Azamacrocyclic Ca^{2+} Sensitive Contrast Agents for MR Imaging

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Introduction. As calcium plays an important role in regulating a great variety of neuronal processes, many efforts are already made to generate gadolinium complexes that can act as a calcium-sensors in MRI.[1] We developed a series of the DO3A-based macrocyclic and bismacrocyclic gadolinium chelates, bearing phosphonate groups as an additional coordination sites. These complexes are hypothesized to change the MRI contrast dynamically with Ca^{2+} concentration. Different lengths of the phosphonate side chains are exploited for fine-tuning the sensitivity of the agent to calcium ion concentration.

Methods. The macrocyclic ligands DO3A-**alkyl** aminobis(methylenphosphonates) (alkyl = propyl **1;** amyl **2;** hexyl **3)**, and the bismacrocyclic bisDO3A-ethyleneaminobis (**alkyl**)phosphonates (alkyl = methyl **4**; ethyl **5**) were prepared in multistep reactions from cyclen. Gadolinium complexes were obtained by treating the ligands with $GdCl_3$ at pH 7.0 -7.5 and 70°C for 24h. Longitudinal and transverse relaxivities r_1 and r_2 were measured on a vertical 7 T/60 cm MRI Biospec system (Bruker Biospin, Germany), at pH 7.4 and different concentrations of Ca^{2+}.

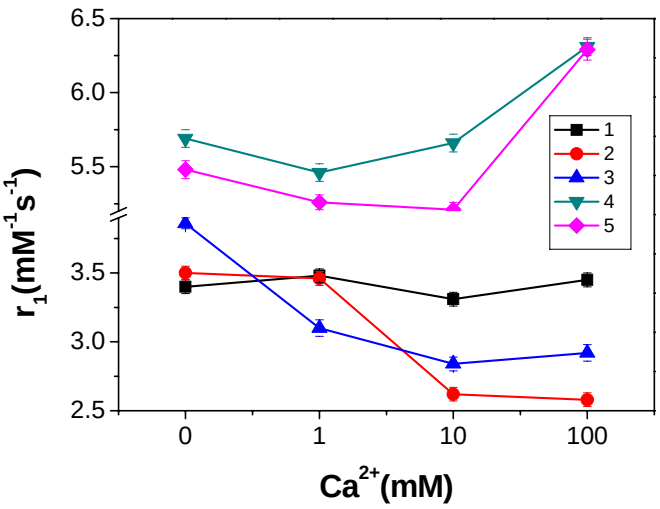

Figure 1. Dependence of the complex relaxivity to the Ca^{2+}ions concentration

Results. The sensitivity of the complexes **1**-**3** for the changes in Ca^{2+} concentrations increased with the chain length between the DO3A unit and the phosphonate functions (Fig. 1). Maximal observed change in relaxivity in presence of the physiological extracellular concentration of calcium (~1 mM) was up to 35% for compound **3**, and was selective to Ca^{2+} compared to other physiologically important metals such as magnesium or zinc. The significant changes in the relaxivity of the bismacrocyclic compounds **4** and **5** were found in the presence of a higher concentration of Ca^{2+} ions.

1. Li et al. J.Am.Chem.Soc., **1999**,121,1413-1414

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