmetry and is rigid at 20 °C on the NMR time scale. ^{17}O NMR studies of the paramagnetic lanthanides indicate that the hydration number is 3, [Ln(bped)(H₂O)₃]$^+$, and that an overall coordination number of 9 is maintained across the lanthanide series.

Introduction

The aqueous chemistry of the lanthanide(III) ions (Ln(III)) is dominated by their oxophilicity.[1] In aqueous solution, saturated or unsaturated neutral nitrogen donors have a low affinity for lanthanides; however, when incorporated into a chelate ring containing an oxygen donor, the neutral nitrogen donor readily coordinates to lanthanides. There are numerous reports of stability constants for Ln(III) complexes of picolinate and amino carboxylate derivatives.[2] The neutral nitrogen donor is ubiquitous in macrocyclic lanthanide complexes through the use of polyaza macrocycles (*e.g.* cyclen), Schiff base condensation reactions to give imines, and 2,6-pyridinedicarboxaldehyde as a macrocyclic building block.[3−6]

Thompson *et al.*[7] compared the difference in stability constant between N-substituted iminodiacetic acids and iminodiacetic acid (ida). Their results are summarized in Figure 1. The added stability imparted by the fourth donor was approximately the same for each lanthanide. The value for amide substitution was taken from Paul-Roth and Raymond,[8] who compared the stabilities of Gd(III) dtpa-bm and dtpa-bma complexes (see Chart 1 for abbreviations). The neutral donors which give the greatest increase in stability are alcoholic oxygen, pyridyl nitrogen, and amide oxygen.

The use of Gd(III) complexes in magnetic resonance imaging (MRI) has spawned many studies on lanthanide complexes of polyamino carboxylates. The two most studied ligand frameworks are based on dota[9] and dtpa[10] (Chart 1). However, these
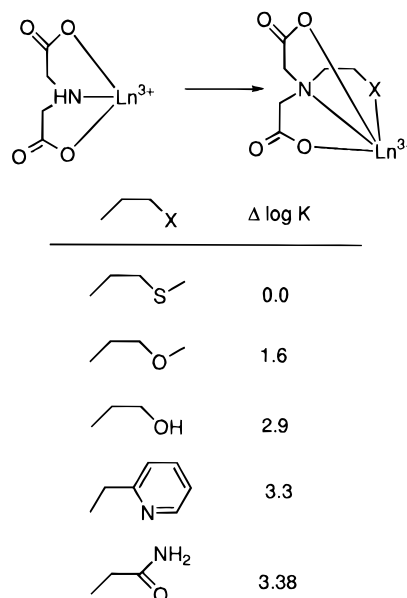

Figure 1. Comparison of neutral donors for Ln(III) chelation after Thompson *et al.*[7] The amide value is taken from Paul-Roth and Raymond.[8]

ligands form anionic and dianionic complexes, respectively, with gadolinium. In order to reduce osmolality and concomitant osmotic shock upon intravenous administration, one of the carboxylato donors in dota has been replaced with an alcohol or an amide, to yield an overall neutral Gd(III) complex. The same approach has been taken with dtpa, where two carboxylato donors are replaced with two amide (dtpa-bma) or 2-pyridyl-methyl (dtpa-bp) moieties.

Although the lanthanide coordination chemistry with alcohol and amide derivatives of dota and dtpa has been well studied, less is known about the 2-methylpridyl derivative. Cacheris *et*
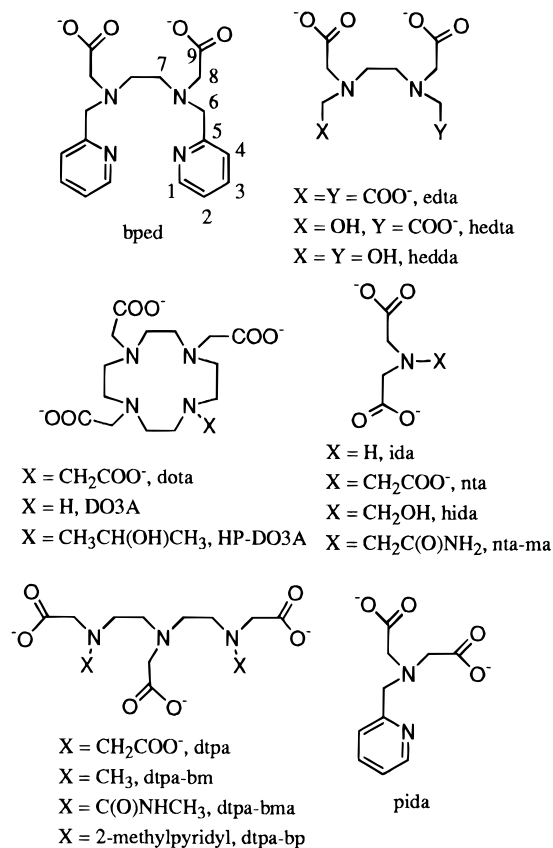
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Chart 1

bped

X = Y = COO⁻, edta
X = OH, Y = COO⁻, hedta
X = Y = OH, hedda

X = CH$_2$COO⁻, dota
X = H, DO3A
X = CH$_3$CH(OH)CH$_3$, HP-DO3A

X = H, ida
X = CH$_2$COO⁻, nta
X = CH$_2$OH, hida
X = CH$_2$C(O)NH$_2$, nta-ma

X = CH$_2$COO⁻, dtpa
X = CH$_3$, dtpa-bm
X = C(O)NHCH$_3$, dtpa-bma
X = 2-methylpyridyl, dtpa-bp

pida

al.[11] showed that while the Gd(III) complexes of dtpa-bma and dtpa-bp have similar formation constants, dtpa-bp had a much lower selectivity for Gd(III) over Zn(II), which in turn led to a higher toxicity in rats because of Gd(III) displacement by endogenous Zn(II). Presumably, this negative result has precluded the use of the 2-pyridylmethyl group in other ligands for Gd(III) MRI applications.

