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Gadolinium Complexation by a New DTPA-Amide Ligand. Amide Oxygen Coordination

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A new type of neutral gadolinium complex with promise as an enhancement agent for magnetic resonance imaging has been prepared and characterized. The reaction of the bicyclic anhydride of diethylenetriaminepentaacetic acid (DTPA) with ethylamine gives the DTPA-bis(ethylamide) derivative DTPA-BEA (**1**) in 71% yield. The Gd(III) complex (**2**) was obtained in high yield from Gd_2O_3 and the acid form of **1**, and crystals were obtained from methanol solution. The most notable feature of the structure is coordination of the two amide carbonyl oxygen atoms to gadolinium. The gadolinium coordination polyhedron is a nine-coordinate tricapped trigonal prism with sites occupied by the three amine nitrogens, three carboxylate oxygens, two amide oxygens, and a water molecule. Amide coordinate bonds (Gd-O) average 2.39 Å versus a carboxylate (Gd-O) average of 2.36 Å, a Gd-N average of 2.70 Å, and water bond (Gd-O) of 2.42 Å. Crystal data: orthorhombic, *Pbca* (No. 61), $a = 13.490$ (2) Å, $b = 18.436$ (3) Å, $c = 25.343$ (3) Å, and $Z = 8$. Final residuals were $R = 3.61\%$ and $R_w = 4.27\%$ following full-matrix least-squares refinement of 3448 independent data with $I > 0$.

Introduction

We have undertaken the preparation and characterization of novel lanthanide complexes for evaluation as constrast agents for magnetic resonance imaging (MRI). Contrast agents are paramagnetic substances that enhance water proton T_1 and T_2 relaxation rates.[1] Since Gd(III) is a nine-coordinate, spin $^7/_2$, paramagnetic ion[2] with a high relaxivity in aqueous solution, it has been an early target of study.[1] Polyamino polycarboxylic acids such as diethylenetriaminepentaacetic acid (DTPA) and ethylenediaminetetraacetic acid (EDTA) have been among the chelating agents used in such studies. However, gadolinium complexes of these ligands are salts under physiological conditions, and the requirement of nonparamagnetic cationic counterions increases the osmolality of the solution. Minimum osmolality is predicted for a neutral complex, which would behave in aqueous solution as one particle. In order to prepare a neutral gadolinium complex that retains high water solubility and relaxivity, DTPA-bis(amide) ligands have been prepared.[3] The structure of the Gd(DTPA-bis(ethylamide)) complex shows that the amide carbonyl oxygens play a prominent role in the metal ion coordination.

Experimental Section

All reagents were obtained from commercial sources unless otherwise noted. Elemental analyses were performed at Galbraith Laboratories. Infrared spectra were obtained on a Nicolet 5DX FTIR spectrometer. NMR spectra were obtained on a Bruker AM 250 spectrometer. Positive ion FAB mass spectra were obtained on an HP 5985A spectrometer using a glycerol matrix and xenon gas.

Synthesis of DTPA-Bis(ethylamide) Dihydrate (1). DTPA-bis(anhydride)[4] (50.3 g, 140 mmol) was added in portions over 30 min to an ice-cold stirred solution of 70% ethylamine (63.1 mL, 780 mmol). Water (30 mL) was added, and the mixture was stirred for an additional 12 h at ambient temperature. The mixture was concentrated under reduced pressure to an oil, diluted with water (100 mL), and adjusted to pH 2.5 with concentrated HCl. The tan crystals that formed were collected and recrystallized from ethanol to give colorless crystals of **1** (44.2 g, 71%), mp 105-109 °C. ^1H NMR (250 MHz, D_2O): δ 3.68 (s, 4 H, terminal NCH_2CO_2), 3.56 (s, 4 H, NCH_2CON), 3.49 (s, 2 H, central NCH_2CO_2), 3.19 (m, 4 H, NCH_2CH_2N), 3.06 (m, 8 H, NCH_2CH_2N and NCH_2CH_3), 0.91 (t, $J = 7.0$ Hz, 6 H, CH_3). IR (KBr): 3610 (m), 3317 (s), 3269 (s), 3090 (m), 2979 (m), 2523 (br), 1717 (s), 1657 (vs), 1632 (vs), 1559 (s), 1384 (s), 1377 (s), 1223 (s), 1100 (m), 701 (m) cm^{-1}. Anal. Calcd (found) for $C_{18}H_{37}N_5O_{10}$: C, 44.71 (44.64); H, 7.71 (7.85); N, 14.48 (14.19).

