Potentially Multidentate Tripodal Amine Catechol Ligands as Chelators for Ga(III) and In(III)

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Received June 6, 2009, Accepted July 10, 2009

The binding abilities of two multidentate tripodal amine catechol ligands, *cis,cis*-1,3,5-tris[(2,3-dihydroxybenzylamino)aminomethyl]cyclohexane (TMACHCAT, L^1) and N^1,N^3,N^5-tris(2-(2,3-dihydroxybenzylamino)ethyl)cyclohexane-1,3,5-tricarboxamide (CYCOENCAT, L^2) with Ga(III) and In(III) have been investigated by potentiometric and spectrophotometric methods in an aqueous medium of 0.1 M KCl at 25 ± 1 °C. The ligands L^1 and L^2 formed various monomeric species MLH_3, MLH_2, MLH and ML (M = Ga^{+3} and In^{+3}) and showed potential to form strong encapsulated tris(catechol) type complexes. The coordination modes, binding ability and selectivity of the ligands towards Ga(III) and In(III) have been discussed with the help of experimental evidences, and supported with molecular modeling calculations.

Key Words: Tripodal amine-catechol ligand, Ga(III), In(III), Potentiometry, Spectrophotometry

Introduction

The proliferation in coordination chemistry of Ga(III) and In(III) ions stems from the potential application of ^{67}Ga, ^{68}Ga and ^{111}In complexes as diagnostic radiopharmaceuticals.[1-4] The ligands used for the radiopharmaceuticals containing gallium and indium must satisfy, at first, two criteria: the metal complex must be stable with respect to hydrolysis to the metal hydroxide, and it must be stable with respect to demetallation by other chelators like the serum protein transferrin. Also, because of their tripositive charge, their ionic forms are unable to permeate membrane barriers and thus suitably designed multidentate ligands which can formed neutral complexes with the metal ions is an essential requirement for the radiopharmaceuticals use.

In search of new chelators, which can fulfilled the above requirements, efforts are made to mimic the molecular structure and binding sites of the natural chelators through simple synthetic molecules.[5,6] Enterobactin (Fig. 1) is a siderophore produced and excreted by bacteria in iron deficient media in order to bind and assimilate extracellular iron.[1,7-9] Its efficiency as Fe(III) ion scavenger with formation constant log K = 49 has stimulated the synthesis of many analogues containing three catechol units in tripod with respect to their use in iron overload treatment.[10] It is worthwhile to mentioned that Fe(III) and Ga(III) showed similar affinity for a variety of ligands.[11,12] That is why, these natural and synthetic chelating agents of Fe(III) are also implemented as chelators for Ga(III) because of their common preference towards the hard donor atoms, such as oxygen and similar coordination behaviors.[13,14] Again, since the aqueous coordination chemistry of In(III) is moreover similar to Ga(III), the same Fe(III) chelators can also be applied for the development of In(III) sequestration with respect to their use as imaging agents.[15]

In our recent studies,[16-18] we demonstrated that C_3-symmetrical tripodal amine catechol ligands, *cis,cis*-1,3,5-tris[(2,3-dihydroxybenzylamino)aminomethyl]cyclohexane (TMAC HCAT, L^1), N^1,N^3,N^5-tris(2-(2,3-dihydroxybenzylamino)ethyl) cyclohexane-1,3,5-tricarboxamide (CYCOENCAT, L^2) and tris((2,3-dihydroxybenzylamino)ethyl)amine (TRENCAT, L^3) (Fig. 1) formed strong encapsulated tris(catechol) type complexes in solution with various tripositive metal ions *viz.*, Al(III), La(III), Gd(III) and Lu(III). Also, it has been observed that (i)

