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Lipophilic Hexadentate Aluminum, Gallium, Indium, and Iron Complexes of a New Phenolate-Derivatized Cyclohexanetriamine Ligand

James E. Bollinger, Joel T. Mague, and D. Max Roundhill*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118

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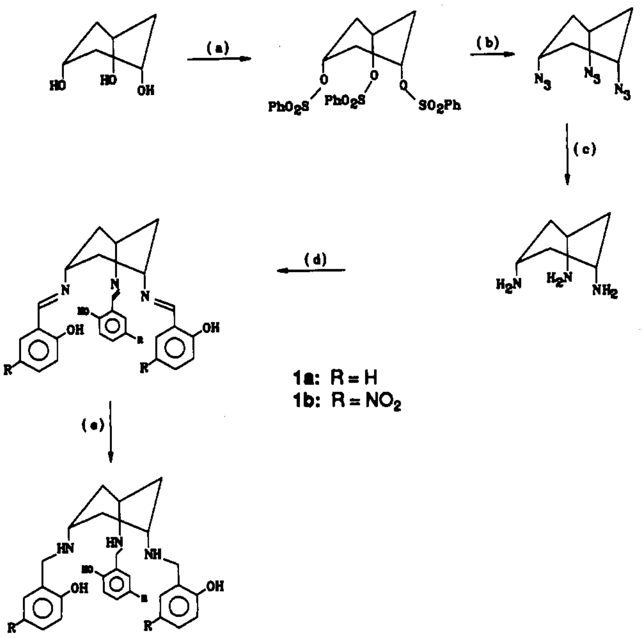
The coordination chemistry of the group 13 (IIIA) metal ions is of biomedical interest because of the association of aluminum with neurological dysfunctions[1] and also because of the use of gallium and indium radioisotopes for imaging applications.[2] Gallium and indium are potentially useful as radiopharmaceutical imaging agents because the isotopes ^{67}Ga, ^{68}Ga, ^{111}In, and ^{113}In have the appropriate energies and half-lives for either γ-ray imaging or positron emission tomography. In order for these isotopes to be selectively transported in solution to the *in vivo* target, one of the necessary prerequisites is that their complexed trivalent ions remain tightly bound to a carrier ligand. High binding constants for metal ions are generally obtained with multidentate hard ligands, and for the particular cases of Ga(III) and In(III) the phenolate anion is a strongly coordinating ligand.[3]

In this communication we report the synthesis of a new hexadentate ligand that is specifically designed for complexation with a trivalent metal ion and the characterization of water-stable complexes with Al(III), Ga(III), In(III), and Fe(III). These ligands have phenolate groups appended to a *cis*-cyclohexanetriamine backbone, and they are among the first examples of a nonmacrocyclic hexadentate ligand that is specifically designed for complexation with these trivalent metal ions.[4] These ligands have phenolate groups appended to a *cis*-cyclohexanetriamine backbone, and they are among the first examples of a nonmacrocyclic hexadentate ligand that is specifically designed for complexation with these trivalent metal ions.[4] The ligands have been designed to avoid the presence of the C=N functionality since it is believed to undergo *in vivo* degradation.[5] The ligands are designed to yield uncharged complexes when coordinated to a trivalent metal ion in order that they can potentially be used to prepare Ga(III) and In(III) myocardial perfusion agents.[6] These new uncharged hexadentate complexes of Al(III), Ga(III), and In(III) are soluble and stable both in aqueous solution and in organic solvents such as benzene, alcohols, and diethyl ether. As a measure of the lipophilicity of these complexes, the 1-octanol:water partition coefficients have the respective values of 9.0, 8.4, 49, and 13 for Al(L), Ga(L), In(L), and Fe(L) (L = hexadentate ligand **1b**).

Scheme 1[a]



1a: R = H
1b: R = NO$_2$

[a] Key: (a) PhO$_2$SCl, pyridine, 10 °C; (b) NaN$_3$, diethylene glycol, 100 °C; (c) LiAlH$_4$, THF, reflux; (d) salicylaldehyde, EtOH, reflux for **1a** and 5-nitrosalicylaldehyde, EtOH, reflux for **1b**; (e) KBH$_4$, EtOH, reflux.

