Syntheses and Characterizations of Metal Complexes Derived from *cis,cis*-1,3,5-Triaminocyclohexane-*N,N′,N″*-triacetic Acid

Hongyan Luo,† Natashia Eberly,† Robin D. Rogers,‡ and Martin W. Brechbiel*,†

Radioimmune & Inorganic Chemistry Section, Radiation Oncology Branch, NCI, NIH, Bethesda, Maryland 20892, and Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487

Received June 6, 2000

A convenient six-step procedure is developed to routinely prepare the hexadentate ligand *cis,cis*-1,3,5-triaminocyclohexane-*N,N′,N″*-triacetic acid (H_3tachta) as an HCl salt. Complexes of gallium(III) and indium(III), [Ga(tachta)] and [In(tachta)], are synthesized from the reactions of the ligand and the corresponding metal precursors. Copper(II), palladium(II), and cobalt(II) complexes, [Cu(Htachta)], [Pd(Htachta)], and [Co(Htachta)], are obtained from the reactions of H_3tachta with the corresponding metal chlorides. The structures of H_3tachta·3HCl·2H_2O ($C_{12}H_{28}Cl_3N_3O_8$) and [Ga(tachta)] ($C_{12}H_{18}GaN_3O_6$) are characterized. The crystal of H_3tachta·3HCl·2H_2O is monoclinic, of the space group $P2_1/c$, with $a = 15.1688(4)$ Å, $b = 8.4708(2)$ Å, $c = 15.9408(2)$ Å, $\beta = 108.058(1)°$, and $Z = 4$; that of [Ga(tachta)] is cubic, of space group $Pa3$, with $a = 14.0762(1)$ Å and $Z = 8$. The gallium atom of [Ga(tachta)] is six-coordinated in the solid state, and the complex assumes a pseudooctahedronal geometry with the completely deprotonated hexadentate ligand encapsulating the metal ion.

Introduction

Neutral, lipophilic radiopharmaceuticals are of interest for possible use in diagnostic imaging of the heart, brain, and tumors.[1,2] Gallium has isotopes that are useful in radiopharmaceutical applications;[2] thus, tripodal triprotic N_3O_3 hexadentate chelating ligands have been developed to form neutral, stable Ga complexes, as exemplified by those chelates based on 1,4,7-triazacyclononane (TACN), *cis,cis*-1,3,5-triaminocyclohexane (tach), and 1,1,1-tris(aminomethyl)ethane (tame) frameworks. The N_3O_3 donor sets provide potential octahedral coordination spheres for metal ions such as Ga(III).[3−12] Radiopharmaceutical studies of the corresponding gallium isotopes complexed with a few N_3O_3 chelating ligands have been reported.[13−16]

cis,cis-1,3,5-Triaminocyclohexane (tach) as a base is especially interesting because of its well-known tripodal framework that may provide a geometric arrangement appropriate for relatively small metal ions that contains three amine donor atoms. Efforts to develop triprotic N_3O_3 hexadentate tach-based chelating agents have been focused on phenolate derivatives (Chart 1).[3,7,12,17−19] However, the tricarboxylic acid counterpart *cis,cis*-1,3,5-triaminocyclohexane-*N,N′,N″*-triacetic acid (H_3tachta) has been virtually unexplored for its chemistry, despite its being a known ligand for over 30 years.[20] The lack of study of the coordination chemistry of this ligand might be attributable to the fact that the previous synthesis involved the use of highly toxic cyanide in a Mannich reaction to introduce the carboxylates, a method which also lacks flexibility to synthesize other related derivatives.[20] Additionally, until recently, synthesis of tach itself has been sufficiently challenging so as to contribute to minimizing investigations into the chemistry of its derivatives.[12,21,22]

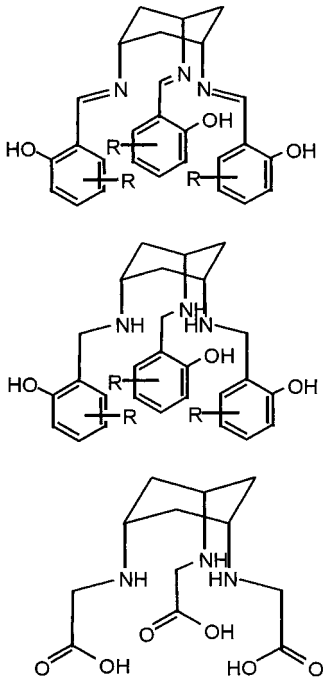
We previously developed an improved synthesis of tach and prepared its nonprotic $N_3N'_3$ and N_3S_3 hexadentate chelates.[22−24] Extending these prior studies, we report herein a general route

* Corresponding author. Phone: (301) 496-0591. Fax: (301) 402-1923. E-mail: martinwb@box-m.nih.gov.
† NIH.
‡ The University of Alabama.

