Inorg. Chem. **2001,** *40,* 3734−3738

Lanthanide Chemistry with Bis{[bis(carboxymethyl)amino]methyl}phosphinate: What Does an Extra Phosphinate Group Do to EDTA?

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Received December 18, 2000

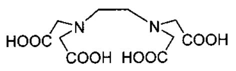
H_5XT (bis{[bis(carboxymethyl)amino]methyl}phosphinic acid) is an $EDTA^{4-}$-like ligand containing an extra phosphinate group. $[Co^{II}(XT)]^{3-}$, $[Co^{III}(XT)]^{2-}$, and a series of $[Ln(XT)]^{2-}$ complexes have been prepared. The phosphinate group is not coordinated in the Co complexes but is bound in the lanthanide complexes. Solid state and solution behaviors of Ln−XT species are consistent: both monoprotonated and nonprotonated species have been found. Protonation of the metal complex does not lead to dissociation of a carboxylate; rather, the proton distributes around the molecular ion. The pM values of Ln−XT are comparable to those of Ln−EDTA but are higher than those of Ln−TMDTA. The inclusion of a phosphinate eases the selectivity of an EDTA-type ligand for late lanthanides.

Introduction

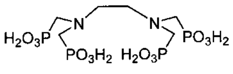
Lanthanides are important in the field of medicinal chemistry.[1,2] The most successful examples are Gd complexes, which are widely used commercially as contrast agents in magnetic resonance imaging (MRI).[3,4] A ^{153}Sm complex is commercially available for palliation of bone pain, and complexes of a number of metalloradionuclides are under clinical and preclinical investigation as radiotherapeutic agents.[5,6] Because both the free ligands and the metal ions are toxic, and the complexes are not, these drugs have to be thermodynamically stable and/or kinetically inert. Ligand design for these complexes, therefore, typically employs a polyamine backbone incorporating anchoring groups such as carboxylate, phosphonate, and (to a lesser extent) amides. The benchmark for these ligands is DTPA; EDTA complexes are often cited for comparison but are not stable enough under the challenging conditions found in vivo.[4]

In a continuing quest for new chelating ligands,[7−13] we rediscovered an old ligand whose sheer resemblance to EDTA demands attention. As part of a series of amine phosphinate compounds, XT was first synthesized by Maier,[14] and was reported again while our study was under way.[15] Amine phosphinates are generally less coordinating at neutral pH than are amine carboxylates or amine phosphonates because of the low basicity of the phosphinates.[16,17] They are, however, derivatives of secondary phosphines, and as such they can act as linkers, rather than only as terminal ligating groups, a limitation of carboxylates and phosphonates. Interestingly, XT incorporates an easily prepared $R_2NCH_2P(O)(OH)CH_2NR_2$ motif. While amines are poor donors for lanthanides by themselves, with carboxylate anchors they contribute to the overall stability of the complexes.[18] By the same argument, we are interested in how a phosphinate flanked between amines would contribute to the binding of a well-studied amine carboxylate system.

In this study, the chemistry of XT with the lanthanides is reported. Two questions are essential in this study: whether or how the phosphinate group coordinates, and how it contributes to the overall stability of the system. Co chemistry was studied for comparison. Some interesting protonation behavior of the lanthanide complexes was also noted.



H_4EDTA



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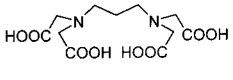

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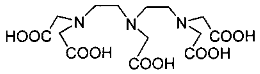

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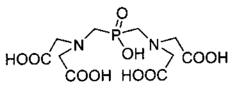

H_5XT

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10.1021/ic0014179 CCC: $20.00

Experimental Section

Materials. Lanthanide starting materials, lanthanide atomic absorption standards, iminodiacetic acid, phosphinic acid (50%), NaOD (40%), DCl (12 M), and formaldehyde (37%) were obtained from Aldrich, Alfa, or Fisher Chemicals and used without further purification. NaOD and DCl solutions were used to adjust the pD of the NMR solution. pD values were calculated by adding 0.4 to the pH meter reading.[19]

Instrumentation. IR (infrared) spectra were recorded as KBr disks in the range 4000−500 cm^{-1} on a Mattson Galaxy Series 5000 FTIR spectrophotometer. Mass spectra (Cs^+, LSIMS (liquid secondary ion mass spectrometry)) were obtained on a Kratos Concept II H32Q with thioglycerol as the matrix. C, H, and N analyses were performed by Mr. Peter Borda in this department. All ^1H NMR spectra were recorded on a Bruker AC-200E spectrometer at 200 MHz and are reported as δ in parts per million downfield from TMS. All $^{31}P\ \{^1H\}$ NMR spectra were recorded on the same instrument at 81 MHz and are reported as δ in parts per million downfield from external phosphoric acid.