Because of the established affinity of the 2-pyridylmethyl moiety for Ln(III) (see Figure 1), the bis(2-pyridylmethyl) derivative of edta (bped) was synthesized. Stability constants for some Ln−bped complexes have been determined to support the previous evidence regarding the replacement of an acetato group by a 2-pyridylmethyl group. Multinuclear (^{1}H, ^{13}C, ^{17}O) NMR studies have been carried out in order to examine further the effect of changing donor atom types with regard to hydration number, number of isomers present, and rigidity of the complexes.

Experimental Section

Materials. H$_2$bped·2HCl was prepared as described previously.[12] Sodium perchlorate, sodium hexafluorophosphate, sodium deuterioxide (NaOD, 40%), deuterium chloride (DCl, 12 M), and the lanthanide atomic absorption standards were obtained from Aldrich. Hydrated lanthanide nitrates and chlorides were purchased from Alfa. Deuterium oxide (D$_2$O) was purchased from Isotec. All were used without further purification.

Instrumentation. ^{1}H NMR (200 and 300 MHz) spectra were referenced to external DSS and recorded on Bruker AC-200E and Varian XL300 spectrometers, respectively. ^{17}O NMR (40.7 MHz, referenced to external H$_2$O) and ^{13}C NMR (75.5 MHz, referenced to external DSS) spectra were recorded on the Varian XL300 spectrometer.

The ^{17}O NMR spectral parameters have been previously detailed.[13] Mass spectra were obtained with a Kratos Concept II H32Q (Cs⁺, LSIMS) instrument. Infrared spectra were obtained as KBr disks in the range 4000−400 cm^{-1} on an ATI Mattson 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[14] was used to relate the acid concentration of the NMR samples (pD) to the potentiometric results (pH).

Synthesis of Metal Complexes. *Caution! Perchlorate salts of metal complexes are potentially explosive and should be handled with care and only in small amounts.* The synthetic procedure for the [Ln-(bped)]X (X = ClO$_4$, PF$_6$) complexes was the same in all cases. Only one representative example is given for each counterion.

[Lu(bped)]PF$_6$. To a solution of H$_2$bped·2HCl (150 mg, 0.35 mmol)) in 25 mL of methanol was added 164 mg of Lu(NO$_3$)$_3$·6H$_2$O (0.35 mmol), followed by 115 mg of sodium acetate (1.40 mmol, 4 equiv) to yield a colorless solution. The solution was filtered into a 50 mL Erlenmeyer flask, and sodium hexafluorophosphate (60 mg, 0.35 mmol) was added with stirring. The resulting colorless solution was filtered into a 30 mL beaker and allowed to stand. A white precipitate formed after the solution was allowed to stand overnight at room temperature. The precipitate was collected on a Büchner funnel and dried *in vacuo* overnight at 60 °C to yield 118 mg (50%). Anal. Calc (found) for [LuC$_{18}$H$_{20}$N$_4$O$_4$]PF$_6$: C, 31.97 (31.90); H, 2.98 (3.21); N, 8.28 (8.21). MS (+LSIMS): m/z = 531 ([M]⁺, [LuC$_{18}$H$_{20}$N$_4$O$_4$]⁺). IR (cm^{-1}, KBr disk): 1599 (b, vs, $\nu_{C=O}$), 1447 (s), 1421 (s), 1308 (m), 1262 (m), 1090 (m), 1019 (m), 934 (m), 843 (vs, ν_{P-F}), 766 (s), 558 (s, ν_{P-F}).

[Sm(bped)]ClO$_4$. To a solution of H$_2$bped·2HCl (83 mg, 0.19 mmol)) in 25 mL of methanol was added 72 mg of SmCl$_3$·6H$_2$O (0.19 mmol), followed by 63 mg of sodium acetate (0.77 mmol, 4 equiv) to yield a colorless solution. To this solution was added dropwise a sodium perchlorate solution in methanol (30 mg, 0.25 mmol, in 1 mL) while a white precipitate gradually formed. After the addition was complete, the white suspension was stirred for 30 min and cooled to 4 °C for 1 h. The off-white solid was collected on a Hirsch funnel, washed with acetone (5 mL), and dried overnight *in vacuo*. Yield: 60 mg (49%). Anal. Calc (found) for [SmC$_{18}$H$_{20}$N$_4$O$_4$]ClO$_4$·CH$_3$OH: C, 35.75 (36.13); H, 3.79 (3.83); N, 8.78 (8.87). MS (+LSIMS): m/z = 508 ([M]⁺, [SmC$_{18}$H$_{20}$N$_4$O$_4$]⁺). IR (cm^{-1}, KBr disk): 1604 (b, vs, $\nu_{C=O}$), 1444 (s), 1410 (s), 1326 (m), 1310 (m), 1121, 1108 (s, ν_{Cl-O}), 1088 (s), 1013 (m), 926 (m), 769 (s), 624 (s).