(1) Reichert, D. E.; Lewis, J. S.; Anderson, C. J. *Coord. Chem. Rev.* **1999**, *184*, 3−66.
(2) Anderson, C. J.; Welch, M. J. *Chem. Rev.* **1999**, *99*, 2219−2234.
(3) Bollinger, J. E.; Mague, J. T.; Roundhill, D. M. *Inorg. Chem.* **1994**, *33*, 1241−1242.
(4) Broan, C. J.; Cox, J. P. L.; Craig, A. S.; Kataky, R.; Parker, D.; Harrison, A.; Randall, A. M.; Ferguson, G. *J. Chem. Soc., Perkin Trans. 2* **1991**, 87−99.
(5) Clarke, E. T.; Martell, A. E. *Inorg. Chim. Acta* **1991**, *186*, 103−111.
(6) Craig, A. S.; Parker, D.; Adams, H.; Bailey, N. A. *J. Chem. Soc., Chem. Commun.* **1989**, 1793−1794.
(7) Green, M. A.; Welch, M. J.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 3689−3691.
(8) Liu, S.; Wong, E.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1993**, *32*, 4268−4276.
(9) Liu, S.; Wong, E.; Karunaratne, V.; Rettig, S. J.; Orvig, C. *Inorg. Chem.* **1993**, *32*, 1756−1765.
(10) Moore, D. A.; Fanwick, P. E.; Welch, M. J. *Inorg. Chem.* **1989**, *28*, 1504−1506.
(11) Moore, D. A.; Fanwick, P. E.; Welch, M. J. *Inorg. Chem.* **1990**, *29*, 672−676.
(12) Bollinger, J. E.; Mague, J. T.; O'Connor, C. J.; Banks, W. A.; Roundhill, D. M. *J. Chem. Soc., Dalton Trans.* **1995**, 1677−1688.
(13) Green, M. A.; Welch, M. J.; Mathias, C. J.; Fox, K. A. A.; Knabb, R. M.; Huffman, J. C. *J. Nucl. Med.* **1985**, *26*, 170−180.
(14) Green, M. A. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 1227−1229.
(15) Green, M. A.; Mathias, C. J.; Neumann, W. L.; Fanwick, P. E.; Janik, M.; Deutsch, E. A. *J. Nucl. Med.* **1993**, *34*, 228−233.
(16) Bollinger, J. E.; Banks, W. A.; Kastin, A. J.; Welch, M. J.; Roundhill, D. M. *Nucl. Med. Biol.* **1996**, *23*, 645−652.
(17) Greener, B.; Cronin, L.; Wilson, G. D.; Walton, P. H. *J. Chem. Soc., Dalton Trans.* **1996**, 401−403.
(18) Lions, M. *J. Am. Chem. Soc.* **1957**, *79*, 1572−1574.
(19) Caravan, P.; Orvig, C. *Inorg. Chem.* **1997**, *36*, 236−248.
(20) Zompa, L. J.; Shindler, J. M. *Chem. Commun.* **1971**, 65−66.
(21) Bollinger, J. E.; Mague, J. T.; Banks, W. A.; Kastin, A. J.; Roundhill, D. M. *Inorg. Chem.* **1995**, *34*, 2143-2152.
(22) Bowen, T.; Planalp, R. P.; Brechbiel, M. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 807−810.
(23) Hilfiker, K. A.; Brechbiel, M. W.; Rogers, R. D.; Planalp, R. P. *Inorg. Chem.* **1997**, *36*, 4600−4603.

10.1021/ic000603b CCC: $20.00
Published on Web 12/07/2000

Chart 1. Currently Known tach-Based Tripodal N_3O_3 Chelating Complexes



to a triprotic N_3O_3 tach-based ligand, H_3tachta, which contains three methylene carboxylic acid donor atoms on tach. We also report an investigation of the Ga(III) coordination chemistry of H_3tachta, as well as the syntheses of In(III), Cu(II), Pd(II), and Co(II) complexes of this ligand. This presents our initial investigation into understanding the coordination chemistry of H_3tachta and its derivatives, although structural data of the latter complexes are not available at this time. The radiolabeling of the H_3tachta ligand and the serum stability and murine biodistribution of the ^{67}Ga-labeled compound will be reported elsewhere.[25]

Experimental Section

General Information. All solvents and reagents were obtained from either Aldrich or Fluka and were used as received. NMR spectra were obtained on a Varian Gemini 300 spectrometer, with δ referenced to internal TMS. CIMS and FAB mass spectra were recorded on a Finnigan 3000 and an Extrel 4000 mass spectrometer (with positive-ion detection), respectively. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

The triamine *cis,cis*-1,3,5-triaminocyclohexane trihydrobromide (tach·3HBr, **1**) was prepared according to a literature procedure.[22]