$H_5XT\cdot HCl\cdot 0.5H_2O$. This synthesis is slightly modified from literature preparations.[14,15] Iminodiacetic acid (2.7 g, 20 mmol) and a 50% solution of H_3PO_2 (1.3 g, 10 mmol) were combined in 6 M HCl (4.0 mL) and heated to reflux. An aqueous solution (37%) of formaldehyde (3.2 g, 40 mmol) was added dropwise to the mixture and the reflux continued overnight. A white precipitate formed when the reaction mixture was cooled to room temperature. This precipitate was collected by filtration, washed with methanol, and dried under vacuum. The filtrate was concentrated, and a second crop of precipitate was recovered by filtration. This material was subsequently redissolved in a minimum amount of 6 M HCl, and the product was precipitated with methanol and similarly collected. Anal. Calcd (found) for $C_{10}H_{19}ClN_2O_{10.5}P$: C, 29.90 (29.91); H, 4.77 (4.96); N, 6.97 (6.73). ^{31}P NMR (D_2O): δ 17. ^1H NMR (D_2O): δ 4.2 (8H, s, NCH_2COO), 3.6 (4H, d, NCH_2P).

$K_3[Co(XT)]\cdot 2H_2O$. $H_5XT\cdot HCl\cdot 0.5H_2O$ (0.157 g, 0.392 mmol) and $CoCl_2\cdot 6H_2O$ (0.110 g, 0.401 mmol) were dissolved in water (10 mL)/methanol (10 mL). A KOH solution (1 M) was added dropwise in order to neutralize the solution (pH paper). More methanol was then added to the solution to precipitate the pink product, which was filtered out and dried under vacuum to yield 0.20 g (91%). Single crystals were grown by diffusing methanol (∼1 mL) into an aqueous solution (∼1 mL) of the product (10 mg). Anal. Calcd (found) for $C_{10}H_{16}CoK_3N_2O_{12}P$: C, 21.32 (21.24); H, 2.86 (3.03); N, 4.97 (4.79). Mass spectrum (−LSIMS): $m/z = 450$ ($[KCo(XTH)]^-$), 488 ($[K_2Co(XT)]^-$). IR (cm^{-1}): $\nu_{CO\ asym} = 1613\ cm^{-1}$, $\nu_{CO\ sym} = 1395$ and 1383 cm^{-1}, $\nu_{PO\ asym} = 1164\ cm^{-1}$ $\nu_{PO\ sym} = 1042\ cm^{-1}$.

$K_2[Co(XT)]$ for NMR Study. $K_3[Co(XT)]\cdot 2H_2O$ (50 mg) was dissolved in H_2O (10 mL), and charcoal was suspended in the solution. A few drops of H_2O_2 were added, and the suspension was stirred overnight. The solution was filtered and concentrated; the purple residue was dissolved in water and precipitated with methanol. The precipitate was collected and dried under vacuum. $^{31}P\ \{^1H\}$ NMR (D_2O): δ 12. ^1H NMR (D_2O): δ 4.5 (2H, d, 19 Hz), 4.0 (2H, d, 17 Hz), 3.7 (2H, d, 19 Hz), 3.6 (2H, d, 16 Hz), 3.0 (4H, 2 sets of overlapping doublets).

General Synthesis of $M_2[Ln(XT)](H_2O)_x$ (M = K, Na). $H_5XT\cdot HCl\cdot 0.5H_2O$ (40 mg, 0.10 mmol) and $LnCl_3\cdot xH_2O$ (Ln = La, Ho) or $Ln(NO_3)_3\cdot xH_2O$ (Ln = La, Sm, Gd, Lu) (0.10 mmol) were dissolved in 2 mL of water. NaOH (1 M, in the case of $LaCl_3\cdot xH_2O$) or 1 M KOH (for the rest of the experiments) was added dropwise until the solution pH was 6−8 (pH paper). The solution was then concentrated. To the residue were added a few drops of water; then methanol (3−5 mL) and acetone (5−10 mL) were added in order to precipitate the product, which was isolated by centrifugation. The residue was dissolved in methanol, precipitated with acetone, and centrifuged again. The product was dried under vacuum. The IR spectra of all the lanthanide complexes, including the monoprotonated ones, were almost superimposable, some with additional ν_{NO3} absorptions. Representative IR bands (cm^{-1}): $\nu_{CO\ asym} = 1593\ cm^{-1}$, $\nu_{CO\ sym} = 1412$ and 1347 cm^{-1}, $\nu_{PO\ asym} = 1160\ cm^{-1}$, $\nu_{PO\ sym} = 1046\ cm^{-1}$.

