

Relaxometric properties of gadolinium chelates of DOTA-like ligands with axially uneven distribution of donor atoms

Miloslav Polasek¹ and Peter Caravan¹

¹Radiology, A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital/Harvard Medical School, Charlestown, Massachusetts, United States

Introduction

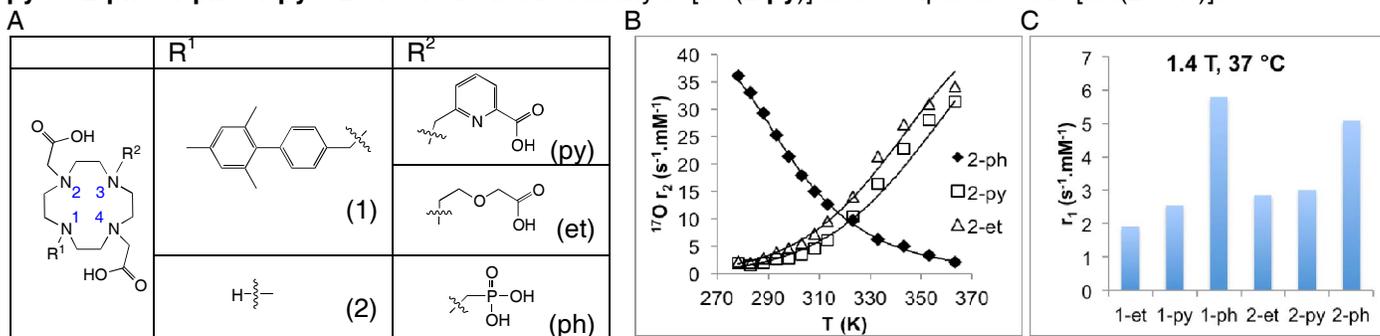
Molecular magnetic resonance (MR) imaging is often impeded by low relaxivity of gadolinium-based MR probes. Relaxivity can be optimized by careful control of the water exchange rate ($1/T_M$, where T_M is lifetime of the coordinated water) and the rotational dynamics of the molecule.[1] Water exchange rates can be controlled by the choice of metal donor groups, while rotational dynamics can be best controlled if the Gd-chelate is linked to a targeting vector by a short linkage. However, methods for such attachment of DOTA-like chelators are limited. Simple amide coupling of an acetate arm slows water exchange and limits relaxivity. Modifications of the backbone of DOTA are synthetically difficult and often provide rather flexible attachment. Here we explore a third possibility: direct alkylation of the nitrogen atom in the macrocycle. We synthesized a small library (N = 6) of DOTA-like chelators (Panel A) where atom N1 was alkylated with a biphenyl moiety (BM) or remained as a secondary amine. To account for the loss of a donor group on N1, the opposite N7 bears either a bidentate or bulky monodentate coordinating unit to complete the number of donor atoms to 8 or 7, respectively (Panel A). We studied the effect of these substituents on the properties of the Gd and Eu chelates.

Methods

Chelators were synthesized from 1,7-DO2A bis(t-butyl)ester by an alkylation reaction with a corresponding alkylating agent. Methyl phosphonate derivatives were synthesized through Mannich reaction with tris(t-butyl)phosphite. Products were purified by preparative RP-HPLC and deprotected with trifluoroacetic acid. Gd and Eu chelates were prepared under standard conditions. Concentrations were measured by ICP-MS. Number of coordinated water molecules (q) was determined from the difference of the luminescence decay rates of Eu chelates in H₂O and D₂O. Water exchange was determined from temperature dependence of ¹⁷O transversal relaxivity at 11.7 T by fitting to a 4-parameter model. Relaxivity was measured at 1.4 T and 37 °C. Kinetic stability was assessed by following relaxivity of 2.5 mM solutions of Gd chelates in the presence of 2.5 mM Zn in 30 mM phosphate buffer at pH = 7.4 and 37 °C.

Results

The Eu chelates of **2-py**, **2-et** and **2-ph** each had one coordinated water ligand, $q = 1$, confirming that all donor atoms coordinated to the central ion. However, the choice of the coordinating group had dramatic effect on the water exchange rate (Panel B). The bidentate pendant arms in **2-py** and **2-et** presented Gd chelates with very slow water exchange ($T_M = 2850 \pm 180$ ns and 1960 ± 170 ns at 37 °C, respectively) while the derivative **2-ph** showed very fast exchange ($T_M = 13.1 \pm 0.7$ ns). Water exchange had profound effect on the relaxivities. Fast exchanging [Gd(**1-ph**)] and [Gd(**2-ph**)] showed 2-times higher relaxivities compared to the slow exchanging derivatives (Panel C). Presence of the non-coordinating BM group had only little effect on the relaxivities (Panel C), however it had a profound effect on kinetic inertness, increasing lability 1.6- to 10-fold compared to the unsubstituted analogs. The order of kinetic inertness with respect to Gd loss was **2-py** >> **2-ph** > **1-ph** > **1-py** > **2-et** > **1-et**. Kinetic stability of [Gd(**2-py**)] was comparable with [Gd(DTPA)].



Conclusions

We explored a novel design of DOTA-like compounds where removal of an acetate arm on N1 is counterbalanced by a donor arm on N7. Surprisingly, presence of a non-coordinating moiety on N1 lowered kinetic stability of the Gd chelates. Choice of the donor arm on N7 influenced both kinetic stability and water exchange rate, the latter could be tuned over 2 orders of magnitude.

References: [1] Caravan et al. Contrast Media Mol. Imaging, 2009, 4, 89–100.