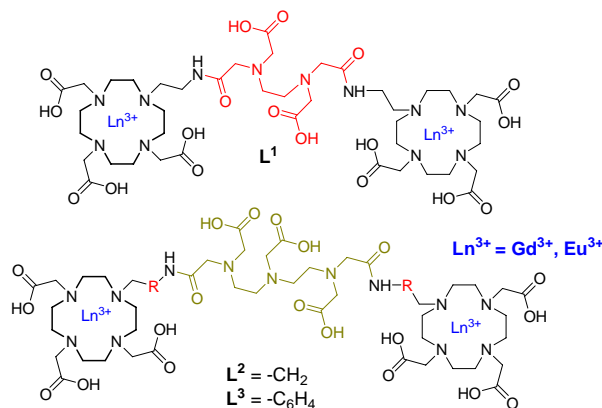


# Synthesis and Relaxation Properties of Three Novel Bis-macrocycles: Attempt towards Calcium Sensitive MRI Contrast Agents

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MR contrast agents whose efficiency depends on the concentration of signaling molecules may be used to directly visualize neuronal activation. The so-called ‘*smart*’ contrast agents for magnetic resonance imaging exhibit dynamic and reversible modulation of their relaxivity by specific physiological or biochemical triggers such as changes in pH, Ca<sup>2+</sup> concentration or enzymatic activity. The extracellular concentration of Ca<sup>2+</sup> plays an important role in the physiological and pathological processes of the nervous system; it led us to design chelating systems in which the relaxivity is influenced by the Ca<sup>2+</sup> concentration. We synthesized three novel bifunctional bismacrocycles based on DO3A-EA coupled to EDTA/DTPA-bis-anhydride via amide bonds.



**Results:** The relaxivity changes upon increasing Ca<sup>2+</sup> concentration of our three novel Gd(III) complexes largely depends on the structure of the ligands. In contrast to no significant relaxivity change of Gd<sub>2</sub>L<sup>3</sup> upon Ca<sup>2+</sup> addition, Gd<sub>2</sub>L<sup>1</sup> and Gd<sub>2</sub>L<sup>2</sup> exhibit a relaxivity increase of 34% and 15%, respectively, which is related to an increase in the hydration number of the complexes. The HRUV-Vis spectra of Eu<sup>3+</sup> complexes of L<sup>1</sup>-L<sup>3</sup> confirm two different coordination environments. They are temperature dependent only for Eu<sub>2</sub>L<sup>3</sup> which we relate to hydration equilibrium between zero and one coordinated water molecule. For complexes with L<sup>1</sup> and L<sup>2</sup> we assume equilibrium between two non-

coordinated species with a coordination of either a carboxylates from the central part of the complex or a molecule of water. Upon  $\text{Ca}^{2+}$  coordination in the central part of the complex, this equilibrium shifts towards the more hydrated complex, which has a direct impact on its relaxivity. The hydration numbers found are in accordance with the relaxivity values.

Reference: 1) Louie et.al (2000) *Nat. Biotechnol.* 18, 321-325.