$Na_2[La(XT)](H_2O)_3$. Anal. Calcd (found) for $C_{10}H_{18}LaNa_2N_2O_{13}P$: C, 20.35 (20.61); H, 3.07 (3.34); N, 4.75 (4.60). $^{31}P\{^1H\}$ (D_2O) NMR: δ 44, 39.

$K_{2.5}[Sm(XT)](H_2O)_5(NO_3)_{0.5}$. Anal. Calcd (found) for $C_{10}H_{22}K_{2.5}N_{2.5}O_{16.5}PSm$: C, 16.67 (16.52); H, 3.08 (3.18); N, 4.86 (4.69). IR (additional peak): $\nu_{NO3free} = 1385\ cm^{-1}$. $^{31}P\{^1H\}$ (D_2O) NMR: δ 57 (from pD 2.3−10.0).

$K_2[Gd(XT)](H_2O)_4$. Anal. Calcd (found) for $C_{10}H_{20}GdK_2N_2O_{14}P$: C, 18.23 (18.56); H, 3.06 (3.51); N, 4.25 (4.13).

$Ca[Ho(XT)](H_2O)_7$. The synthesis is the same as for the other Ln complexes except that excess $CaCl_2$ was added to the reaction mixture. Anal. Calcd (found) for $C_{10}H_{26}CaHoN_2O_{17}P$: C, 17.60 (17.37); H, 3.84 (3.70); N, 4.11 (3.93).

$K_3[Lu(XT)](NO_3)(H_2O)_3$. Anal. Calcd (found) for $C_{10}H_{18}K_3LuN_3O_{16}P$: C, 15.81 (15.75); H, 2.39 (2.21); N, 5.53 (5.36). IR (additional peak): $\nu_{NO3free} = 1385\ cm^{-1}$. $^{31}P\{^1H\}$ (D_2O) NMR: δ 44 (pD 2.3−10.0).

General Synthesis of $K[Ln(HXT)]\cdot xH_2O$. $H_5XT\cdot HCl\cdot 0.5H_2O$ (40 mg, 0.10 mmol) and $Ln(NO_3)_3\cdot xH_2O$ (Ln = Nd, Gd, Lu) or $DyCl_3\cdot xH_2O$ (0.10 mmol in any case) were dissolved in 2 mL of water. KOH solution (1 M) was added dropwise until the solution pH was 6−8 (pH paper). Concentrated hydrochloric acid was then added to the neutral aqueous solution until pH = 2−3. Methanol (3−5 mL) was then added in order to precipitate the product, which was isolated by centrifugation. The residue was washed with methanol and dried under vacuum.

$K[La(HXT)](H_2O)_{2.5}$. Anal. Calcd (found) for $C_{10}H_{18}KLaN_2O_{12.5}P$: C, 20.88 (21.06); H, 3.15 (3.27); N, 4.87 (4.54).

$K[Nd(HXT)](H_2O)_{2.5}$. Anal. Calcd (found) for $C_{10}H_{18}KN_2NdO_{12.5}P$: C, 20.69 (20.86); H, 3.12 (3.47); N, 4.83 (4.66).

$K[Gd(HXT)](H_2O)_5$. Anal. Calcd (found) for $C_{10}H_{23}GdKN_2O_{15}P$: C, 18.81 (18.66); H, 3.63 (3.60); N, 4.39 (4.28).

$K[Dy(HXT)](H_2O)_5$. Anal. Calcd (found) for $C_{10}H_{23}DyKN_2O_{15}P$: C, 18.65 (18.76); H, 3.60 (3.43); N, 4.35 (4.08).

