Preparation of the Novel Chelating Agent *N*-(2-Aminoethyl)-*trans*-1,2-diaminocyclohexane-*N*,*N*′,*N*″-pentaacetic Acid (H_5CyDTPA), a Preorganized Analogue of Diethylenetriaminepentaacetic Acid (H_5DTPA), and the Structures of $Bi^{III}(CyDTPA)^{2-}$ and $Bi^{III}(H_2DTPA)$ Complexes

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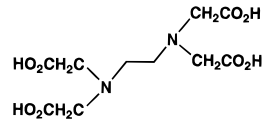
Received October 18, 1995

Introduction

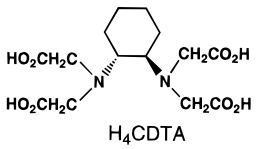
There is a need for chelating agents that have high affinity for metals in biological environments. Radioisotopic metal ions may be used in the selective imaging and therapy of tumors if their complexes are stable *in vivo*.[1,2] An important ligand property that increases metal complex stability is preorganization, the tendency of the free ligand to assume the conformation necessary for metal ion complexation.[3] Thus, *trans*-cyclohexylenediamine tetraacetic acid (CDTA) has a higher affinity for most metal ions than does EDTA, because the bridging cyclohexylene group holds the two $N(CH_2CO_2H)_2$ chelate groups in a mutually *cis* arrangement.[4−6]

The α-particle-emitting isotope ^{212}Bi is of particular interest in the localized killing of tumor cells by an antibody-linked chelate.[7] The requirement of the large Bi^{3+} ion (ionic radius 1.17 Å) for high coordination numbers led to use of DTPA and its derivatives linked to monoclonal antibodies for *in vivo* tests of tumor imaging and treatment. However, these were not sufficiently stable chelators.[8] Therefore, we applied a preorganization strategy in the synthesis of a cyclohexylene analogue of DTPA, *N*-(2-aminoethyl)-*trans*-1,2-diaminocyclohexane-*N*,*N*′,*N*″-pentaacetic acid (**1**, referred to herein as H_5CyDTPA), and its C-functionalized version for antibody conjugation.[9]

This paper reports the preparation of H_5CyDTPA and the synthesis and structural characterization of bismuth(III) complexes of $CyDTPA^{5-}$ and H_2DTPA^{3-}.



H_4EDTA



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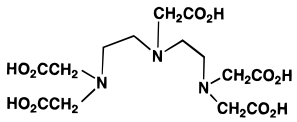
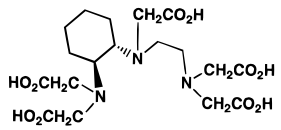


H_5DTPA



H_5CyDTPA

Experimental Section

Materials and Methods. Anhydrous solvents (THF, dioxane, and DMF) and 1 M diborane in THF were obtained from Aldrich. *trans*-(±)-1,2-diaminocyclohexane was purchased from Aldrich and distilled from 5 Å sieves prior to use. The 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide (EDC) was obtained from Sigma Chemical. *N*-Hydroxysuccinimide was obtain from Aldrich and used as received. Ion-exchange resins were obtained from Bio-Rad. Silica gel 60 (70−230 mesh ASTM) used for column chromatography was purchased from EM Science.

^1H and ^{13}C NMR were obtained by using a Varian 300XL instrument. Chemical shifts are reported in ppm on the δ scale relative to TMS (C_6D_6 solutions), or TSP (D_2O) solutions. Proton chemical shifts are annotated as follows: ppm (multiplicity, integral, coupling constant (Hz)). Chemical ionization mass spectra (CI-MS) were obtained by use of a Finnnegan 3000 instrument. Fast atom bombardment (FAB-MS) mass spectra were obtained at the Mass Spectroscopy Laboratory, College of Chemistry, University of California, Berkeley, CA. Elemental analyses were performed by Atlantic Microlabs (Atlanta, GA).

Arsenazo III yttrium dye complex (AA-III) was used to visualize the purified compound **1** after being eluted from the ion-exchange column. The testing solution was prepared from 5×10^{-4} *M* arsenazo III (50 mL), 5 M and pH 4.5 NH_4OAc (50 mL), H_2O (150 mL), and 0.012 M YCl_3 (500 μL).

***trans*-1,2-Diaminocyclohexane−CBZ−Glycine Monoamide (2).** *N*-CBZ-glycine[10] (15.0 g, 49.2 mmol), *N*-hydroxysuccinimide (5.66 g, 49.2 mmol), and EDC (9.43 g, 49.2 mmol) were combined in EtOAc (400 mL) with DMF (200 mL), and the reaction was stirred under argon for 18 h. The reaction solution was diluted with EtOAc (200 mL) and extracted with saturated NaCl solution (400 mL) and 5% $NaHCO_3$ (2 × 400 mL) and again with saturated NaCl solution (400 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to a solid. The solid was taken up in DMF (150 mL) and added dropwise to freshly distilled *trans*-1,2-diaminocyclohexane (250 mL) over ca. 12 h while vigorously stirring under argon. The cloudy solution was filtered and concentrated to a thick oil. The oil was taken up in $CHCl_3$ (400 mL) and washed with saturated salt solution (2 × 200 mL), 5% $NaHCO_3$ (2 × 200 mL), and salt solution (2 × 200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to a gelatinous oil that was solidified with $CHCl_3$ and hexanes (ca. 30 mL each). Column chromatography (silica, 2.6 × 40 cm, 200-mL fractions) was employed to isolate the product. A portion of the crude product (3.0 g) in minimal $CHCl_3$ was applied to the column. The column was eluted with $CHCl_3$ and the impurities were eluted while gradually increasing the percentage of methanol in the eluent in successively greater steps (0, 1, 2, 3, 5, 10, 20%). At 20% methanol, the product started to elute, whereafter the column was eluted with 100% methanol. The fractions were combined and concentrated to a white solid (9.02 g, 77.6%). ^1H NMR ($CDCl_3$): δ 7.342 (s, 5H), 6.351 (d, 1H, J = 8.5), 6.009 (br s, 1H), 5.113 (s, 2H), 3.837 (m, 2H), 3.488 (m, 1H), 2.361 (m, 1H), 1.924 (br d, 2H), 1.691 (m, 2H), 1.554 (s, 2H), 1.40−1.00 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 169.16, 156.69, 136.20, 128.51,

