Synthesis and Characterization of Racemic Mixture and Meso Isomers of Bis(*trans*-2-aminocyclohexyl)aminepentaacetic Acid and the Stabilities of Their Gd(III) Complexes

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The synthesis and characterization of two multidentate ligands, the racemic mixture and meso isomers of bis(*trans*-2-aminocyclohexyl)aminepentaacetic acid, are described. Equilibrium constants for their Gd(III) complexes were determined by direct potentiometry. The formation constants (K_{ML} = [ML]/[M][L]) of Gd(III)−$Cycy_{racemic}$ in 0.10 M KCl at 25.0 °C is $10^{20.71}$; that for the meso isomer is $10^{20.42}$. The crystal structure of (1S,2S,1′S,2′S)-bis(*trans*-2-aminocyclohexyl)amine-*N*,*N*,*N*′,*N*′′,*N*′′-pentaacetic acid, penta-*tert*-butyl ester ($C_{42}H_{75}N_3O_{10}$), is reported. This compound crystallizes in the triclinic system with space group *P*1 with cell parameters a = 10.805(2) Å, b = 11.382(2) Å, c = 20.999(4) Å, α = 91.41(3)°, β = 98.23(3)°, γ = 113.88(3)°, V = 2327.8(8) Å^3, Z = 2, D_x = 1.116 g mL^{-1}. The results are compared to the crystal structures of the gadolinium complexes and the predictions derived from molecular mechanics.

Introduction

Magnetic resonance imaging (MRI) has become one of the primary imaging methods in modern medicine.[1,2] With the widespread use of MRI has come a demand for efficient paramagnetic contrast agents used to enhance the contrast between normal and diseased tissue or to indicate specific organ functions. Research has been focused mostly on complexes of gadolinium(III), iron(III), and manganese(II) because of their high magnetic moments. The signal intensity in MRI depends largely on the longitudinal relaxation rate ($1/T_1$) and the transverse rate ($1/T_2$) of water protons. Contrast agents of gadolinium(III) complexes belong to the "T_1 agents",[2] which induce larger relaxation enhancement and are strongly favored in MRI development.[2] Current MRI contrast agents in clinical use are all polyamino−polycarboxylate complexes of gadolinium, e.g., Magnevist, $[Gd(DTPA)(H_2O)]^{2-}$;[3] Omniscan, $[Gd(DTPA\text{-}BMA)(H_2O)]$;[4] Dotarem, $[Gd(DOTA)(H_2O)]^{-}$;[5] ProHance, $[Gd(HP\text{-}DO3A)(H_2O)]$;[6] Gadovist, $[Gd(DO3A\text{-}butrol)(H_2O)]$;[7] MultiHance, $[Gd(BOPTA)(H_2O)]^{2-}$.[8]

The gadolinium ion is extremely toxic and is retained in the liver, spleen, and bone.[9] High stability is therefore imperative for gadolinium chelates that are being considered as MR contrast agents. In general, a chelate with greater degree of lipophilicity will have greater hepatobiliary clearance. For example, substitution of an ethoxybenzyl group to the backbone of the DTPA chelate $[Gd(EOB\text{-}DTPA)]^{-2}$ enhances hepatobiliary clearance compared to the parent chelate.[10] Lipophilic agents will have greater uptake in certain organs and may have potential as organ-specific agents.

CDTA (*trans*-1,2-cyclohexylenedinitrilotetraacetic acid) is an analogue of EDTA. By the substitution of the ethylene backbone with a cyclohexylene ring, the lipophilicity is increased, and the trans arrangement of the two aminodiacetate groups may better fit the requirement of the coordination site of the metal ion and greatly increases the complex stability of some divalent and trivalent transition metal complexes.[11] From the data in Table 1, it can be seen that the CDTA chelates are more stable than the EDTA chelates by 2−5 orders of magnitude. Part of this increase in stability is due to the greater basicity of CDTA ($\sum\{[H_nL]/([H_{n-1}L][H])\}$ = 25.9, n = 1, 2, 3, 4) over that of EDTA ($\sum\{[H_nL]/([H_{n-1}L][H])\}$ = 22.5, n = 1, 2, 3, 4). However, most of the increase is due to the greater preorganization of the donor groups of CDTA over those of EDTA, as explained by Martell and Hancock.[13] On that basis, it was decided to investigate a DTPA analogue in which the ethylene

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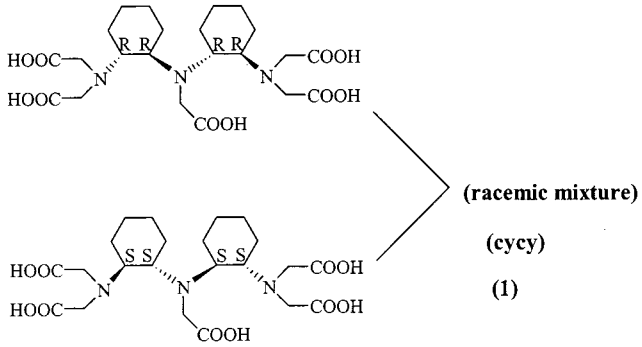
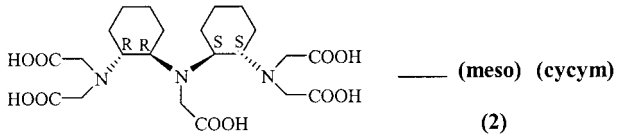
Table 1. Protonation Constants of EDTA and CDTA and Their Stability Constants for Cu(II), Gd(III), and Fe(III) (μ = 0.10 M KCl, T = 25.0 °C)

equilibrium quotient	protonation constants and log K of EDTA[12] complexes	protonation constants and log K of CDTA[12] complexes
HL/H·L	10.19	12.3
H_2L/HL·H	6.13	6.11
H_3L/H_2L·H	2.69	3.49
H_4L/H_3L·H	2.0	2.4
H_5L/H_4L·H	1.5	1.6
GdL/Gd·L	17.4	19.5
Fe(III)L/Fe(III)·L	25.1	30.0
Cu(II)L/Cu(II)·L	18.8	22.0

groups are replaced by cyclohexylene groups with the diamino groups in the trans position. This gives rise to two isomers: a racemic mixture and a meso form, as indicated by formulas **1**