$Na[Lu(HXT)](H_2O)_3(CH_3COOH)$. To a methanolic solution (5 mL) of $Lu(OOCCH_3)_3(H_2O)_4$ (42 mg, 10 mmol) and $H_5XT\cdot HCl$ (40 mg, 0.10 mmol) was added sodium acetate (50 mg, 0.61 mmol). Acetone was added liberally to this solution in order to precipitate the product. The precipitate was isolated by centrifugation. The solid residue was redissolved in methanol and precipitated out with acetone addition, and the mixture was centrifuged again to deposit the product, which was dried under vacuum. Anal. Calcd (found) for $C_{12}H_{23}LuN_2NaO_{15}P$: C, 21.70 (22.01); H, 3.49 (3.55); N, 4.22 (4.23). ^{31}H (D_2O) NMR: δ in addition to the overlapped multiplet from the complex, 2.2 (s, CH_3COOH).

Potentiometric Equilibrium Measurements. Experiments were performed with a Fisher Acumet 950 digital pH meter or an Orion EA 920 digital pH meter, and a Metrohm Dosimat automatic buret (Dosimat 665), both interfaced with a PC. A Metrohm 6.0222.100 (combination) electrode was used. All pH readings were calibrated daily by a titration with HCl. A Gran plot[20] was made using this data set, and the working slope and intercept of a plot of millivolts (measured) vs pH (calculated) were determined and applied to the measurements of that day (pH = $-\log[H^+]$ herein). The NaOH concentration (0.1−0.2 M) was determined by titrating against potassium hydrogen phthalate. The temperature of the solutions was kept constant at 25.0 ± 0.1 °C by a Julabo circulating water bath. The ionic strength was fixed at 0.16 M NaCl. Each batch of ligand stock solution was titrated to determine its concentration. Lanthanide solutions were prepared by appropriate dilutions of atomic absorption standard solutions (Aldrich). The final solution under study typically contained 0.5−2 mM of each of the ligand and the metal, with a slight excess (0.1−0.3 times) of the ligand. Three to 10 titrations were performed for each metal−ligand system and for the free ligand; data were collected in the range $2 < pH < 11$. Titrations with 2:1 and 0.5:1 ligand to lanthanum ratios were performed, but only 1:1 species were found at the concentrations under study. Equilibration times between 1 and 7.7 min were used to ensure that equilibrium was achieved.

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Table 1. Selected Crystallographic Data for $K_3[(Co^{II}(XT)]\cdot 2H_2O$

formula	$C_{10}H_{16}CoK_3N_2O_{12}P$
fw	563.44
cryst syst	orthorhombic
space group	$P2_12_12$
a, Å	11.8931(5)
b, Å	8.4428(11)
c, Å	9.6761(4)
V, $Å^3$	971.6(2)
Z	2
ρ_{calc}, g/cm^3	1.926
F(000)	570.00
temp, °C	-93 ± 1
radiation	Mo Kα ($\lambda = 0.71069$ Å)
μ, cm^{-1}	16.74
transm factors	0.7308−1.000
$2\theta_{max}$	60.1°
total reflns	8942
unique reflns	1603
observations with $I > 3\sigma(I)$	2002
no. of variables	165
R; R_w[a]	0.036; 0.040

[a] $R = \sum||F_o^2| - |F_c^2||/\sum|F_o^2|$, $I > 3\sigma(I)$; $R_w = (\sum(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)^{1/2}$.

The titration data were processed with SUPERQUAD.[21] At least 50% of the metal was not bound to the ligand at the starting pH. Only ML and MHL species were found in the range 2 < pH < 11, and inclusion of other species worsened the fit. The errors reported represent the discrepancies among the same metal titrations, which are significantly larger than the error of the fitting.

X-ray Crystallographic Analysis. A pink crystal of $K_3[Co(XT)]\cdot 2H_2O$ was mounted on a glass fiber for data collections on a Rigaku/ADSC CCD area detector at −93 °C (Table 1) to a maximum 2θ value of 60.1°. A sweep of data was done using φ oscillations from 0.0° to 190.0° at $\chi = -90°$, and a second sweep was performed using ω oscillations between −23.0° and 18.0° at $\chi = -90°$. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[22] and expanded using Fourier techniques.[23] The Co anion has crystallographic C_2 symmetry. K(2) also lies on a 2-fold axis. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were refined isotropically.

