

## Computational Insight into a Mechanistic Overview of Water Exchange Kinetics and Thermodynamic Stabilities of Bis and Tris-Aquated Complexes of Lanthanides

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**Abstract :** A thorough investigation of  $\text{Ln}^{3+}$  complexes with more than one inner-sphere water molecule is crucial for designing high relaxivity contrast agents (CAs) used in magnetic resonance imaging (MRI). This study accomplished a comparative stability analysis of two hexadentate ( $\text{H3cbda}$  and  $\text{H3dpaa}$ ) and two heptadentate ( $\text{H4peada}$  and  $\text{H3tpaa}$ ) ligands with  $\text{Ln}^{3+}$  ions. The higher stability of the hexadentate  $\text{H3cbda}$  and heptadentate  $\text{H4peada}$  ligands has been confirmed by the binding affinity and Gibbs free energy analysis in aqueous solution. In addition, energy decomposition analysis (EDA) reveals the higher binding affinity of the  $\text{peada4-}$  ligand than the  $\text{cbda3-}$  ligand towards  $\text{Ln}^{3+}$  ions due to the higher charge density of the  $\text{peada4-}$  ligand. Moreover, a mechanistic overview of water exchange kinetics has been carried out based on the strength of the metal-water bond. The strength of the metal-water bond follows the trend  $\text{Gd-O47 (w)} > \text{Gd-O39 (w)} > \text{Gd-O36 (w)}$  in the case of the tris-aquated  $[\text{Gd}(\text{cbda})(\text{H}_2\text{O})_3]$  and  $\text{Gd-O43 (w)} > \text{Gd-O40 (w)}$  for the bis-aquated  $[\text{Gd}(\text{peada})(\text{H}_2\text{O})_2]-$  complex, which was confirmed by bond length, electron density ( $\rho$ ), and electron localization function (ELF) at the corresponding bond critical points. Our analysis also predicts that the activation energy barrier decreases with the decrease in bond strength; hence  $k_{\text{ex}}$  increases. The  $^{17}\text{O}$  and  $^1\text{H}$  hyperfine coupling constant values of all the coordinated water molecules were different, calculated by using the second-order Douglas-Kroll-Hess (DKH2) approach. Furthermore, the ionic nature of the bonding in the metal-ligand (M-L) bond was confirmed by the Quantum Theory of Atoms-In-Molecules (QTAIM) and ELF along with energy decomposition analysis (EDA). We hope that the results can be used as a basis for the design of highly efficient Gd(III)-based high relaxivity MRI contrast agents for medical applications.

**Keywords :** MRI contrast agents, lanthanide chemistry, thermodynamic stability, water exchange kinetics

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