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S0020-1669(95)01326-7 CCC: $12.00

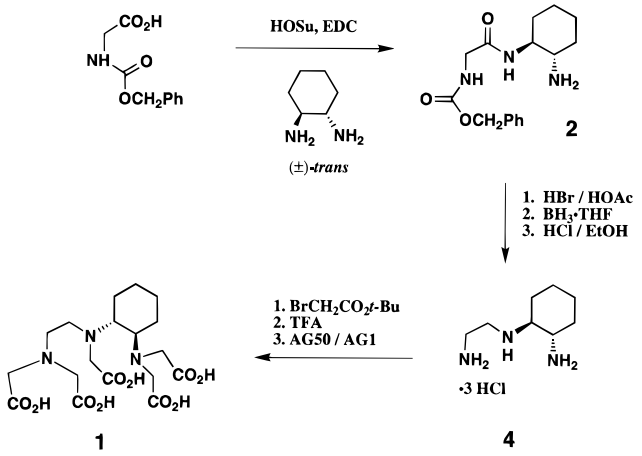
128.19, 128.03, 67.12, 56.16, 55.21, 44.91, 35.26, 24.96(2). MS (CI/NH_3) 306 (M + 1). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 62.95; H, 7.54; N, 13.77. Found: C, 62.78; H,7.64; N, 13.70.

***trans*-1,2-Diaminocyclohexane−Glycine−Monoamide Dihydrobromide (3).** Hydrobromic acid (33% in HOAc, Fluka) (100 mL) was added to monoamide **2** (6.25 g, 20.6 mmol) under argon. The resulting clear solution formed a precipitate after 1 h. Diethyl ether (100 mL) was added, and the suspension was stirred for an additional hour. The precipitate was then collected on a Hirsch funnel under an argon umbrella. The product was washed with ether and vacuum dried (6.60 g, 96%). ^{1}H NMR (D_2O, pH 1.0): δ 3.845 (s, 2H), 3.130 (ddd, 1H, J = 11.5, 11.5, 4.0), 2.113 (br d, 2H), 1.941 (m, 1H), 1.802 (m, 2H), 1.60−1.26 (m, 4H). ^{13}C NMR (D_2O, pH 1.0, ref = **C**D_3CN): δ 168.16, 55.37, 52.03, 41.61, 31.60, 30.21, 24.48, 23.99. MS (CI/NH_3): 172 (M + 1). Anal. Calcd for $C_8H_{17}N_3O(HBr)_2$: C, 28.83; H, 5.71; N, 12.61. Found: C, 28.78; H, 5.81; N, 12.53.

***N*-(2-Aminoethyl)-*trans*-1,2-diaminocyclohexane Trihydrochloride (4).** Amide **3** (6.27 g, 18.8 mmol) was suspended in THF (100 mL) in a three-necked round-bottom flask under argon. The flask was cooled (0 °C) and 1 M diborane (120 mL) was added via syringe. The suspension was vigorously refluxed for 36 h. The resulting clear solution was treated with MeOH (50 mL) at 0 °C. The solution was concentrated to a solid and the residue was taken up in 100% EtOH (110 mL). The solution was saturated with HCl(g) while cooling the flask in an ice bath. The acidic solution was refluxed for 7 h and left stirring under argon for an additional 12 h at room temperature. The precipitating suspension was moved to 4 °C for 24 h after which the product was collected on a Buchner funnel and vacuum dried (2.78 g, 55%). ^{1}H NMR (D_2O, pH 1.8): δ 3.70−3.30 (m, 6H), 2.313 (br d, 1H), 2.192 (br d, 1H), 1.84 (m, 2H), 1.70−1.30 (m, 4H). ^{1}H NMR (D_2O, pH 13.0): δ 2.80−2.70 (m, 3H), 2.60 (m, 1H), 2.463 (ddd, 1H, J = 10, 10, 4.0), 2.214 (ddd, 1H, J = 9.5, 9.5, 3.5), 1.960 (br d, 1H), 1.763 (br d, 1H), 1.682 (m, 2H), 1.30−0.95 (m, 4H). ^{13}C NMR (D_2O, pH 1.0, ref = **C**D_3CN): δ 59.61, 51.86, 42.27, 36.15, 29.67, 26.57, 22.72, 22.37. MS (CI/NH_3): 158 (M + 1). Anal. Calcd for $C_8H_{19}N_3(HCl)_3$: C, 36.04; H, 8.26; N, 15.77. Found: C, 35.98; H, 8.19; N, 15.72.

