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Study of Structural Influence on the Formation Constants of Lanthanide–Polyamino Polycarboxylate Complexes

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This contribution describes the synthesis of three polyamino polycarboxylic acids (thiobis(ethylenenitrilo)tetraacetic acid, TEDTA; *N,N*-bis(2-aminoethyl)aniline-*N',N',N'',N''*-tetraacetic acid, BEATA; *N,N*-bis(2-aminoethyl)ethylamine-*N',N',N'',N''*-tetraacetic acid, DEATA) and reports the stability constant sequences of chelates formed by their anions with the lanthanide elements, as well as the consecutive anion protonation constants (at $I = 0.10$ and 25 °C). The data are compared to corresponding values for a number of analogous polyamino polycarboxylate species derived from tervalent lanthanons.

Introduction

Recently, we reported the formation constants of chelates of the lanthanides with 1,5-diaminopentane-*N,N,N',N'*-tetraacetic acid (PMDTA),[1] (bis(3-aminopropyl) ether)-*N,N,N',N'*-tetraacetic acid (BPETA), and (bis(3-(bis(carboxymethyl)amino)propyl)methylammonio)acetate (BCPA).[2] At about the same time, several research groups[3-5] discussed amino carboxylate structures that affect the formation constants of lanthanide complexes.

We are interested in lanthanide-ion-selective reagents for two reasons. From a theoretical point of view, a better understanding of coordination properties of lanthanide complexes is needed. From a practical point of view, one would like to synthesize new proficient reagents for separating lanthanides from actinides, which also may have wide analytical and/or pharmaceutical applications.

Lanthanide elements commonly form 3+ ions that exhibit the "lanthanide contraction" (i.e., cationic radius decreases gradually and rather uniformly with increasing atomic number). The coordination numbers of such cations are reported to be 8 or 9 in aqueous solution.[6-8] Spedding's group,[9] for example, found that the light lanthanons have a coordination number of 9, the heavy lanthanons have a coordination number of 8, and those cations in the middle of the series have a coordination number between 8 and 9 (by an X-ray scattering technique). More recently, Narten and Hahn[10] used neutron diffraction to study $NdCl_3$ in water and found an average coordination of 8.5.

Diethylenetriaminepentaacetic acid (DTPA) has been known for several decades as a promising chelating agent in lanthanide and actinide separations.[11,12] Since the first DTPA studies, additional polyamino polycarboxylic acids have been prepared, but only a few of them have been studied with regard to their potential use in lanthanide–actinide separations.

There are essentially two types of stability trends for lanthanide–polyamino polycarboxylate species: (1) "ideal", such as with Ln–PMDTA complexes,[1] where the behavior appears to be based on a simple electrostatic charge density (or acid–base) concept involving cationic size and charge. (2) "Nonideal", such as with Ln–DTPA and Ln–EEDTA chelates, where the curve shapes first parallel type 1 behavior for lighter lanthanides (usually with a break at gadolinium) but then deviate in the case of the heavier lanthanides, with chelate stability decreasing instead of increasing with increasing atomic number.[13,14] Experimental results show that type 2 chelating agents are the most promising agents for promoting lanthanide–actinide separation.[1]

The present research illustrates that the stabilities of lanthanide ion complexes are affected greatly by changing the central atom in the diethylene backbone, and this paper also reports synthetic methods used to prepare *N,N*-bis(2-aminoethyl)ethylamine-*N',N',N'',N''*-tetraacetic acid (DEATA), *N,N*-bis(2-aminoethyl)aniline-*N',N',N'',N''*-tetraacetic acid (BEATA) and thiobis(ethylenenitrilo)tetraacetic acid (TEDTA).