Results and Discussion

XT forms complexes with a number of lanthanides. They are synthesized by mixing the respective metal salt and $H_5XT\cdot HCl$, adjusting the pH with a base, and precipitating the complex with organic solvents. The series has been characterized by EA, IR spectroscopy, and, in the case of La, Sm, and Lu, ^{31}P NMR spectroscopy.

Solid Ln−XT complexes have been isolated in both deprotonated and monoprotonated forms, consistent with the findings in solution (vide infra). The formation of the monoprotonated samples is unmistakable; either they showed drastically different solvation behavior from the respective deprotonated species (La, Nb, and Gd complexes of XT are hygroscopic when deprotonated but sparingly soluble in water when protonated) or, when they dissolved in water, they buffered the solution at low pH (Dy and Lu complexes). Protonated EDTA complexes with divalent and trivalent metals have been studied extensively and shown to exist both in solution and in the solid state.[24−26] In most reported examples one carboxylate was protonated and a noncoordinating COOH group was evident in the IR spectra. The IR spectra of all the Ln−XT complexes, protonated or not, are virtually identical, indicating a close structural relationship across the series. Lacking an X-ray structure, one can only speculate that one of the carboxylates coordinates in a protonated form, and the proton is stabilized by extensive hydrogen bonding. Similar [Ln(HEDTA)] complexes have been reported for late lanthanides, and protonated carboxylate coordination was postulated from IR evidence.[27] A vanadium complex (amavadin) containing a bond between a neutral carboxylic acid and V has been structurally characterized.[28]

The numbers of included solvents or salts in these solid materials (from EA) seems to be random. The difference in these solid state complexes lies in the additional coordination sites on the metal and how they interact with each other, the solvent, and small ligands, i.e., the packing of the solid material. While structurally characterized Ln−EDTA complexes have been shown to be di- or trihydrates,[29] monohydrated and nonhydrated species form from extensive drying.[27] Thus drying affects the packing of the solid material, and, consequently, the coordination behavior of the complex changes. With a potentially hexadentate ligand (so that the metal coordination sphere is unsaturated) it has been shown crystallographically that the formation of mono-, di-, and trinuclear species is very sensitive to the size of the lanthanide atom.[30] This result was rationalized on the basis of the difference of the coordination number among the lanthanides and the resultant packing of the crystals. Following this argument, one expects that Ln−XT complexes are possibly oligomeric in the solid state. The lack of detectable ionized species in the LSIMS experiments is consistent with this speculation. Also, in the ^{31}P NMR experiments of the La−XT and Lu−XT complexes, extra peaks appear when the solutions are concentrated. (Concentration dependence is a good indication that the species is more than mononuclear.)

Suitable crystals of Ln−XT for X-ray diffraction experiments were not forthcoming, hence various transition metals were tried. $H_5XT\cdot HCl$ reacts with $CoCl_2\cdot H_2O$ in the presence of KOH to form $K_3[Co(XT)]\cdot 2H_2O$, which was characterized by EA, IR spectroscopy, LSIMS, and X-ray crystallography. Single crystals of $K_3[Co(XT)]\cdot 2H_2O$ were grown by diffusing methanol into an aqueous solution of the complex. The complex anion is C_2 symmetric, with the ligand coordinating to the Co center via two N and four carboxylate O atoms (Figure 1). The phosphinate is not coordinated. The coordination geometry is distorted octahedral with N(1)N(1)*O(3)O(3)* forming a rectangular equatorial plane and O(1) and O(1)* occupying the axial positions. The bond lengths are comparable to those in similar Co^{II} species (Table 2).[24,31]

When $K_3[Co(XT)]\cdot 2H_2O$ is oxidized by H_2O_2, a Co^{III}−XT complex is obtained. The ^{31}P and ^{1}H NMR experiments showed that the ligand coordinates to the Co^{III} in a fashion similar to that found in the Co^{II} analogue. One resonance at 12 ppm was seen in the ^{31}P NMR spectrum. Coordination normally causes

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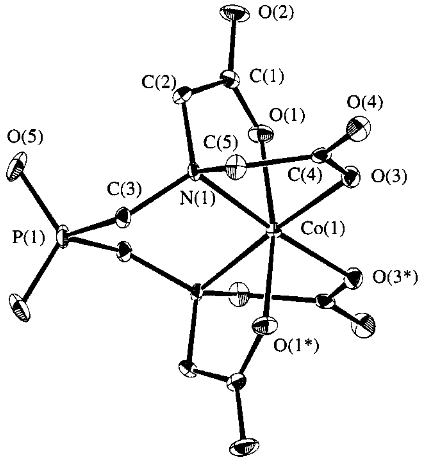

Figure 1. ORTEP drawing of the $[Co^{II}(XT)]^{3-}$ anion in $K_3[Co(XT)]\cdot 2H_2O$. Thermal ellipsoids for the non-hydrogen atoms are drawn at the 33% probability level.