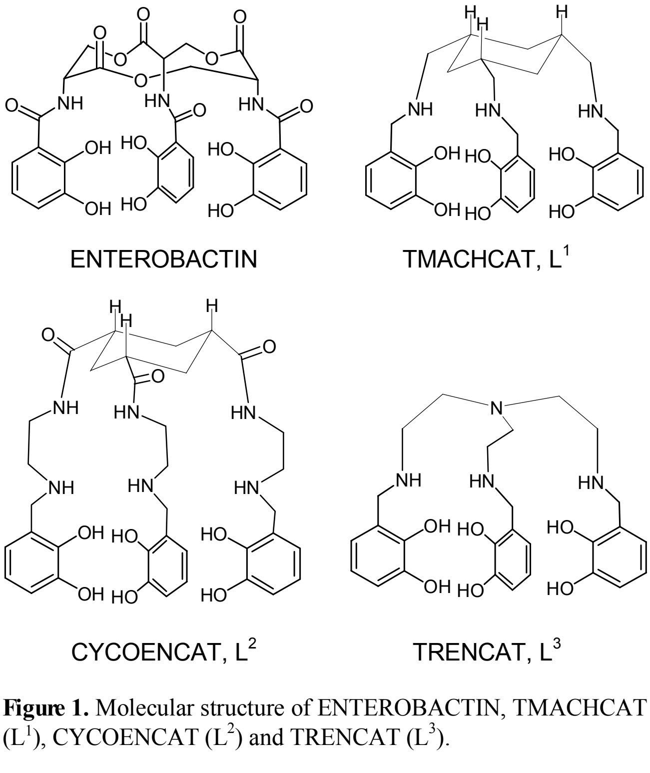

Figure 1. Molecular structure of ENTEROBACTIN, TMACHCAT (L^1), CYCOENCAT (L^2) and TRENCAT (L^3).

the calculated pAl (= −log [Al^{+3}]) values of these ligands are found to be higher than the well known chelating agents like EDTA, DTPA, transferrin and comparable with that of DFO (DFO is the one of the approved drug used in Al^{+3}-intoxication),[17] (ii) the ligand L^1 shows potential to form mononuclear encapsulated complex at nearly physiological condition with lanthanide(III) ions, which is important for use as contrast agents in magnetic resonance imaging[16] and (iii) the stability order found for ligand L^3 with the group-13 metal ions is Al(III) > Ga(III) > In(III), which is unusual for catechol type ligand.[18] Considering the unique solution coordination behavior of tripodal amine catechol ligands, present work aimed to study the thermodynamic stability and selectivity of the ligands L^1 and L^2 towards Ga(III) and In(III).

Experimental

Materials and titration procedure. The compounds *cis*,*cis*-1,3,5-tris[(2,3-dihydroxybenzylamino)aminomethyl]cyclohexane (TMACHCAT, L^1) and N^1,N^3,N^5-tris(2-(2,3-dihydroxybenzylamino)ethyl)cyclohexane-1,3,5-tricarboxamide (CYCOENCAT, L^2) were synthesized as per our previously reported methods.[16,17] Nitrate salts of gallium and indium were obtained from Sigma-Aldrich and used directly. All other chemicals: potassium hydroxide, hydrochloric acid and potassium chloride were obtained from Merck.

The detail procedure for potentiometric and spectrometric titrations were given in our previous communications.[16,18] All solutions were prepared prior to the experiments in double distilled deoxygenated water. KOH solution of 0.1 M was prepared and standardized against potassium hydrogen phthalate. HCl solution (0.1 M) was prepared and standardized against standard KOH. The ionic strength was maintained at 0.1 M by adding appropriate amount of 1 M KCl. Solutions of 0.01 M ligand and 0.01 M metal ions were also prepared in deoxygenated water. Final concentration of ligand (1×10^{-3} M) and metal (1×10^{-3} M and 5×10^{-4} M) were maintained for the different titrations. Following titrations with metal-to-ligand molar ratios: $C_M/C_L = 0 : 1$; $C_M/C_L = 1 : 1$, $1 : 2$ were carried out. A non-linear least square computer program Hyperquad 2000 has been used to calculate the formation constants of the metal complexes.[19] The log K values of L^1 (11.26, 10.65, 9.80, 8.48, 7.61 and 6.20) and L^2 (11.36, 10.67, 9.82, 8.49, 7.62 and 6.27) determined previously[17] were used to evaluate the formation constants of the metal complexes. The first three values were assigned to the hydroxyl groups of catechol units at *ortho* whereas last three values to the secondary amines. Protonation constants for the hydroxyl groups of catechol units at *meta* were not evaluated within the adopted experimental conditions (pH ~2.5 - 11.5).[16-17] Thus, in the following discussion, the neutral and fully protonated form of the ligands are represented by H_3L and H_6L^{3+}, respectively.

In the spectrophotometric studies, a dilute solution of ligand (4.02×10^{-5} M) and metal ion (4.02×10^{-5} M) was acidified with 0.1 N HCl at an ionic strength of 0.1 M KCl and 25 ± 1 °C, and then titrated with 0.1 N KOH. After each adjustment of pH, an aliquot was taken and spectra were recorded. The formation constants were calculated by global fitting of the whole spectral data using a non-linear least-square fitting program, pHAb.[20]

Molecular modeling calculations. All calculations were carried out on a Pentium IV 3.0 GHz machine on Windows 2000 environment using the computer program CAChe (Computer Aided Chemistry) version 6.1.1 software from the Oxford Molecular Group.[21] The probable structure of the metal complexes formed in solution were drawn using CAChe workspace and then the geometry was optimized through molecular mechanics calculation using MM3 force field and adopting the Eigen-vector following (EF) method. Since, the ligands L^1 and L^2 have the probability to undergo ring flipping from their *cis*,*cis*-equatorial to axial conformer upon complexation, optimization process were undertaken for the same complex, where the coordinating arms are present either at equatorial or axial position with respect to the cyclohexane ring. For all possible metal chelates, six coordinated structure were drawn by adding appropriate number of water molecules with the metal ion. Semi-empirical calculations were carried out using MOPAC 2000 program implemented in CAChe. The MM3 minimized structures are re-optimized using semi-empirical PM3 self-consistent fields (SCF) method, at the Restricted Hartree-Fock (RHF) level with convergence limit of 0.0001 kcal/mol and RMS gradient of 0.001 kcal/mol.