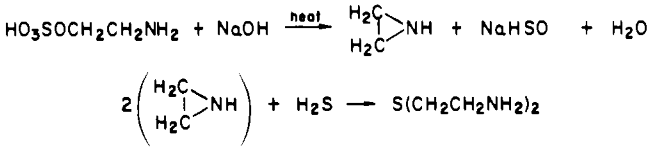
Experimental Section

Starting Materials. *N,N*-Bis(2-chloroethyl)aniline was purchased from Alfa Products. Bis(2-hydroxylethyl)ethylamine was obtained from ICN Pharmaceutical, Inc., and chloroacetic acid and ethanolamine were obtained from Aldrich Chemical Co. These chemicals were used without further purification. Reagent grade solvents were used without additional purification. Approximately 0.1 M lanthanide nitrate solutions were prepared by dilution of concentration stock solutions. These more concentrated reagents were originally prepared from the corresponding oxides, which had been purified up to 99.999% purity in this laboratory by our technical staff, from the method described by Adolphson.[15] The diluted metal nitrate solutions were standardized by both a gravimetric technique (in which the metal ion was precipitated as the oxalate and ashed to the oxide) and by complexometric titration with EDTA, with the use of xylenol orange as an indicator.[16]

Physical Measurements. Mass spectra were recorded on a Finnigan 400 GC MS DS. Nuclear magnetic resonance spectra were obtained by using either the JEOL FX 90Q fourier transform NMR spectrometer or the Bruker WM300 instrument. All the elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Molecular weights of product acids were determined by the potentiometric titration method, with standardized carbonate-free potassium hydroxide used as the titrant.

Thiobis(ethylenenitrilo)tetraacetic Acid (TEDTA). TEDTA was prepared from ethanolamine via ethylenimine and the intermediate bis(2-aminoethyl) sulfide according to literature directions[17-19] by condensing the latter with an excess of chloroacetate.

$$HOCH_2CH_2NH_2 + H_2SO_4 \longrightarrow HO_2SOCH_2CH_2NH_2 + H_2O$$



$$S(CH_2CH_2NH_2)_2 + 4ClCH_2COONa \longrightarrow S[CH_2CH_2N(CH_2COOH)_2]_2$$

Only the last stage of the preparation (which varied significantly from previous syntheses) is described here.

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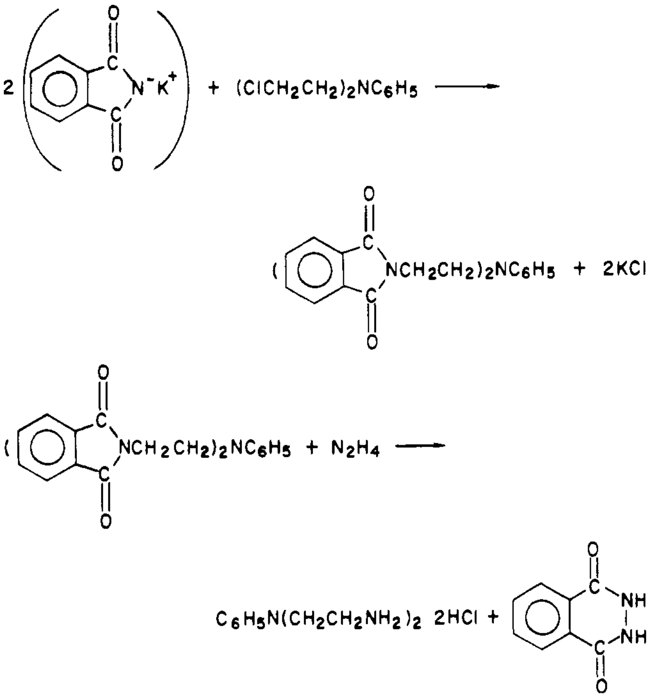
The required 146.25 mL (1.46 mol) of 10 M NaOH was added slowly to 138.2 g (1.46 mol) of chloroacetic acid in 150 mL of water (up to pH ~5 at a temperature below 10 °C. After neutralization of the acid, 35.1 g (0.293 mol) of bis(2-aminoethyl) sulfide was added to the solution, whereupon the color of the solution changed to green. In a period of 6 h, 150 mL of 10 M NaOH was added to the solution to maintain the pH above 10, while the temperature was kept under 40 °C. After the addition was completed, the solution was diluted to 2 L and loaded on four (1 in. × 4 ft) Dowex 50-W hydrogen-form cation-exchange columns. As the solution was loaded and the system was flushed with water, a distinguishable light band of TEDTA formed in front of (below) the sodium ion band. Highly pure TEDTA was next obtained by eluting the complex from the column with 0.1 M NH_4OH. After the eluate was evaporated, white crystalline TEDTA was obtained. The product was dried at 100 °C overnight; yield 53.3 g (51.8%). The molecular weight was found by titration to be 352.8, which compared very well to the expected 352.36. The solubility of TEDTA in water is only 1.0×10^{-2} M at 25 °C. Anal. Calcd for $C_{12}H_{20}N_2O_8S$: C, 40.95; H, 5.73; N, 7.96. Found: C, 40.64; H, 5.87; N, 7.95.