[Dy(bped)]PF$_6$. Yield: 145 mg (66%). Anal. Calc (found) for [DyC$_{18}$H$_{20}$N$_4$O$_4$]PF$_6$·0.5H$_2$O: C, 32.13 (32.26); H, 3.15 (3.33); N, 8.33 (8.07). MS (+LSIMS): m/z = 520 ([M]⁺, [DyC$_{18}$H$_{20}$N$_4$O$_4$]⁺). IR (cm^{-1}, KBr disk): 1591 (b, vs, $\nu_{C=O}$), 1446 (s), 1422 (s), 1309 (m), 1263 (m), 1086 (m), 1019 (m), 914 (m), 842 (vs, ν_{P-F}), 764 (s), 558 (s, ν_{P-F}).

[Gd(bped)]ClO$_4$. Yield: 35 mg (28%). Anal. Calc (found) for [GdC$_{18}$H$_{20}$N$_4$O$_4$]ClO$_4$·CH$_3$OH: C, 35.37 (35.57); H, 3.75 (3.79); N, 8.68 (8.86). MS (+LSIMS): m/z = 514 ([M]⁺, [GdC$_{18}$H$_{20}$N$_4$O$_4$]⁺). IR (cm^{-1}, KBr disk): 1605 (b, vs, $\nu_{C=O}$), 1445 (s), 1408 (s), 1326 (m), 1310 (m), 1121, 1108 (s, ν_{Cl-O}), 1086 (s), 1014 (m), 926 (m), 768 (s), 624 (s).

[La(bped)]ClO$_4$. Yield: 85 mg (60%). Anal. Calc (found) for [LaC$_{18}$H$_{20}$N$_4$O$_4$]ClO$_4$·CH$_3$OH: C, 36.41 (36.28); H, 3.50 (3.86); N, 8.94 (8.90). MS (+LSIMS): m/z = 495 ([M]⁺, [LaC$_{18}$H$_{20}$N$_4$O$_4$]⁺). IR (cm^{-1}, KBr disk): 1602 (b, vs, $\nu_{C=O}$), 1443 (s), 1410 (s), 1329 (m), 1120, 1107 (s, ν_{Cl-O}), 1087 (s), 1011 (m), 929 (m), 767 (s), 624 (s).

Multinuclear NMR Studies. The hydration number of [Dy(bped)]⁺ was determined by the method of Alpoim *et al.*[15] An equimolar (35 mM) solution of Dy^{3+} and H$_2$bped·2HCl was prepared, and a stoichiometric amount (4 equiv) of standardized NaOH was added so that the complex was fully formed. Five solutions of differing dysprosium concentrations were prepared by serial dilution of the stock solution. The ^{17}O NMR spectra were recorded at 20 °C.

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Solutions of [Ln(bped)]$^+$ in D_2O were prepared by adding an equimolar amount of the appropriate lanthanide salt to a D_2O solution of Na_2bped. The solutions were approximately 90 mM at pD ~4.5. The ^1H, ^{13}C, and ^{17}O NMR spectra were recorded at 20 °C. The ^1H and ^{13}C NMR spectra of [La(bped)]$^+$ and [Lu(bped)]$^+$ were identical to those obtained by dissolving solid samples of [Ln(bped)]PF$_6$ (Ln = La, Lu).

Potentiometric Equilibrium Measurements. The equilibrium constants were determined by potentiometric methods described previously.[13] The ionic strength was fixed at 0.16 M (NaCl), and the solutions were maintained at 25 °C. Argon, which had been passed through 10% NaOH, was bubbled through the solutions to exclude CO_2.

The ligand was checked for purity by NMR and elemental analysis before titration. Titrations were also employed to verify the molecular weight obtained by elemental analysis. The 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 Gran's method.[16]

The ratios of ligand to metal used were in the range 1:2 < L:M < 1.2:1, and concentrations were in the range 1.0−2.5 mM. At least four titrations were performed on the Ln(III)−H$_2$bped equilibria, each titration consisting of about 100 data points. The metal−ligand solutions were titrated over the pH range 2−11. Complexation was usually rapid (1−3 min per point to give a stable pH reading); however, caution was taken to ensure that no trace hydrolysis or precipitation was occurring by monitoring up to 30 min for pH drift.

The data were refined using the program BEST.[17] The stepwise deprotonation constants for H$_2$bped·2HCl at 0.16 M NaCl and 25 °C are ~1.5, 3.11(2), 5.53(3), and 8.67(8).[12] The hydrolysis constants used were taken from Baes and Mesmer.[18] The data could be explained satisfactorily only by the presence of two species, [Ln(bped)]$^+$ and [Ln(bped)(OH)].