***N,N′,N″*-Tribenzyl-*cis,cis*-1,3,5-triaminocyclohexane (tach(Bz)$_3$, 2).** A solution of sodium hydroxide (1.94 g, 48.40 mmol) in water (10 mL) was added to tach·3HBr (6.0 g, 16.13 mmol). To the resultant clear solution was added benzene (120 mL), the mixture was heated to reflux, and the refluxing solution was azeotropically dried using a Dean−Stark trap. After all of the water had been removed, the solution was cooled to room temperature. Benzaldehyde (5.129 g, 4.9 mL, 48.40 mmol) was then added, and the resulting mixture was refluxed for 18 h. The solution was decanted, and the solvent was removed by rotary evaporation, resulting in a yellow oil, which was dried in vacuo to yield a semisolid (4.45 g, 70%). The identity of the oil was confirmed as the expected Schiff base by CIMS (*m*/*e* 394, M + 1) and ^{1}H NMR spectroscopy. This material was taken up in methanol (120 mL), and sodium borohydride (1.84 g, 48.40 mmol) was added in small portions, after which the mixture was stirred at room temperature for 18 h. The solution was concentrated to dryness by rotary evaporation, and the residue was taken up in $CHCl_3$ (120 mL). Brine (50 mL) and NaOH solution (1 M, 50 mL) were added, and the mixture was stirred vigorously at room temperature for 1 h. The resulting solution was poured into a separatory funnel, and the volume was doubled with $CHCl_3$. The organic layer was retained, washed with brine (100 mL), dried over $MgSO_4$, and filtered, and the filtrate was concentrated to yield the product as an oil, which was then dried in vacuo for 18 h (4.52 g, 93%). CIMS: *m*/*e* = 400 (M + 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4−7.2 (m, 15H, overlapped Ph *o,m,p-H*), 3.83 (s, 6H, N−CH_2), 2.58 (tt, $^3J_{HH}$ = 18.3 Hz, 3H, backbone C*H*−N), 2.23 (d, $^3J_{HH}$ = 18.3 Hz, 3H, backbone CH_aH), 1.10 (q, $^3J_{HH}$ = 18.3 Hz, 3H, backbone CHH_e). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.05 MHz): δ 140.32, 128.43, 128.06, 126.92, 126.89 (nontertiary phenyl *C*), 53.17 (methyl *C*), 50.96 (backbone methine *C*H), 40.19 (backbone *C*H_2).

***N,N′,N″*-Tribenzyl-*cis,cis*-1,3,5-triaminocyclohexane-*N,N′,N″*-tris-(*tert*-butyl acetate) ((*t*-Bu)$_3$tachta(Bz)$_3$, 3).** To a solution of *tert*-butyl bromoacetate (7.29 g, 37.38 mmol) and Na_2CO_3 (3.96 g, 37.38 mmol) was added **2** (4.52 g, 11.33 mmol) in DMF (200 mL). The mixture was allowed to stir while being heated to ∼90 °C for 18 h. It was then cooled to room temperature and extracted with $CHCl_3$ (100 mL). The organic phase was collected and washed with water (100 mL) and then with brine (2 × 100 mL), dried over $MgSO_4$, and filtered, and the filtrate was concentrated by rotary evaporation to an orange oil, which was then left to dry in vacuo for 18 h (6.96 g, 83%). CIMS: *m*/*e* = 742 (M + 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40−7.18 (m, 15H, overlapped Ph *o,m,p-H*), 3.80 (s, 6H, N−CH_2−Ph), 3.20 (s, 6H, N−CH_2−CO_2−*t*-Bu), 2.58 (t, 3H, backbone C*H*−N), 2.12 (d, 3H, backbone CH_aH), 1.52−1.38 (m, 27H, *t*-Bu *H*), 1.08 (q, 3H, backbone CHH_e).

***cis,cis*-1,3,5-Triaminocyclohexane-*N,N′,N″*-tris(*tert*-butyl acetate) ((*t*-Bu)$_3$tachta, 4).** To a solution of the alkylation product (6.96 g, 9.39 mmol) in EtOH (100 mL) was added 10% Pd/C catalyst (2.5 g). The resulting mixture was subjected to hydrogenation by agitation with excess H_2(g) at 40 psi on a Parr hydrogenation apparatus at room temperature for 1 week. The reaction mixture was filtered through Celite 577, and the filtrate was concentrated by rotary evaporation and left in vacuo for 18 h (1.53 g, 34%). CIMS: *m*/*e* = 472 (M + 1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.33 (s, 6H, N−CH_2), 2.52 (t, $^3J_{HH}$ = 18.6 Hz, 3H, backbone C*H*−N), 2.66 (d, $^3J_{HH}$ = 18.3 Hz, 3H, backbone CH_aH), 1.77 (q, $^3J_{HH}$ = 18.3 Hz, 3H, backbone CHH_e). ^{13}C{^{1}H} NMR ($CDCl_3$, 75.05 MHz): δ 171.96 (carbonyl *C*), 81.31 (*t*-Bu *C*Me$_3$), 53.20 (methylene *C*), 48.83 (backbone methine *C*H), 39.60 (backbone *C*H_2), 28.00 (*t*-Bu *C*H_3).