Results and Discussion

Metal complex formation. Potentiometric titration curves of ligands L^1 and L^2 in the absence and presence of metal ions (Ga^{+3} and In^{+3}) at $\mu = 0.1$ M KCl and 25 ± 1 °C in aqueous medium are shown in Fig. 2. The deviation in the metal-ligand titration curves from the free ligands curves implies the formation of metal complexes. The shape of titration curves qualitatively indicates that the ligands have considerable affinity for the metal ions. The first break in the metal-ligand titration curves obtained at $a = 3$ (a = moles of base added/moles of ligand), where the curve for Ga(III) lying at low pH region was expected to form stronger complexes than In(III). When the pH increases further, the turbidity starts to appear from $a = {\sim}6$ indicates that ligands are able to deprotonate from six sites. Considering these preliminary observations, the experimental curves were tested in the minimization programme Hyperquad 2000 with different possible models. The best-fit models were obtained when formation of species of the types MLH_3, MLH_2, MLH and ML were considered. The calculated overall formation constants (log β) of these metal species alongwith their pK (pK = −log K) values are summarized in Table 1. The equilibrium reactions for the overall formations of the metal species are given by the equations 1 to 4; whereas the pK values are derived by using equations 5 to 7 (charges are omitted for clarity).

$$\mathrm{M + L + 3H \rightleftharpoons MLH_3}, \quad \beta_{113} = \frac{[\mathrm{MLH_3}]}{[\mathrm{M}][\mathrm{L}][\mathrm{H}]^3} \tag{1}$$

$$\mathrm{M + L + 2H \rightleftharpoons MLH_2}, \quad \beta_{112} = \frac{[\mathrm{MLH_2}]}{[\mathrm{M}][\mathrm{L}][\mathrm{H}]^2} \tag{2}$$

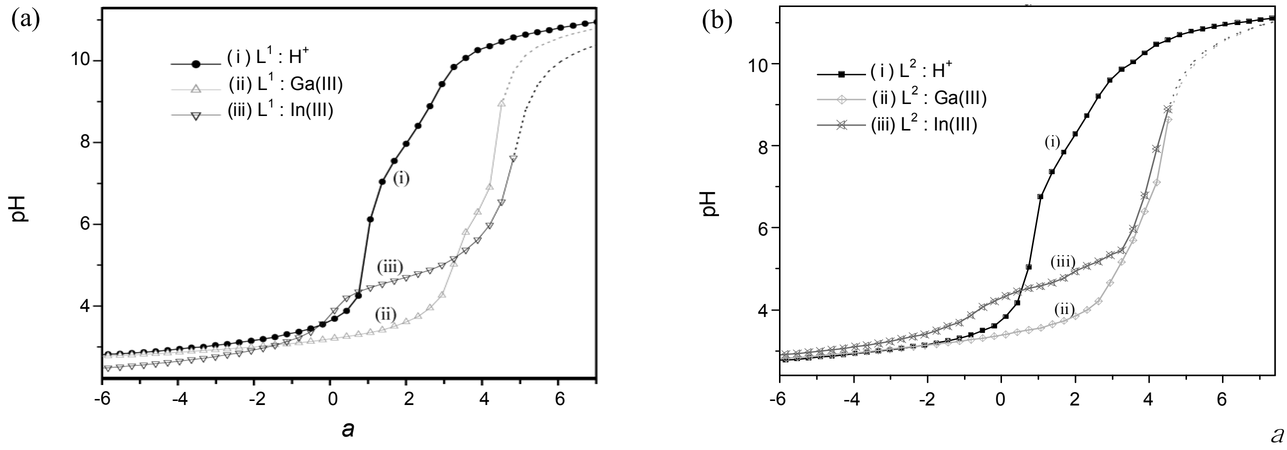

Figure 2. Potentiometric titration curves of (a) L^1 and (b) L^2 in absence (i) and presence of metal ions (ii) Ga(III) and (iii) In(III) in 1 : 1 ligand-metal molar ratio, where '*a*' is moles of base added per mole of ligand present (the solid symbols represent equilibrium points collected when no solid phase was present in solution while dotted lines represent points collected when turbidity or precipitation appeared in the solution).