The synthesis of these new hexadentate ligands first involves the transformation of *cis*-1,3,5-cyclohexanetriol into *cis*-1,3,5-

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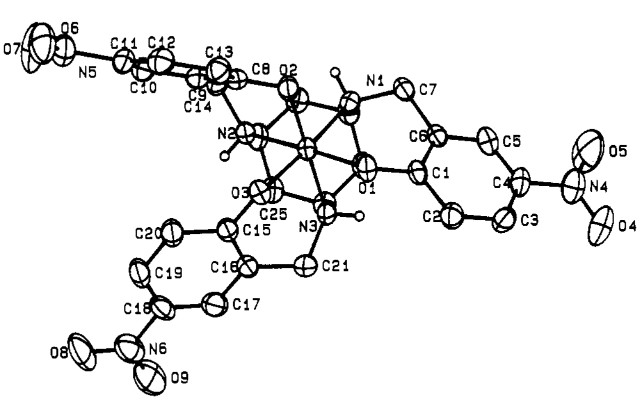

Figure 1. ORTEP representation of the structure of Al(L).

cyclohexanetriamine using the method of Fleisher.[7,8] This procedure involves converting the triol to the tris(benzenesulfonate), followed by substitution with azide ion and reduction to the amine with lithium aluminum hydride. (*Caution! Polyazides are potentially explosive.*) Condensation of *cis*-1,3,5-cyclohexanetriamine with salicylaldehyde or 5-nitrosalicylaldehyde,[9] followed by the reduction of the resulting Schiff base with potassium borohydride, gives the respective *cis*-tris((hydroxybenzyl)amino)cyclohexane products **1a,b** (Scheme 1).[10] The NO_2 group has been appended because it allows for changes to be made in the lipophilicity of the complex and also because it offers a potential binding site for attachment to an antibody *via* an isothiocyanate group.[11] Complexes of **1b** (L) have been obtained with the Al(III), Ga(III), In(III), and Fe(III). Complexation is achieved by dissolving the metal nitrate or chloride in absolute ethanol along with an equimolar amount of the L·3HCl, followed by addition of an excess of noncoordinating base such as diisopropylethylamine.[12] Upon refluxing of the solution, the complexes precipitate. The complexes have been characterized in solution by a combination of IR, NMR, and UV spectroscopy. The X-ray crystal structures of the Al(L) and Fe(L) complexes confirm that they have an uncharged monomeric structure in the solid state.[13] The distances and angles within the structures do not indicate the presence of any significant strain.

An ORTEP representation of the Al(L) complex is shown in Figure 1. The corresponding iron complex is isostructural. Both complexes crystallize with a molecule of ethanol which is weakly hydrogen bonded to one metal-coordinated oxygen atom of the ligand. The crystal structure has the metal in an octahedral coordination environment with the ligand acting as a hexadentate species. This results in the creation of a network of skewed six-membered rings such that each oxygen moiety is *trans* to the amine of a neighboring pendant arm. In Figure 1 two of the pendants assume a propeller-like conformation while the third does not, reflecting an inversion of one six-membered ring as compared to the other two. The ^1H NMR spectra indicate that the three coordinating pendants are equivalent on the NMR time scale and the structure is semirigid. This feature is evident from the presence of distinct and separate resonances for the two pendant methylene protons individually coupled to the adjacent amine proton. *In vivo* studies with these ligands and complexes are presently underway.

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Supplementary Material Available: Text giving details of the data collection and structure solution and tables of crystallographic data, positional parameters, bond distances, bond angles, and general displacement parameters for Al(L) and Fe(L) (32 pages). Ordering information is given on any current masthead page.

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(7) Fleisher, E. B.; Gebala, A. E.; Levey, A.; Tasker, P. A. *J. Org. Chem.* **1971**, *36*, 3042–4.

(8) We find that this route to *cis*-1,3,5-cyclohexanetriamine from *cis*-1,3,5-cyclohexanetriol is more reliable than the published procedure *via* the reduction of the trioxime of phloroglucinol with sodium in liquid ammonia (Lions, F.; Martin, K. V. *J. Am. Chem. Soc.* **1957**, *79*, 1572–5).