***N*,*N*-Bis(2-aminoethyl)aniline-*N′*,*N′*,*N″*,*N″*-tetraacetic Acid–0.25-Water (BEATA).** BEATA was prepared from *N*,*N*-bis(2-chloroethyl)-aniline via *N*,*N*-bis(phthalimidoethyl)aniline (from which the diamine was first displaced in ethanol solution by hydrazine and then recovered as its dihydrochloride).[20]



The synthetic method used to prepare BEATA from *N*,*N*-bis(2-aminoethyl)aniline was similar to that used in the case of TEDTA except that the cation-exchange eluant was 0.05 M NH_4OH. The product was a violet, finely crystalline solid, yield 75.6%. It was dried at 100 °C overnight and found to decompose at 235 °C. The molecular weight of the acid (based on titration) was 418.7, which compared well with the calculated 415.9. The solubility of BEATA in water is 5×10^{-3} M at 25 °C.

$$C_6H_5N(CH_2NH_2)_2 + 4ClCH_2COONa \rightarrow C_6H_5N[CH_2CH_2N(CH_2COOH)_2]_2 + 4NaCl$$

Anal. Calcd for $C_{18}H_{25}N_3O_8\cdot{}^1/_4H_2O$: C, 51.98; H, 6.17; N, 10.10; O, 31.73. Found: C, 52.00; H, 6.44; N, 9.96; O, 31.77.

***N*,*N*-Bis(2-aminoethyl)ethylamine-*N′*,*N′*,*N″*,*N″*-tetraacetic Acid (DEATA).** The method for synthesizing DEATA was similar to that for BEATA, except that the starting material was bis(2-hydroxyethyl)-ethylamine, which had to be converted first to bis(2-chloroethyl)ethylamine (the analogue of bis(2-chloroethyl)aniline). The hygroscopic product was a glassy white solid, yield 65.5%. The solid decomposed at 120 °C. The determined molecular weight was 385.0, which was quite close to the calculated 381.4. Anal. Calcd for $C_{14}H_{25}N_3O_8\cdot H_2O$: C, 44.09; H, 7.14; N, 11.05; O, 37.76. Found: C, 43.98; H, 7.11; N, 11.47; O, 37.44. ^1H NMR (300 MHz D_2O/Me_4Si): δ 3.79 (8 H, s), 3.68 (8 H, p), 3.40 (2 H, q), 1.30 (3, t). ^{13}C NMR: (D_2O/CD_3CN) δ 164.60, 49.22, 42.28, 41.59, 41.13.

Table I. Protonation Constants of TEDTA at 25 °C and Ionic Strength (μ) = 0.1

	25 °C[a]	25 °C[b]	20 °C[c]
log ([HL]/[H][L])	9.29	9.33	9.42
log ([H_2L]/[H][HL])	8.34	8.39	8.47
log ([H_3L]/[H][H_2L])	2.68		2.52
log ([H_4L]/[H][H_3L])	1.97		1.80

[a] This work. [b] Reference 22. [c] Reference 21.