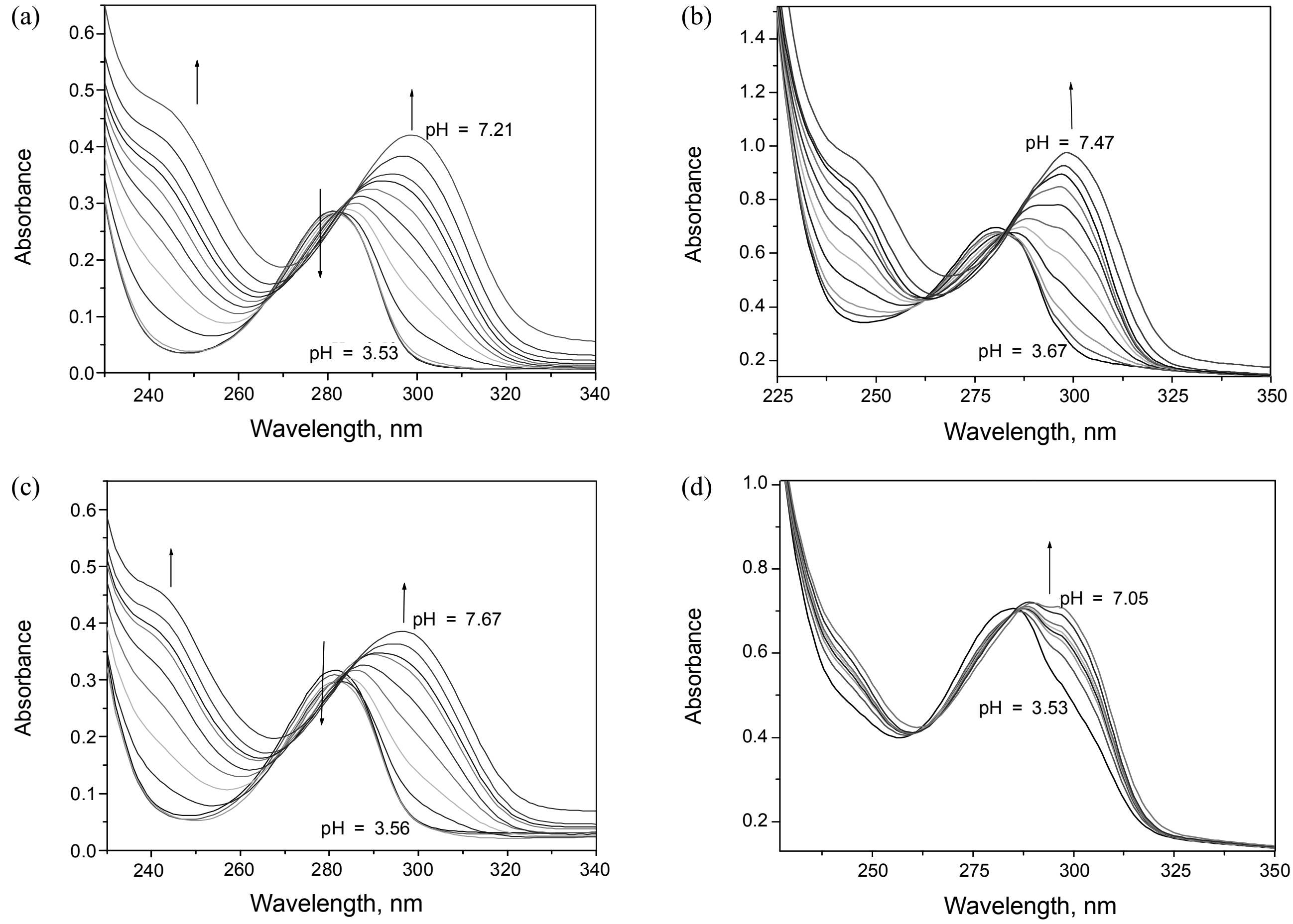

Figure 3. Experimental electronic spectra at 1:1 metal to ligand ratio for (a) GaL^1, (b) GaL^2, (c) InL^1, and (d) InL^2 systems.

$$M + L + H \rightleftharpoons MLH, \quad \beta_{111} = \frac{[MLH]}{[M][L][H]} \tag{3}$$

$$M + L \rightleftharpoons ML, \quad \beta_{110} = \frac{[ML]}{[M][L]} \tag{4}$$

$$MLH_3 \rightleftharpoons MLH_2 + H, \quad K_{MLH_3}^{MLH_2} = \frac{[MLH_2][H]}{[MLH_3]} \tag{5}$$

$$MLH_2 \rightleftharpoons MLH + H, \quad K_{MLH_2}^{MLH} = \frac{[MLH][H]}{[MLH_2]} \tag{6}$$

$$MLH \rightleftharpoons ML + H, \qquad K_{MLH}^{ML} = \frac{[ML][H]}{[MLH]} \qquad (7)$$