***N*-(2-Aminoethyl)-*trans*-1,2-diaminocyclohexane-*N*,*N*′,*N*″-pentaacetic Acid (1).** Triamine **4** (1.0 g, 3.75 mmol) and Na_2CO_3 (3.58 g, 33.8 mmol) were combined in DMF (20 mL). While this was being heated to ca. 90 °C, *tert*-butyl bromoacetate (4.39 g, 22.5 mmol) was added. The reaction was stirred under argon at 90 °C for 18 h, cooled to room temperature, and extracted into CH_2Cl_2 (100 mL) and washed with a saturated salt solution (3 × 100 mL). The CH_2Cl_2 solution was dried over $MgSO_4$, filtered and rotary evaporated to a thick oil (MS (CI/NH_3): 728 (M + 1)). The oil was then treated with trifluoroacetic acid (TFA) (25 mL) and stirred under argon for 18 h. The acid was removed via rotary evaporation and the residue was taken up in water (20 mL). The solution was loaded onto an AG50WX8 cation exchange resin column (200−400 mesh, H^+ form, 2.6 × 20 cm) and washed with water until the eluent was neutral. The crude product was eluted from the column with 2 M NH_3(aq) (1.0 L). The basic solution was concentrated to a solid which was vacuum dried. The solid (300−400 mg portions per run) was dissolved in water (ca. 5 mL) and loaded onto an AG1X8 anion exchange resin column (200−400 mesh HCO_2H form, 1.6 × 30 cm). The column was washed with water (11 fractions, 18 × 150 mm tubes) after which a 2 L gradient of 0.0−2.25 M formic acid was run through the column to elute the product (88 18 × 150 mm tubes). The product was routinely found in tubes 65−77 and visualized by use of AA-III dye yttrium complex. The dye complex (0.25 mL) was diluted with an equal amount of H_2O, and each fraction was tested by adding a 10 μL aliquot of the fraction to the blue solution. A positive test resulted in formation of a purple-pink color change. The relevant fractions were combined and concentrated to ca. 10 mL and the solution lyophilized to leave a white powder. The column was washed back to neutral and the purification sequence repeated until all of the ammonium salt had been purified through the AG1 column. The isolated product from each run was combined and dried for 72 h at 90 °C, 0.01 mm (766 mg, 45.7%). ^{1}H NMR (D_2O, pH 12.0): δ 3.30−2.35 (br series of multiplets, 16H, within which was 3.176 (dd, J = 23.5, 16.0), 1.980 (m, 2H), 1.720 (m, 2H), 1.122 (m, 4H). ^{13}C NMR (D_2O, pH 12.0, ref = TSP): δ 183.21, 182.79, 182.28, 63.26, 55.88, 27.97, 27.85, 26.61. MS (FAB/thioglycerol/glycerol): 448 (M + 1). Anal. Calcd for $C_{18}H_{29}N_3O_{10}$: C, 48.32; H, 6.49; N, 9.39. Found: C, 47.37; H, 6.46; N, 9.19.

Scheme 1



Bis(guanidinium)[*N*-(2-aminoethyl)-*trans*-1,2-diaminocyclohexane-*N*,*N*′,*N*″-pentaacetato]bismuth(III) (5). Bismuth subcarbonate (0.085 g, 2.2 × 10^{-4} mol) was added to a solution of **1** (0.075 g, 1.7 × 10^{-4} mol) in water (20 mL). The white suspension was refluxed 85 min and filtered. Guanidine carbonate (0.032 g, 1.7 × 10^{-4} mol) in water (10 mL) was added to the filtrate. The clear solution was refluxed 2 h, then dried under reduced pressure. The solid was taken up in water (3 mL), and the resulting suspension was filtered. Methanol (3 mL) was mixed with the filtrate and the solution was layered with ether (5 mL). After 2 d the crop of clear prisms was harvested, washed with ether, and dried (0.11 g, 1.4 × 10^{-4} mol, 82% yield). Crystallization by slow evaporation of an aqueous solution of **5** yielded the same product. ^{1}H NMR (D_2O, pH 7.8, 25 °C): δ 4.80 (NH_2 and H_2O), 4.70−2.70, many overlapping multiplets including AB spin systems at lower field (NCH_2CO$_2$), more complex multiplets centered at 3.98, 3.53, 3.19, 3.06, and 2.82 (NCH_2CH$_2$ and NCHR$_2$), total 16H; four multiplets centered at 2.13, 1.81, 1.36, and 1.22 (cyclohexyl CH_2, 8H). ^{13}C NMR (D_2O, pH 7.8, 25 °C): δ 183.4, 183.1, 182.7, 181.5, 180.6 (-CO$_2$), 72.6, 65.1, 64.3, 63.5, 62.4, 60.8, 59.5, 56.9, 56.3 (NCH$_2$), 28.8, 28.1, 27.3 (cyclohexyl CH$_2$; third signal has twice the intensity of others). The guanidinium carbon was not observed. Anal. Calcd for $C_{20}H_{36}N_9O_{10}Bi$: C, 31.14; H, 4.70; N, 16.34. Found: C, 31.03; H, 4.70; N, 16.22.

Bi(H_2DTPA)·2H_2O (6). $Bi(NO_3)_3$·$5H_2O$ (4.85 g, 0.01 mol) was added to a 25 mL aqueous solution containing H_5DTPA (3.93 g, 0.01 mol) and 5 mL of 4.0 M NaOH (0.02 mol). The cloudy solution was heated at 75 °C until clear, filtered, and allowed to slowly evaporate at room temperature. After 2 weeks, an amorphous white solid was isolated by filtration, washed with cold water, and dried over anhydrous $MgSO_4$ (3.0 g, 47%). ^{1}H NMR (D_2O, 25 °C, pH 7): δ 4.24 (br, 2H, NCH_2C(O)), 4.02 (m, 4H, NCH_2C(O)), 3.7 (m, 6H, NCH_2C(O) and NCH_2CH$_2$), 3.25 (m, 4H, NCH_2CH_2), 2.96 (m, 2H, NCH$_2$CH_2). Spectrum identical at pH 2 (HCl added) except for slight (<0.1 δ) shifts of peaks. MS (FAB/nitrobenzyl alcohol): 600 (M + H)$^+$. Anal. Calcd for $C_{14}H_{24}N_3O_{12}Bi$: C, 26.47; H, 3.81; N, 6.61; Bi, 32.89. Found: C, 26.99; H, 3.65; N, 7.10; Bi, 31.48.