Table 2. Selected Bond Lengths (Å) and Angles (deg) in the $[Co(XT)]^{3-}$ Anion in $K_3[(Co^{II}(XT)]\cdot 2H_2O$

Co−O(1)	2.051(15)	Co−N(1)	2.165(2)
Co−O(3)	2.081(2)		
N(1)−Co−O(3)	80.46(2)	O(1)−Co−O(3)	92.45(6)
O(3)−Co−O(3)[a]	98.09(9)	O(1)−Co−O(3)[a]	94.63(6)
N(1)−Co−N(1)[a]	101.24(9)	O(1)−Co−N(1)[a]	91.42(7)
O(1)−Co−O(1)[a]	169.19(10)		

[a] Symmetry operation −*x*, 1 − *y*, *z*.

a significant downfield shift in phosphinate ^{31}P NMR signals: this 12 ppm signal indicates that, most likely, the phosphinate does not coordinate to the metal. The ^{1}H NMR spectrum showed six sets of doublets, and coupling constants are consistent with geminal coupling, implying that the complex has reduced symmetry; most likely the C_2 symmetry of the $[Co^{II}XT]^{3-}$ is retained in its Co^{III} analogue.

The ^{31}P NMR spectra of the Lu and Sm complexes showed single resonances at 44 and 57 ppm, respectively, indicating a single species in each solution. The drastic difference in ^{31}P chemical shifts between the Co^{III} and the lanthanide complexes infers that the phosphinate in Ln−XT is coordinated and that in $[Co(XT)]^{2-}$ it is not. The ^{31}P chemical shift difference between Lu−XT and Sm−XT is attributed to differences in magnetic properties of the respective metals, Sm being paramagnetic. The ^{1}H NMR spectrum showed sharp but overlapped signals with clear geminal coupling, corresponding to a rigid solution structure. The ^{1}H NMR resonances are more numerous and more spread out in the Sm−XT complex, and they are not as simple as those in Co^{III}−XT, evincing that an asymmetric complex exists in solution. Two species are observed in the ^{31}P NMR spectrum of the La−XT complex, regardless of pD.

Corresponding to the solid state result, the protonated species were observed at low pD. The single ^{31}P NMR signal remains unchanged, but the ^{1}H NMR signals broadened at pD 2.4, indicating that the aminophosphinate portion of the molecule is hardly affected by the protonation but that the carboxylates are affected, consistent with the expected protonation of the latter.

The stepwise protonation constants (pK_n, eq 1) of XT are remarkably similar to those of EDTA, less so to those of TMDTA (Table 3).

$$H_{n-1}XT + H = H_nXT \qquad K_n \tag{1}$$

Table 3. Stepwise Protonation Constants (25 °C) for XT and Related Ligands

	XT[a]	XT[b]	EDTA[c]	EDTA[d]	TMDTA[d]
log K_1	9.27(5)	10.27	9.52	10.37	10.27
log K_2	6.56(6)	6.76	6.14	6.19	7.91
log K_3	2.84(13)	2.86	2.88	2.87	2.67
log K_4	2.32(18)	2.26	2.11	2.26	2.00

[a] μ = 0.16 M NaCl, this study. [b] μ = 0.1 M $[(CH_3)_4N]Cl$.[32] [c] μ = 0.12 M NaCl.[35] [d] μ = 0.1 M $[(CH_3)_4N]Cl$.[36]

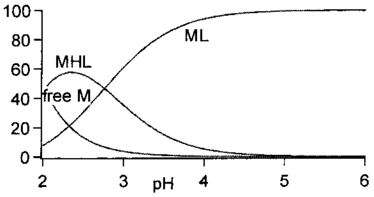

Figure 2. Speciation diagram of the Gd−XT system ([Gd] = [XT] = 1 mM, *T* = 25 °C, μ = 0.16 M NaCl).