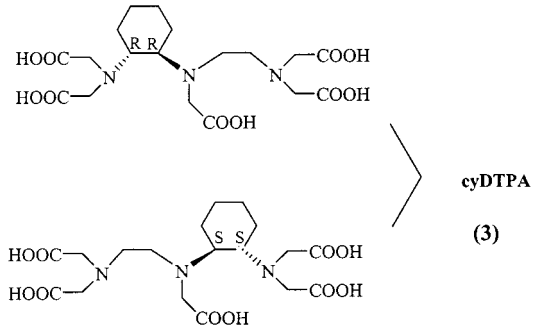


and **2**. These two ligands have different physical properties and



should produce Gd(III) complexes with different stabilities.

A German patent by M. Dexter (J. R. Geigy A.G.)[14] claimed the preparation of the sodium salt of the monocyclohexyl derivative of DTPA, i.e., CyDTPA (**3**). However, the ligand



they prepared is a mixture of the cis and trans isomers. M. W. Brechbiel et al.[15,16] published the synthesis of the trans isomers of CyDTPA and the stabilities of their Bi(III) and Y(III) complexes. Caulfield and co-workers[17] reported preparation of the DTPA analogue with two cyclohexylene rings on the backbone (cycy, **1**; cycym, **2**), i.e., dicyclohexenetriaminepentaacetic acid [Gd(DCTPA)$^{2-}$, WIN 70197] and the crystal structure of its gadolinium chelate. The preliminary relaxation studies and toxicological evaluations of the complex showed that it is a promising liver-targeted MRI constrast agent. The present study is focused on the coordination chemistry of these ligands, the separation and characterization of the stereoisomers, and the stability constants of their gadolinium complexes.

Experimental Section

Synthesis and Characterization of the Ligands. Materials and Methods. *Trans*-1,2-diaminocyclohexane, *tert*-butyl bromoacetate, and trifluoroacetic acid were obtained from Aldrich Chemical Co. and were used as supplied. [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (**4**),[18] *N*-(*p*-tolylsulfonyl)-7-azabicyclo[4,1,0]heptane (**5**),[18] and the meso form of bis(*trans*-2-aminocyclohexyl)amine (**6′**)[19] were prepared by previously reported procedures. Two solutions for the chromatographic separation of the racemic and meso isomers were prepared: (A) CH_2Cl_2/MeOH = 8:2 (v/v); (B) dry NH_3 (gas) dissolved in a solution of 640 mL of CH_2Cl_2 and 160 mL of MeOH in an ice−water bath until the total volume became 900 mL.

The proton and carbon-13 NMR were recorded on a VXR-300 spectrometer operating at 300 MHz, and the chemical shifts are reported in ppm relative to tetramethylsilane. The mass spectra were obtained with the Chemistry Department VG analytical 70S high-resolution double-focusing magnetic sector spectrometer with an attached VG analytical 11/250J data system. Measurements were made by the Chemistry Department mass spectrometry specialist, Dr. Lloyd W. Sumner. Fast atom bombardment (FAB) technique was used for ionization. The C, H, N analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. The melting point was determined with a Fisher-Johns melting point apparatus and was uncorrected.

Synthetic Route and Procedures. The routes used for the synthesis of cycy (**1**) and cycym (**2**) are shown in Scheme 1.

(a) Racemic Mixture of Bis(*trans*-2-aminocyclohexyl)amine (6). The procedure described by Henrichs et al.[19] was followed and modified. (±)-*trans*-1,2-Diaminocyclohexane, 15.7 g (0.137 mol) was dissolved in 30 mL of anhydrous acetonitrile and was heated to reflux. A solution of 5.7 g (0.023 mol) of *N*-tosylcyclohexylaziridine (**5**) in 8 mL of acetonitrile was added dropwise within 20 min. The reaction solution was refluxed under Ar for 3 h and was allowed to stand at room temperature for 20 h. The solvent and excess (±)-*trans*-1,2-diaminocyclohexane were removed in vacuo. To the pale-yellow oil 50 mL of hexane was added, and the mixture was stirred at room temperature for 1 h. The colorless hexane solution was removed by decantation. Another 50 mL of hexane was added to the sticky oil and heated to reflux for 2 h. After it was cooled, the pale-yellow precipitate that separated was collected by filtration and washed with hexane. The solid isolated was dissolved in 35 mL of concentrated sulfuric acid and heated in a 120 °C bath for 24 h. After the solution was cooled, the reaction mixture was placed in an ice−water bath and 200 mL of anhydrous ether was added portionwise to complete the precipitation. The mixture was filtered under Ar and washed with 2 × 30 mL of dry ethyl ether. The solid material was transferred to a flask cooled in an ice−water bath; 12−13 mL of 50% NaOH solution was added portionwise and cautiously. A large amount of solid and ether solution separated. This mixture was extracted with 6 × 30 mL of ether. The combined ether solutions were filtered and dried with anhydrous $MgSO_4$. From this dry ether solution, 3.3 g of pale-yellow precipitate was obtained. This 3.3 g of crude product was loaded on 60 g of silica gel 60 and was eluted by solvents A and B. The pure racemic mixture

