Facile Synthesis of Gd-DO3A-EA Conjugated with DTPA: A Novel Calcium Dependent MR Contrast Agent

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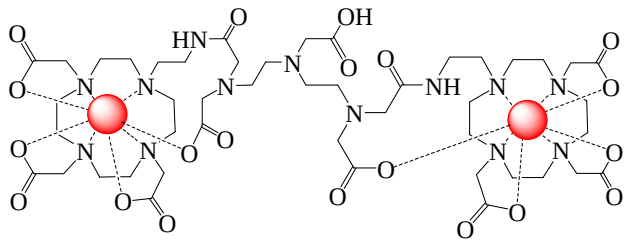
'*Smart*' contrast agents (CA) exhibit dynamic and reversible modulation of their relaxivity by specific physiological or biochemical triggers such as changes in pH, Ca^{2+} concentration or enzymatic activity (1-3). The extracellular concentration of Ca^{2+} plays important role in physiological and pathological processes in the nervous system. This led to the designing of a chelating system in which relaxivity is influenced as a function of Ca^{2+} concentration by changing coordination number around the paramagnetic metal ion. We synthesized a novel bifunctional bismacrocycle [Gd-(DO3A-DTPA-DO3A); Fig.] based on DO3A-EA [{4,7-Bis-carboxymethyl-10-(2-aminoethyl)-1,4,7,10-tetraaza-cyclododec-1-yl}-acetic acid] coupled to DTPA-bis-anhydride via a flexible alkyl spacer to form the amide linkages. The overall yield of the four step synthesis starting from cyclen was 54%. This gadolinium-based agent has two limiting conformational states with different Ca^{2+} concentrations. It is hypothesized that in the absence of Ca^{2+}, the carboxylates of the DTPA ligand interact with the Gd^{3+} ions which were held in DO3A, but in the presence of Ca^{2+}, these carboxylates rearrange to chelate Ca^{2+} thereby allowing water to bind directly to Gd^{3+}.



Gd-(DO3A-DTPA-DO3A)

Results: MR relaxivity of Gd-(DO3A-DTPA-DO3A) at pH 7.4 in the absence of Ca^{2+} was found to be r_1 = (5.02±0.05) $s^{-1}mM^{-1}$. In the presence of 1mM Ca^{2+} r_1 was (6.18±0.06) $s^{-1}mM^{-1}$ and 100mM Ca^{2+} r_1 was (7.69±0.06) $s^{-1}mM^{-1}$. These data indicate 23% relaxivity enhancement from 0-1mM Ca^{2+} concentration under physiological conditions thus exhibiting a possibility for use as extracellular calcium sensitive CA.

References: (1). Zhang, S., *et. al* (1999) *Angew. Chem. Int. Ed. 38*, 3192-3194. (2). Li, W-H., *et. al* (1999) *J. Am. Chem. Soc. 121*, 1413-1414. (3) Louie, A.Y., *et. al* (2000) *Nat Biotechnol 18*, 321-325.

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