Spectrophotometric titrations of the ligands L^1 and L^2 in presence of Ga(III) and In(III) were carried at 1 : 1 metal-ligand ratio by keeping the ligand concentration $[L] = 4.02 \times 10^{-5}$ M and metal ion concentration $[M(III)] = 4.02 \times 10^{-5}$ M. The pH values were varied between 3.5 ~ 7.5. Above pH 7.5, the solution became turbid. The experimental electronic spectra for L^1/L^2-M(III) systems are given in Fig. 3. The ligand peak at 280 nm was shifted towards higher wavelength with concomitant rise in the absorbance upon successive rise in pH. This indicates the complexation of metal ions with the ligands. Also, the variations in electronic spectra for all metal ions at different pH are almost similar with respect to ligands suggesting similar mode of complexation. The formation constants calculated for the best-fit models using the program pHAb were summarized in Table 1 alongwith the potentiometric results, which accord well each other.

The speciation curves (Fig. 4) indicate that the complex formation occurred from pH ~ 3. The first species, MLH_3 is formed with the interaction of M with LH_3. The coordinated species LH_3 is formed with the release of three protons from the fully protonated form of the ligands LH_6^{3+} (Fig. 5a), and it is obvious that the three protons should be released from the more acidic catecholic units. Thus, the metal species MLH_3 can be structurally represented by a monocapped type geometry (Fig. 5b), where the three secondary amine nitrogen atoms remain in protonated form. Similar monocapped type coordination mode in tripodal ligands with different trivalent metal ions has been reported both in solid and solution state.[22] As the pH increases subsequently, successive deprotonation from MLH_3 leads to the formation of three different complexes MLH_2, MLH and ML (Fig. 4) before the solid phase appeared in the titrations. The extrusion of protons from the complex MLH_3 may take place either from the NH_2^+ groups for which the protonation constant values have been evaluated or from catechol ones, for three of which the protonation constant values are unknown. From Fig. 3, it can be observed that as the pH increases the absorption maxima (λ_{max}) shifted bathochromically. Since, the catechol units is the only chromophore in the ligands, the red shift in λ_{max} can be assignable to the deprotonation and/or coordination of catecholic oxygens. Such competitive coordination mode is expected for Ga(III) and In(III) metal ions because the 'hard' cations will show more preference towards 'hard' negatively charged oxygen donors than the 'soft' secondary amine nitrogen donors. Thus, it can be suggested that both the ligands L^1 and L^2 are encapsulating Ga(III) and In(III) in ML species to form tris(chatechol)