Synthesis of Gd(DTPA-bis(ethylamide)) Trihydrate (2). The complex was prepared in situ in quantitative yield. A mixture of **1** (12.1 g, 25.0 mmol) and Gd_2O_3 (4.53 g, 12.5 mmol) in water (30 mL) was refluxed for 5 h. The solution was adjusted to pH 6.5 with 1 M NaOH. Colorless crystals of **2** soon formed; mp >200 °C. IR (KBr): 3450 (br, H_2O), 3239 (s), 3086 (m), 2977 (m), 2882 (m), 1636 (vs), 1590 (vs), 1439 (m), 1401 (s), 1358 (m), 1325 (m), 1155 (m), 1094 (m), 939 (m) cm^{-1}. Positive ion FAB MS: 603, $(M + H)^+$. Anal. Calcd (found) for $C_{18}H_{36}GdN_5O_{11}$: C, 32.97 (33.39); H, 5.53 (5.58); N, 10.68 (10.55).

Table I. Crystal Data and Intensity Collection for **2**[a]

empirical formula	$C_{18}H_{44}GdN_5O_{15}$
fw	727.83
crystal dimens mm	0.33 × 0.26 × 0.23
temp K	148
cell params	
a, Å	13.490 (2)
b, Å	18.436 (3)
c, Å	23.343 (3)
V, $Å^3$	5806 (3)
space group	*Pbca* (No. 61)
Z	8
calcd density, g/cm^3	1.67
abs coeff μ, cm^{-1}	23.66
λ(radiation), Å	0.71073
scan type	$\theta-2\theta$
scan speed, deg/min	1.54-6.67
scan width, deg	0.80 + 0.35 (tan θ)
bkgd/scan ratio	0.5
2θ limits, deg	3.00-45.00
reflcns measd	$-14 \leq h \leq +14$ $0 \leq k \leq 19$ $0 \leq l \leq 25$
no. of unique data	3735
no. of obsd data, $I > 0$	3448
discrepancy indices	
R, %	3.61
R_w, %	4.27
R_{all}	5.50
goodness of fit	1.43
no. of variables	352
final diff ρ_{max}, e/$Å^3$	0.86

[a] Data were collected while monitoring three intensity standards (3,11,8; 8,5,5; 2,6,13) every 1 h of exposure time and checking the same three reflections as orientation standards every 200 reflections. Reorientation was necessary once during data collection (after 400 data).

Relaxivity Measurements. Relaxation times (T_1) in water of compound **2** were measured on a RADX Model 530 proton spin analyzer at 10 MHz, 37 °C, for a range of gadolinium concentrations. The data were fit by nonlinear regression to the equation $T_1 = 1/(A[Gd] + B)$ to

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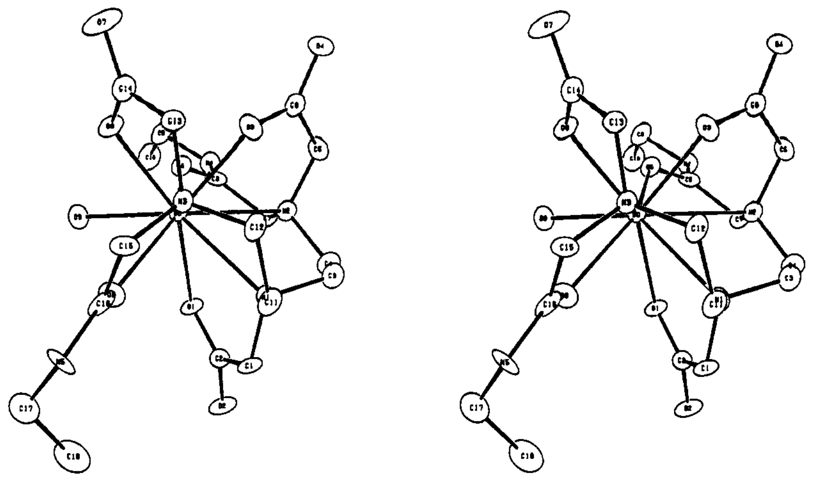
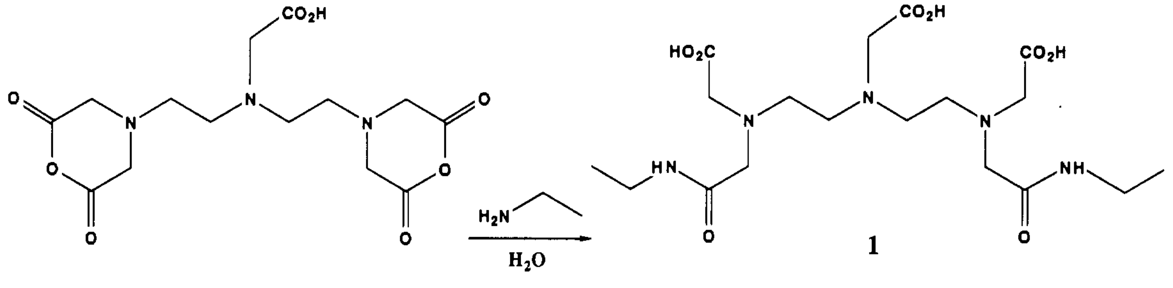