X-ray Data Collection, Structure Determination, and Refinement for 5 and 6. Suitable crystals of **5** were obtained by slow diffusion of ether into a water−methanol solution. Suitable crystals of **6** grew slowly from a sealed vial of an aqueous solution. Transparent single crystals were mounted on fibers and transferred to the goniometer. The space groups were determined from the systematic absences. A summary of data collection parameters is given in Table 1.

Structures were solved using direct methods. Full-matrix least-squares refinement was carried out with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms attached to oxygen in **6** were located from difference Fourier maps and refined isotropically. The other hydrogen atoms were placed in calculated positions and were assigned isotropic thermal parameters which were 20% greater than the B_{eqv} of the atom to which they were bonded.

Table 1. Crystal Data and Structure Refinement for [guanidinium$^+$]$_2$[Bi(CyDTPA)$^{2-}$] (**5**) and Bi(H_2DTPA)·2H_2O (**6**)

	5	**6**
color/shape	colorless/parallelepiped	colorless/flat
empirical formula	$C_{20}H_{36}BiN_9O_{10}$	$C_{14}H_{24}BiN_3O_{12}$
fw	771.56	635.34
temp, K	295(2)	153
crystal system	orthorhombic	monoclinic
space group	Pbca	$P2_1/n$
unit cell dimens		
a, Å	16.176(4)	8.994 (5)
b, Å	18.003(5)	8.182 (4)
c, Å	18.487(5)	25.687(4)
β, deg	x	92.47(3)°
V, Å^3	5384(2)	1889(1)
Z	8	4
D(calcd), Mg/m^3	1.904	2.234
abs coeff, mm^{-1}	6.620	9.376
diffractometer/scan	Siemens SMART/CCD area detector	Rigaku AFC6R/$\omega-2\theta$ 16.0°/min (in ω), max 4 rescans
radiation/wavelength, Å	Mo Kα (graphite monochrom)/0.710 73	Mo Kα/0.710 73
F(000)	3056	1232
crystal size, mm	0.30 × 0.30 × 0.10	0.40 × 0.10 × 0.02
θ range for data collcn, deg	2.02−23.28	1.5−25.05
index ranges	$-17 \le h \le 17$, $-20 \le k \le 14$, $-20 \le l \le 20$	$0 \le h \le 10$, $0 \le k \le 9$, $-20 \le l \le 30$
no. of reflcns collcd	19 249	3856
no. of independent reflcns	3865 ($R_{int} = 0.0565$)	3613 ($R_{int} = 0.061$)
abs cor	semiempirical from φ-scans	semiempirical from φ-scans
range of relat transm factors	0.965 and 0.510	1.0 and 0.719
sec extinction cor	none	coefficient = 6.8303 × 10^{-8}
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
computing	SHELXS-86, SHELX-93[a]	TEXSAN[b]
data/restraints/params	3860/0/361	2700/0/296
goodness-of-fit on F^2	1.084	1.35
weighting scheme	SHELX-93 weight params 0.0268, 4.4830	$w_i = 4F_o^2/\sigma^2(F_o^2)$; *p*-factor = 0.01
final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0316$, $wR_2 = 0.0602$	$R_1 = 0.020$, $wR_2 = 0.020$
R indices (all data)	$R_1 = 0.0510$, $wR_2 = 0.0673$	$R_1 = 0.0387$, $wR_2 = 0.0216$
largest diff peak and hole, e Å^3	0.520 and −0.659	0.580 and −0.55

[a] Reference 17. [b] Reference 18.

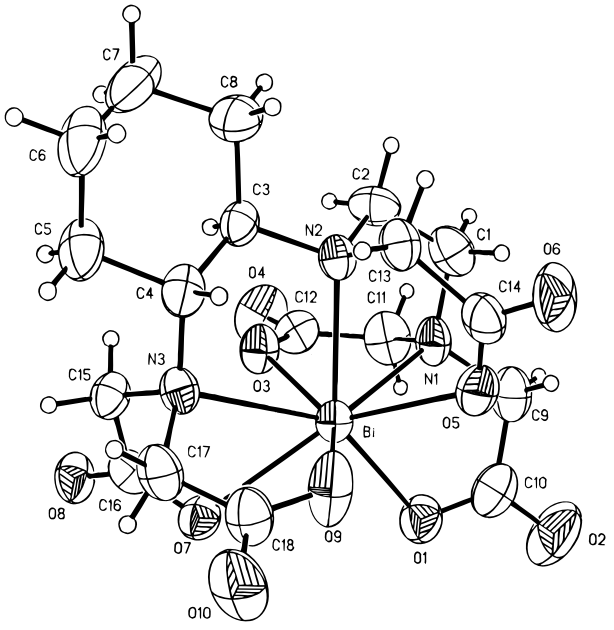


Figure 1. Molecular structure of Bi(CyDTPA)$^{2-}$ (**5**).