Results

Metal Complexes. The lanthanide complexes of bped^{2-} were all prepared in a similar manner. These cations, [Ln(bped)]$^+$, were isolated from methanol as either the hexafluorophosphate or perchlorate salts. Better yields were obtained for the heavier lanthanides with hexafluorophosphate, while the lighter lanthanide complexes were better isolated as perchlorate salts. Lanthanide nitrate or chloride salts could be used to prepare the Gd−Lu complexes, but only chloride salts were used for the lighter lanthanides; otherwise, the complexes were isolated as nonstoichiometric salts of the added counterion and nitrate. The use of ethanol as a solvent or heating of the reaction mixture led to the inclusion of inorganic salts. The metal complexes prepared in methanol gave acceptable elemental analyses, with the perchlorates being isolated as methanol solvates. Positive LSIMS mass spectral studies showed strong parent ion peaks for [Ln(bped)]$^+$ with the expected isotopic patterns. The infrared spectra were similar for all the [Ln(bped)]$^+$X complexes with strong bands typical of noncoordinated hexafluorophosphate (842, 558 cm^{-1})[19] or perchlorate (1120, 1108 cm^{-1}).[20] There was a small splitting in the perchlorate Cl−O stretch, which may indicate some weakly bonding interaction, although this splitting was much less than that of coordinated perchlorate.[20] The carboxylato asymmetric stretch underwent a considerable bathochromic shift upon coordination, from 1728 cm^{-1} (H$_2$bped·2HCl) to about 1600 cm^{-1} ([Ln(bped)]$^+$). The complexes did not readily dissolve in water or DMSO; however, upon standing or heating, they
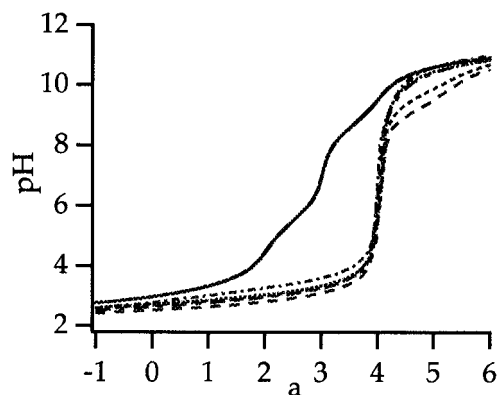
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Figure 2. Titration curves (pH vs *a*; *a* = mol of OH$^-$/mol of bped) for H$_2$bped·2HCl (—) and equimolar (2 mM) bped−Ln(III) solutions: La(III) (-·-·); Nd(III) (···); Gd(III) (—·—·); Ho(III) (- - -), Yb-(III) (− − −).

Table 1. Logarithms of the Formation Constants for Complexation of Ln(III) with bped^{2-} (Abbreviated L) at 25 °C and μ = 0.16 M (NaCl)

Ln(III)	[ML]/[M][L]	[ML(OH)][H]/[M][L]	[ML]/[ML(OH)][H]
La(III)	10.81(4)	0.06(8)	10.75(4)
Nd(III)	11.99(2)	1.45(8)	10.45(8)
Gd(III)	12.37(3)	2.10(3)	10.25(3)
Ho(III)	12.31(2)	3.00(2)	9.31(2)
Yb(III)	13.42(8)	4.43(4)	8.98(4)

did dissolve and were quite soluble (>0.2 M), suggesting that the solid state structures may be polymeric.

Potentiometric Titrations. Titration curves for H$_2$bped· 2HCl in the presence of La(III), Nd(III), Gd(III), Ho(III), and Yb(III) are shown in Figure 2. The 1:1 curves display an inflection at *a* (mol of OH$^-$/mol of dbped^{2-}) = 4, as expected for the formation of a [Ln(bped)]$^+$ complex. The curves diverge beyond *a* = 4, with a second buffer region occurring at decreasing pH as the lanthanide series is traversed, indicating the formation of a [Ln(bped)(OH)] complex which becomes increasingly stable with increasing atomic number. The formation constants of the Ln−bped complexes are listed in Table 1, and are displayed graphically in Figure S1 (Supporting Information).

Solution NMR Studies. The ^1H and ^{13}C NMR spectra of [Ln(bped)]$^+$ (Tables 2 and 3, respectively) were assigned on the basis of COSY spectra and by comparison of the chemical shifts with those determined for [In(bped)]PF$_6$ and [Co(bped)]-PF$_6$.[12] ^1H and ^{13}C NMR spectra of the [Ln(bped)]$^+$ complexes indicate the presence of only one isomer, and this isomer has 2-fold symmetry in solution. Only 9 of a possible 18 ^{13}C NMR resonances and 10 out of a possible 20 ^1H NMR resonances are observed for each complex. The splitting of H(6), H(7), and H(8) into three AB patterns suggests that all six donor atoms are coordinated and that the complex is rigid on the NMR time scale. As the ionic radius decreases from La(III) to Y(III) to Lu(III), some marked changes occur in the ^1H NMR spectra. The chemical shift separation between H(6$_a$) and H(6$_b$) decreases from 0.50 ppm (La) to 0.10 ppm (Y) to 0.08 ppm (Lu). The same trend is observed for the chemical shift separation between H(7$_a$) and H(7$_b$): from 0.45 ppm (La) to 0.22 ppm (Y) to 0.12 ppm (Lu). However H(8$_a$) and H(8$_b$) remain separated by 0.19 ppm for all three. Of the paramagnetic lanthanides, the only spectra assignable were those of [Sm(bped)]$^+$. The other lanthanide complexes exhibited broad resonances in their ^1H NMR spectra, resonances which were shifted to both higher and lower frequency.

