

INVESTIGATION OF EQUILIBRIUM, KINETIC, RELAXATION PROPERTIES OF Mn(II) COMPLEXES FORMED WITH PC2A DERIVATIVE LIGANDS

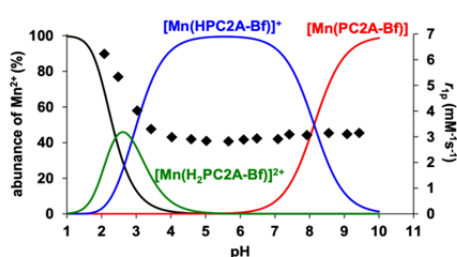
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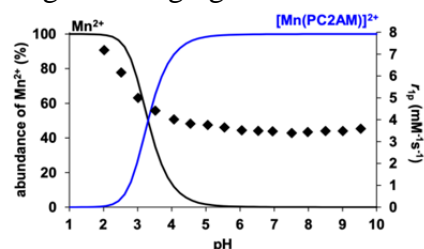
Manganese (II) complexes are gaining attention as alternatives to gadolinium-based contrast agents for magnetic resonance imaging (MRI) due to their lower toxicity and robust relaxometric properties. This study focuses on the synthesis, equilibrium, kinetic, and relaxometric characterization of Mn (II) complexes with pyridine-containing cyclen (PC2A, PC2A_BF and PC2AM) derivatives. Synthesis of the ligand (PC2A, PC2A_BF) are followed according to the previous work^[1]. The PC2AM was synthesized by coupling PC2A and Dimethylamine using DIC as a coupling agent^[2]. Protonation constants ($\log K_{iH}$) and conditional stability constants ($\log K_{ML}$, pMn) were meticulously determined under physiological conditions, demonstrating that specific ligand modifications significantly enhance the stability and selectivity of Mn(II) complexes.

Relaxometric studies revealed a strong dependence of longitudinal relaxivity (r_1) on pH and ligand coordination environments. Notably, PC2AM derivatives exhibited improved relaxivity profiles attributed to optimized water exchange kinetics and rotational correlation times. Transmetalation kinetics with Cu (II) were investigated, and pseudo-first-order rate constants (k_d) were measured across various pH levels. The results highlighted the superior kinetic inertness of Mn (PC2AM) complexes, with half-lives ($t_{1/2}$) exceeding several hundred hours under physiological conditions.

Furthermore, nuclear magnetic relaxation dispersion (NMRD) studies provided detailed insights into the molecular mechanisms governing relaxivity, confirming the potential of PC2AM derivatives as next-generation MRI contrast agents. This work establishes a comprehensive framework for the rational design of Mn (II) based contrast agents, with applications extending to clinical diagnostics and targeted imaging.



Relaxivity values (◆) and species distribution of Mn^{2+} - PC2A-Bf system as a function of pH ($[Mn^{2+}] = [PC2A-Bf] = 1.0$ mM, 26 MHz, 0.15 M NaCl, 25°C)



Relaxivity values (◆) and species distribution of Mn^{2+} - PC2AM system as a function of pH ($[Mn^{2+}] = [PC2AM] = 1.0$ mM, 26 MHz, 0.15 M NaCl, 25°C)

[1] Marie Devreux, Céline Henoumont, Fabienne Dioury, Sébastien Boutry, Olivier Vacher, Luce Vander Elst, Marc Port, Robert N. Muller, Olivier Sandre, and Sophie Laurent. *Mn²⁺ Complexes with Pyclyen-Based Derivatives as Contrast Agents for Magnetic Resonance Imaging: Synthesis and Relaxometry Characterization*. *Inorg chem* (60)(6),3604-3619 (2021).

[2] Roeser, Katharina, et al. *Chiral Quaternary Ammonium Salt-Catalyzed Enantioselective Addition Reactions of Hydantoins*. s.l.: 107, e202300 Verlag Helvetica Chimica Acta (2024).