Table 4. Logarithms of the Formation Constants for Complexation of Ln^{III} with XT (*T* = 25 °C, μ = 0.16 M NaCl)

	log K_{MHL}	log K_{ML}	log K_a	log β_{MHL}
La	7.9(3)	13.0(3)	4.14(6)	17.14(22)
Nd	8.64(15)	14.64(11)	3.27(2)	17.91(12)
Sm	9.30(11)	15.60(15)	2.97(5)	18.57(8)
Gd	9.22(16)	15.73(25)	2.76(6)	18.48(15)
Ho	8.8(4)	15.8(5)	2.2(5)	18.1(3)
Yb	8.73(20)	15.56(14)	2.44(12)	18.01(18)

(Charges of the species are omitted for simplicity in the equations and pertinent discussion.) The ionic strength of the solutions was fixed with 0.16 M NaCl in this study, but EDTA and a number of polyaminocarboxylate ligands are known to bind sodium weakly at basic pH; thus the protonation constants reported herein should be viewed as apparent, or conditional, constants specifically pertinent to isotonic conditions. Protonation constants of this ligand and its metal binding stability constants (with divalent metal cations) were published when our study was under way.[32] The experiments of Varga et al. were performed in tetramethylammonium chloride, and the first proton association constant was about 10 times higher than ours.[32] This difference was also noted in the EDTA system.[33]

The complex formation constants of a few lanthanides with XT (K_{ML}) were determined potentiometrically. The following equilibria (eqs 2 and 3) were included to describe the system.

$$M + HL \rightleftharpoons MHL \qquad K_{MHL} \tag{2}$$

$$M + L \rightleftharpoons ML \qquad K_{ML} \tag{3}$$

Inherent in the above two equations are the K_a of MHL (eq 4) and the conventional β_{MHL} (eq 5).

$$ML + H \rightleftharpoons MHL \qquad K_a \tag{4}$$

$$M + H + L \rightleftharpoons MHL \qquad \beta_{MHL} \tag{5}$$

Consistent with solid state and NMR evidence, MHL complexes were found at low pH and were completely deprotonated to ML species by pH 4.5 (Figure 2, Table 4).

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(32) Varga, T. R.; Király, R.; Brücher, E. *ACH*—*Models Chem.* **1999**, *136*, 431.

(33) Kumar, K.; Jin, T.; Wang, X.; Desreux, J. F.; Tweedle, M. F. *Inorg. Chem.* **1994**, *33*, 3823.

Interestingly, log K_a values of these MHL species decrease across the series, with an exception at Ho. (The latter data set has larger error which invalidates the comparison.) The metal complex becomes a better acid going across the series from La to Yb. Along with the solid state IR evidence that there is no free carboxylic acid donor group in the MHL species, this result points to a curious behavior of these protonated complexes. Instead of dissociation of one carboxylate group upon protonation, all carboxylate coordinations seem to remain intact, with the proton distributed around the complex, probably close to the carboxylates. In other words, the complex, rather than a single group, acts as an acid.

It is difficult to compare the formation constants of the Ln−XT complexes with those of other systems because of the aforementioned Na−XT association. The stability constants determined will be slightly lower than the actual values; however, pM, (eq 6) an often quoted conditional quantity, is less biased in this regard.[34] The free metal (aqua or hydroxo species) concentration depends on the pH, as well as on metal ion and ligand concentrations; thus pM nullifies the inherent dependence of K on the basicity of the ligands in potentiometric determinations, and is often used to compare the thermodynamic stability of different chelates at a fixed pH. The expression of basicity correction intrinsic in pM is $K_{\rm eff}$ (eq 7), which is often used on its own in simple systems.[4]

$$\mathrm{pM} = -\log [\mathrm{M}_{\rm free}] \qquad (6)$$

$$K_{\rm eff} = K/(1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{H}^+]^2 + ... + K_1K_2 ... \mathrm{K}_n [\mathrm{H}^+]^n) \qquad (7)$$

