

Hexameric Mn(II)-EDTA Complex as Contrast agent for High Field MR Imaging

Jiang Zhu^{1,2}, Eirc Gale¹, Iliyana Atanasova³, and Peter Caravan¹

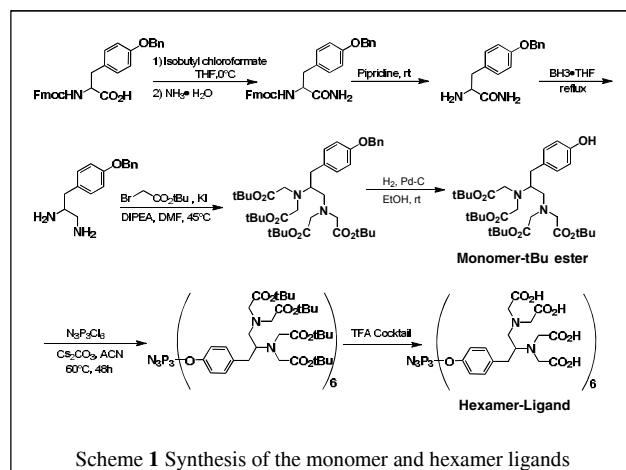
¹Martinos Center for Biomedical Imaging, Charlestown, MA, United States, ²Sichuan

Key laboratory of Medical Imaging, Nanchong, Sichuan, China, ³Massachusetts

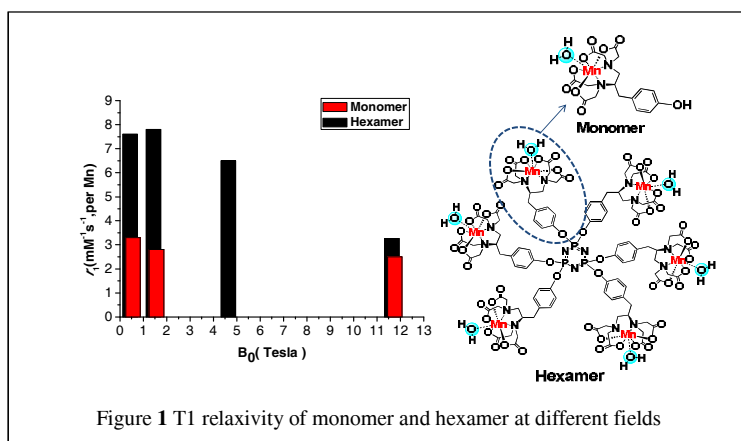
Institute of Technology, Cambridge, MA, United States

Target audience: Molecular imaging.

Purpose: High field MRI offers enhanced signal-to-noise ratio (SNR), higher spatial resolution and/or reduced acquisition times. However, the T_1 relaxivity (r_1) of lanthanide contrast agents is field-dependent and generally decreases as field strength increases above 1.5T. High field preclinical imaging and the growing base of higher field clinical scanners demand a new generation of contrast agents offering optimized relaxivity above 3T. Our aim is to design and synthesize a new Mn(II)-based T_1 agent, exhibiting rotational dynamics (τ_R) and the mean residency time (τ_m) finely tuned for high-field MRI applications¹.



Methods: Starting from L-tyrosine, we synthesized an EDTA derivative with a pendant phenol (monomer). Reaction of this derivative with $N_3P_3Cl_6$, followed by



deprotection and chelation of Mn(II) gave the novel rigid, hexameric complex shown in Scheme 1. Relaxivities of the monomeric and hexameric complexes were determined through measurement of T_1 using an inversion recovery sequence at different field strengths, ranging from 0.47 T to 11.7T. The hydration state of the Mn(II) complex and water exchange kinetics for the inner-sphere were determined by measurement of the temperature dependence of the transverse relaxation time T_2 of $H_2^{17}O$ in the presence and absence of the hexamer Mn(II) complex².

Results: The hexameric Mn(II) complex shows greater relaxivity on a per ion basis at low, intermediate and high fields compared to the monomeric

analog. ($r_1 = 7.6$ (45.6), 7.8(46.8), 6.5(39.0) and 3.3(19.8) $mM^{-1}s^{-1}$ per Mn (per molecule), at 0.5, 1.5, 4.7, and 11.7T, respectively in HEPES buffer, 37°C, Figure 1). O-17 NMR confirmed the presence of one water co-ligand ($q = 1$), with the mean residency time of $\tau_m = 2.2 \pm 0.1$ (ns), at 37 °C. Preliminary MRI data in a mouse xenograft tumor model indicates that the hexamer shows tumor enhancement consistent with its relaxivity.

Discussion and Conclusion: The small, compact size of the hexamer offers favorable properties for high field applications. First, the intermediate size between a simple chelate and a macromolecule results in an intermediate rotational correlation time well suited to higher relaxivity at high fields. The compound achieves this size by condensation of 6 Mn-EDTA chelates and thus the molecular relaxivity is 6-fold higher (e.g. 39 $mM^{-1}s^{-1}$ at 4.7T). The compact structure (MWt = 2932.6) also enables this complex to rapidly extravasate into the interstitium and may prove useful for more sensitive lesion detection. This system represents a promising entry towards MR contrast suitable for usage at high field.

Reference:

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- Gale, E. M.; Zhu, J.; Caravan, P., Direct Measurement of the Mn(II) Hydration State in Metal Complexes and Metalloproteins through ^{17}O NMR Line Widths. *Journal of the American Chemical Society* **2013**.ASAP