



Studies of Binary Complexes of Tripodal Ligand *cis,cis*-1,3,5-tris(methylamino)cyclohexane with Cr(III) and Fe(III)

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Abstract The formation of binary complexes of Cr(III) and Fe(III) with a tripodal ligand *cis,cis*-1,3,5-tris(methylamino)cyclohexane (*tmach*) (L) has been investigated in solution. The overall stability constants of *tmach* with Cr(III) and Fe(III) were determined by potentiometric method at an ionic strength of 0.1M NaClO₄ at 25±1°C in aqueous medium. The formation of species like MLH₂⁵⁺, MLH⁴⁺, ML³⁺, ML(OH)²⁺ and ML(OH)₃ were observed. Fe(III) was found to form more stable complexes than Cr(III). Molecular mechanics calculations were performed to explain the mode of coordination in solution.

Key words: Tripodal amine ligand, potentiometry, stability constants and molecular mechanics

Introduction

The coordination chemistry of tripodal ligands has undergone rapid development and varieties of tripodal ligands exist and most form stable complexes with various transition metal ions¹. These transition metal complexes have been widely investigated, since they may serve as candidates for a magnetic resonance imaging agent² and models for the unique coordination polyhedra³⁻⁵ in addition to their special chemical, physical, and structural properties. The molecule *cis,cis*-1,3,5-triaminocyclohexane (*tach*) (Fig.1) is a well known versatile face capping N₃ tripodal amine ligand which can coordinate with several transition metals giving stable complexes and also derivatised to give different multidentate ligands^{3,6,7}. The molecule *tach* and its derivatives have wide applications in the field of bioinorganic chemistry for the synthesis of *vivo* metal chelators^{8,9} and in the modeling of metallo enzyme active sites¹⁰⁻¹².

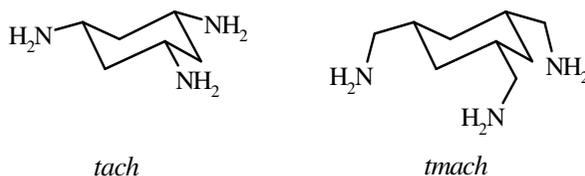


Figure- 1. Schematic drawing of *tach* and *tmach*.

Introduction of a methylene group in each arm of *tach* gives *tmach*, its higher homologue (**Fig.1**), which is more flexible and expected to form better complexes than *tach*. In this paper, we report the complexation behavior of *tmach* with Fe(III) and Cr(III) in aqueous medium by potentiometric method, and coordination behavior using molecular mechanics.

Experimental

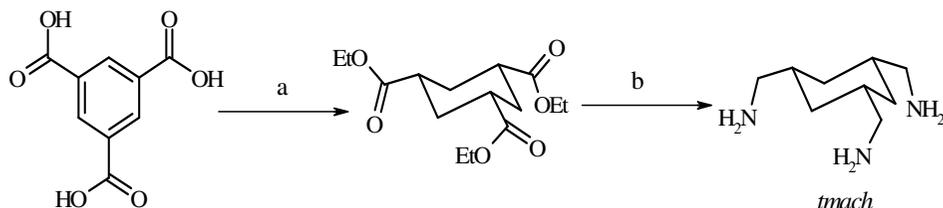
All chemicals for the synthesis of *tmach* were obtained from Aldrich Chemicals Ltd. The chemicals used for potentiometric study were obtained from Ranbaxy Chemicals Ltd., India and were used directly. The metal ions solutions of 0.01 M were prepared by dissolving their chloride salts. A stock solution of 0.01 M *tmach* was prepared. KOH (~0.1 M) solution was made from carbon dioxide free doubly distilled water and standardized against potassium hydrogen phthalate¹⁸. HClO₄ of 0.1 M solution was used after standardizing against KOH.