Figure 3 shows a plot of the dysprosium-induced ^{17}O NMR shift (Dy IS) of H$_2$O versus concentration of [Dy(bped)]$^+$. The

Table 2. ^{1}H (300 MHz) Spectral Data^{a,b} for H₂bped^c and Its La(III), Sm(III), Y(III), and Lu(III) Complexes^d in D₂O

	H₂bped	[La(bped)]⁺	[Sm(bped)]⁺	[Y(bped)]⁺	[Lu(bped)]⁺
H(1)	8.59 (4.4)	8.66 (5.1)	8.39 (3.4)	8.71 (4.6)	8.78 (5.1)
H(2)	7.76 (4.4, 7.7)	7.48 (5.1, 7.8)	7.23 (3.4, 7.5)	7.48 (4.6, 7.8)	7.57 (5.1, 7.1)
H(3)	8.28 (7.7, 7.8)	7.95 (7.8, 7.5)	7.62 (7.5, 7.8)	7.95 (7.8, 7.5)	8.05 (7.1, 8.2)
H(4)	7.85 (7.8)	7.49 (7.5)	6.90 (7.8)	7.47 (7.5)	7.55 (8.2)
H(6ₐ)	4.43	4.33 (−15.0)	4.15 (−17.2)	4.20 (−15.3)	4.24 (−15.5)
H(6ᵦ)		3.83 (−15.0)	3.34 (−17.2)	4.10 (−15.3)	4.16 (−15.5)
H(7ₐ)	3.34	2.84 (−10.4)	1.46 (−9.3)	3.04 (−10.1)	3.18 (−10.2)
H(7ᵦ)		2.39 (−10.4)	1.28 (−9.3)	2.82 (−10.1)	3.06 (−10.2)
H(8ₐ)	3.67	3.30 (−16.8)	3.13 (−14.6)	3.51 (−17.3)	3.57 (−17.3)
H(8ᵦ)		3.11 (−16.8)	3.03 (−14.6)	3.32 (−17.3)	3.31 (−17.3)

^{a} For labeling, see Chart 1. ^{b} Numbers in parentheses refer to coupling in Hz (H(1), $^3J_{12}$; H(2), $^3J_{12}$ and $^3J_{23}$; H(3), $^3J_{23}$ and $^3J_{34}$; H(4), $^3J_{34}$; H(6), $^2J_{ab}$; H(7), $^2J_{ab}$; H(8), $^2J_{ab}$. ^{c} pD = 2.3. ^{d} pD = 4.6.

Table 3. ^{13}C (75.5 MHz) Spectral Data^a for H₂bped^b and Its La(III), Sm(III), Y(III), and Lu(III) Complexes^c in D₂O

	H₂bped	[La(bped)]⁺	[Sm(bped)]⁺	[Y(bped)]⁺	[Lu(bped)]⁺
C(1)	147.52	151.45	151.74	152.00	152.30
C(2)	129.65	127.12	125.71	126.72	127.10
C(3)	146.53	142.37	142.15	143.02	143.87
C(4)	128.91	126.58	125.05	126.72	126.95
C(5)	152.94	159.50	158.01	159.38	160.43
C(6)	58.90	64.89	67.00	66.20	64.72
C(7)	50.03	54.40	57.65	59.48	60.98
C(8)	57.40	63.00	66.87	64.52	63.95
C(9)	175.18	182.58	188.92	182.46	182.81

^{a} For labeling, see Chart 1. ^{b} pD = 2.3. ^{c} pD = 4.6.
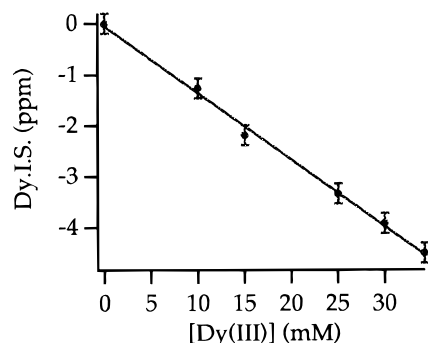
Figure 3. Plot of dysprosium-induced ^{17}O NMR chemical shift (Dy IS) of H₂^{17}O vs [Dy(III)] for [Dy(bped)]⁺ at 20 °C and pH 4.5.

slope of the line is proportional to the hydration number of the complex.[15,21] For Dy³⁺$_{aq}$, the slope is −358 ppm/M.[13] The hydration number of Dy³⁺$_{aq}$ has been shown to be 8,[22,23] which yields a slope of 45 ppm/M per bound water molecule. The slope of the line in Figure 3 is −131 ± 3 ppm/M (r^2 = 0.998), which corresponds to a hydration number of 2.93 ± 0.07.

The shift, Δ, induced at a nucleus of a ligand binding to a Ln(III) cation can be expressed as the sum of the diamagnetic shift (Δ_d), the contact shift (Δ_c), the pseudocontact shift (Δ_p), and the shift due to the bulk magnetic susceptibility (Δ_χ), eq 1.

$$\Delta = \Delta_d + \Delta_c + \Delta_p + \Delta_\chi \quad (1)$$

The diamagnetic shift is usually relatively small, and this has been estimated using the shift of the La(III) complex. Since the magnetic moment of each Ln(III) ion is relatively constant, the bulk magnetic susceptibility shift can be estimated from eq

2,[24] which applies to a superconducting solenoid, where C is

$$\Delta_\chi = 4\pi C(\mu_{eff}/2.84)^2/3T \quad (2)$$

the concentration (mM) of Ln(III), μ_{eff} is the effective magnetic moment for Ln(III), and T is the temperature (K). Calculated μ_{eff} values were taken from Figgis.[25]

