Assessment of Bis-macrocyclic Compounds as Calcium-sensitive MR Contrast Agents

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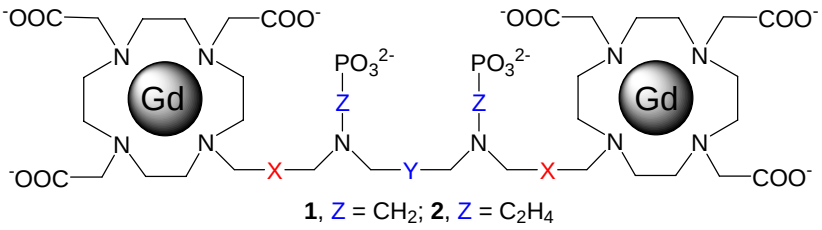
Introduction. The ability of non-invasively observing changes in the Ca^{2+} concentrations is important in the understanding of a great variety of neuronal processes. Several compounds were designed (Fig.1) to take advantage of the different binding abilities of carboxylates and phosphonates to gadolinium. Furthermore the different affinities of the two functional groups to Ca^{2+} permit to obtain free coordination sites at gadolinium. The generation of these coordination sites, which are mandatory for water relaxivity, depends on the structure of the complexes and the Ca^{2+} concentration. Gadolinium complexes **1** and **2** were synthesized and relaxivity studies were performed.

Methods. For measurements of the relaxivities r_1 and r_2, concentrations of 0.1, 0.4, 0.7, and 1 mM of the CA and different concentrations of Ca^{2+} (0, 1.0, 10.0 and 100.0 mM) were used at pH 7.2 in a KMOPS buffer. Relaxivity $r_{1,2}$ was calculated from the slope of $R_{1,2(c)}$ versus the CA concentration by an error-weighted linear regression.



1, Z = CH_2; **2**, Z = C_2H_4

Figure 1. Gadolinium complexes of the bis-macrocyclic compounds with the variable length of the side chain

Results. Changes of relaxivity was observed for the different Ca^{2+} concentrations (Fig. 2). An increase of the Ca^{2+} concentration between 10 to 100 mM enlarged relaxivity up to 20%. According to the results shown it is expected that by the incorporation of more structural constraints into the acyclic part (X and Y) changes in relaxivity can be moved towards the range of physiological conditions (i.e. 1mM in the extracellular space).

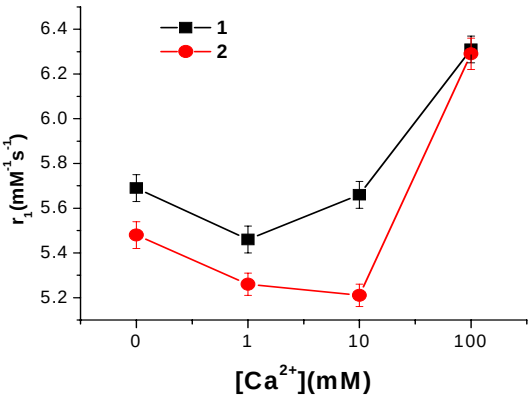


Figure 2. Relaxivity studies of the complexes in the presence and absence of Ca^{2+}

This work was supported by the Louis-Jeantet Foundation, and the Hertie Foundation.