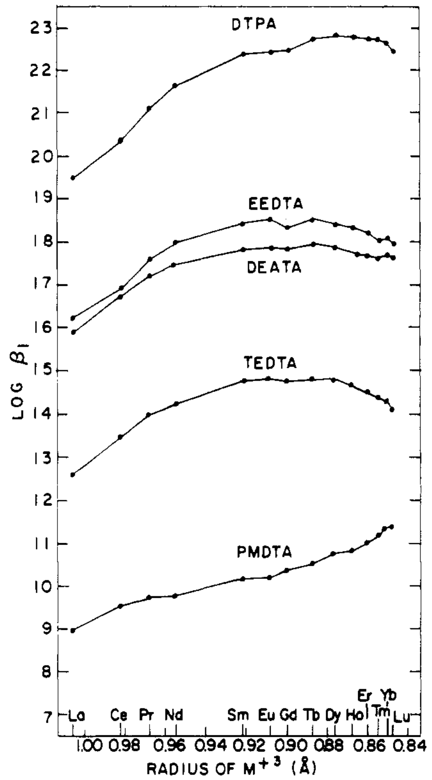


Figure 1. Stability constants of lanthanides with several polyamino polycarboxylates.

Anion Protonation Constants. In each case, the anions' protonation constants were obtained from pH_c measurements on a series of independently prepared chelating agent solutions, each containing a different amount of KOH or HNO_3 and enough KNO_3 to adjust the ionic strength to 0.10 M.[20]

Lanthanum Polyamino Polycarboxylate Stability Constants. The stability constants for the ML^- (β_1 = [ML]/[M][L]) complexes formed by the various lanthanides were determined potentiometrically at 25.00 ± 0.05 °C and ionic strength (KNO_3) 0.10 M. These values were calculated from pH_c measurements on a series of independently prepared solutions of chelating agent, $M(NO_3)_3$, KNO_3, and KOH. The nonlinear calculation method that was employed has been described in detail elsewhere.[20]

Results

The protonation constants for TEDTA were determined by other groups.[21,22] However, in order to verify their results, measurements were performed again under appropriate conditions. Our results and the literature values are displayed in Table I.

The values of the first and second stepwise protonation constants at 25 °C are comparable to those reported in Martell and Smith.[22] The values that were determined in this work are slightly different from those determined by Anderegg[21] at 20 °C, as might be expected due to different standardization techniques and conditions.

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Table II. Formation Constants of Lanthanides with Polyamino Polycarboxylates at 25 °C and $\mu = 0.1$

Ln	DTPA CH_2COOH –N–	CEDTA CH_2CH_2COOH –N–	HDTTA CH_2CH_2OH –N–	BEOTA CH_2CH_2OH –N–	DEATA C_2H_5 –N–	BEATA C_6H_5 –N–	BEBTA $CH_2C_6H_5$ –N–	EEDTA –O–	TEDTA –S–
La	19.48	15.0	14.17	15.15	15.86	13.10	15.20	16.21[a] (16.17)[b]	12.60 (12.80)[c]
Ce	20.33				16.73	13.91		16.90	13.47
Pr	21.07	15.70			17.20	14.82		17.57	13.97
Nd	21.60	16.14	15.13	16.64	17.44	15.10	16.52	17.98	14.22 (14.7)[d]
Sm	22.34	16.16	15.44	16.79	17.79	15.66	17.94	18.40	14.76
Eu	22.39	16.46			17.82	15.71		18.52	14.82
Gd	22.46	16.71	15.44	16.23	17.79	15.42	17.50	18.34	14.76
Tb	22.71	16.71			17.92	15.48		18.52	14.83
Dy	22.82	16.71	15.96	16.53	17.84	15.35	16.50	18.42	14.83
Ho	22.78	16.71			17.72	15.02		18.34	14.67
Er	22.74	16.46	15.86	16.79	17.70	14.81	17.98	18.20	14.51
Tm	22.72	16.71			17.60	14.79		18.04	14.41
Yb	22.62	16.46			17.70	14.88		18.06	14.32
Lu	22.44	16.28	15.35	16.79	17.68	14.74	16.42	17.96	14.10
Y	22.05				17.13			17.75	