Figure 1. ORTEP stereoview of **2** that includes the atom numbering scheme. Atoms are represented at the 50% probability level. Hydrogen atoms and second coordination sphere waters of solvation are not shown for clarity. The view is toward the capped rectangular face (see Figure 2) with the approximate trigonal axis vertical.

Scheme I. Synthesis of Gd(DTPA-BEA) (**2**)



$1 + Gd_2O_3 \xrightarrow{H_2O}$ Gd[DTPA bis-(ethylamide)], 2

determine relaxivities, where *A* is the relaxivity, and *B* is $1/T_1$ for pure water.

X-ray Crystallography. Colorless single crystals suitable for X-ray structure analysis were obtained by slow evaporation of a methanol solution. Preliminary cell constants and space group assignment were from precession photographs. Data collection was performed on a CAD4 diffractometer at −125 °C.[5] A summary of crystal data and intensity collection is presented in Table I. Reflections collected during the first 4 h of data collection were eliminated from the data set because of extreme fluctuations in the intensities of the standards. Data collected from 4.0 to 17.8 h were corrected for a 6.3% rise in the intensity of the three standards while the data collected from 17.8 to 40.0 h were corrected to account for a 4.7% rise in the standards. No further change was noted for the duration of data collection (95 h). A total of 996 additional reflections were rejected on the basis of the following: (1) the scattering vector deviated more than 0.1° from the calculated position (956 reflections), (2) abnormally high backgrounds (24 reflections), and (3) bad background ratios (16 reflections). Intensity data were converted to structure factor amplitudes after rejecting bad data. Of 8075 observations, 3448 unique data resulted with $I > 0$ after merging ($R_{av} = 3.39$). No absorption correction was applied. The structure was solved by the heavy-atom method. Seven water molecules were located in the structure. Hydrogen atoms attached to carbon and nitrogen atoms were included in the refinement at their calculated positions, with d(C–H) = 0.95 Å and d(N–H) = 0.85 Å[6] and isotropic thermal parameters 1.2 times the equivalent isotropic thermal parameter of the atom to which they are attached. All hydrogen atoms associated with the water molecules were located from Fourier syntheses and were included in subsequent refinements at these fixed positions with isotropic thermal parameters 1.2 times the equivalent isotropic thermal parameter of the oxygen atom to which they are attached. [An abnormally short O(10)–H(33) distance, 0.59 Å, was lengthened along the O–H vector to 0.86 Å.[16] The final cycle of least squares yielded $R = 3.61\%$, $R_w = 4.27\%$, GOF = 1.43, and $(\Delta/\sigma)_{max} < 0.01$.

Table II. Selected Bond Lengths (Å) for **2**

	$Gd–O_{carboxylate}$		
Gd–O(1)	2.351 (3)	Gd–O(6)	2.384 (3)
Gd–O(3)	2.356 (3)	av	2.364 (10)
	$Gd–O_{amide}$		
Gd–O(5)	2.425 (3)	av	2.39 (3)
Gd–O(8)	2.362 (3)		
	$Gd–O_{water}$		
Gd–O(9)	2.423 (3)		
	Gd–N		
Gd–N(1)	2.645 (4)	Gd–N(3)	2.702 (4)
Gd–N(2)	2.759 (4)	av	2.70 (3)
	Average Ligand Bond Lengths[a]		
$N_{amine}–C_{sp^3}$	1.488 (9, 3)	$C–O_{carboxylate}$	1.265 (3, 5)
$N_{amide}–C_{amide}$	1.333 (2, 10)	$C=O_{amide}$	1.248 (2, 11)
$N_{amide}–C_{sp^3}$	1.468 (2, 5)	$C_{sp^3}–C_{sp^2}$	1.509 (5, 7)
$C=0_{carboxylate}$	1.259 (3, 5)	$C_{sp^3}–C_{sp^3}$	1.520 (4, 3)

[a] The first number in parentheses represents the number of observations; the second number represents the standard deviation of the averaged observations.