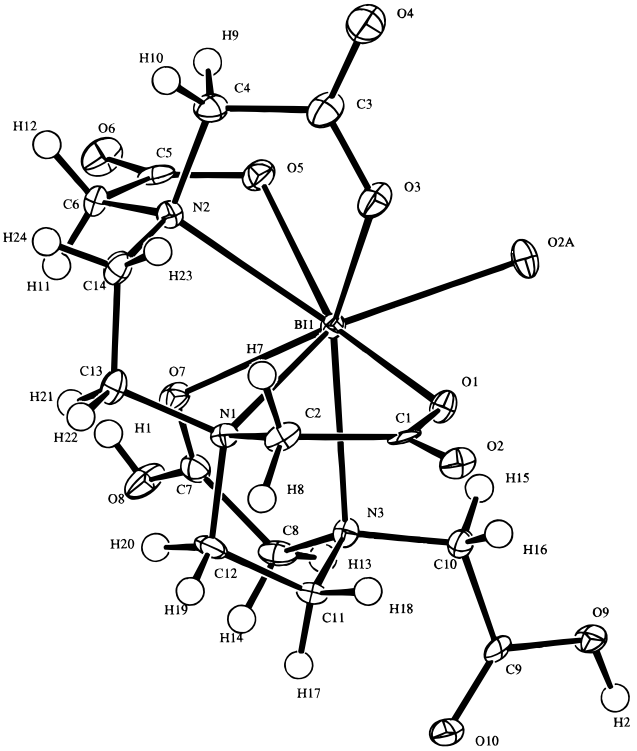


Figure 2. Structure of Bi(H_2DTPA)$^{2-}$ (**6**). Atom O2A is from a neighboring molecule.

Results and Discussion

Synthetic Studies. Prior reports of H_5CyDTPA were limited to the patent literature and a conference abstract with few applicable details.[11] Therefore, H_5CyDTPA (**1**) was prepared via modification of the previously reported route to the C-functionalized version of this ligand designed for modification of proteins (Scheme 1).[9]

The components of the triamine were assembled directly from the transiently isolated active ester of CBZ-glycine which was

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Table 2. Selected Bond Distances (Å) and Bond Angles (deg) in [guanidinium$^+$]$_2$[Bi(CyDTPA)$^{2-}$] (**5**) and Bi(H$_2$DTPA)·2H$_2$O (**6**)

[guanidinium$^+$]$_2$[Bi(CyDTPA)$^{2-}$] (**5**)

Bi−O(3)	2.371(4)	O(5)−C(14)	1.269(7)	N(2)−C(3)	1.522(7)	C(3)−C(4)	1.527(8)
Bi−O(5)	2.405(4)	O(6)−C(14)	1.235(7)	N(3)−C(15)	1.486(7)	C(3)−C(8)	1.532(8)
Bi−N(2)	2.458(5)	O(7)−C(16)	1.251(7)	N(3)−C(17)	1.503(7)	C(4)−C(5)	1.536(8)
Bi−O(9)	2.479(4)	O(8)−C(16)	1.260(7)	N(3)−C(4)	1.522(7)	C(5)−C(6)	1.516(10)
Bi−O(1)	2.528(4)	O(9)−C(18)	1.261(7)	N(4)−C(19)	1.344(9)	C(6)−C(7)	1.504(11)
Bi−N(1)	2.548(5)	O(10)−C(18)	1.234(7)	N(5)−C(19)	1.291(8)	C(7)−C(8)	1.521(9)
Bi−N(3)	2.592(5)	N(1)−C(9)	1.473(8)	N(6)−C(19)	1.366(9)	C(9)−C(10)	1.514(10)
Bi−O(7)	2.610(4)	N(1)−C(1)	1.480(8)	N(7)−C(20)	1.316(7)	C(11)−C(12)	1.500(9)
O(1)−C(10)	1.274(8)	N(1)−C(11)	1.490(7)	N(8)−C(20)	1.323(7)	C(13)−C(14)	1.539(9)
O(2)−C(10)	1.230(8)	N(2)−C(13)	1.484(7)	N(9)−C(20)	1.314(7)	C(15)−C(16)	1.546(8)
O(3)−C(12)	1.290(7)	N(2)−C(2)	1.507(8)	C(1)−C(2)	1.515(9)	C(17)−C(18)	1.479(9)
O(4)−C(12)	1.225(7)						

