Synthesis and Physicochemical Characterization of New Gd-TTDA-bisamide Complexes, Potential Contrast Agents for MRI

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INTRODUCTION:

Ideally at 310K, the water residence time τ_M of a gadolinium complex should be equal to ca 10 to 30 ns, depending on the imaging field, allowing so for the highest relaxivity after motion restriction by covalent or non-covalent binding. Recent works have shown that derivatives of Gd-TTDA have exchange lifetime τ_M significantly shorter than Gd-DTPA (τ_M<10 ns) [1, 2]. This work reports the synthesis and the physicochemical characterization of two new Gd-TTDA-bisamide complexes which could be further substituted to enhance their specificity in the context of molecular imaging.

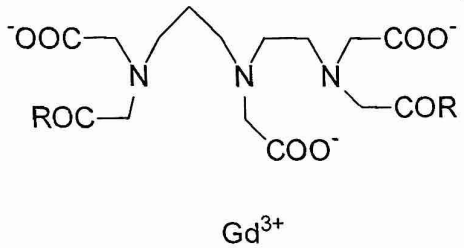

Figure 1: Structure of the parent complex Gd-TTDA **1** (R= O^-) and of the two bisamides Gd-TTDA-BA **2** (R=NH_2) and Gd-TTDA-BMA **3** (R=$NHCH_3$)

MATERIALS AND METHODS

The TTDA ligand (3,6,10-tri(carboxymethyl)-3,6,10-triazadodecanedioic acid) was prepared following the protocol described by Wang et al. [3]. The TTDA-bisamides, obtained by reaction of TTDA bisanhydride with the corresponding amine, were identified by ^1H, ^{13}C NMR spectroscopy and by mass spectrometry. The Gd-complexes were prepared by mixing the ligand with gadolinium chloride. Proton longitudinal relaxation dispersion profiles (NMRD) were recorded at 310K on a field cycling relaxometer (Stelar). The water residence time τ_M of the complexes was obtained from the analysis of the temperature dependence of the oxygen-17 transverse relaxation rate (Bruker AMX-300) [4]. Transmetallation by zinc ions was evaluated by the decrease of the water longitudinal relaxation rate at 310K and 20 MHz (Bruker Minispec) of buffered phosphate solutions containing equal amount of gadolinium complex and $ZnCl_2$ [5].

RESULTS :

At low temperature, no limitation of r_1 by τ_M is observed in good agreement with the low τ_M determined by ^{17}O NMR at 310 K : 22.0 ns and 32.4 ns for **2** and **3** respectively. At 310 K, NMRD profiles are quite similar for the 3 complexes ; their r_1 at 20 MHz is slightly higher than for the parent compound Gd-DTPA **4**. These compounds are less stable than the Gd-DTPA **4** as proven by their faster transmetallation against Zn .