Paramagnetic CEST Agents: Imaging Sugar *via* the Bulk Water

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Synopsis

Europium (III) complex of a DOTA-tetraamide ligand containing two phenyl boronate pendent arms was synthesized and characterized as a prototype of contrast agent for imaging sugar in tissues. Upon sugar binding, the exchange between single Eu^{3+}-bound water molecule and bulk water was slowing down and this can be imaged by MRI using chemical exchange saturation transfer (CEST) imaging sequence. Therefore, it offers the possibility of high-sensitivity MR imaging sugars in tissues using bulk water protons as antenna.

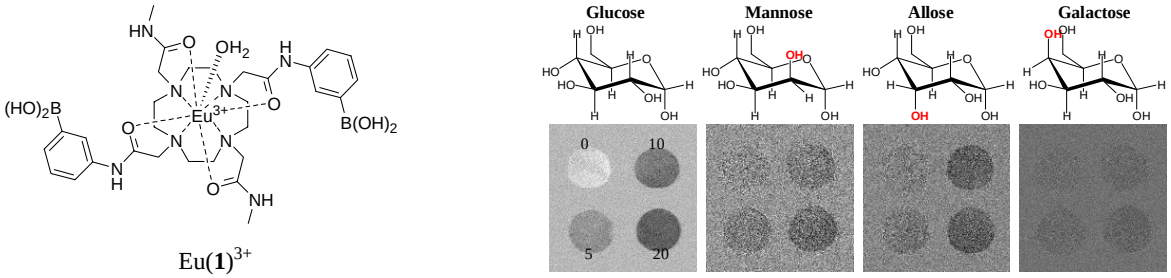
Introduction

Balaban *et al.*[1] were first to report a new class of diamagnetic MRI contrast agents based on chemical exchange saturation transfer (CEST) between biomolecules and bulk water. More recently, Van Zijl *et al.*[2] have shown that the effect can be amplified by using exogenous macromolecules with large numbers of exchanging sites or endogenous proteins/peptides. This idea was further extended to paramagnetic systems.[3,4] The benefits of paramagnetic CEST agents over diamagnetic systems is that 1) one can more easily avoid partial saturation of the bulk water resonance *in vivo*, 2) faster exchange systems that satisfy the intermediate exchange requirement, $\Delta\omega \bullet \tau_M > 1$, may be used, and 3) it is relatively easier to design new responsive agents. In this abstract, we report on the design of a sugar responsive paramagnetic CEST agent.

Results and Discussion

Boronic acids are known to bind selectively and reversibly with cis-diols, a property that has been widely exploited in design of new sacharide senors.[5] With this background, we set out to build a new DOTA-tetraamide ligand and the corresponding europium complex, $Eu(\mathbf{1})^{3+}$. UV spectroscopy studies reveal that different sugars do have a very different binding abilities towards $Eu(\mathbf{1})^{3+}$ even though there are only subtle configuration variations among the sugars. For example, the association constants obtained by UV spectroscopy at pH 10.2 are 2272 ±266, 56±3, 30±2, 198±20 M^{-1} for glucose, mannose, allose and galactose, respectively.

High resolution ^{1}H NMR spectra revealed that Eu^{3+}-bound water exchange rate is slowing down upon the sugar binding. To test whether this can be used to image sugars by MRI, a phantom consisting of four plastic tubes (ID 4 mm) each containing 10 mM $Eu(\mathbf{1})^{3+}$ and different amounts of sugars was prepared in 100 mM PIPES buffer at pH 7.0. Two sets of Images were acquired after alternatively applying identical presaturation pulses (B_1=1020 Hz for 2 s) at 50 ppm (Eu^{3+}-bound water) *versus* 30 ppm (between the bound and bulk water peaks). CEST images presented here (Figure 1) were obtained by subtracting the images saturated at 50 ppm from those at 30 ppm. These images show clear intensity gradations that parallel the sugar concentration.



$Eu(\mathbf{1})^{3+}$

Figure 1. CEST images for phantoms containing 10 mM $Eu(\mathbf{1})^{3+}$ and different amount of sugars (mM as labeled on the images).

Conclusion

In summary, a new DOTA-tetraamide ligand with bis-(phenyl boronate) arms was prepared and its europium complex was found to bind sugars reversibly. Upon sugar binding, the Eu^{3+}-bound water exchange rate is modulated which makes it possible to image sugar, especially glucose for the first time by MRI using the bulk water protons as antenna.

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