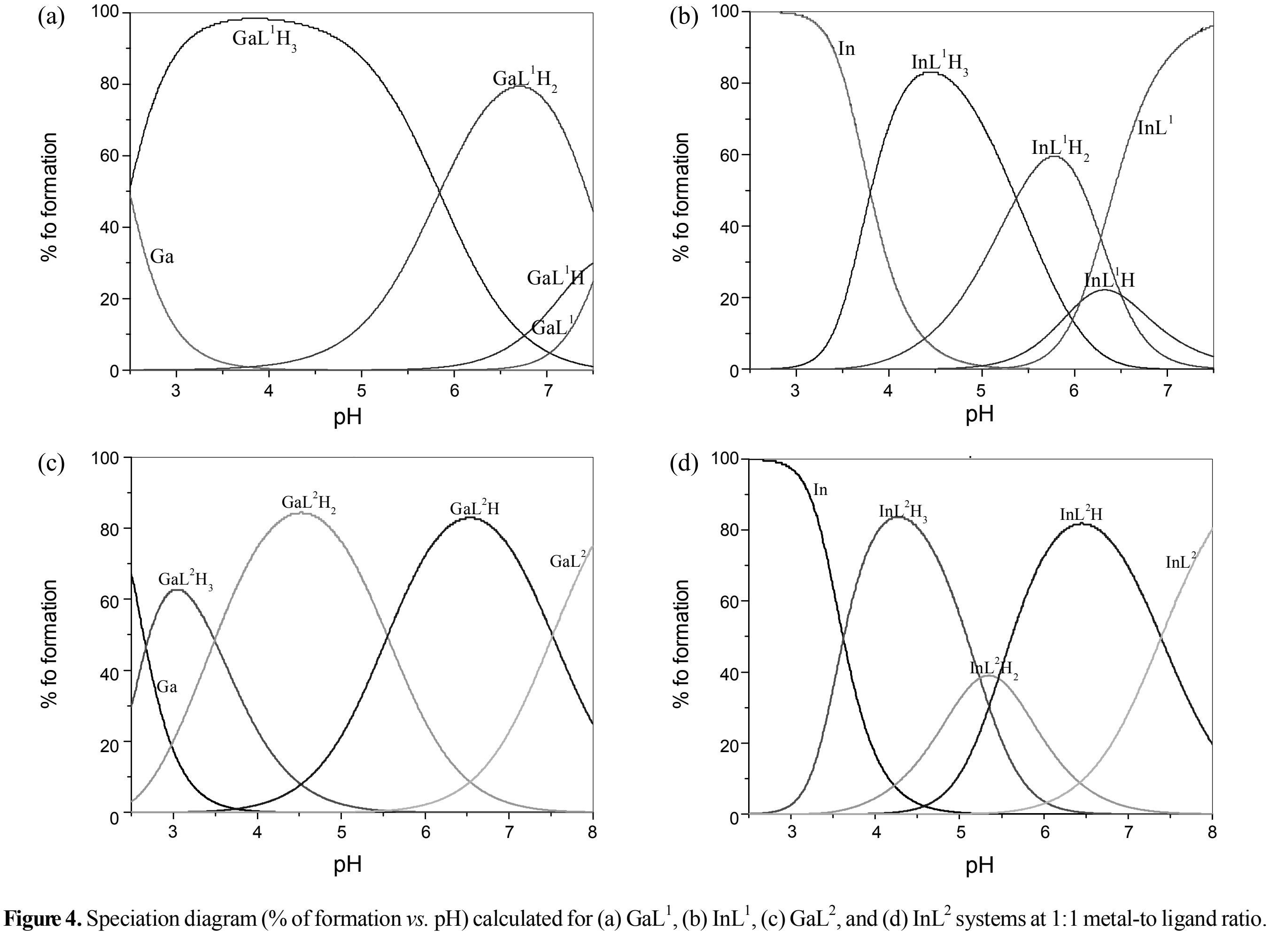

Figure 4. Speciation diagram (% of formation *vs.* pH) calculated for (a) GaL^1, (b) InL^1, (c) GaL^2, and (d) InL^2 systems at 1:1 metal-to ligand ratio.

Table 1. Overall (log β) and pK values (pK = −log K) of the metal complexes at 25 ± 1 °C and μ = 0.1 M KCl, (**A** = potentiometry and **B** = spectrophotometry)*

Equilibrium	*TMACHCAT*				*CYCOENCAT*				*TRENCAT* [*18*]	
	Ga(III)		In(III)		Ga(III)		In(III)		Ga(III)	In(III)
	A	B	A	B	A	B	A	B	A	A
$[MLH_3]/[M][L][H]^3$	47.56	47.37	43.64	43.61	47.25	47.22	44.37	44.35	46.82	42.97
$[MLH_2]/[M][L][H]^2$	41.72	41.71	38.27	38.13	43.76	43.74	39.13	39.11	41.12	37.86
$[MLH]/[M][L][H]$	34.05	34.15	31.77	31.68	38.21	38.23	33.67	33.68	33.41	31.23
$[ML]/[M][L]$	26.47	26.27	25.71	25.65	30.69	30.70	26.28	26.25	26.13	25.56
$[MLH_2][H]/[MLH_3]^{**}$	5.84	5.66	5.37	5.48	3.49	3.48	5.24	5.24	5.70	5.11
$[MLH][H]/[MLH_2]^{**}$	7.67	7.56	6.50	6.46	5.55	5.51	5.46	5.43	7.71	6.63
$[ML][H]/[MLH]^{**}$	7.58	7.88	6.06	6.03	7.52	7.53	7.39	7.43	7.28	5.67

*Standard deviations ranges from 0.01 to 0.1; **Represents pK values (pK = −log K).

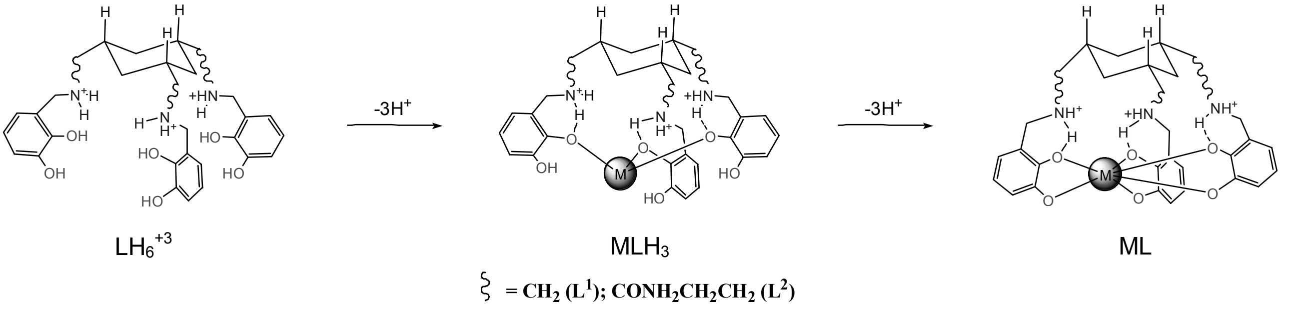

Figure 5. Possible coordination mode for ligands, L^1 and L^2 with the metal ions.

type complex (Fig. 5c).