***cis,cis*-1,3,5-Triaminocyclohexane-*N,N′,N″*-triacetic Acid Trihydrochloride (H_3tachta·3HCl, 5).** The hydrogenation product was taken up in EtOH (85 mL). Concentrated HCl (50 mL) was slowly added to the solution, and the white suspension was allowed to stir vigorously at room temperature for 18 h. The solid product was collected by suction filtration, washed with Et_2O (2 × 25 mL), and dried in vacuo. The filtrate was concentrated to ca. 20 mL and filtered over a glass frit funnel to collect any additional product. This was also washed with Et_2O (2 × 25 mL) and dried in vacuo (0.98 g, 20%). Anal. Calcd (found): C, 37.40 (37.43); H, 7.12 (6.97); Cl 21.23 (21.05); N, 8.39 (8.12). CIMS: *m*/*e* = 304 (M + 1). ^{1}H NMR (D_2O, 300 MHz): δ 3.94 (s, 6H, N−CH_2), 3.53 (tt, $^3J_{HH}$ = 18.3 Hz, 3H, backbone C*H*−N), 2.66 (d, $^3J_{HH}$ = 18.3 Hz, 3H, backbone CH_aH), 1.77 (q, $^3J_{HH}$ = 18.3 Hz, 3H, backbone CHH_e). ^{13}C{^{1}H} NMR (D_2O, 75.05 MHz): δ 172.43 (carbonyl *C*), 54.95 (methylene *C*), 48.69 (backbone methine *C*H), 32.85 (backbone *C*H_2).

[Ga(tachta)]. To a solution of H_3tachta·3HCl (65.1 mg, 0.157 mmol) in MeOH/$CHCl_3$ (9:1, 40 mL) was added Ga(acac)$_3$ (46.6 mg, 0.127 mmol) in MeOH/$CHCl_3$ (1:1, 8 mL). The resultant cloudy solution was stirred and refluxed overnight, during which a fine white precipitate was formed, which was collected by filtration, washed with MeOH (3 × 2 mL), and dried in air (33.0 mg, 66%). The product was only marginally soluble in H_2O, Et_2O, MeOH, EtOH, CH_2Cl_2, $CHCl_3$, and DMSO-d_6, thus hindering acquisition of NMR data. Anal. Calcd (found) for $C_{12}H_{18}GaN_3O_6$·0.5H_2O·0.5CH_3OH: C, 38.01 (38.00); H, 5.36 (5.25); N, 10.64 (10.62).

(24) Ye, N.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. *Polyhedron* **1998**, *17*, 603−606.
(25) Dadachova, E.; Park, C. W.; Eberly N.; Paik, C.; Brechbiel, M. W. *Nucl. Med. Biol.*, submitted for publication.

Table 1. Crystal Data and Structure Refinement Details for H_3tachta·3HCl·2H_2O (**A**) and [Ga(tachta)] (**B**)

	A	**B**
empirical formula	$C_{12}H_{28}Cl_3N_3O_8$	$C_{12}H_{18}GaN_3O_6$
fw	448.72	370.01
crystal system	monoclinic	cubic
space group	$P2_1/c$	$Pa3$
a, Å	15.1688(4)	14.0762(1)
b, Å	8.4708(2)	14.0762(1)
c, Å	15.9408(2)	14.0762(1)
α, deg	90	90
β, deg	108.058(1)	90
γ, deg	90	90
V, Å^3	1947.37(7)	2789.05(3)
Z	4	8
d_{calc}, g cm^{-3}	1.531	1.762
μ, mm^{-1}	0.515	2.009
radiation (λ, Å)	Mo Kα (0.710 73)	Mo Kα (0.710 73)
diffractometer	Siemens SMART/CCD	Siemens SMART/CCD
h, k, l ranges	17 to 19, −9 to 11, −20 to 20	−18 to 17, −16 to 18, −18 to 16
θ range, deg	1.41−27.86	2.51−27.83
F_{000}	944	1520
no. of data collected	11 880	16 583
no. of unique data (R_{int})	4512 (0.0606)	1121 (0.0789)
no. of data with $I > 2.0\sigma(I)$	3044	885
refinement method	full-matrix least squares	full-matrix least squares
computing	SHELXTL, version 5	SHELXTL, version 5
R1 ($I > 2.0\sigma(I)$)	0.0558	0.0430
wR2 ($I > 2.0\sigma(I)$)	0.1010	0.0860
goodness of fit	1.095	1.139

[In(tachta)]. To a solution of H_3tachta·3HCl (166.6 mg, 0.402 mmol) and $InCl_3$·4H_2O (120.2 mg, 0.410 mmol) in MeOH (25 mL) was added *i*-Pr_2NEt (12 drops) dropwise until a bluish cloudiness was observed. The resultant suspension was stirred and refluxed for 2 h, during which more fine white precipitate was formed. The solid was collected by filtration, washed with MeOH (2 × 5 mL), and air-dried (143.9 mg, 81%). The product was only marginally soluble in H_2O, Et_2O, MeOH, EtOH, CH_2Cl_2, $CHCl_3$, and Me_2SO. Anal. Calcd (found) for $C_{12}H_{18}InN_3O_6$·0.5H_2O·0.5CH_3OH: C, 34.11 (33.97); H, 4.81 (4.78); N, 9.55 (9.36).