[a] At 20 °C. [b] at 25 °C. [c] Reference 22. [d] Reference 32.

Table III. Protonation Constants (log *K*) of Different N-Substituted Ligands at $\mu = 0.1$

	MEDTA CH_3[a]	DEATA C_2H_5[b]	BEOTA C_8H_{17}	BEBTA $C_6H_5CH_2$	BEATA C_6H_5[b]	HDTTA CH_2CH_2OH	DTPA CH_2CO_2H[b]	CEDTA $CH_2CH_2CO_2H$
$\log([HL]/[H][L]$	10.89	10.44	9.6	9.05	10.15	9.3	10.45	9.31
$\log([H_2L]/[H][HL])$	7.39	7.42	8.8	7.99	9.18	8.00	8.53	8.14
$\log([H_3L]/[H][H_2L])$	3.65	4.00	4.1	3.98	3.46	3.54	4.28	4.7
$\log([H_4L]/[H][H_3L])$	2.8	2.80	2.9	2.52	1.91	2.58	2.65	2.97
$\log([H_5L]/[H][H_4L])$							1.82	2.58

[a] At 20 °C. [b] At 25 °C.

The values of each of the trivalent lanthanide chelate formation constants ($\log \beta_1$) for TEDTA are shown together with those for DTPA, EEDTA, and PMDTA in Table II. Plots of $\log \beta_1$ vs. lanthanide cationic radius for these chelates are displayed in Figure 1 for easier comparison. It is apparent that the formation constants in the sequence of Ln–TEDTA complexes parallel those of Ln–EEDTA. Both sets of values increase gradually from La up to Eu and drop at Gd (the "gadolinium break"). This could be attributed to a small ligand field stability energy associated with splitting of partially filled f orbitals. However, the main reason for this change is not well understood. After Gd, the complex formation constant increases slightly for Tb and then decreases continually for the remainder of the sequence. The most surprising features of this graph are the large formation constant differences between the DTPA–EEDTA data and the EEDTA–TEDTA data. The difference in a set is a factor of ca. 10^4 in each case (due in one instance to the replacement of the amine nitrogen atom with attached CH_2COO^- in DTPA by –O– and in the other case by replacement of the ether oxygen atom by a sulfur atom. Comparison of these three strategically placed atoms shows that all have at least one set of lone pair of electrons. X-ray crystallographic determination of the bond angles of substances having resemblances of these moieties, however, show that the bond angle, C–X–C, of the central atom (X = O, N, or S) does not vary drastically; $O(CH_3)_2 = 111 \pm 3°$, $N(CH_3)_3 = 108 \pm 4°$ and $S(CH_3)_2 = 105 \pm 3°$.[23] The bond angle thus does not seem to be the primary cause for such large differences in the formation constants of the respective complexes. It is easy to rationalize that the formation constants of Ln–EEDTA complexes should be higher than those of the Ln–TEDTA complexes since the greater polarization effect should cause the central O atom to be more strongly attracted to a metal ion than the sulfur is. The difference between the Ln–EEDTA and Ln–DTPA formation constants is more subtle and will be discussed later.