Selectivity and binding ability. Table 1 reveals that both the ligands, L^1 and L^2 are forming strong complexes with Ga(III) and In(III). The ligand L^2 showed higher affinity for both the metal ions than the ligand L^1. The longer arms in L^2compared to L^1 allow the ligand to more easily self-organize around the metallic centre and to fulfil the octahedral coordination requirements of Ga(III) and In(III). Again, the stability order found for the metal chelates is Ga(III) > In(III). Such trend is expected because of the larger ionic radius and lower "hardness" of In(III) result lower stability than Ga(III) towards hard donor ligands.[23] Similar trend in stability order has been reported earlier for several types of complexes.[24] On comparing the log β_{FeL}(L^1 = 27.14 and L^2 = 31.02)[25] with log β_{ML} (L = L^1 and L^2; M = Ga^{3+} and In^{3+}), it can be observed that Ga(III) and Fe(III) showed similar affinity with the ligands. This is presumably due to their similar charge/radius ratio, coordination properties, and ligand substitution kinetics, and also unperturbed by ligand field effects. It is one reason for which Ga(III) serve as an excellent surrogate maker of iron(III) for structural elucidation of the active molecules in the solution.[11,12,26] Furthermore, as the formation of metal complexes are depending on the protonation constants of ligands (L^1 and L^2) and the pH, pM (pM = −log [M^{n+}]) is a better value for the relative comparison of complexation efficiency of the ligands under given conditions of pH, M^{n+} and L concentrations. The pM (M = Ga^{3+} and In^{3+}) values calculated within the pH range 3.0 ~ 7.5 for the ligands at $[L]_{total} = 5 \times 10^{-4}$ M (L= L^1 or L^2) and $[M^{3+}]_{total} = 5 \times 10^{-5}$ M is shown in Fig. 6. From Fig. 6, it can be pointed out that (i) the selectivity of ligands for both the metal ions is maintained over the pH range, (ii) the ligand L^2 is selectively forming complexes than ligand L^1 with respect to the metal ions and (iii) the ligands showing much selectivity towards Ga(III) than In(III). More importantly, both the ligands L^1 and L^2 derived from the cyclohexane-based tripod showed higher

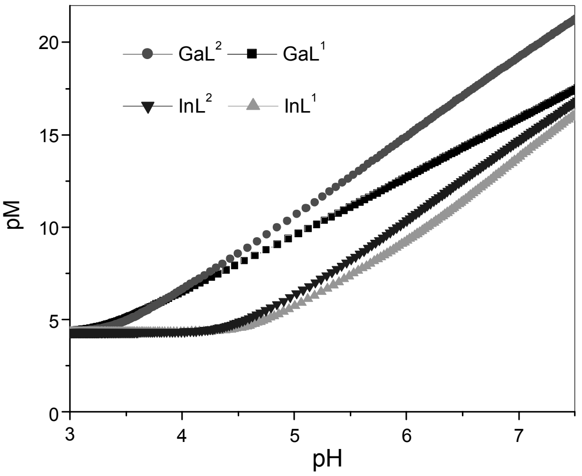

Figure 6. Plot of pM (pM = -log [M^{n+}]) *vs* pH. pM was calculated for [L] = 5 × 10^{-4} M (L= L^1 or L^2), [M^{n+}] = 5 × 10^{-5} M (M^{n+} = Ga^{3+} and In^{3+}) using the deprotonation constants of ligands L^1 and L^2, and the complexation constants β_{11n}.