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(10) Anal. Calcd for $C_{27}H_{39}Cl_3N_6O_{12}$: C, 43.5; H, 5.28; N, 11.3; O, 25.7 (*m/e* 583). Found: C, 43.5; H, 5.54; N, 11.4; O, 25.6 (*m/e* 583(1) (FAB)). Spectral data for **1b**·3HCl are as follows. IR (KBr) (cm^{-1}): ν(NH) 2900–3100, br, w; δ(NH) 1593, s; 5123, s; $\nu(NO_2)$ 1496, m; 1338, s. ^1H NMR ($CDCl_3$): δ 1.8 m (3H), 2.74 m (3H), 3.33 m (3H), 4.20 m (6H), 7.18 d (3H), 8.18 d (3H), 8.47 s (3H), 9.65 bs (1H), 12.1 bs (3H). $^{13}C\{^1H\}$ NMR: δ 30.3, 52.6, 42.4, 119.7, 139.6, 116.2, 127.1, 163.1, 128.5

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(12) Data for Al(L)·C_3H_6O are as follows. Anal. Calcd for $C_{30}H_{33}N_6O_{10}$-Al: C, 54.2; H, 5.02; N, 12.7 (*m/e* 607). Found: C, 54.4; H, 5.32; N, 12.6 (*m/e* 607(1) (FAB)). IR (KBr) (cm^{-1}): ν(NH) 3246, w; δ(NH) 1601, m; $\nu(NO_2)$ 1482, s; 1332, s. ^1H NMR ($CDCl_3$): δ 1.83 b (3H), 2.56 b (3H), 3.03 bs (3H), 3.34 b (3H), 4.13 t (3H), 6.21 d (3H), 7.99 d (3H), 7.94 s (3H), 5.31 b (3H). UV (MeCN): λ_{max} 360 nm (4.59×10^4), 238 nm (1.32×10^4). Data for Ga(L)·H_2O are as follows. Anal. Calcd for $C_{27}H_{29}N_6O_{10}Ga$: C, 48.8; H, 4.41; N, 12.7 (*m/e* 636). Found: C, 48.8; H, 4.53; N, 12.9 (*m/e* 636(1) (FAB)). IR (KBr) (cm^{-1}): ν(NH) 3244, w; δ(NH) 1601, m; $\nu(NO_2)$ 1482, s; 1332, s. ^1H NMR ($CDCl_3$): δ 1.86 b (3H), 2.60 b (3H), 3.14 b (3H), 3.37 b (3H), 4.24 t (3H), 6.26 d (3H), 7.96 d (3H), 7.95 s, 5.58 b (3H). UV (MeCN): λ_{max} 366 nm (4.57×10^4), 226 nm (1.60×10^4). Data for In(L)·H_2O are as follows. Anal. Calcd for $C_{27}H_{29}N_6O_{10}In$: C, 45.5; H, 4.11; N, 11.8 (*m/e* 695). Found: C, 45.8; H, 4.46; N, 11.7 (*m/e* 695(1) (FAB)). IR (KBr) (cm^{-1}): ν(NH) 3244, w; δ(NH) 1599, m; $\nu(NO_2)$ 1491, s; 1336, s. ^1H NMR ($CDCl_3$): δ 1.89 b (3H), 2.56 b (3H), 3.23 b (3H), 3.39 b (3H), 4.37 t (3H), 6.48 d (3H), 7.96 d (3H), 7.99 s (3H), 5.56 b (3H). UV (MeCN): λ_{max} 368 nm (5.70×10^4), 234 nm (1.54×10^4). Data for Fe(L)·H_2O are as follows. Anal. Calcd for $C_{27}H_{29}N_6O_{10}Fe$: C, 49.6; H, 4.48; N, 12.9 (*m/e* 649). Found: C, 49.4; H, 4.95; N, 12.72 (*m/e* 649(1) (FAB)). IR (KBr) (cm^{-1}): ν(NH) 3238, w; δ(NH) 1597, m; $\nu(NO_2)$ 1491, s; 1336, s. UV (MeCN): λ_{max} 500 nm (2.99×10^3), 368 nm (4.04×10^4), 240 nm (1.73×10^4).

(13) Crystallographic data for Fe(L) (Al(L) in parentheses): $P2_1/n$ ($P2_1/n$), with a = 12.271(2) Å (12.305(1) Å), b = 12.069(3) Å (12.072(2) Å), c = 20.540(2) Å (20.229(3) Å), V = 3042(2) $Å^3$ (3005(1) $Å^3$), ρ_{calc} = 1.49 g cm^{-3} (1.44 g cm^{-3}), Z = 4 (4). From 2672 (3105) unique reflections with $I \geq 2\sigma(I)$ out to 25 °C (Mo Kα) the structure was solved by direct methods and refined with anisotropic thermal parameters to R = 4.5% (4.0%) and R_w = 4.9% (4.7%).