Results

The gadolinium complex of DTPA-BEA, **2**, was obtained in 71% overall yield in two steps (Scheme I). The structure of Gd(DTPA-BEA)(H_2O) (**2**) is shown in Figure 1 along with the atomic numbering scheme. A summary of crystal data and intensity collection is given in Table I. A list of important bond lengths appears in Table II.[7]

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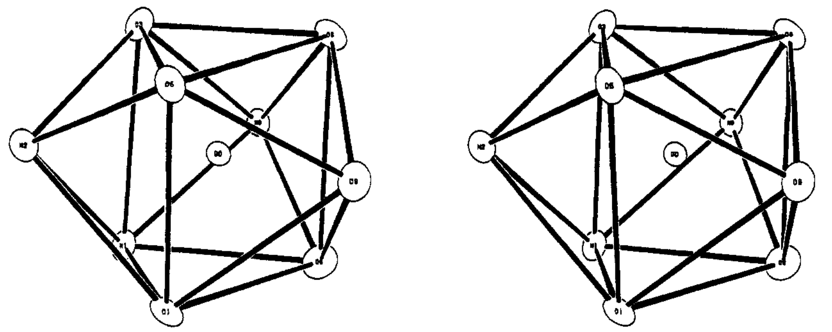


Figure 2. ORTEP stereoview of the inner coordination polyhedron of **2** showing the tricapped-trigonal-prismatic coordination of the Gd atom. Atoms are represented at the 50% probability level. The 3-fold axis is vertical.

Table III. Polyhedral Angles (deg) for **2**

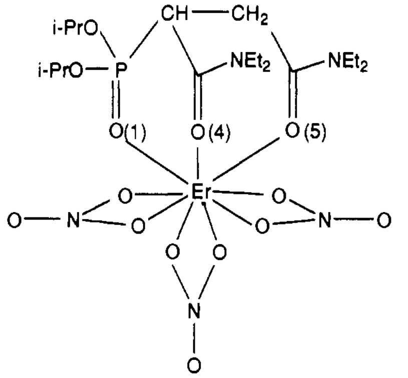
face 1	face 2	angle	av angle	idealized[a] angle, D_{3h}
O(3),O(5),O(6)	O(1),O(8),N(1)	175.9		180.0
O(3),O(5),O(6)	O(9),N(2),N(3)	171.1	173.6	180.0
O(9),N(2),N(3)	O(1),O(8),N(1)	173.8		180.0
N(2),O(3),N(1)	O(9),O(6),O(8)	139.2		146.4
N(1),N(3),O(3)	O(1),O(5),O(9)	146.6	142.6	146.4
N(3),O(6),O(8)	N(1),O(1),O(5)	141.9		146.4
N(2),O(3),N(1)	N(1),N(3),O(3)	19.8		26.4
N(3),O(6),O(8)	O(9),O(6),O(8)	20.5	23.2	26.4
O(1),O(5),O(9)	N(1),O(1),O(5)	29.2		26.4
O(1),O(5),O(6),O(8)	O(1),O(5),N(1),O(3)	56.9		60.0
O(1),O(5),O(6),O(8)	N(1),O(3),O(6),O(8)	58.6	60.1	60.0
O(1),O(5),N(1),O(3)	N(1),O(3),O(6),O(8)	64.7		60.0

[a] For the tricapped trigonal prism, from ref 8.

The gadolinium ion is in a nine-coordinate ligand environment comprising the three amine nitrogens, N(1), N(2), and N(3); three carboxylic acid oxygens, O(1), O(3), and O(6); two amide oxygens, O(5) and O(8); and one water molecule, O(9). The asymmetric unit contains six additional water molecules, which form a hydrogen bond network with the coordinated water molecule and the three uncoordinated carboxylic acid oxygens, O(2), O(4), and O(7). The metrical parameters associated with the primary coordination sphere of the gadolinium ion provide useful information in assigning the geometry of this complex. The coordination geometry is best described as a distorted tricapped trigonal prism with the outer amine nitrogens, N(2) and N(3), together with the coordinated water oxygen, O(9), forming the three rectangular face caps (Figure 2). The dihedral angles compare well with those calculated for the idealized D_{3h} geometry[8] (Table III).