O(3)−Bi−O(5)	133.93(14)	N(2)−Bi−N(3)	72.4(2)	C(9)−N(1)−C(1)	112.2(5)	C(17)−N(3)−Bi	107.3(3)
O(3)−Bi−N(2)	77.7(2)	O(9)−Bi−N(3)	65.6(2)	C(9)−N(1)−C(11)	111.1(5)	C(4)−N(3)−Bi	108.4(3)
O(5)−Bi−N(2)	70.0(2)	O(1)−Bi−N(3)	148.9(2)	C(1)−N(1)−C(11)	112.3(5)	N(1)−C(1)−C(2)	113.6(5)
O(3)−Bi−O(9)	146.71(14)	N(1)−Bi−N(3)	138.4(2)	C(9)−N(1)−Bi	106.4(4)	N(2)−C(2)−C(1)	113.3(5)
O(5)−Bi−O(9)	68.3(2)	O(3)−Bi−O(7)	69.93(14)	C(1)−N(1)−Bi	107.1(3)	N(2)−C(3)−C(4)	111.3(5)
N(2)−Bi−O(9)	92.9(2)	O(5)−Bi−O(7)	155.74(14)	C(11)−N(1)−Bi	107.4(4)	N(3)−C(4)−C(3)	111.1(5)
O(3)−Bi−O(1)	96.52(14)	N(2)−Bi−O(7)	128.55(14)	C(13)−N(2)−C(2)	109.7(5)	N(1)−C(9)−C(10)	114.1(6)
O(5)−Bi−O(1)	86.6(2)	O(9)−Bi−O(7)	93.1(2)	C(13)−N(2)−C(3)	112.1(4)	O(1)−C(10)−C(9)	117.4(6)
N(2)−Bi−O(1)	137.7(2)	O(1)−Bi−O(7)	85.87(14)	C(2)−N(2)−C(3)	108.8(4)	N(1)−C(11)−C(12)	115.0(5)
O(9)−Bi−O(1)	111.0(2)	N(1)−Bi−O(7)	124.51(14)	C(13)−N(2)−Bi	108.4(4)	O(3)−C(12)−C(11)	117.6(6)
O(3)−Bi−N(1)	68.0(2)	N(3)−Bi−O(7)	64.06(14)	C(2)−N(2)−Bi	108.0(4)	N(2)−C(13)−C(14)	115.0(5)
O(5)−Bi−N(1)	72.1(2)	C(10)−O(1)−Bi	116.0(4)	C(3)−N(2)−Bi	109.8(3)	O(5)−C(14)−C(13)	118.1(6)
N(2)−Bi−N(1)	74.1(2)	C(12)−O(3)−Bi	121.3(4)	C(15)−N(3)−C(17)	109.0(5)	N(3)−C(15)−C(16)	112.6(5)
O(9)−Bi−N(1)	140.4(2)	C(14)−O(5)−Bi	118.4(4)	C(15)−N(3)−C(4)	112.7(5)	O(7)−C(16)−C(15)	119.9(5)
O(1)−Bi−N(1)	65.1(2)	C(16)−O(7)−Bi	111.5(4)	C(17)−N(3)−C(4)	112.4(5)	C(18)−C(17)−N(3)	115.7(5)
O(3)−Bi−N(3)	81.15(14)	C(18)−O(9)−Bi	119.7(4)	C(15)−N(3)−Bi	106.8(3)	O(9)−C(18)−C(17)	118.3(6)
O(5)−Bi−N(3)	117.4(2)						

Bi(H$_2$DTPA)·2H$_2$O (**6**)

Bi(1)−O(1)	2.309(3)	O(2)−C(1)	1.247(5)	O(10)−C(9)	1.222(6)	N(3)−C(11)	1.473(6)
Bi(1)−O(2)[a]	2.620(3)	O(3)−C(3)	1.293(6)	N(1)−C(2)	1.498(6)	C(1)−C(2)	1.524(7)
Bi(1)−O(3)	2.290(3)	O(4)−C(3)	1.233(6)	N(1)−C(12)	1.502(6)	C(3)−C(4)	1.512(7)
Bi(1)−O(5)	2.699(3)	O(5)−C(5)	1.275(6)	N(1)−C(13)	1.517(6)	C(5)−C(6)	1.521(7)
Bi(1)−O(7)	2.602(3)	O(6)−C(5)	1.245(6)	N(2)−C(4)	1.486(6)	C(7)−C(8)	1.499(7)
Bi(1)−N(1)	2.449(4)	O(7)−C(7)	1.220(6)	N(2)−C(6)	1.478(6)	C(9)−C(10)	1.527(6)
Bi(1)−N(2)	2.563(4)	O(8)−C(7)	1.311(6)	N(2)−C(14)	1.482(6)	C(11)−C(12)	1.516(7)
Bi(1)−N(3)	2.723(4)	O(9)−C(9)	1.318(6)	N(3)−C(8)	1.475(6)	C(13)−C(14)	1.507(7)
O(1)−C(1)	1.274(6)			N(3)−C(10)	1.462(6)		