Table 2. Calculated least strain energy (E_T in kcal/mol) structures for MLH_3 and ML type complexes (L = L^1 and L^2)

M(III)	ML^1H_3		ML^1	
	3-axial	3-equitorial	3-axial	3-equitorial
Ga(III)	-478.57	-521.89	-357.03	-363.63
In(III)	-451.71	-494.39	-346.65	-349.39
	ML^2H_3		ML^2	
Ga(III)	-569.68	-574.98	-368.88	-409.77
In(III)	-537.63	-537.14	-358.96	-398.81

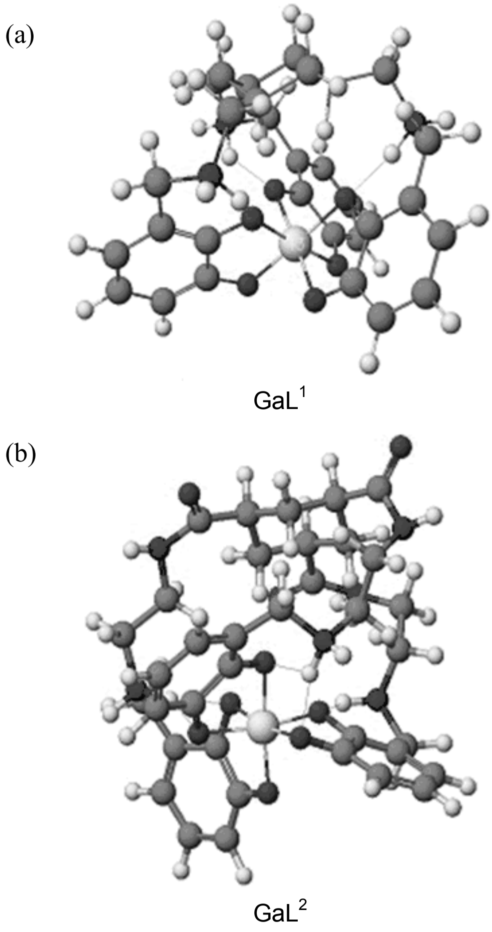

Figure 7. Optimized structures of GaL^1 and GaL^2 complexes through semi-empirical PM3 method.

thermodynamic stability towards Ga(III) and In(III) compared to that of TRENCAT.[18] This result inferred to a more flexible and preorganized architecture for the derivatives from cyclohexane-based tripod than TREN.

Structural simulations. Molecular modeling studies were undertaken to simulate the possible structure of the metal complexes formed in the solution. The experimentally proposed possible coordination modes for the metal species formed in solution are shown in Fig. 5. The first important thing needs to be predicted through molecular modeling calculations is the conformation of ligands in their complexes. Since, the ligands are isolated in *cis*,*cis*-equatorial form, it may be expected that the encapsulation of metal ion may takes place with or without any change in conformation to *cis*,*cis*-axial form. Molecular mechanics calculations using MM3 force field were performed for the proposed complexes by considering both axial as well as equatorial form of the ligands. The calculations were done for the initial (MLH_3) and final (ML) species. The calculated strain energies (Table 2) revealed that sterically the conformation of ligands retained their equatorial conformation both in monocapped MLH_3 and encapsulated ML complex.

The least strain structures of ML^1 and ML^2 complexes were re-optimized by applying semi-empirical PM3 method. The calculations predicted similar structure for Ga(III) and In(III) chelates. Some important calculated structural parameters are also given in Table 3 and the optimized structure of GaL^1 and GaL^2 chelates are shown in Fig. 7. The optimized structures have distorted octahedral geometry for all the complexes. All complexes showed the presence of intramolecular hydrogen bond between protonated amine nitrogen proton and catecholic oxygen. Such intramolecular H-bonds known to provide extra stability for the formation of tripodal tris(catechol) type encapsulated complex, and this effect was reported for the complexes of enterobactin and its analogs.[5]

Conclusion

The tripodal amine catechol ligands L^1 and L^2 on interactions with Ga(III) and In(III) formed stable complexes, where only the catechol units were taken part in complex formation to give tris(catecholate) type complex. Molecular modeling calculations predicted a distorted octahedral type geometry for the metal complexes, where the ligands retained their *cis*,*cis*-equatorial conformation and a strong intramolecular

Table 3. Some calculated structural parameter of the MLH_3 and ML type complex obtained through semi-empirical PM3 method*: (i) total energy (E_T, eV), bond length (Å) and bond angle (°)

M(III)	ML^1H_3			ML^1				
	E_T	$NH\cdots O^1$	$M-O^1$	E_T	$NH\cdots O^1$	$M-O^1$	$M-O^2$	$<O^1MO^2$
Ga(III)	-7422.49	1.701	2.023	-6421.48	1.817	1.860	1.840	90.27
In(III)	-7408.08	1.700	2.187	-6407.79	1.817	2.173	2.125	79.27
	ML^2H_3			ML^2				
Ga(III)	-9640.39	1.780	1.811	-8640.47	1.714	1.831	1.838	92.12
In(III)	-9625.33	1.862	2.098	-8626.49	1.733	2.128	2.131	80.41

*O^1 and O^2 represents oxygen atom in the catechol units at *ortho* and *meta* positions respectively.

H-bond was observed between the amine proton and *ortho*-catecholic oxygen. The ligand L^2 showed higher affinity than L^1. The trend of stability for the ligands is Ga(III) > In(III).

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