The coordination of gadolinium by the amide oxygen atoms is clearly demonstrated by the bond lengths (Table II). The Gd–O(8) bond to one of the amide oxygens is 2.362 (3) Å, shorter than the average Gd–O bond length of 2.384 Å. The other Gd–amide oxygen bond, Gd–O(5), is 2.425 Å. The Gd–O bond lengths range from 2.351 (3) to 2.425 (3) Å and are 0.03–0.11 Å shorter than the sum of their ionic radii.[9] The Gd–N bond lengths range from 2.645 (4) to 2.759 (4) Å with an average of 2.702 Å and are 0.08–0.19 Å longer than the sum of their ionic radii.

The IR data provide support for amide oxygen coordination and are a diagnostic feature for amide oxygen and carboxylate coordination. DTPA-BEA (**1**) has carbonyl stretches at 1717 (s), 1657 (vs), 1632 (vs), and 1559 (s) cm^{-1}. We tentatively assign the two higher energy bands to the amide carbonyl stretches and the two lower energy bands to carboxylate stretches. Gd(DTPA-BEA) exhibits very different carbonyl stretches in this region with bands at 1636 (vs) and 1590 (vs) cm^{-1}. Therefore, complexation has shifted the amide carbonyl bands 20–80 cm^{-1} to lower energy. This trend has been noted before in the erbium complex **3** (Figure 3), which has amide carbonyls coordinated to the metal ion.[10] Coordination of the amide carbonyls led to a shift in the infrared by 10–45 cm^{-1} to lower energy.



Bond Lengths, Å

Er-O(1) 2.298(6)
Er-O(4) 2.326(7)
Er-O(5) 2.267(8)
Er-O(nitrate)$_{av}$ 2.407

Figure 3. Schematic structure (and primary coordination sphere bond lengths) for {diisopropyl [1,2-bis(diethylcarbamoyl)ethyl]phosphonate}erbium(III) nitrate (**3**).[10]

Table IV. Primary Coordination Sphere Bond Lengths (Å) for Lanthanide Polyaminopolycarboxylate Complexes

Ln-(EDTA)-$(H_2O)n^-$							
entry	metal	*n*	Ln–O$_{av}$	Ln–N$_{av}$	ΔΣ(O)[a]	ΔΣ(N)[a]	ref
1	La	3	2.538	2.755	−0.028	+0.079	11
2	Pr	3	2.491	2.714	−0.038	+0.075	12
3	Sm	3	2.455	2.673	−0.027	+0.081	12
4	Gd	3	2.430	2.655	−0.027	+0.088	12
5	Dy	3	2.416	2.651	−0.017	+0.108	12
6	Ho[b]	3	2.401	2.633	−0.020	+0.101	13
7	Er	2	2.292	2.537	−0.062	+0.073	14
8	Yb	2	2.297	2.533	−0.037	+0.088	15
av ΔΣ(σ)					−0.032 (14)	+0.087 (12)	

entry	complex	Ln–O$_{av}$	Ln–N$_{av}$	ΔΣ(O)[a]	ΔΣ(N)[a]	ref
9	$Gd(DTPA)(H_2O)^{2-}$	2.419	2.640	−0.039	+0.073	16
10	$Nd(DTPA)(H_2O)^{2-}$	2.480	2.755	−0.033	+0.132	17
11	$Eu(DOTA)(H_2O)^{-}$[c]	2.411	2.680	−0.051	+0.100	18
12	$Tb(TETA)^{-}$[d]	2.315	2.599	−0.076	+0.099	19
13	Gd(DTPA-BEA)(H_2O)	2.384	2.702	−0.073	+0.135	*e*

[a] ΔΣ(atom) is the difference between the calculated[9] Ln–atom distance and the observed distance. [b] Average for two crystallographically independent molecules. [c] DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate. [d] TETA = 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetate. [e] This work.

Discussion

The single-crystal structure of the neutral, nonionic complex Gd(DTPA–bis(ethylamide)) (**2**) reveals the prominent role played

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(7) See statement regarding supplementary material at the end of this paper.