For all titrations, the observed pH was measured as $-\log [H^+]$ using a Thermo Orion 720A⁺ pH meter equipped with a combined glass electrode. The electrode was calibrated to read pH according to the classical method¹⁹. The value of $pK_w = 13.78 \pm 0.05$ was used in the calculation. All potentiometric titrations were carried out at $25 \pm 1^\circ\text{C}$ maintained from a double wall glass jacketed titration cell connected to a constant temperature circulatory bath. The ionic strength was maintained at 0.1 mol dm^{-3} by adding appropriate amount of 1M NaClO₄ solution. The following titrations were carried out: (a) free ligand (b) ligand and metal ion (1:1) (c) ligand and metal ion (2:1). Each titration was repeated two times to confirm the reliability of the data. The stability constants were calculated using computer program Hyperquad 2000¹⁴. The sigma values lie between 0.03 and 0.10 and the chi squared values for Cr(III) = 9.71 and Fe(III) = 7.82. The species distribution curves of the metal complexes were obtained from calculated stability constants with the program HySS²⁰ and are presented in **Fig. 3**.

Molecular modeling calculations were done using computer program HyperChem version 7.5²¹. The geometry of the complexes was proposed by energy minimization through molecular mechanics calculations. The geometrical optimization was done using force field MM⁺ and Polak-Ribiere algorithm with RMS gradient 0.01kcal/ mole, followed by molecular dynamics and same process was repeated for three times. The strain energy was noted after each calculation and then the structure with minimum strain energy was selected as a possible model of the complexes.

Results and Discussion

The ligand *tmach* was synthesized as per the **scheme I**¹³. Each intermediate product and the final product were characterized through melting point, elemental analysis, mass, IR, ¹H NMR, ¹³C NMR and electronic spectral data. The ligand is a colourless liquid at room temperature and highly soluble in water. Three protonation constants of *tmach*, $\log K_1 = 10.53$, $\log K_2 = 9.84$ and $\log K_3 = 8.88$ have been determined at $\mu = 0.1 \text{ M NaClO}_4$ and $25 \pm 1^\circ\text{C}$ and used as input data to evaluate the stability constants of the metal complexes.

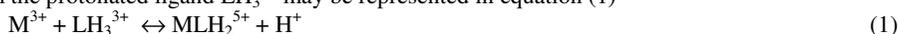


Scheme I. Synthesis of *tmach*: Reagents and Conditions: (a) i. EtOH, dry HCl; ii. PtO₂/H₂, room temp, 24hrs; (b) i. LiAlH₄, dry THF; ii. PhSO₂Cl; iii. NaN₃; iv. LiAlH₄, dry THF.

The potentiometric titrations of the *tmach* (L) with Cr(III) and Fe(III) were carried out in 1:1 and 1:2 metal-ligand molar ratios at $\mu = 0.1 \text{ M NaClO}_4$ and $25 \pm 1^\circ\text{C}$ in aqueous medium.

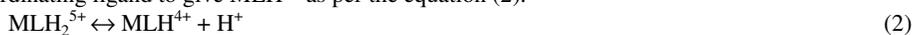
The experimental titration curves for the 1:1 metal-ligand molar ratio for both metal ions are shown as symbols in **Fig. 2** and the curves for 1:2 metal-ligand titration is not shown as ML_2^{3+} complex formation was not observed. The deviation of titration curves of the metal systems from ligand alone after $a = 1$ (where 'a' is moles of base added per mole of ligand present) indicates the complex formation. The overall stability constants ($\log \beta$) of the various species formed were calculated using computer program Hyperquad 2000¹⁴ and are presented in **Table 1**. The best-fit model was obtained when the formation of species MLH_2^{5+} , MLH^{4+} , ML^{3+} , $ML(OH)^{2+}$ and $ML(OH)_3$ were considered. The simulated titration curves obtained using the result (**Table 1**) are shown as solid line in **Fig. 2**.