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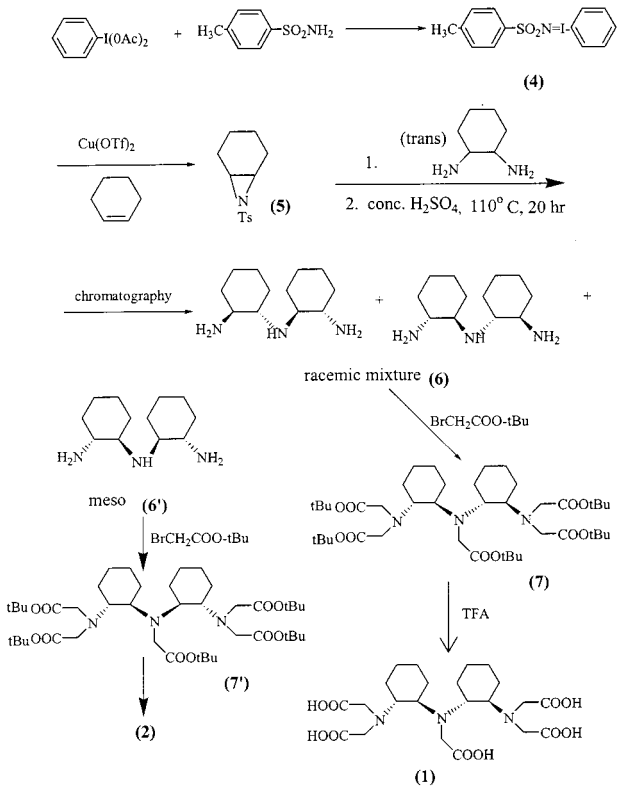
Scheme 1



was obtained by twice chromatographic separation with mixed solvent of A/B = 9:1 and 8:2 (v/v). After all the racemic mixture was eluted from the column, pure meso isomer was obtained by washing with A/B = 7:3, 6:4, and 1:1. ^{1}H NMR of the racemic mixture (in $CDCl_3$; see Figure 1 for numbering system of cyclohexene), δ: 2.31 & 2.11 (m, 4H, −CH− of **1** & **2** of cyclohexylene); 2.01 (m, 4H, **3** of cyclohexylene); 1.87 (m, 4H, **6** of cyclohexylene); 1.67 (b, 5H, NH & NH_2); 1.2−1.0 (m, 8H, **4** & **5** of cyclohexylene). ^{1}H NMR of the meso isomer (in $CDCl_3$), δ: 2.36 & 2.11 (m, 4H, −CH− of **1** & **2** of cyclohexylene); 1.90 (m, 4H, 3 of cyclohexylene); 1.67 (m, 4H, **6** of cyclohexylene); 1.57 (b, 5H, NH & NH_2); 1.2−1.0 (m, 8H, **4** & **5** of cyclohexylene). ^{13}C NMR of the racemic mixture (in $CDCl_3$),δ: 60.2 & 55.5 (−CH− of **1** & **2** of cyclohexylene); 36.3 ($-CH_2-$ of **6** cyclohexylene); 32.3 ($-CH_2-$ of **3** cyclohexylene); 25.33 & 25.28 ($-CH_2-$ of **5** & **4** of cyclohexylene). ^{13}C NMR of the meso isomer (in $CDCl_3$), δ: 63.5 & 56.4 (−CH− of **1** & **2** of cyclohexylene); 34.4 ($-CH_2-$ of **6** cyclohexylene); 33.9 ($-CH_2-$ of **3** cyclohexylene); 25.2 ($-CH_2-$ of **5** of cyclohexylene); 24.5 (CH_2- of **4** of cyclohexylene). For comparison, the ^{13}C NMR spectra of the racemic and meso isomers with the numbering scheme for NMR assignment are shown in Figure 1. Anal. Calcd for $C_{12}H_{25}N_3 \cdot 0.1H_2O$ (racemic): C, 67.67; H, 11.84; N, 19.74. Found: C, 67.60; H, 11.96; N, 19.62.

(b) Racemic Mixture of Bis(*trans*-2-aminocyclohexyl)amine−*N,N,N′,N″,N″*-Pentaacetic Acid, Penta-*tert*-butyl Ester (7). Compound **6**, 0.46 g (2.18 mmol), *tert*-butyl bromoacetate, 4.25 g (21.8 mmol), and potassium carbonate, 1.5 g (10.9 mmol), was mixed with 27 mL of acetonitrile and was heated in a 65 °C bath for 20 h. The reaction mixture was filtered, and the insoluble material was washed with dichloromethane. The filtrate and washings were combined. The excess *tert*-butyl bromoacetate was removed at 2−3 mmHg and 45 °C, and 2.5 g of pale-yellow oil was obtained. This crude product was purified on silica gel 60; the impurities were removed by elution with 98/2 (v/v) of hexane/ethyl acetate. After elution with 95/5 and 9/1 (v/v) of hexane/ethyl acetate mixed solvent, 1.9 g of colorless oil was obtained. One gram of colorless crystalline product was obtained from crystallization of the dichloromethane solution; yield 58%, mp = 118−119 °C. ^{1}H NMR (in $CDCl_3$; see Figure 1 for the numbering scheme of the cyclohexylene), δ: 3.59 & 3.57 (s, 10H, $-CH_2-$ of acetate); 2.75 & 2.55 (t, 4H, −CH− of **1** & **2** of cyclohexylene); 2.1 (m, 4H, **6** of cyclohexylene); 1.66 (m, 4H, **3** of cyclohexylene); 1.48 & 1.45 (s, 45H, *tert*-butyl); 1.2−1.1 (m, 8H, **4** & **5** of cyclohexylene). ^{13}C NMR (in $CDCl_3$), δ: 171.9 (carboxy); 80.1 ($-CH_2-$ of the acetate); 65.2 & 63.8 (−CH− of **1** & **2** of cyclohexylene); 53.5 ($-CH_2-$ of **6** cyclohexylene); 31.4 ($-C-(CH_3)_3$); 29.3 ($-CH_2-$ of **3** cyclohexylene); 28.2 ($-C-(CH_3)_3$); 25.9 ($-CH_2-$ of **4** & **5** of cyclohexylene). FAB MS: [M + 1] = 782. Anal. Calcd for $C_{42}H_{75}N_3O_{10}$: C, 64.47; H, 9.95; N, 5.37. Found: C, 64.70; H, 9.59; N, 5.35.