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by the amide oxygens in the inner coordination sphere of the complex. We are aware of only one other structurally characterized lanthanide complex with bonds to amide oyxgen atoms, namely the erbium complex[10] **3** (Figure 3). In complex **3** the bond lengths d(Er–O) for the two amide oxygens are 2.326 (6) and 2.267 (8) Å, both substantially shorter than the d(Er–O) of 2.412 Å predicted by ionic radii.[9]

This trend of short metal–oxygen bonds and long metal–nitrogen bonds is seen in a variety of polyaminopolycarboxylate complexes (Table IV).[11-19] With the lanthanide–EDTA structures used as a basis for comparison (entries 1–8), it is seen that the average Ln–O bond is 0.0321 (14) Å shorter than that calculated from ionic radii[9] while the average Ln–N bond is 0.087 (12) Å longer than calculated. In an examination of other lanthanide polyaminopolycarboxylate complexes (entries 9–13), only complex 2 (entry 13) and the Nd(DTPA)(H_2O) complex (entry 10) have Ln–N interactions significantly longer than expected (using a 3σ criterion) and only complex **2** and the Tb(TETA) complex (entry 12) have Ln–O interactions significantly shorter than expected. Although the complexes listed in Table IV are similar, the range of bond variation seen in complex **2** is greater than in any of the comparisons.

Chromatographic and solution equilibria behavior of aqueous Gd(DTPA-BEA) is consistent with a neutral, discrete complex. The T_1 proton relaxivity of the complex (4.8 $\mathrm{mM^{-1}\,s^{-1}}$) is in the range indicative of Gd^{3+} ions with one coordinated water molecule.[1] The ligand comprises the remaining eight coordination sites (three amines, three carboxylates, and two carboxamides). This participation of amide or ester groups in the coordination of DTPA derivatives in aqueous solution has also been predicted from nuclear magnetic resonance dispersion studies.[20] The nine-coordinate geometry of Gd(III), which includes one water molecule, seems likely to be a key part of the promising contrast agent properties of this complex. The present work demonstrates the utility of amides as coordinating ligands for lanthanide complexes. This is particularly noteworthy in that amides are neutral chelating groups at physiological pH. Thus, a Gd(DTPA-bis(amide)) complex such as **2** possesses no net charge. As described in the Introduction, this leads to a 3-fold reduction in osmolality relative to salts of Gd DTPA dianions. This has profound implications for the physiological acceptance of the resulting complexes as contrast agents for MRI.[21]

Acknowledgment. We thank Dr. F. Ekkehardt Hahn for providing crystals of **2**. We thank Dr. Fred Hollander for help with the X-ray crystal structure. That portion of the research performed at UCB was supported by a grant from Salutar, Inc.

Supplementary Material Available: Tables of positional parameters (Table S-V), anisotropic thermal parameters (Table S-VI), rms amplitudes of thermal vibration (Table S-VII), and bond lengths and angles for **2** (Table S-IX) and an ORTEP diagram of **2** with the lattice water molecules (Figure S-4) (9 pages); a table of observed and calculated structure factors for **2** (Table S-VIII) (22 pages). Ordering information is given on any current masthead page.

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Geometrical Isomerism of Mixed Tris(amino carboxylato)cobalt(III) Complexes Containing Glycinato and β-Alaninato Ligands. Crystal Structure of *trans*(O_5)-(β-Alaninato)bis(glycinato)cobalt(III) Trihydrate

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The geometry of six meridional isomers of tris(amino carboxylato)cobalt(III) complexes, containing glycinato and β-alaninato ligands, has been determined by considering the influence of the magnetic anisotropy of the cobalt(III) atom on the NMR chemical shifts of the methylene protons. A new synthesis, column chromatography, and electronic absorption spectra of these complexes are presented and discussed. The crystal structure analysis of *trans*(O_5)-(β-alaninato)bis(glycinato)cobalt(III) trihydrate confirmed the NMR deduction. The compound crystallizes in the monoclinic space group $P2_1/c$, with a = 8.958 (2) Å, b = 15.836 (4) Å, c = 10.234 (2) Å, β = 111.55 (3)°, and Z = 4. The structure consists of enantiomeric pairs of (β-alaninato)bis(glycinato)cobalt(III) complex molecules and molecules of water. In the complex molecule, the coordination around cobalt is distorted octahedral. The six-membered chelate ring adopts a twist-boat conformation, and the five-membered chelate rings adopt puckered conformations. The presence of relatively weak hydrogen bonds between the molecules of the complex and water is also established.

Introduction

A series of mixed tris(amino carboxylato)cobalt(III) complexes containing glycinato (Gly) and β-alaninato (β-Ala) ligands consists of eight complexes. They all belong to the CoN_3O_3 type of complexes and possess facial or meridional configuration. However, for the meridional configuration the chelate ligand positions are not equivalent and a redistribution of glycinato and β-alaninato chelate ligands generates three geometrical isomers (Chart I).

The synthesis of one of the tris(amino carboxylato)cobalt(III) complexes containing both α and β-amino carboxylato chelates

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