The close similarity in the experimental titration curves for Cr(III) and Fe(III) systems (**Fig. 2**) indicates similar mode of complexation. It was observed that (**Fig. 4**), $FeLH_2^{5+}$ predominates over LH_3^{3+} at low pH for Fe(III) system, while for Cr(III), LH_3^{3+} predominates. The formation of MLH_2^{5+} from the protonated ligand LH_3^{3+} may be represented in equation (1)



$$\log K_{MLH_2^{5+}}^{M^{3+}} \leftrightarrow \frac{[MLH_2^{5+}][H^+]}{[M^{3+}][LH_3^{3+}]}, \quad (-1.03 \text{ for Fe(III) and } 0.67 \text{ for Cr(III) system})$$

The species $CrLH_2^{5+}$ and $FeLH_2^{5+}$ have maximum concentration of 65% and 95% respectively at pH ~5. On further rise of pH, the species MLH_2^{5+} release one more proton from the coordinating ligand to give MLH^{4+} as per the equation (2).



$$\log K_{MLH^{4+}}^{MLH_2^{5+}} \leftrightarrow \frac{[MLH^{4+}][H^+]}{[MLH_2^{5+}]}, \quad (-5.97 \text{ for Fe(III) and } -6.92 \text{ for Cr(III) system})$$

Also, it is evident that the ML^{3+} complex formation resulted due to stepwise deprotonation of the protonated species MLH^{4+} (equation 3). The concentration of unprotonated complex ML^{3+} is maximum [Cr(III): 85% and Fe(III): 80%] at pH ~7.



$$\log K_{ML^{3+}}^{MHL^{4+}} \leftrightarrow \frac{[ML^{3+}][H^+]}{[MHL^{4+}]}, \quad (-5.71 \text{ for Fe(III) and } -5.81 \text{ for Cr(III) system})$$

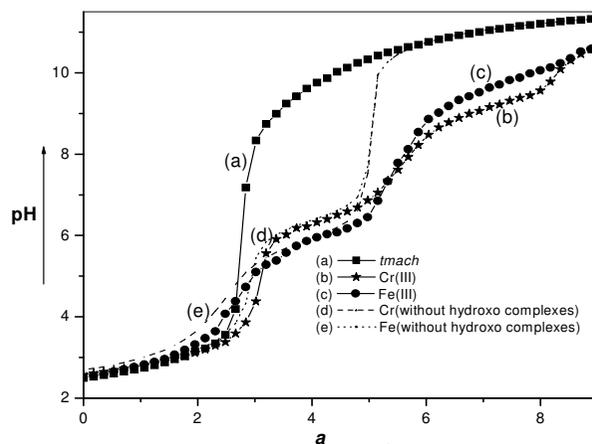


Fig. 2. Potentiometric titration curves of *tmach* (L) with Fe(III) and Cr(III) in 1:1 molar ratio, where 'a' is the moles of base added per mole of ligand present. Symbols and solid lines indicate the experimental values and simulated results respectively.

The inflation of the titration curve (**Fig. 2**) after $a \sim 5$ is due to the formation of hydroxy metal complexes of the types $ML(OH)^{2+}$ and $ML(OH)_3$. Exclusion of hydroxy complexes from the model chosen during calculation did not give a good fit. The theoretical curves (dashed line) calculated by excluding the hydroxy complexes deviates from the experimental curves (shown as symbols), which is more prominent at high pH (**Fig. 2**). No trace of $ML(OH)_2^+$ species was observed. It has been well established that $CrCl_3$ and $FeCl_3$ exist as $[Cr(H_2O)_6]^{3+}$ and $[Fe(H_2O)_6]^{3+}$ in aqueous solution¹⁵. The hexa aqua ion $[Cr(H_2O)_6]^{3+}$, hydrolyses to give hydroxo complexes or condenses to give a dimeric hydroxo bridged species¹⁵. The $[Fe(H_2O)_6]^{3+}$ in aqueous solution has tendency to hydrolyse or to form μ -oxo bridged dimer. But in the present study inclusion of dimeric or polymeric type of complexes did not give a good fit with experimental curves and are rejected. Keeping this in view, it is proposed that the coordination sites, not occupied by the ligand molecule are occupied by the solvent molecule, H_2O to give a hexa-coordinated environment. Accordingly, the formation of hydroxy species can be presented as equations (4) and (5).