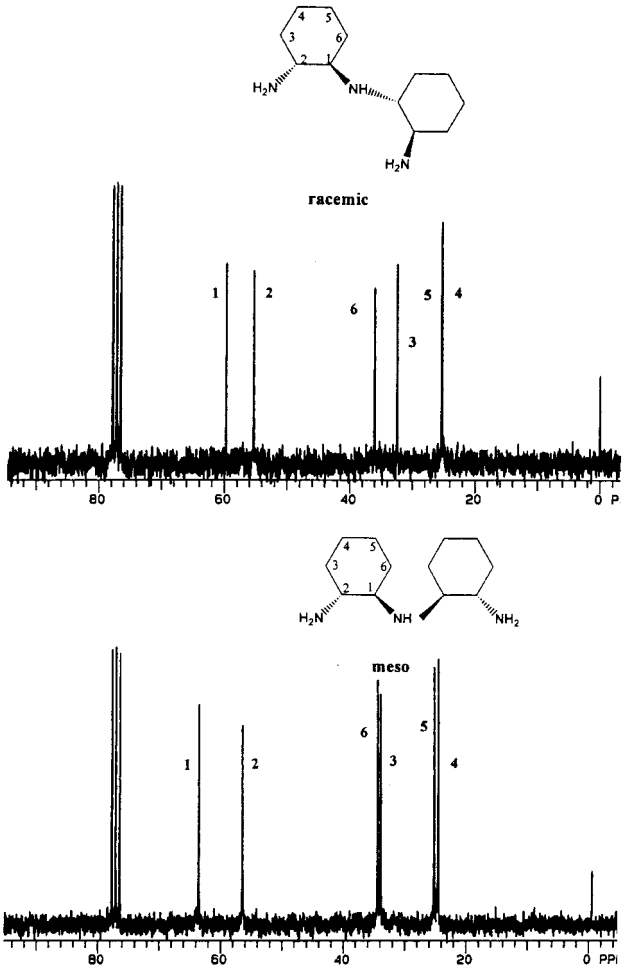


Figure 1. ^{13}C NMR spectra of the racemic and meso isomers of bis(*trans*-2-aminocyclohexyl)amine.

(c) Meso Isomer of Bis(*trans*-2-aminocyclohexyl)amine−*N,N,N′,N″,N″*-Pentaacetic Acid, Penta-*tert*-butyl Ester (7′). A similar procedure was used except that compound **6′** was used as starting material; yield 50%. ^{1}H NMR (in $CDCl_3$), δ: 3.57 & 3.56 (s, 10H, $-CH_2-$ of acetate.); 2.6−2.7 (m, 4H, −CH− of **1** & **2** of cyclohexylene); 2.1 & 1.9 (m, 4H, **6** of cyclohexylene); 1.65 (m, 4H, **3** of cyclohexylene); 1.48 & 1.45 (s, 45H, *tert*-butyl); 1.3−1.1 (m, 8H, **4** & **5** of cyclohexylene).^{13}C NMR (in $CDCl_3$), δ: 171.9 (carboxy); 80.1 ($-CH_2-$ of the acetate); 63.7 & 59.9 (−CH− of **1** & **2** of cyclohexylene); 53.5 ($-CH_2-$ of **6** cyclohexylene); 32.0 ($-C-(CH_3)_3$); 30.1 ($-CH_2-$ of **3** cyclohexylene); 28.2 ($-C-(CH_3)_3$); 25.9 & 26.0 ($-CH_2-$ of **4** & **5** of cyclohexylene). FAB MS: [M + 1] = 782.

(d) Racemic Mixture of Bis(*trans*-2-aminocyclohexyl)amine−*N,N,N′,N″,N″*-Pentaacetic Acid (1). Compound **7**, 1.29 g (1.65 mmol), was dissolved in 60 mL of trifluoroacetic acid (TFA) and was stirred at room temperature for 18 h. The volatile material was removed by rotavaporation. Water, 50 mL, was added and then evaporated under reduced pressure to remove the excess TFA. This procedure was repeated. The white residue was dissolved in 20 mL of water (pH is about 0.8) and was neutralized with 2.5 M NaOH until pH = 6.8, then acidified with 2.5 M HCl to pH = 1.0. This aqueous solution was allowed to stand at 5 °C for 24 h. A large amount of fine crystalline product separated. It was filtered and washed with cold water and dried