DEATA and BEATA. The value of the stepwise protonation constant of DEATA and BEATA together with those of [(octylimino)bis(ethylenenitrilo)]tetraacetic acid (BEOTA),[24] [(benzylimino)bis(ethylenenitrilo)]tetraacetic acid (BEBTA),[24] *N'*-(β-carboxyethyl)diethylenetriamine-*N*,*N*,*N''*,*N''*-tetraacetic acid (CEDTA),[25] *N'*-(β-hydroxyethyl)diethylenetriamine-*N*,*N*,*N''*,*N''*-tetraacetic acid (HDTTA),[26] *N*[(methylnitrilo)bis(ethylenenitrilo)]tetraacetic acid (MEDTA),[24] and DTPA[21] are shown in Table III.

The greatest variation in magnitude with structure occurs with the first protonation (or the last dissociation) constant. The structural substituents can be classified into two kinds: (1) electron-donor CH_3, C_2H_5, C_8H_{17}, and $C_6H_5CH_2$ groups; (2) electron-withdrawing $HO_2CCH_2CH_2$, $HOCH_2CH_2$, C_6H_5, and HO_2CCH_2 groups. Since an electron-donor group enhances the basicity of the lone-pair electron of the central nitrogen atom to a greater extent than does an electron-withdrawing group, one expects to observe a greater affinity for the last proton. It is expected that the octyl-substituted acid should have the highest $\log K_1$ value. However, this does not seem to be true because the *N*-methyl acid exhibits the highest first protonation constant.

The formation constants of Ln–DEATA, Ln–BEATA, and other N-substituted metal chelates are presented in Table II. All the metal chelates of these N-substituted ligands (except DTPA) have $\log \beta_1$ values within the range 15–18. Comparison of the formation constants for the Ln–DEATA and Ln–BEATA series shows the formation constants of the alkyl-substituted Ln–DEATA series to range about 100-fold higher than that of the aryl-substituted Ln–BEATA sequence. The highest formation constant of the DEATA series occurs at Tb, while with BEATA the maximum is at Eu. The higher formation constants observed with DEATA agree with the rationale that alkyl substituents enhance the basicity of Lewis bases whereas aryl groups do not. The shift of the highest formation constant toward the lighter lanthanons (Tb → Eu) noted above provides insight into the relative steric

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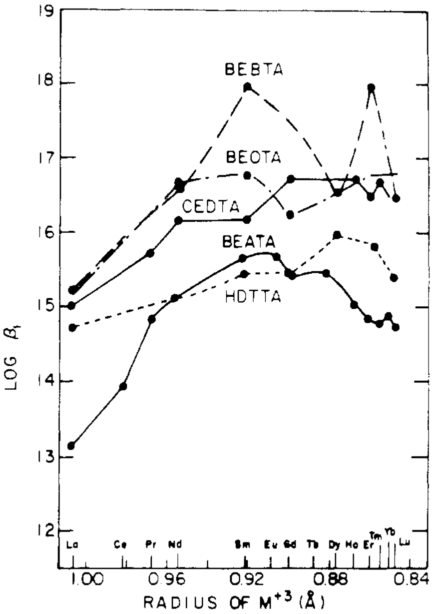

Figure 2. Stability constants of lanthanides with $C_6H_5N[CH_2CH_2N(CH_2COOH)_2]_2$ and different N-substituted chelates.

constraints inherent in these two reagents (DEATA vs. BEATA). The flexibility of the phenyl group in BEATA is much less than that of the ethyl group in DEATA. As the radius of the metal ion becomes smaller and smaller in the lanthanide sequence, steric stress increases and one of the bonds is gradually compromised to relieve this stress. With BEATA, the effect is observed sooner in the sequence.