$$\log K_{ML(OH)^{2+}}^{ML^{3+}} \leftrightarrow \frac{[ML(OH)]^{2+}}{[ML]^{3+}[OH^-]}, \quad (-8.04 \text{ for Fe(III) and } -7.86 \text{ for Cr(III) system})$$



$$\log K_{ML(OH)_3}^{ML(OH)^{2+}} \leftrightarrow \frac{[ML(OH)_3]}{[ML(OH)]^{2+}[OH^-]^2}, \quad (-19.34 \text{ for Fe(III) and } -18.29 \text{ for Cr(III) system})$$

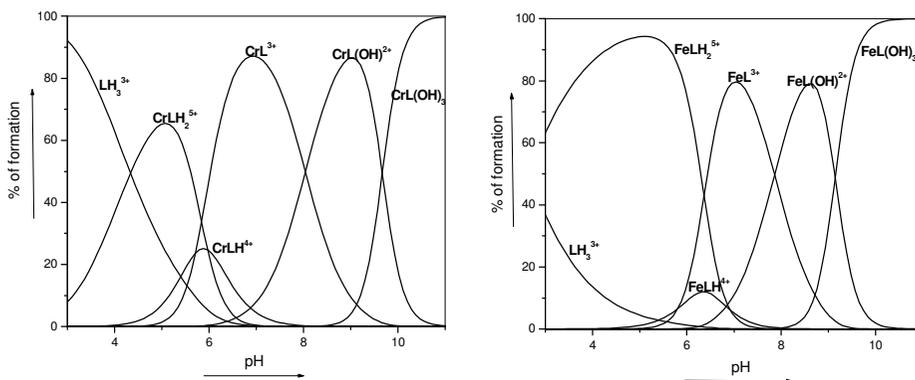


Fig. 3. Species distribution curves for Cr(III)-*tmach* and Fe(III)-*tmach* system in aqueous solution at $\mu = 0.1M NaClO_4$ and $25 \pm 1^\circ C$.

Table 1. The complexation reactions and their overall stability constants ($\log \beta$) values at $\mu = 0.1M NaClO_4$ and $25 \pm 1^\circ C$.

Reactions	Cr(III)	Fe(III)
$M^{3+} + L + 2H^+ \leftrightarrow MLH_2^{5+}$	28.22 ± 0.10	29.92 ± 0.03
$M^{3+} + L + H^+ \leftrightarrow MLH^{4+}$	22.25 ± 0.08	23.00 ± 0.08
$M^{3+} + L \leftrightarrow ML^{3+}$	16.54 ± 0.07	17.19 ± 0.03
$M^{3+} + L + OH^- \leftrightarrow ML(OH)^{2+}$	8.50 ± 0.09	9.33 ± 0.03
$M^{3+} + L + 3OH^- \leftrightarrow ML(OH)_3$	-10.84 ± 0.10	-8.96 ± 0.03

Schwarzenbach *et al.*¹⁶ have studied the formation of metal complexes of *cis,cis*-1,3,5-triaminocyclohexane (*tach*) with divalent copper and zinc. They have reported the formation of