over P_2O_5/1 mmHg at room temperature for 24 h; 0.68 g of product was obtained; yield 79%. ^{1}H NMR (in D_2O, pD = 1, *t*-BuOH as internal standard, 1.29 ppm), δ: 4.1−3.8 (m, 10H, $-CH_2-$ of acetate); 3.38 & 3.17 (t, 4H, −CH− of **1** & **2** of cyclohexylene); 2.27 & 2.15 (m, 4H, **3** of cyclohexylene); 1.78 (m, 4H, **6** of cyclohexylene); 1.6−1.2 (m, 8H, **4** & **5** of cyclohexylene). ^{13}C NMR (in D_2O, pD = 1, *t*-BuOH as internal standard, $-CH_3$ is 31.1 ppm), δ: 171.9 (carboxy); 68.4 & 66.6 ($-CH_2-$ of the acetate); 54.2 & 45.9 (−CH− of **1** & **2** of cyclohexylene); 32.4 ($-CH_2-$ of **3** cyclohexylene); 26.5 ($-CH_2-$ of **6** cyclohexylene); 26.1 & 25.2 ($-CH_2-$ of **4** & **5** of cyclohexylene). FAB MS: [M + Na^+] = 524. Anal. Calcd for $C_{22}H_{35}N_3O_{10}\cdot NaCl\cdot(^1/_4)H_2O$: C, 46.36; H, 6.19; N, 7.38. Found: C, 46.29; H, 6.15; N, 7.01.

(e) Meso Isomer of Bis(*trans*-2-aminocyclohexyl)amine−*N,N,N′,N″,N″*-Pentaacetic Acid (2). A similar procedure was used except compound **7′** (1.7 g, 2.2 mmol) was used as starting material, and 1.2 g of product was obtained; yield 90%. ^{1}H NMR (in D_2O, pD = 1, CH_3OD as internal standard, 3.34 ppm), δ: 3.9−3.6 (m, 10H, $-CH_2-$ of acetate.); 3.6 & 3.3 (t, 4H, −CH− of **1** & **2** of cyclohexylene); 2.27 & 2.13 (m, 4H, **3** of cyclohexylene); 1.78 (m, 4H, **6** of cyclohexylene); 1.2−1.6 (m, 8H, **4** & **5** of cyclohexylene). ^{13}C NMR (in D_2O, pD = 1, CH_3OD as internal standard, 49.0 ppm), δ: 171.3 (carboxy); 65.2 & 64.3 ($-CH_2-$ of the acetate); 53.3 & 46.9 (−CH− of **1** & **2** of cyclohexylene); 32.3 ($-CH_2-$ of **3** of cyclohexylene); 28.2 ($-CH_2-$ of **6** of cyclohexylene); 26.2 & 24.1 ($-CH_2-$ of **4** & **5** of cyclohexylene). FAB MS: [M + Na^+] = 524. Anal. Calcd for $C_{22}H_{35}N_3O_{10}\cdot 0.95CF_3COOH$: C, 47.01; H, 5.89; N, 6.88. Found: C, 47.32; H, 6.58; N, 6.89.

(f) Other Reagents and Standard Solutions. A metal ion solution of Gd(III)) was prepared at about 0.02 M from analytical grade chloride salt with demineralized water and was standardized by complexometric titration with EDTA and by cation exchange (Dowex 50W-X8 cation exchange resin, 20−50 mesh, hydrogen form).

A carbonate-free solution of the titrant, KOH, was prepared by dilution of analytical concentrate "Dilut-It" (J. T. Baker Chemical Co.) with demineralized water under a stream of purified argon gas. The solution was standardized with potassium acid phthalate, and the extent of the carbonate accumulation was checked periodically by titration with a standard hydrochloric acid solution.

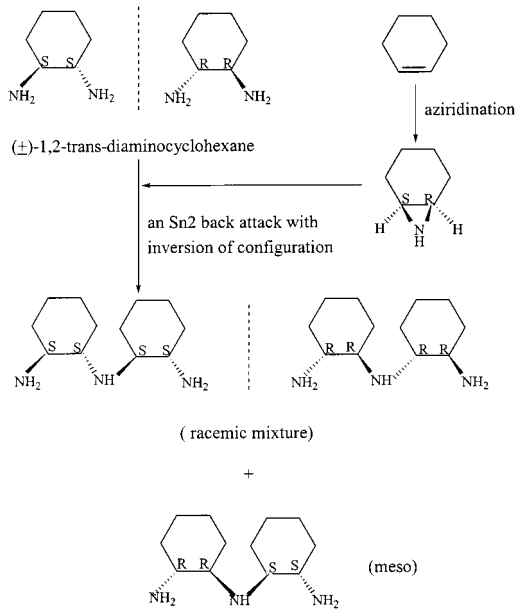
(g) Potentiometric Equipment and Measurements. A Corning pH/ion analyzer 250 instrument was used together with a model S-30056-10C Sargent Welch glass electrode and a Fisher 13-639-52 calomel reference electrode. A completely sealed 75 mL glass-jacketed titration cell was used, and the temperature, 25.0 °C ± 0.1 °C, was controlled with a Fisher model 90 refrigerated bath. Atmospheric CO_2 was excluded from the cell during the titration by passing purified argon through the experimental solution in the reaction cell. The standard base was delivered through a capillary tip just under the surface of the solution by means of a 10 mL capacity Metrohm piston-type buret.[20]

Prior to each potentiometric equilibrium study, a calibration of the pH meter and electrode system was made using standard dilute HCl solutions at an ionic strength of 0.100 M adjusted with KCl in the thermostated cell at 25.0 °C to read hydrogen ion concentration directly. Thus, the term p[H] in this work is defined as $-\log [H^+]$. The value of $K_W = [H^+][OH^-]$ used in the computations was $10^{-13.78}$.