Sodium binds to XT at high pH, hence only the two basic pK_a values differ, depending on whether the measurements were done with or without Na^+. The lanthanides form complexes under acidic conditions in a potentiometric determination: the ML complexes are completely formed by pH 4. It is reasonable to assume that the two events (formation of La and Na complexes) are independent of each other. Thus one can view that the two systems are different mostly because of the pK_a's of the ligand, which is corrected for by $K_{\rm eff}$ or pM. For example, log $K_{\rm Al-EDTA}$ values are 15.3 and 16.5, determined in 0.12 M NaCl[35] and in 0.10 M $[(\mathrm{CH_3})_4\mathrm{N}]\mathrm{Cl}$,[36] respectively, and their pM's are 14.2 and 14.5. To completely reconcile studies done in different media, one has to take deviations caused by sodium binding into account (log $K_{\rm Na-EDTA} = 1.86$, eq 8).[36] As long as its contribution remains very small compared with the basicity correction, as is the case when the set pH value is significantly smaller than the first pK_a of the ligand, pM values can be compared. The advantage of pM is that it reconciles most of the existing studies done in different supporting electrolytes ($[(\mathrm{CH_3})_4\mathrm{N}]\mathrm{Cl}$, KCl, and NaCl at similar ionic strengths), but because this comparison relies heavily on the aforementioned assumptions, it has to be treated cautiously.

$$K_{\rm eff} = K/(1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{H}^+]^2 + ... + K_1K_2 ... \mathrm{K}_n [\mathrm{H}^+]^n + K_{\rm NaL}[\mathrm{Na}^+]) \qquad (8)$$

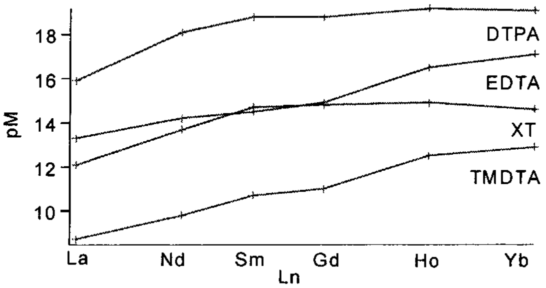

Figure 3. Trends in pM values ([L] = 10^{-5} M, [M] = 10^{-6} M, pH = 7.4, T = 25 °C; DTPA, EDTA, and TMDTA complexes, $\mu = 0.10$ M $[(\mathrm{CH_3})_4\mathrm{N}]\mathrm{Cl}$;[36] XT complexes, $\mu = 0.16$ M NaCl).

Comparison of the pM values of the Gd−XT system with those of the Gd−EDTA and Gd−TMDTA systems shows that the Gd−XT complex is on a par with the Gd−EDTA complex but a few orders of magnitude more stable than the Gd−TMDTA complex. Thus the addition of a phosphinate group has a similar effect on the stability of the Gd complexes as going from a six-membered chelate ring to a five-membered ring (Figure 3).

Although their origins are open to much debate, stability trends for lanthanides with linear polyaminocarboxylate ligands fall into two types:[33,37] (1) the formation constants increase significantly with increasing charge to ionic radius ratios as found in EDTA-type ligands; (2) the stability constants increase, reach a plateau, then slightly decline, as with DTPA. The Ln−XT system follows the second trend (Figure 3). Compared to EDTA, XT binds more selectively to early lanthanides, similarly to middle ones, and less strongly to the late ones. TMDTA, however, is a weaker ligand for Ln than XT. The fact that EDTA and TMDTA have similar trends in pM across the series but XT−Ln shows a different binding profile demonstrates that the phosphinate in XT is significant.

Conclusions

This study probes the chemistry of Ln with XT, specifically, the role of an extra phosphinate in the coordination behavior of an EDTA-like ligand. The phosphinate coordinates to the lanthanides, but not to $\mathrm{Co^{II}}$ or $\mathrm{Co^{III}}$ in their respective complexes. It contributes to the overall stability of the ligand, but not by much. It has a more profound effect on stability trends in the lanthanide series than on the stabilities of the individual complexes: the phosphinate eases the selectivity of an EDTA-type ligand to late lanthanides. Solid state and solution behaviors of Ln−XT species are consistent: both monoprotonated and nonprotonated species have been found. Protonation of the metal complex does not lead to dissociation of a carboxylate; rather, the proton distributes around the molecular ion.

Acknowledgment. The authors gratefully acknowledge DuPont Pharmaceuticals for its support, the Natural Sciences and Engineering Research Council for operating grants, and Mr. Peter Borda for elemental analysis.

Supporting Information Available: X-ray crystallographic files in CIF format for structure $\mathrm{K_3[Co(XT)]\cdot 2H_2O}$. This material is available free of charge via the Internet at http://pubs.acs.org.

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