[Cu(Htachta)]. To a solution of $CuCl_2$ (69.7 mg, 0.518 mmol) and H_3tachta·3HCl (221.5 mg, 0.535 mmol) in MeOH (30 mL) was added *i*-Pr_2NEt (12 drops) dropwise until a bluish cloudiness was observed. The suspension was doubled in volume and refluxed for 3 h, after which 5 drops more of *i*-Pr_2NEt was added to the clear blue solution. The blue solid that precipitated was collected by filtration, washed with MeOH (5 mL), and dried in vacuo (60.7 mg, 32% based on $CuCl_2$). No attempts were made to maximize the yield by isolating additional material from the blue mother liquor. The product was soluble in H_2O, slightly soluble in MeOH, but insoluble in Et_2O. Anal. Calcd (found) for $C_{12}H_{19}CuN_3O_6$·$^1/_6H_2O$: C, 39.18 (39.46); H, 5.30 (5.79); N, 11.42 (11.12). FABMS: m/z = 366 (Cu(Htachta) + 1).

[Pd(Htachta)]. To a solution of $PdCl_2$ (86.4 mg, 0.487 mmol) and H_3tachta·3HCl (206.5 mg, 0.499 mmol) in MeOH (50 mL) was added *i*-Pr_2NEt (15 drops) dropwise until a yellow fluffy precipitate was formed. The suspension was refluxed overnight, then more *i*-Pr_2NEt (25 drops) was added, and the mixture was refluxed for 6 h. The precipitate was removed by filtration, and the green-yellow solution was slowly evaporated to yield yellow crystalline solids mixed with colorless crystals. The solids were washed with Me_2CO, and the remaining undissolved yellow solid was collected by filtration, washed with $CHCl_3$ (3 × 2 mL) and Et_2O (3 × 2 mL), and then air-dried (110.2 mg, 50% based on $PdCl_2$). The product was moderately soluble in H_2O, slightly soluble in MeOH, but insoluble in Et_2O. Anal. Calcd (found) for $C_{12}H_{19}PdN_3O_6$·0.5H_2O·CH_3OH: C, 34.80 (35.02); H, 5.39 (5.60); N, 9.36 (9.50). FABMS: m/z = 408 (Pd(Htachta) + 1).

[Co(Htachta)]. To a purple solution of $CoCl_2$·H_2O (66.5 mg, 0.512 mmol) and H_3tachta·3HCl (213.2 mg, 0.515 mmol) in MeOH (25 mL) was added *i*-Pr_2NEt (27 drops) dropwise. The resultant reddish suspension was refluxed overnight, during which a pink precipitate was formed. This was collected by filtration, washed with MeOH (2 × 5 mL) and Et_2O (10 mL), and then air-dried (153.7 mg, 77% based on $CoCl_2$·H_2O). The product was soluble in H_2O, slightly soluble in MeOH, but insoluble in Et_2O. Anal. Calcd (found) for $C_{12}H_{19}CoN_3O_6$·0.25H_2O·0.75CH_3OH: C, 39.39 (39.51); H, 5.83 (6.16); N, 10.81 (11.02). FABMS: m/z = 361 (Co(Htachta) + 1).

Table 2. Selected Bond Lengths (Å) and Angles (for) for H_3tachta·3HCl·2H_2O

O(1)−C(8)	1.331(4)	N(1)−C(7)	1.481(4)
O(2)−C(8)	1.199(4)	N(1)−C(1)	1.499(4)
O(3)−C(10)	1.331(4)	N(2)−C(9)	1.498(4)
O(4)−C(10)	1.200(4)	N(2)−C(3)	1.505(4)
O(5)−C(12)	1.200(4)	N(3)−C(11)	1.489(4)
O(6)−C(12)	1.319(4)	N(3)−C(5)	1.504(4)
C(7)−N(1)−C(1)	113.8(2)	O(2)−C(8)−C(7)	125.0(3)
C(9)−N(2)−C(3)	113.2(2)	O(1)−C(8)−C(7)	109.9(3)
C(11)−N(3)−C(5)	113.5(2)	N(2)−C(9)−C(10)	111.1(3)
N(1)−C(1)−C(6)	110.9(2)	O(4)−C(10)−O(3)	126.1(3)
N(1)−C(1)−C(2)	109.3(2)	O(4)−C(10)−C(9)	125.1(3)
N(2)−C(3)−C(2)	111.5(2)	O(3)−C(10)−C(9)	108.8(3)
N(2)−C(3)−C(4)	109.3(2)	N(3)−C(11)−C(12)	109.8(3)
N(3)−C(5)−C(4)	108.9(2)	O(5)−C(12)−O(6)	125.9(3)
N(3)−C(5)−C(6)	110.7(2)	O(5)−C(12)−C(11)	123.7(3)
N(1)−C(7)−C(8)	109.8(3)	O(6)−C(12)−C(11)	110.4(3)
O(2)−C(8)−O(1)	125.1(3)		

X-ray Crystallographic Analyses of H_3tachta·3HCl·2H_2O (A) and [Ga(tachta)] (B). Single crystals of **A** and **B** were obtained by slow room-temperature evaporation respectively of a methanolic solution of the ligand and a solution containing the two corresponding reactants in MeOH in open vessels.