The potentiometric equilibrium measurements were made on 40−50 mL of ligand solutions initially 5.30×10^{-3} M, first in the absence of metal ions and then in the presence of the metal ion for which [L]/[M^{3+}] ratios were about 1.04:1. The p[H] values were measured after addition of 0.100 mL increments of standard KOH solution. The protonation constants of the ligands and the stability constants of the Gd(III) chelates were obtained directly from the pH titration data and calculated with the BEST program.[20]

(h) X-ray Diffraction Studies of the Racemic Mixture of Bis-(*trans*-2-aminocyclohexyl)amine−*N,N,N′,N″,N″*-Pentaacetic Acid, Penta-*tert*-butyl Ester (7). Single crystals suitable for X-ray diffraction were prepared by slow evaporation of its dichloromethane solution. A colorless needle of compound **7** having dimensions of 0.44 × 0.20 × 0.20 mm was mounted on a glass fiber. Examination and data collection

Scheme 2



were performed on a Bruker P4 X-ray diffractometer at 296(2) K. The structure was solved by direct method and refined by least-squares[21] to residuals $R = 0.0832$ [$I > 2\sigma(I)$], $R_w = 0.1377$; 7968 reflections were collected [R(int) = 0.0620]. Hydrogen atoms were placed in ideal positions. Selected bond lengths and angles (with the corresponding data of CDTA and DTPA), torsional angles of the two cyclohexylene rings, atom coordinates, equivalent isotropic displacement parameters, and anisotropic displacement parameters are provided in Tables S1 (Supporting Information) and are available from the authors.

(i) Molecular Modeling. All computations were performed with the commercially available modeling package SYBYL[22] utilizing the TAFF force field, running on a Silicon Graphics workstation.[23] The gadolinium parameters and details of the coordination scan have been previously published.[23]

Results and Discussion

Synthetic Methods. The synthetic route for the preparation of Cycy and Cycym is outlined in the Scheme 1. The key step for the preparation of these ligands is the separation of the racemic mixture and meso isomer of bis(*trans*-2-aminocyclohexyl)amine. By the reaction of *trans*-1,2-diaminocyclohexane with the cyclohexylaziridine, only three isomers can be formed. The two that are mirror-image to each other are the racemic mixture, and the third one is the meso isomer (see Scheme 2). The racemic mixture and the meso isomer are diastereomers and have similar chemical properties and different physical properties. They can be separated by silica gel flash chromatography by an dichloromethane−methanol (v/v of $^8/_2$) mixed solvent with 1−2% of $NH_{3(gas)}$. Henrichs and co-workers[18] characterized the meso isomers from racemic mixtures with the combined use of chiral shift reagents and two-dimensional heteronuclear correlation NMR spectroscopy. However, they did not isolate the pure racemic mixture or describe any of their NMR spectra. Figure 1 shows the differences of the ^{13}C NMR of these diastereomers.

Crystal Structure of (1S,2S,1′S,2′S)-Bis(*trans*-2-aminocyclohexyl)amine−*N,N,N′,N″,N″*-Pentaacetic Acid, Penta-*tert*-

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Table 2. Crystal Data for (1S,2S,1′S,2′S)-Bis(*trans*-2-aminocyclohexyl)amine−*N*,*N*,*N*′,*N*″,*N*″-Pentaacetic Acid, Penta-*tert*-butyl Ester

empirical formula	$C_{42}H_{75}N_3O_{10}$
fw	782.05
temp, K	296(2)
λ, Å	0.710 73
cryst syst	triclinic
space group	*P*1
a, Å	10.805(2)
b, Å	11.382(2)
c, Å	20.999(4)
α, deg	91.41(3)
β, deg	98.23(3)
γ, deg	113.88(3)
V, Å^3	2327.8(8) Å^3
Z	2
calcd density, Mg/m^3	1.116
abs coeff, mm^{-1}	0.078
F(000)	856
reflns collected/unique	8214/7968 [*R*(int) = 0.0620]
abs correction	ψ scan
max and min transm	0.995 and 0.970
refinement method	full-matrix least-squares on F^2
final *R* indices[a] [$I > 2\sigma(I)$]	R1 = 0.0832, wR2 = 0.2336
R indices[b] (all data)	R1 = 0.1377, wR2 = 0.2800

[a] $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR(F^2) = \sum|w(F_o^2 - F_c^2)^2|/\sum wF_o^4$.

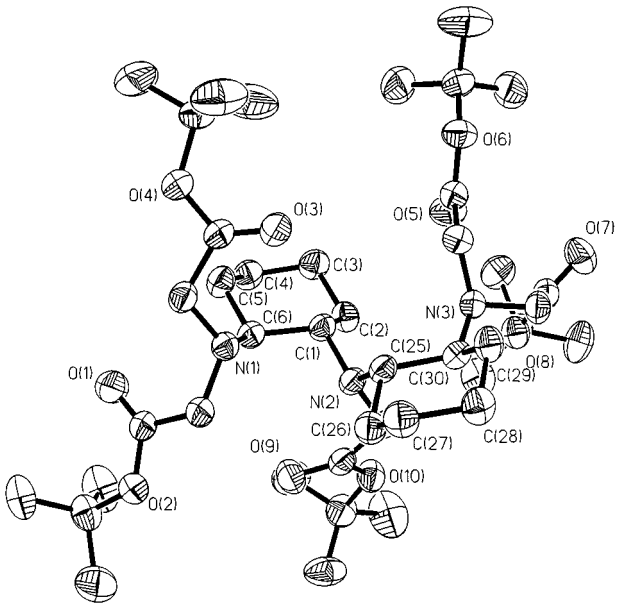

Figure 2. Thermal ellispoid (30%) plot of (1S,2S,1′S,2′S)-bis(*trans*-2-aminocyclohexyl)amine−*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid, penta-*tert*-butyl ester.