MLH³⁺, ML²⁺, ML(OH)⁺ and ML(OH)₂ types of complexes for both the metal ions. They suggested that initially one of the protonated amine groups remain uncoordinated for MLH³⁺ type of complexes. At the higher pH the proton dissociates from the protonated amine group to form ML²⁺ and further ML(OH)⁺ and ML(OH)₂ types of complexes. They also proposed that in MLH⁴⁺, the ligand coordinate through the two N atoms of the cyclohexane ring in the boat form. However in the present case two and one protonated amines remain uncoordinated in MLH₂⁵⁺ and MLH⁴⁺ respectively for both Cr(III) and Fe(III). No MLH₂⁴⁺ type of complex has been reported by Schwarzenbach *et al.*¹⁶ for Cu(II) and Zn(II). In the present study, removing the species MLH₂⁵⁺ from the model during the calculation did not give a good fit for the metal-ligand systems in the lower pH region. Keeping the above facts in view it is suggested that at lower pH (<6), the ligand coordinate through one N of *tmach* in the complex MLH₂⁵⁺, through two N in the complex MLH⁴⁺ and three N in ML³⁺ with all unprotonated amine group. Obviously the other coordination sites are occupied by the solvent molecules to give a hexa coordinated species. The species MLH₂⁵⁺ and MLH⁴⁺ exist in the pH region 2.5-7 and 4-8 respectively. The ML³⁺ is a major species at pH 7 and span over pH 5-10.

For MLH₂⁵⁺, complexes of Cr(III) was found to be more stable than Fe(III) by energy 0.99 kcal/mole. In case of CrLH⁴⁺ and FeLH⁴⁺ where the ligand coordinates with the metal ion with two N, the one where *tmach* has a boat conformation has low strain energy 35.39 and 35.50 kcal/mole respectively as compared to the complex where *tmach* has a chair conformation with strain energy of 37.94 and 41.09 kcal/mole. This further support the coordination mode of mono protonated species suggested for *tach* by Schwarzenbach¹⁶. For CrL(H₂O)₃³⁺ and FeL(H₂O)₃³⁺ where *tmach* coordinates through three-amine N atoms, the lowest energy structure had *tmach* with axial N coordination. The difference in energy between axial and equatorial coordination was 129.42 and 135.01 kcal/mole respectively. Thus, a definite ring flipping was observed from equatorial to axial

conformation during coordination. Also a definite ring flipping was observed, for metal complexes of *tach*, and the complex formation takes place through axial conformation¹⁷. The ligand *tmach* exists in similar form in all hydroxy complexes also. The strain energy obtained from the molecular mechanics for the species including free ligand is given in **Table 2**.

Table 2. Strain energy (kcal/mole) of MLH₂⁵⁺, MLH⁴⁺, ML³⁺, ML(OH)²⁺, ML(OH)₃ obtained from MM⁺ calculation:

Species	equitorial	axial	MLH ₂ ⁵⁺	MLH ⁴⁺		ML ³⁺		ML(OH) ²⁺	ML(OH) ₃
				Chair	boat	axial	equitorial		
<i>tmach</i>	3.36	10.39	-	-	-	-	-	-	-
Cr(III)	-	-	17.84	37.94	35.39	48.75	178.17	54.38	48.42
complex	-	-	18.83	41.09	35.50	50.45	180.46	56.20	50.13
Fe(III)									
complex									

Conclusion

The tripodal triamine *tmach* coordinates to both Fe(III) and Cr(III) as unidentate, bidentate and tridentate ligand which is pH dependent, and two or one amino groups of *tmach* remains protonated at low pH. Assuming the coordination number of the metal ions as 6, which also evident from formation of ML(OH)₃ type of complex, it is assumed that five, four and three solvent water molecules are coordinated to the metal ion in MLH₂⁵⁺, MLH⁴⁺ and ML³⁺ respectively. Though there is possibility for the tridentate ligand *tmach* to form ML₂³⁺ type of complexes, such complex was not formed. Non-existence of ML₂³⁺ type of complex may be due to the repulsion of charge between the ML³⁺ complex and the protonated ligand, steric factor and large cavities between the coordination sites of the *tmach*. At higher pH, the coordinated water molecules undergo stepwise hydrolysis and lose protons to form ML(OH)²⁺ and ML(OH)₃ complexes.

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