The contact and pseudocontact shifts can be expressed by eq 3,[24] where Δ_c and Δ_p are each expressed as the product of two

$$\Delta' = \Delta - (\Delta_d + \Delta_\chi) = \Delta_c + \Delta_p = \langle S_z \rangle F + C^D G \quad (3)$$

terms. The first term ($\langle S_z \rangle$ or C^D) is characteristic of the lanthanide but independent of the ligand, while the second term (F or G) is characteristic of the ligand in question but independent of the Ln(III) cation. Values for the lanthanide-dependent contact term, $\langle S_z \rangle$, and pseudocontact term, C^D, have been calculated.[26–30] Equation 3 can be separated into two linear forms, eqs 4 and 5. Although, both (4) and (5) are

$$\Delta'/C^D = F(\langle S_z \rangle/C^D) + G \quad (4)$$

$$\Delta'/\langle S_z \rangle = G(C^D/\langle S_z \rangle) + F \quad (5)$$

mathematically identical, Reilley *et al.*[31] have advocated the use of eq 4 when $F \gg G$ (and eq 5 when $G \gg F$), since the dependence on theoretical C^D (or $\langle S_z \rangle$) will be minimized by a small intercept. In Figure 4 (top), the lanthanide-induced chemical shifts (LIS) for the ^{17}O nucleus in D₂O (after correcting for Δ_d (−366 ppm for La) and Δ_χ) are listed in Table 4 and have been plotted according to eq 4 and according to eq 5 in Figure 4 (bottom). By the procedure of Peters *et al.*,[32] the shifts were extrapolated to [Ln(bped)⁺] = [D₂O]; the values for C^D and $\langle S_z \rangle$ were taken from ref 21. Plotting the LIS data according to eq 4 gives $F = -245 \pm 5$, $G = -9.2 \pm 4$, $r^2 = 0.999$; eq 5 gives $F = -268 \pm 13$, $G = -13.4 \pm 3$, $r^2 = 0.83$.

Discussion

The metal complexes were formed readily by mixing H₂bped·2HCl with the appropriate lanthanide salt in methanol in the

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Table 4. Lanthanide-Induced ^{17}O NMR Chemical Shifts of D$_2$O for [Ln(bped)]$^+$ at pD = 4.6 at 20 °C

Ln(III)	[Ln(III)] (mM)	LIS (ppm)	
		a	*b*
La	92.0	−0.67	0
Ce	92.4	−0.14	+288
Pr	90.8	+1.03	+934
Nd	92.1	+1.42	+1135
Eu	85.4	−5.10	−2618
Gd	92.7	−14.27	−7331
Tb	89.9	−16.21	−8650
Dy	92.1	−13.79	−7119
Ho	91.9	−10.94	−5587
Er	90.5	−9.08	−4653
Tm	91.5	−6.20	−3021
Yb	91.0	−2.76	−1150

^{a} LIS measured at [Ln(III)] given in column 2. ^{b} LIS extrapolated to [Ln(III)] = [D$_2$O] and corrected for the diamagnetic contribution by +366 ppm (the shift for La(III)).
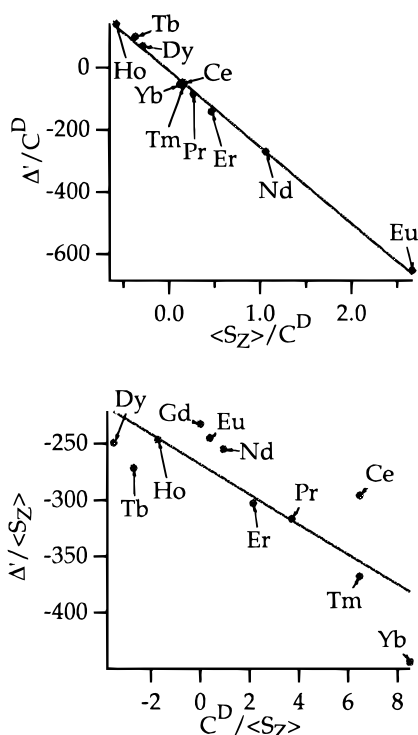
Figure 4. Plots of Δ'/C^D vs $\langle S_z \rangle/C^D$ (top) and $\Delta'/\langle S_z \rangle$ vs $C^D/\langle S_z \rangle$ (bottom).

presence of sodium acetate. As was the case with the Al(III), Ga(III), In(III), and Co(III) complexes,[12] the lanthanide complexes could be isolated by the addition of the appropriate anion, either hexafluorophosphate or perchlorate. No crystalline samples could be prepared despite trying a variety of solvents (methanol, ethanol, 2-propanol, and water), solvent mixtures (addition of acetone, diethyl ether, and acetonitrile), and counterions (chloride, bromide, iodide, tetrafluoroborate, perchlorate, sulfate, and nitrate). The infrared spectra of the lanthanide complexes were superimposable across the series, suggesting similar solid state structures. The asymmetric C=O stretch shifted upon coordination from 1728 cm^{-1} (H$_2$bped·2HCl) to 1690 cm^{-1} ([Al(bped)]$^+$)[12] to 1631 cm^{-1} ([In-(bped)]$^+$)[12] to 1600 cm^{-1} ([Ln(bped)]$^+$). The +LSIMS spectra gave strong peaks for [Ln(bped)]$^+$ in the correct isotopic pattern, as expected for monocationic complexes.