O(1)−Bi(1)−O(2)	77.1(1)	O(5)−Bi(1)−N(1)	126.1(1)	C(12)−N(1)−C(13)	108.0(4)	O(4)−C(3)−C(4)	117.5(5)
O(1)−Bi(1)−O(3)	72.6(1)	O(5)−Bi(1)−N(2)	60.7(1)	Bi(1)−N(2)−C(4)	106.7(3)	N(2)−C(4)−C(3)	113.5(4)
O(1)−Bi(1)−O(5)	159.0(1)	O(5)−Bi(1)−N(3)	120.3(1)	Bi(1)−N(2)−C(6)	110.4(3)	O(5)−C(5)−O(6)	125.3(5)
O(1)−Bi(1)−O(7)	132.4(1)	O(7)−Bi(1)−N(1)	74.4(1)	Bi(1)−N(2)−C(14)	107.8(3)	O(5)−C(5)−C(6)	117.1(4)
O(1)−Bi(1)−N(1)	70.4(1)	O(7)−Bi(1)−N(2)	74.5(1)	C(4)−N(2)−C(6)	108.5(4)	O(6)−C(5)−C(6)	117.6(4)
O(1)−Bi(1)−N(2)	122.1(1)	O(7)−Bi(1)−N(3)	63.5(1)	C(4)−N(2)−C(14)	110.3(3)	N(2)−C(6)−C(5)	111.8(4)
O(1)−Bi(1)−N(3)	75.2(1)	N(1)−Bi(1)−N(2)	72.8(1)	C(6)−N(2)−C(14)	112.9(4)	O(7)−C(7)−O(8)	123.1(5)
O(2)−Bi(1)−O(3)	75.7(1)	N(1)−Bi(1)−N(3)	71.3(1)	Bi(1)−N(3)−C(8)	111.5(3)	O(7)−C(7)−C(8)	124.0(4)
O(2)−Bi(1)−O(5)	85.7(1)	N(2)−Bi(1)−N(3)	130.2(1)	Bi(1)−N(3)−C(10)	101.9(3)	O(8)−C(7)−C(8)	112.8(4)
O(2)−Bi(1)−O(7)	130.9(1)	Bi(1)−O(1)−C(1)	119.8(3)	Bi(1)−N(3)−C(11)	103.7(2)	N(3)−C(8)−C(7)	113.8(4)
O(2)−Bi(1)−N(1)	147.5(1)	Bi(1)−O(2)−C(1)	129.3(3)	C(8)−N(3)−C(10)	112.5(4)	O(9)−C(9)−O(10)	124.5(4)
O(2)−Bi(1)−N(2)	128.1(1)	Bi(1)−O(3)−C(3)	119.8(3)	C(8)−N(3)−C(11)	113.0(4)	O(9)−C(9)−C(10)	111.6(4)
O(2)−Bi(1)−N(3)	100.2(1)	Bi(1)−O(5)−C(5)	112.0(3)	C(10)−N(3)−C(11)	113.3(4)	O(10)−C(9)−C(10)	124.0(4)
O(3)−Bi(1)−O(5)	91.6(1)	Bi(1)−O(7)−C(7)	116.7(3)	O(1)−C(1)−O(2)	125.6(5)	N(3)−C(10)−C(9)	117.1(4)
O(3)−Bi(1)−O(7)	142.2(1)	Bi(1)−N(1)−C(2)	106.3(3)	O(1)−C(1)−C(2)	117.6(4)	N(3)−C(11)−C(12)	111.8(4)
O(3)−Bi(1)−N(1)	94.9(1)	Bi(1)−N(1)−C(12)	112.3(3)	O(2)−C(1)−C(2)	116.8(4)	N(1)−C(12)−C(11)	113.5(4)
O(3)−Bi(1)−N(1)	67.7(1)	Bi(1)−N(1)−C(13)	110.3(3)	N(1)−C(2)−C(1)	113.2(4)	N(1)−C(13)−C(14)	112.2(4)
O(3)−Bi(1)−N(3)	147.7(1)	C(2)−N(1)−C(12)	109.7(4)	O(3)−C(3)−O(4)	124.9(5)	N(2)−C(14)−C(13)	112.4(4)
O(5)−Bi(1)−O(7)	68.4(1)	C(2)−N(1)−C(13)	110.1(3)	O(3)−C(3)−C(4)	117.6(4)		

[a] Symmetry operator = $^1/_2 - x$, $^1/_2 + y$, $^1/_2 - z$.

reacted with excess (±)-*trans*-1,2-diaminocyclohexane to provide exclusively monoamide **2**. The carbamate was removed by acid and the resultant dihydrobromide reduced directly by BH_3 generating the requisite triamine **4**. Alkylation of the triamine with *tert*-butyl bromoacetate provided the crude pentaester. Cleavage of the ester groups with trifluoroacetic acid followed by purification via ion-exchange chromatography afforded **1**.

The bismuth complexes were prepared by reaction of bismuth subcarbonate (as described previously[12] for the synthesis of Bi(DTPA)$^{2-}$) or bismuth nitrate with the free ligands.

Structure Analysis. The solid-state structures of [(guanidinium)$_2$][Bi(CyDTPA)$^{2-}$] (**5**) and Bi(H$_2$DTPA)·2H$_2$O (**6**) are shown in Figures 1 and 2. Bond-length parameters of these and of [(guanidinium)$_2$][Bi(DTPA)$^{2-}$]·4H$_2$O (**7**)[12] and K[Bi(HDTPA)]·4 H$_2$O (**8**)[13] are compared in Table 3. The conformational preorganization effect of the cyclohexylene bridge substituent may be assessed by comparing complex **5** with **7**.

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Table 3. Comparison of Bond Distances in **5**−**8**

parameter	Structure			
	(guanidinium)$_2$ Bi(CyDTPA) (**5**)	Bi(H_2DTPA)·2H_2O (**6**)	(guanidinium)$_2$ Bi(DTPA)·4H_2O (**7**)	K[Bi(HDTPA]·4H_2O (**8**)
ligand charge	5-	3-	5-	4-
Bi coordination no.	8	8	9	9
Bi−N (central N)	2.458(5)	2.449(4)	2.536(7)	2.489(7)
Bi−N (terminal N 1)	2.548(5)	2.563(4)	2.626(6)	2.55(1)
Bi−N (terminal N 2)	2.592(5)	2.723(4)[a]	2.639(6)	2.669(8)
Bi−O from central N	2.405(4)	2.309(3)	2.479(5)	2.384(7)
Bi−O from terminal N 1	2.371(4)	2.290(3)	2.494(5)	2.362(8)
Bi−O from terminal N 1	2.528(4)	2.699(3)[b]	2.599(5)	2.525(8)
Bi−O from terminal N 2	2.479(4)	2.602(3)[c]	2.368(5)	2.568(8)
Bi−O from terminal N 2	2.610(4)		2.562(5)	2.734(8)[c]
Bi−O (intermolecular or H_2O)		2.620(3)[d]	2.686(6)[d]	2.749(7)[e]

[a] Only one carboxylate of this nitrogen is coordinated. [b] Strong H-bonding of this oxygen to another molecule. [c] Other oxygen of this carboxylate is protonated. [d] Ligand carbonyl oxygen of nearby molecule. [e] Bi−O of coordinated water.