Colorless plates of approximate dimensions 0.06 × 0.14 × 0.22 mm for **A** and 0.10 × 0.10 × 0.12 mm for **B** were mounted on glass fibers and transferred to the goniometer. The crystals were cooled to −100 °C during data collection by using a stream of cold nitrogen gas. The space groups were determined from the systematic absences. A summary of data collection parameters is listed in Table 1.

Both structures were solved by direct methods and difference Fourier syntheses. Hydrogen atoms were included in the refinements riding on the bonded atom with U fixed to 1.2U_{eq} of the parent atom. The unique N−H and O−H hydrogen atoms were located in difference Fourier maps prior to riding refinement; all other hydrogen atoms were placed in calculated positions. Selected bond lengths and angles are given in Tables 2 and 3 for **A** and **B**, respectively.

Results and Discussion

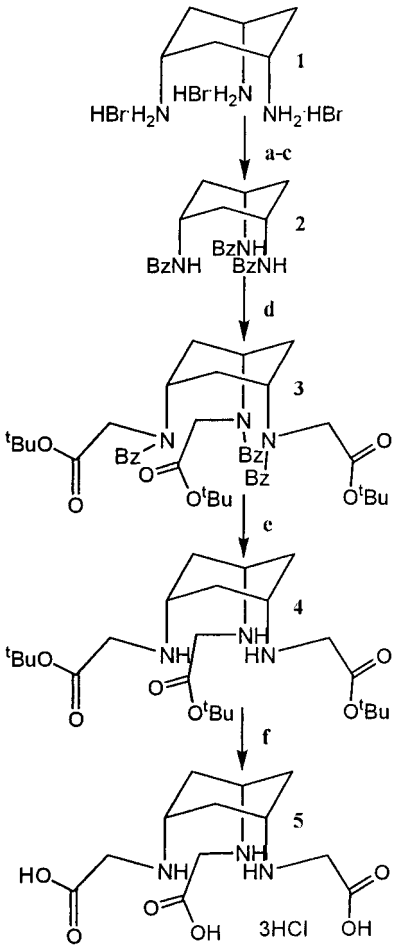
Ligand Synthesis. The precursor tach was prepared according to our improved procedure.[22] There were several choices

Table 3. Selected Bond Lengths (Å) and Angles (deg) for [Ga(tachta)][a]

Ga−O(1)	1.949(2)	O(2)−C(4)	1.228(4)
Ga−N	2.084(2)	N−C(3)	1.483(4)
O(1)−C(4)	1.284(4)	N−C(1)	1.505(4)
O(1)−Ga−O(1)#2	90.77(9)	C(1)−N−Ga	116.4(2)
O(1)−Ga−N#1	96.53(10)	N−C(1)−C(2)	112.1(2)
O(1)−Ga−N	83.11(9)	N−C(1)−C(2)#2	108.1(2)
O(1)−Ga−N#2	170.52(10)	N−C(3)−C(4)	111.6(2)
N−Ga−N#2	90.37(9)	O(2)−C(4)−O(1)	124.1(3)
C(4)−O(1)−Ga	117.9(2)	O(2)−C(4)−C(3)	118.7(3)
C(3)−N−C(1)	113.5(2)	O(1)−C(4)−C(3)	117.2(3)
C(3)−N−Ga	108.5(2)		

[a] Key: (#1) symmetry code *y*, *z*, *x*; (#2) symmetry code *z*, *x*, *y*.

Scheme 1. Synthesis of H_3tachta·3HCl



(a) NaOH; (b) Benzaldehyde; (c) $NaBH_4$; (d) $BrCH_2CO_2{}^tBu$, Na_2CO_3; (e) H_2, Pd/C; (f) HCl.

as to how one could introduce the carboxylate functionality selectively into the tach framework. The route employed here (see Scheme 1) was chosen because of its directness and simplicity and for the potential to later introduce additional groups at the secondary amines. In brief, each of the primary amines were selectively monobenzylated by first forming benzylimines with benzaldehyde and subsequently reducing the imines with excess borohydride. Alkylation of the formed secondary amines with *tert*-butyl bromoacetate then introduced the protected acetic acids of the target compound. The benzyl groups were removed at this point by simple hydrogenation,[26] and the *tert*-butyl esters cleaved with acid yielded the final product. The sequence of these two steps could in fact be reversed; however, for both convenience and solubility, as well as avoiding contamination with any extraneous metal ions, the order of events presented herein was deemed appropriate. It was also clear that the use of tosylate, or a sulfonate derivative, rather than the benzyl group might make the synthesis more direct; however, we anticipated that the harsh conditions required for removal of such groups could potentially interfere with both yields and later choices of additionally introduced functional donor groups.

Overall, the triprotic, hexadentate (N_3O_3) ligand was formed in moderate yields from tach·3HBr with this six-step procedure. All of the steps are convenient, and no extremely toxic materials are used. This general method appears superior to the previous procedure for generation of H_3tachta and its structural derivatives. This route also provides a routine entry to intermediates **2** and **4** that could be employed to prepare numerous other tach-based ligands.