The potentiometric measurements substantiate the stoichiometry of these complexes. The titration curves show a buffering effect up to 4 equiv (*a* = 4) of hydroxide. The stability constants (Table 1, Figure S1 (bottom)) increase from

La(III) to Nd(III) and then plateau at Gd(III) and Ho(III), before increasing again to Yb(III). This is a common effect in Ln(III) solution chemistry. Although the formation constant for a lanthanide complex with a given ligand usually increases across the series, this increase is rarely monotonic; plateaus and decreases often appear somewhere in the lanthanide series in a plot of free energy of formation versus atomic number.[33] As may be expected from a hydrated ternary monocationic [La-(bped)(H$_2$O)$_3$]$^+$ complex, further addition of hydroxide leads to the formation of a quaternary [Ln(bped)(H$_2$O)$_2$(OH)] complex. The stability of this complex increases across the lanthanide series from La(III) to Yb(III).

In Figure S1 (bottom), the stability constants[2] for La(III), Nd(III), Gd(III), Ho(III), and Yb(III) for edda^{2-}, bped^{2-}, and edta^{2-} are plotted against inverse ionic radius (coordination number 9). The formation constants for [Ln(bped)]$^+$ are intermediate between those for [Ln(edda)]$^+$ and [Ln(edta)]$^-$, which is to be expected on the basis of the results presented in Figure 1. The mean change in stability constant upon adding two 2-pyridylmethyl groups to edda^{2-} to give bped^{2-} is $\Delta \log K = 4.1 \pm 0.3$; replacement of the 2-pyridylmethyl groups in bped^{2-} with two acetato groups in edta^{4-} gives $\Delta \log K = 5.3 \pm 0.8$. The same effect is seen on going from ida to pida ($\Delta \log K = 2.1 \pm 0.1$) to nta ($\Delta \log K = 2.6 \pm 0.1$) except the magnitude of the effect is halved.

Thompson *et al.*[7] estimated the stability of certain donors (Figure 1) by considering a series of N-substituted iminodiacetic acid derivatives. They plotted log K_1(Ln) versus the second deprotonation constant of the ligand for a series of nonbonding substituents (hydrogen, methyl, phenyl, and benzyl) and obtained a straight line. The substituted ligands in Figure 1 were treated in the same manner, and the deviation from this line was used to infer the added stability from the substituent. This allows for the differences in basicities of the varying ligands. There are few available data on lanthanide complexes of N-substituted edda derivatives with which to make an analogous comparison. To account for differing ligand basicity, equilibrium 6 can be

$$H_3L^+ + Ln^{3+} \rightleftharpoons LnL^+ + 3H^+ \quad K_6 \qquad (6)$$
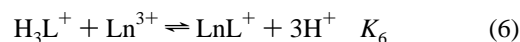
considered, where L = edda^{2-} or bped^{2-}. Equation 6 corrects for competition with H$^+$. For this equilibrium, the difference in Ln(III) stability between bped^{2-} and edda^{2-} is $\Delta \log K_6 = 5.3 \pm 0.3$. This gives an added stability of 2.65 ± 0.15 log units per 2-pyridylmethyl group. The same approach used in a comparison of edda and hedda[34] for La(III) (see Chart 1) gives $\Delta \log K_6 = 5.0$, or 2.5 log units per 2-hydroxyethyl group. Although these numbers are lower than those given in Figure 1, the trend is the same.

In Figure S1 (top), the hydrolytic tendencies of [Ln(bped)]$^+$ and [Ln(hedta)] are compared. Plotting the pK_a of bound water versus inverse ionic radius shows that both complexes become more acidic as the lanthanide ionic radius decreases. Somewhat surprising is the fact that neutral [Ln(hedta)] is more acidic than cationic [Ln(bped)]$^+$.

The Dy IS of H$_2^{17}$O (Figure 3) is indicative of a complex containing three bound water molecules, *i.e.* [Dy(bped)(H$_2$O)$_3$]$^+$. In order to determine whether or not the coordination number of [Ln(bped)]$^+$ was constant across the lanthanide series, *i.e.* [Ln(bped)(H$_2$O)$_3$]$^+$, the LIS of D$_2^{17}$O was determined for the lanthanide series (excluding Pm). The ^{17}O NMR shifts were

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greater than 75% contact in nature for all the lanthanides. It was expected that if the hydration number changed across the series, there would be a break in a plot of Δ'/C^D versus $\langle S_z \rangle / C^D$. The linearity of this plot (Figure 4, top), suggests that the hydration number is constant across the series. It has been shown[35] that a coordinated ^{17}O nucleus has an F value of -70 ± 11 at 346 K. Since the ^{17}O NMR shifts are predominantly contact and since F is linearly proportional to $1/T$,[26] $F = -83$ per coordinated ^{17}O at 20 °C. The value of F determined from eq 4 was -245 ± 5. Dividing this by -83 yields 2.95 ± 0.06 coordinated D$_2$O molecules, which is in excellent agreement with the value obtained from the Dy IS experiment, 2.93 ± 0.07. Separating the data in Figure 4 into heavy (Tb–Yb) and light (Ce–Eu) lanthanides does not yield a better result; in fact, the nature of the scatter is such that $|F|$ is slightly larger for the heavier lanthanides. Peters and co-workers[32] have shown that, for the lanthanide–glycolate (ga) system, the 1:3 complex exists as [Ln(ga)$_3$(D$_2$O)$_3$], and this complex has a constant hydration number across the lanthanide series. They obtained a value for F of 231 (converted to 20 °C), in good agreement with the result for [Ln(bped)(D$_2$O)$_3$]$^+$.