CyDTPA has a stronger interaction with bismuth(III) as seen by a lower Bi coordination number of eight in **7** and correspondingly shorter Bi−ligand bond distances on average. Solid-state structures of complexes **6** and **7** have intermolecular donation of a DTPA carbonyl oxygen to a neighboring bismuth center, giving rise to infinite polymer chains in **6** and to a dimer in **7**. Because this intermolecular interaction may not persist in aqueous solution, the Bi(DTPA)$^{2-}$ may be labile by comparison to Bi(CyDTPA)$^{2-}$ due to the presence of an open coordination site. *In vivo* studies of lability of C-functional analogues of **5** and **7** are in accord with this.[8,14]

Partial protonation of the DTPA ligand has interesting effects on structure, as seen in the structures of the complex of H_2DTPA^{3-} (**6**) and of HDTPA^{4-} (**8**). In both of these the Bi−N(terminal) distances are asymmetric, reflecting a lengthening of the Bi−N distance for which a protonated carboxylate is bound to the nitrogen. Interestingly, the two protonated carboxyl groups in **6** are bonded to the same nitrogen atom with one of them (C9) not coordinated to the Bi center. The Bi−O separations in all four compounds are quite asymmetric. This asymmetry is greatest for the complex (**6**) of the most highly protonated ligand H_2DTPA^{3-}. The Bi−O distances range from 2.3 to 2.7 Å with the shortest distances being found in the diprotonated **6**, followed by the monoprotonated **8**, the eight-coordinate fully-deprotonated **5**, and the nine-coordinate fully-deprotonated **7**. In all structures, the two short Bi−O contacts come from carboxylates bonded to different N atoms. In each case one of the two shortest Bi−O separations belongs to the carboxylate bonded to the central N atom.

The coordination spheres of **5** and **6** may be examined for evidence of lone pair activation.[19] The coordination spheres of both **5** and **6** may be derived from a square antiprism.[15a] The coordination sphere of **5** (Figure 3) lies along a D_2-symmetric interconversion pathway between the square antiprism and the dodecahedron.[15b] This geometry is obtained by a folding of the two square faces of a square antiprism. The folded square faces of the antiprism are defined by N(2)−N(3)−O(5)−O(9) and N(1)−O(1)−O(3)−O(7), and their deviations from planarity are 0.20 and 0.21 Å respectively. The folding bends N(3), O(5), N(1), and O(7) toward the equatorial plane of Figure 3. With respect to a dodecahedron, this leads them to the ***B*** sites[16−18] and the remaining donors toward the ***A*** sites of the dodecahedron.

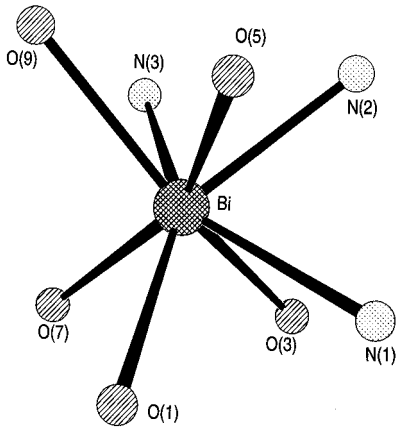

Figure 3. Bismuth coordination sphere of Bi(CyDTPA)$^{2-}$ (**5**).

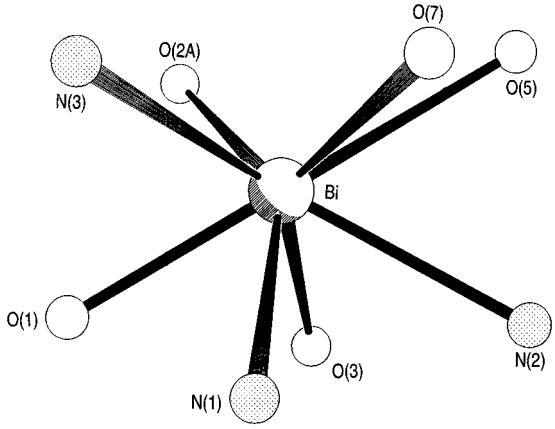

Figure 4. Bismuth coordination sphere of Bi(H_2DTPA) (**6**).

The coordination sphere of **6** is derived from a folding of one square face of the square antiprism, giving rise to a bicapped trigonal prism. Thus, in reference to Figure 4, the square face N(1)−N(2)−O(1)−O(3) is folded (deviation from planarity 0.21 Å) while the other face N(3)−O(2A)−O(5)−O(7) is relatively planar (deviation 0.042 Å). This distortion creates a bicapped trigonal-prismatic coordination sphere in which the capping atoms (N(2) and O(1)) come from the square face that is folded.[15c] Structural analysis of $BiCl_3$ crown ether complexes suggests a lone pair on Bi(III) located at the center of three weak Bi−O interactions and a highly distorted bicapped trigonal prismatic coordination sphere geometry.[19] While **6** contains relatively disparate Bi−(N, O) bond lengths (see above) and

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(18) *The teXsan Crystal Structure Analysis Package*; Molecular Structure Corp.: The Woodlands, TX, 1985.

the bicapped trigonal prism is somewhat irregular (angles of Table 2), there is neither a clear location at the center of the weakest Bi−(N,O) interactions nor an empty coordination site[19c] for a lone pair, and we therefore believe the disparity in bond lengths in **6** is due to protonation of $DTPA^{5-}$ rather than lone pair activation.

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Acknowledgment. We thank the National Institutes of Health for financial support (R.P.P.). The technical assistance of Mr. Neng Ye is acknowledged.

Supporting Information Available: Tables of positional parameters, anisotropic thermal parameters, bond lengths and angles, and hydrogen atom parameters for **5** and **6** (16 pages). Ordering information is given on any current masthead page.

IC951326P