Complex Syntheses and Characterizations. The Ga(III) tachta complex was the initial target of interest because of the potential use of this chelating agent with the Ga(III) isotopes, ^{66}Ga, ^{67}Ga, and ^{68}Ga, which possess emissions suitable for radiopharmaceutical applications. To this end, the synthesis and determination of the absolute structure of this complex were pursued in conjunction with ongoing radiopharmaceutical studies. Some preliminary results of this parallel investigation include observations of a strong hydrophilic nature with <1% of the [^{67}Ga(tachta)] complex being found in 1-octanol and combined in vitro and in vivo stability studies which indicate that the [^{67}Ga(tachta)] complex is stable in both environments and is essentially 100% excreted after 24 h. These and other related studies will be reported in detail elsewhere.[25] Although initially of secondary interest, studies to address the structural natures of the remaining complexes are continuing, as ^{111}In, ^{109}Pd, ^{64}Cu, and ^{67}Cu also possess emissions suitable for applications in the field of nuclear medicine.

White fine powdery gallium and indium complexes, [Ga(tachta)] and [In(tachta)], were prepared from $Ga(acac)_3$ and $InCl_3·4H_2O$, respectively, and the corresponding ligands in good yields upon refluxing in methanolic solutions. For the indium complex, addition of a base was necessary to initiate precipitation of the desired product and possibly to produce crystals as well. For the gallium complex, slow reaction of the ligand and $Ga(NO_3)_3.xH_2O$ in MeOH afforded products that were suitable for X-ray crystallographic analysis. Attempts to produce crystals of this Ga(III) complex under the same conditions as those used in the analogous In(III) case generated colorless crystals that proved to be the HCl salt of the uncoordinated ligand, as verified by X-ray crystallographic analysis (vide infra).

The reactions of $CuCl_2$, $PdCl_2$, and $CoCl_2$ with H_3tachta were carried out in MeOH. In all cases, the presence of a base was necessary to form the desired products, [Cu(Htachta)], [Pd(Htachta)], and [Co(Htachta)]. The isolated yields of these complexes were much lower than those of the gallium and indium complexes, possibly due to greater solubility of the complexes in MeOH.

All the isolated complexes are stable in air. The analytical data for the Ga(III) and In(III) complexes fit the general formula [M(tachta)], with one metal atom per triply deprotonated ligand. The poor solubility of the two complexes prevented NMR spectroscopic or mass spectrometric identification. For the gallium complex, the neutral form was confirmed by X-ray crystallography (vide infra).

(26) Rylander, P. *Catalytic hydrogenation in organic syntheses*; Academic Press: New York, 1979; pp 280−282.

Table 4. Structural Comparison of Ga(III) Complexes of Tripodal N_3O_3 Chelating Ligands[a]

	[Ga(tachta)]	[Ga(tstach)][12]	[Ga(NOTA)][11]	[Ga(TX-TACN)H]$^{+}$ [10]	[Ga(5-MeOsal)$_3$tame][7]	[Ga(**IIa**)][9]
Ga−O	1.949[b]	1.93(2)	1.930(4)	1.94(5)	1.941(0)[b]	1.920(4)
Ga−N	2.084[b]	2.15(3)	2.09(1)	2.11(1)	2.105(0)	2.13(5)
O−Ga−O	90.77[b]	90.4(3)	95.0(7)	90(2)	92.6(0)	93(1)
N−Ga−N	90.37[b]	92(5)	84.5(2)	83.2(6)	83(0)	86(3)
trans O−Ga−N	170.52[b]	175.6(7)	167.6(3)	174(2)	171(0)	174(2)
cis O−Ga−N	90(7)	88.6(6)	90(8)	94(3)	92(5)	91(1)
all cis angles	90(5)	91(3)	90(7)	90(5)	90(5)	90(3)

[a] Mean values of the three parameters with the standard deviations. [b] Unique value.

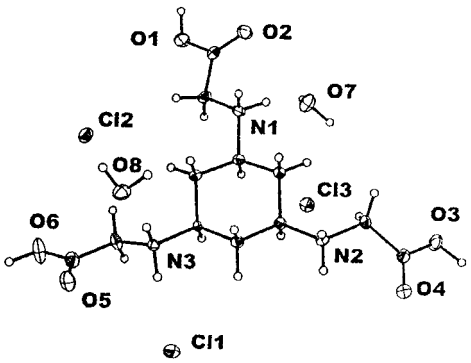


Figure 1. ORTEP drawing of H_3tachta·3HCl·2H_2O (**A**), showing 50% probability thermal ellipsoids.

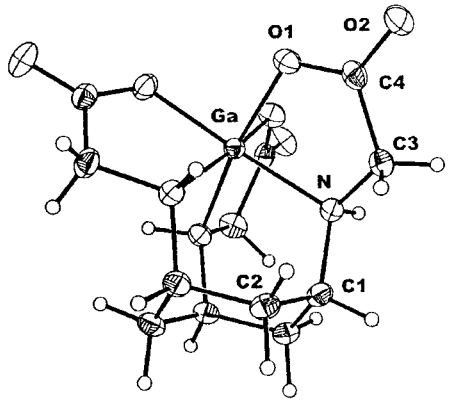


Figure 2. ORTEP drawing of [Ga(tachta)] (**B**), showing 50% probability thermal ellipsoids.