In the Ln(III)–edta system, it is believed that there is a hydration/dehydration equilibrium (eq 7) occurring across the series in the vicinity of Eu(III). Two species are observed in

$$[Ln(edta)(H_2O)_x]^- \rightleftharpoons [Ln(edta)(H_2O)_{x-1}]^- + H_2O \quad (7)$$
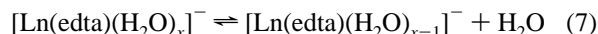
the UV–vis spectrum of [Sm(edta)]$^-$: [Eu(edta)]$^-$ and [Gd(edta)]$^-$.[36] This has been interpreted in terms of a hydration equilibrium where one water molecule is displaced (eq 7).[37,38] Ots[39,40] has given thermodynamic arguments for a hydration equilibrium. Luminescence spectroscopy studies have given hydration numbers of 2.5[41] and 3.5[42] for [Eu(edta)]$^-$ and 2.4[43] and 2.6[44] for [Tb(edta)]$^-$. A Dy IS study of [Dy(edta)]$^-$ gave a slope of -90 ppm/M, which corresponds to two bound water molecules.[15] X-ray crystal structures of M^I[Ln(edta)]·nH$_2$O show water coordination numbers of 3 for Ln = La,[45] Pr,[46] Sm,[46] Gd,[46] Dy,[47] and Ho,[48] and 2 for Ln = Yb.[47] This suggests that the hydration number changes from 3 to 2 across the series (*i.e.*, $x = 3$ in eq 7).

Bryden *et al.* reported lanthanide-induced ^{17}O NMR shifts of D$_2$O for [Ln(edta)]$^-$ complexes.[49] After extrapolation of the

shifts to [Ln] = [D$_2$O] and correction for the temperature difference, $F = 206$ for the lighter lanthanides (Pr–Eu) and $F = 163$ for the heavier lanthanides (Tb–Yb). This gives a hydration number of 2.5 for the lighter lanthanides and 2.0 for the heavier lanthanides. These values support the argument for a change in coordination number and also illustrate the difference in hydration number between [Ln(edta)]$^-$ and [Ln(bped)]$^+$.

The ^{1}H and ^{13}C spectra indicate that the [Ln(bped)]$^+$ complexes have 2-fold symmetry in aqueous solution. All six donor atoms are coordinated, since H(6), H(7), and H(8) are split into AB quartets in the lanthanide complexes. This also suggests that the complexes are rigid at 20 °C on the NMR time scale. As the ionic radius decreases from La^{3+} (1.216 Å, CN = 9)[50] to Y^{3+} (1.075 CN = 9, intermediate between Dy^{3+} and Ho^{3+})[50] to Lu^{3+} (1.032, CN = 9),[50] there is no change in the number of peaks in the ^{1}H NMR spectrum, but the chemical shifts vary (Table 2). The largest effect is the chemical shift difference between H(6$_a$) and H(6$_b$). These two resonances are well separated for [La(bped)]$^+$ at 0.50 ppm; however, as the ions become smaller, this shift separation drops to 0.10 ppm for Y(III) and 0.08 ppm for Lu(III). A similar effect is observed for H(7$_a$) and H(7$_b$). Since the coordination number does not change across the series, the chelate ring angles must adjust to the smaller size of the ion.

The coordination number of the Ln(III) aquo ions is known to change from 9 to 8 across the lanthanide series.[51] The complexes, [Ln(bped)(H$_2$O)$_3$]$^+$, have a constant hydration number of 3. The formation of [Ln(bped)(H$_2$O)$_3$]$^+$ involves three factors: the dehydration of Ln$^{3+}_{aq}$, which loses six waters for the early lanthanides and five waters for the late lanthanides; the increasing charge to radius ratio as the lanthanides become heavier; and any changing steric effects within the bped^{2-} ligand as the lanthanide is changed. This combination is responsible for the plateau in stability constant in the middle of the lanthanide series. However, the formation of [Ln(bped)(OH)(H$_2$O)$_n$] should depend primarily on the acidity of the ion, and this is what is observed.

Conclusions

The neutral pyridine donor is an effective ligating group for the lanthanide(III) ions and offers an alternative to the neutral amide or neutral alcoholic oxygen donor in the design of stable lanthanide complexes. The Ln(III) complexes formed with bped^{2-} are intermediate in stability between [Ln(edda)]$^+$ and [Ln(edta)]$^-$. In contrast to [Ln(edta)]$^-$, which undergoes a change in hydration number across the lanthanide series from 3 to 2, [Ln(bped)]$^+$ has a constant hydration number of 3. The acidity of bound water is strongly dependent on the lanthanide in question; the pK_a of bound water varies by 2 orders of magnitude from La(III) to Yb(III).

Supporting Information Available: Figure S1, showing plots of the pK_a of bound water and log K_{ML} vs inverse ionic radius for [Ln(bped)]$^+$ (1 page). See any current masthead page for ordering information.

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