butyl Ester. To further prove the stereochemical property of our ligands, the single-crystal structure of the penta-*tert*-butyl ester (**7**) was also determined. A summary of crystallographic results is given in Table 2. The structure was solved and refined in the space group *P*1. Figure 2 illustrates the structure of one of the isomers of the racemic mixture: (1S,2S,1′S,2′S)-bis(*trans*-2-aminocyclohexyl)amine−*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid, penta-*tert*-butyl ester. The average N−C bond distance is 1.47 Å and compares well with that of CDTA (1.462 Å).[24] The C−N−C bond angles of the two peripheral nitrogen are almost identical to those of DTPA,[25] and the difference in the angles of the middle nitrogen is probably due to the formation of a hydrogen bond in DTPA.[25]

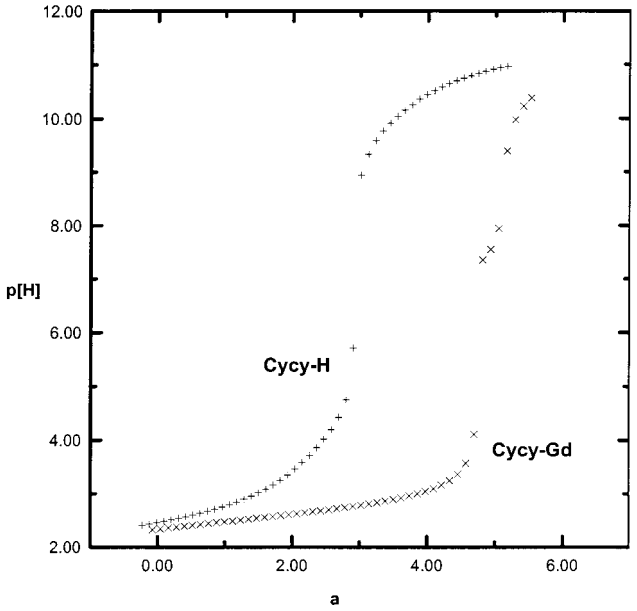

Figure 3. Potentiometric p[H] profile of Cycy and its complexes with Gd(III) at μ = 0.10 M KCl, T = 25.0 °C ± 0.1 °C: a = moles of base added per mole of ligand present (Cycy−H, T_{Cycy} = 0.002 18 M; Cycy−Gd, T_{Cycy} = 0.001 97 M, T_{Gd} = 0.001 89 M).

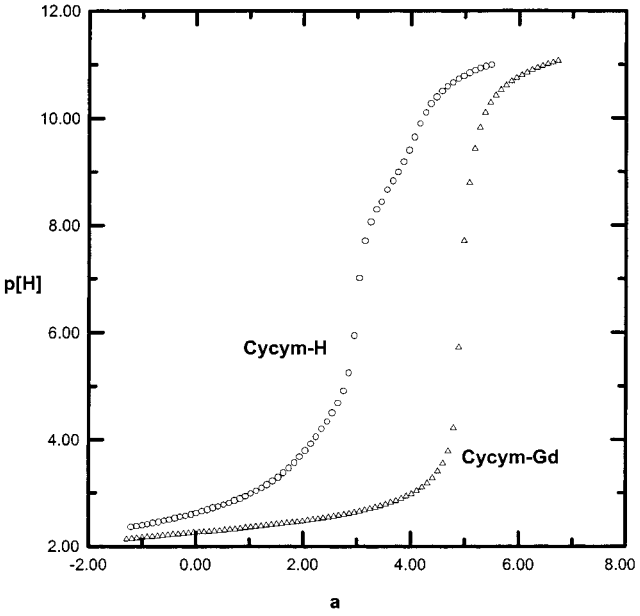

Figure 4. Potentiometric p[H] profile of Cycym and its complexes with Gd(III) at μ = 0.10 M KCl, T = 25.0 °C ± 0.1 °C: a = moles of base added per mole of ligand present (Cycym−H, T_{Cycym} = 0.00232 M; Cycym-Gd, T_{Cycym} = 0.00244 M, T_{Gd} = 0.00228 M).

The cyclohexane rings of the molecules have the chair conformation with standard values of both valence angles and the C−C distances at the carbon atoms. The average value of the C−C−C angle is 110.9(3)°, comparable with that of CDTA, 110.5(3)°,[24] and the average of C−C distances is 1.530(5) Å, very close to that of CDTA, 1.523(5) Å.[24] The values of the torsional angles are also characteristic of cyclohexane. The C^6−N^1 and C^1−N^2 bonds are equatorial, confirming the trans configuration of the nitrogen atoms relative to the plane of the

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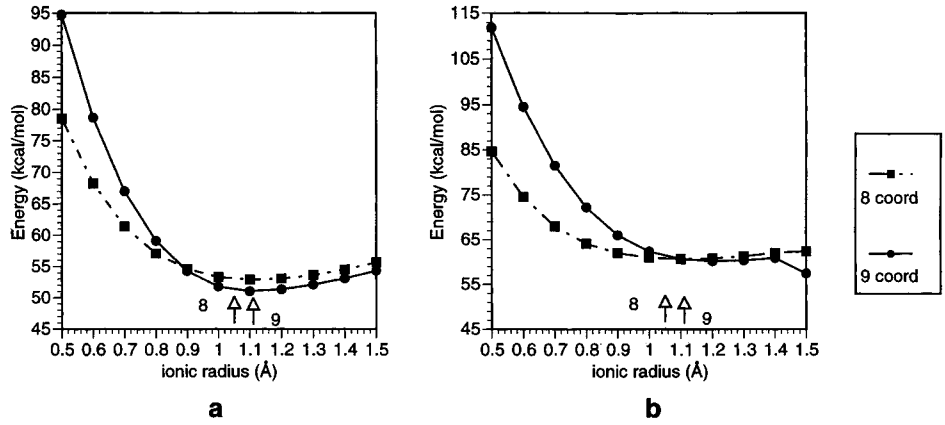

Figure 5. (a) Coordination scan for Gdcycy indicating the preferred ionic radii for eight- and nine-coordinate Gd(III) (1.053 and 1.107 Å, respectively). (b) Coordination scan for Gdcycym indicating the preferred ionic radii for eight- and nine-coordinate Gd(III).