A general formula of [M(Htachta)] for the Cu(II), Pd(II), and Co(II) complexes was determined by the mass spectrometric measurements and microanalyses. It was a mild surprise that the Co(II) complex also appeared to be an [M(Htachta)] species from these data, instead of [*i*-Pr_2NHEt]$^{+}$[M(tachta)]$^{-}$, as previously a six-coordinate geometry was proposed for a Co(III) complex of tachta^{3-}.[20] The absolute determination of the coordination spheres and geometries will have to be determined by obtaining X-ray crystallographic data for these complexes. However, all efforts to obtain suitable crystals for this purpose have met with failure but remain an ongoing aspect of studies to evaluate these complexes as radiopharmaceuticals.

X-ray Structures. The ORTEP diagrams of the structures of H_3tachta·3HCl·2H_2O (**A**) and [Ga(tachta)] (**B**) are shown in Figures 1 and 2.

H_3tachta·3HCl·2H_2O (A). There are four H_6tachta^{3+} cations in each monoclinic cell, together with twelve Cl^{-} ions and eight H_2O molecules, which are associated with one another via H-bonds, with hydrogen-bond lengths ranging from 1.848 to 2.652 Å. There is no significant intramolecular hydrogen bonding. The cyclohexane is in a chair conformation, with the three carbon atoms in the 1-, 3-, and 5-positions each being bonded to ammonium N atoms equatorially. The whole compound is present as an open proligand, ready to bind a metal ion on either side of the planar chelating molecule (Figure 1).

[Ga(tachta)] (B). There are eight [Ga(tachta)] molecules (as pairs of Δ and Λ enantiomers) in each cubic cell. Each complex molecule forms intermolecular hydrogen bonds to three adjacent complex molecules, each from an amine H to an adjacent carbonyl O atom, with a value of 1.914(3) Å. The hydrogen bond is almost linear (178.2(1)°).

The gallium atom in the neutral molecule **B** is encapsulated by a triply deprotonated hexadentate N_3O_3 chelating ligand, with three coordination sites occupied by the amino N donors in a facial manner, the other three sites being occupied by the carboxylate O donors of the three carboxylic arms (Figure 2). All three arms attached to the cyclohexane framework are identical, related by a C_3 axis. This symmetry is rarely present in most of the Ga(III) complexes of tripodal N_3O_3 chelating ligands, such as tach-based [Ga(tstach)],[12] TACN-based [Ga(NOTA)][11,12] and [Ga(TX-TACN)H]$^{+}$,[10,12] and tame-based [Ga(**IIa**)].[9] The only other 3-fold symmetric structure of a Ga(III) complex of a tripodal N_3O_3 chelating ligand was that found for tame-based Ga[(5-MeOsal)$_3$tame].[7]

The Ga coordination geometry of **B** can be described as pseudooctahedral with a slight trigonal distortion ($\phi = 48.5°$; $\phi = 60°$ corresponds to regular octahedron and $\phi = 0°$ to trigonal prism). Further distortions are caused by the smaller O(1)−Ga−N bite angle (83.11(9)°) formed by the O_2C-CH_2-N portion of the ligand as compared to the intramolecular O(1)−Ga−N#1 angle (96.5(1)°). The cis angles O(1)−Ga−O(1)#2 (90.77(9)°) and N−Ga−N#2 (90.37(9)°) are relatively close to the right angles for an ideal octahedron (Table 3). The average of the four unique cis bond angles is 90(5)°. For [Ga(tstach)], where tstach^{3-} is the phenolic congener of tachta^{3-}, the average of the cis bond angles is 91(3)°.

The bond to the tertiary amine N and that to a carboxylato O atom in [Ga(tachta)] are found to be 2.084(2) and 1.949(2) Å, similar to those found in the gallium(III) complexes formed with tripodal N_3O_3 chelating ligands, as shown in Table 4. The data in Table 4 also show that while the Ga−O bonds are slightly different (≤0.015 Å) from the mean value of 1.933 Å (regardless of carboxylato O or phenolato O), the Ga−N bonds, on the other hand, differ from the average value (2.112 Å) by 0.28−0.44 Å.

In conclusion, the triprotic N_3O_3 hexadentate tach-based chelating agent H_3tachta was synthesized by an improved route. Complexes of this chelating ligand with Ga(III), In(III), Cu(II), Co(II), and Pd(II) were also prepared and characterized. The structure of the Ga(III) complex was solved. This chelate and derivatives that bear further substituents on the amine N-position currently are being evaluated for possible use as radiopharmaceuticals. This ongoing research will be reported in the appropriate venue in due course.[25]

Acknowledgment. We thank Mr. Noel Wittaker and Mr. Wesley White for assistance with the MS and NMR measurements, respectively.

Supporting Information Available: X-ray crystallographic files, in CIF format, and complete tables of crystallographic data, final atomic coordinates and equivalent isotropic thermal parameters, anisotropic thermal parameters, bond lengths, bond angles, torsion angles and intermolecular contacts, and least-squares planes for **A** and **B**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC000603B