Discussion

Three of the new chelate sets (Ln–TEDTA, Ln–DEATA, and Ln–BEATA) exhibit the decreasing trend in the stability with the heavy lanthanides observed earlier in the cases of Ln–DTPA and Ln–EEDTA. As the cationic radius becomes smaller and smaller toward the end of the family, steric effects become more critical. In order to relieve the steric stress, which increases as the average number of coordination sites observed by Spedding et al.[9] decreases, it seems that one of the bonds of the heptadentately bound ligand must be gradually compromised or broken. In the Ln–PMDTA sequence,[1] where a methylene group replaces oxygen, sulfur, or nitrogen but provides no lone pair of electrons to form the two additional five-membered chelate rings, the respective chelate formation constants decrease tremendously (10^7-fold from EEDTA, Figure 1). Because of this, it appears that the gradual downturn midway through the formation sequences must imply some disarrangement between the complexed metal ion and donor atoms of the chelating agent. The formation constants of amino polycarboxylates are related to the number of chelating rings formed.[3] Thus, it seems more reasonable that one of the terminal carboxylate groups is gradually being detached instead of the central donor atom as cationic size is diminished.

The plots of log β_1 vs. lanthanide cationic radius for BEATA, BEOTA, BEBTA, CEDTA, and HDTTA are displayed in Figure 2. It is notable that the formation constants (log β_1) of these five chelating agents (BEATA, BEOTA, BEBTA, CEDTA, and HDTTA) ($\sim 1 \times 10^{13}$ to 1×10^{18}) are so much lower than those of DTPA ($\sim 1 \times 10^{22}$). The formation constants of the N-substituted ligands (see also DEATA), except DTPA, lie between those of EEDTA and TEDTA. It is without doubt that the basicity of the central nitrogen greatly affects the formation constants of the metal complexes (DEATA vs. BEATA in Table II). A study of the trend in formation constants across the lanthanide series has been conducted for several chelating ligands.[27] Factors that affect the complex formation constants include ionic size, ligand cavity size, and changes in total coordination number across the series, as well as entropy and enthalphy effects. No simple relationship has been observed between ionic radii and formation constants.

Choppin et al.[28] published ^1H and ^{13}C NMR spectra for the DTPA complexes of La and Lu. It was suggested that DTPA is heptadentately (not octadentately) coordinated to the metal ion by three nitrogen atoms and an average of four carboxylic groups. If one accepts Choppin et al.'s view regarding DTPA complexes, it is extremely difficult to explain the more than 10^5-fold increase of β_1 values compared to those values for complexes formed by analogous heptadentate ligands. There is without doubt heptadentate coordination of DEATA, BEOTA, BEBTA, and BEATA to the lighter, larger lanthanons by three nitrogen atoms and all four carboxylate groups. There is another difference between DTPA and the analogous DEATA, DEOTA, BEBTA, and BEATA ligands. The DTPA anion has a 5– formal charge compared to 4– for the others. Nevertheless, it appears that the fifth carboxylate group of DTPA does play a major role in bonding; otherwise, the 10^5-fold increase in stability does not make sense. If one compares respective light lanthanon chelate stabilities (i.e. log β_1 values) in the cases of ethylenediamine-*N,N,N′,N′*-tetraacetate[29] (hexadentate, 4–) and *N*-hydroxyethylethylenediamine-*N,N′,N′*-triacetate[30] (hexadentate, 3–) (e.g., in the case of neodymium, 16.61 and 15.16), it becomes obvious that formal charge of the ligand anion alone does not play that large a role in chelate formation. The ability to form one or more additional chelate rings, on the other hand, does have a very large effect on chelate stability. This phenomenon is obvious when one compares log β_1 for neodymium *N*-methylethylenediamine-*N,N′,N′*-triacetate (12.51)[31] to that of neodymium *N*-hydroxyethylethylenediamine-*N,N′,N′*-triacetate (15.16).[31] Only when formal charge and dentate character both increase (all else equal) does the magnitude of the change in stability exceed 10^4 (compare 16.61 for NdEDTA to 12.51 for the case in which one CH_2COO^- of EDTA is replaced by CH_3).

Registry No. TEDTA, 923-74-0; BEATA, 87732-99-8; DEATA, 97315-55-4.

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