Table 3. Protonation Constants of Cycy, Cycym, and DTPA, and Their Stability Constants for Gd(III) (μ = 0.10 M KCl, T = 25.0 °C ± 0.1 °C)

equilibrium quotient	log K[a] of Cycy	log K[a] of Cycym	log K of DTPA[6]
HL/H·L	11.02	10.77	10.49
H_2L/HL·H	10.28	8.56	8.53
H_3L/H_2L·H	3.94	4.39	4.28
H_4L/H_3L·H	2.22	2.80	2.65
H_5L/H_4L·H	1.53	2.33	1.82
GdL/Gd·L	20.71	20.42	22.46
GdHL/GdL·H	1.92	2.38	2.34 (20 °C)
pM[b]	12.9	14.7	17.0

[a] The estimated error of protonation constants is ±0.01, and that of the stability constants is ±0.02. [b] 100% excess ligand at pH 7.4.

cyclohexane fragment established in the literature.[26] This compound crystallizes in space group $P1$, which means it does not have a plane of symmetry in its molecule. It is one of the racemic mixture. This structure also shows that the precursor of this compound and the following product, the pentaacetic acid derivative, are also racemic mixtures.

Protonation Constants and Stability Constants. The titration curves of the two ligands and their Gd(III) complexes are shown in Figures 3 and 4. The protonation constants of the two ligands and the stability constants of their Gd(III) complexes are shown in Table 3. The species distribution curves of the Cycy−Gd and Cycym−Gd systems are provided in Figures 1 and 2 of S2 of Supporting Information, respectively, and are available from the authors.

The stability constants of both ligands (racemic and meso) for Gd(III) are about 2 log units lower than that of log K of DTPA. This was not anticipated in view of the prediction (see Introduction) that the cyclohexane rings would increase the stabilties of the complexes formed. In a previous study of gadolinium complexes, the coordination scan was utilized to develop a linear relationship between the thermodynamic stability constant log K and the quantity referred to as ΔE_{coord}.[23] This term, ΔE_{coord}, is the energy difference between the solvated complex, with the appropriate number of waters bound to the Gd, and the desolvated complex. It represents the energetic cost in changing the coordination state of a complex from the preferred state, in the case of GdCycy, 9, to that due entirely to the coordinating ability of the ligand alone. A remarkable feature is that this effect is due entirely to steric interactions. Electronic and electrostatic effects are not considered in the coordination scan.

The coordination scans of both complexes GdCycy and GdCycym are shown in Figure 5. In order for a given coordination state to be favorable, the preferred ionic radius must be on the correct side of the crossover point; the closer an ionic radius is to a crossover point the more the other coordination state contributes to the equilibrating system. In addition, the energy difference between the "ideal radii" of a particular coordination number and the crossover point indicates how readily the coordination of a particular complex will change; a small difference in energies is favorable, while a large difference would disfavor a change in coordination. As can be seen in Figure 5, GdCycy would prefer to be nine-coordinate, with the ionic radius (1.107 Å) well to the right of the crossover point (0.89 Å). GdCycym would prefer to be eight-coordinate (ionic radius 1.053 Å) with the crossover point located at 1.15 Å.

Since GdCycy is predicted to favor a coordination number of 9, our previously developed relationship should be valid. For gadolinium polyaminopolycarboxylate complexes,

$$\log K = (-1.115124)(\Delta E_{coord}) + 27.37513$$

The calculated value of ΔE_{coord} for GdCycy of 3.6 leads to a predicted stability constant of 23.4. In comparison GdDTPA has a ΔE_{coord} of 3.2, leading to a predicted log K of 23.8. While the absolute value of predicted log K's may be higher than found experimentally (see Table 3), the model does predict that GdCycy would be less stable than GdDTPA.

Caulfield et al.[17] reported the X-ray structure of the GdCycy complex. As expected, the ligand occupied eight of the nine coordination sites of the gadolinium ion. The remaining coordination sites of the metal ions are bound with a water molecule with a Gd(III)−O distance of 2.42 Å, a value similar to the 2.49 Å reported for $Gd(DTPA)^{2-}(H_2O)$. This report disclosed limited information about the bond distances and angles. Caravan et al.[2] show that the Gd−N distances (2.80 Å) to the central nitrogen is long in Gd(CycyDTPA) relative to that of the DTPA complexes (2.62 Å average). The difference in crystal structure is stated to be due to a steric effect, in agreement with our work on the differences of Gd(III) stability constants.

The synthesis and Gd(III) stability determination of another derivative with one cyclohexylene group substituted on the backbone of DTPA[15] are in progress.

Acknowledgment. This research was supported by U.S. Public Health Service, National Cancer Institute, CA-42925

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(A.E.M. and M.J.W.). National Science Foundation Grant CHE-8705697 supported the purchase of the mass spectrometer.

Supporting Information Available: X-ray crystallographic files in CIF format. Eight tables listing the atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and torsion angles, and figures showing the thermal ellispoid (50%) of compound **7** (S,S,S,S), and species distribution curves of Gd(III)−Cycy system and Gd(III)−Cycym system. This material is available free of charge via the Internet at http://pubs.acs.org.

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