Optimization of the inner-sphere water molecule exchange rate to increase the contrast of paraCEST contrast agents

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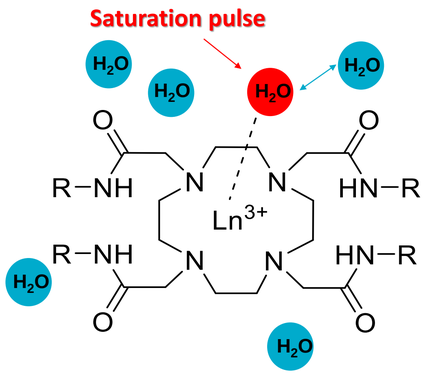
Introduction

ParaCEST MRI

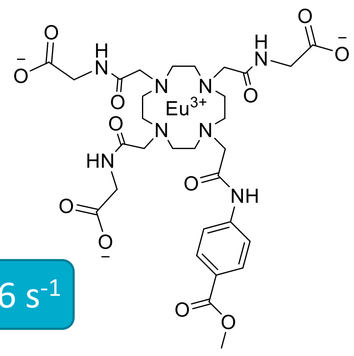
ParaCEST agents show a great interest in MRI imaging. This imaging technique, which is based on a saturation transfer from exchangeable protons to bulk water molecules, has several advantages over the common MRI contrast agents. The contrast can easily be turned-on or turned-off by the application of the saturation pulse. Thus, the exam does not require a pre-injection image. Then, several contrast agents can be injected at the same time and turned-on separately, their biodistribution can hence be differentiated. It is called multi-color imaging.



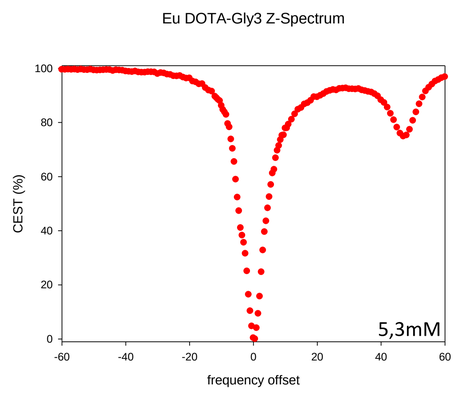
Europium based DOTA derivatives have interesting CEST properties. Indeed, after the modification of the carboxylate functions into amides, some paramagnetic complexes show an increased water residence time, which is one of the most significant parameter for the CEST effect. [1] The saturation transfer can either occur with the innersphere water molecule or with the amide protons.

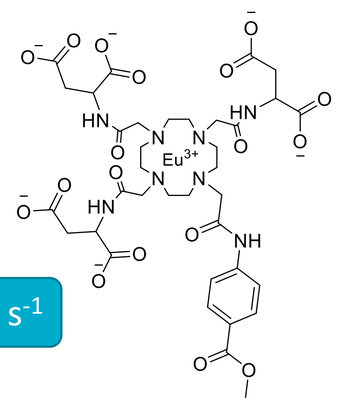
However, the sensitivity of paraCEST contrast agents is limited, mostly after injection *in-vivo*. To overcome this issue, the design of new complexes tends to decrease the innersphere water molecule exchange rate. This research will focus on that subject.

Goal of the study



K_{ex}=18866 s^{-1}

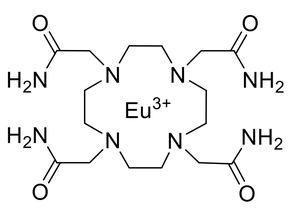




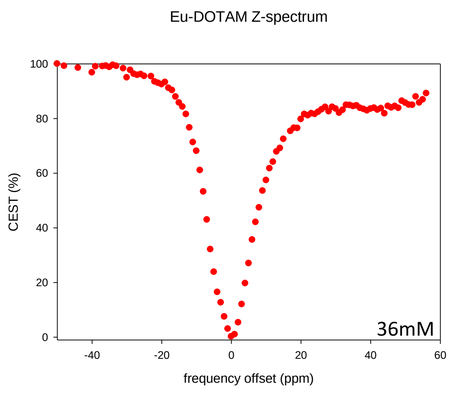
K_{ex}= 9239 s^{-1}

In this study, a DOTA derivative was substituted by 3 glycine, to ensure water solubility of the complex. The same ligand was also substituted by aspartic acid pendant arms and a strong decrease of the innersphere water molecule exchange rate was observed. This property leads to an increase of sensitivity of the contrast agent.
To further study this phenomenom, tetra-substituted europium complexes were studied, to comprehend the influence of the carboxylic acids on the exchange rate.
Finally, an amphiphilic complex was synthesized to prepare active nanostructures in paraCEST MRI: micelles. The influence of the distance between the complexes on the exchange rate will hence be evaluated.

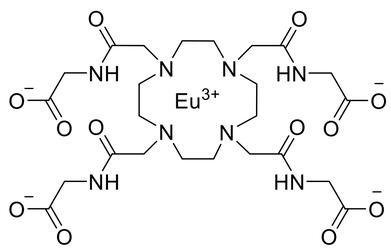
Results



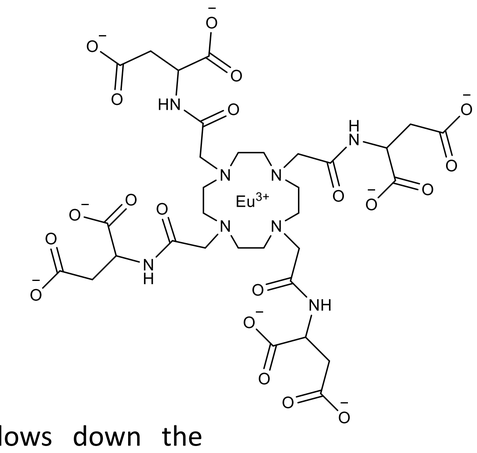
K_{ex}= 39400 s^{-1}

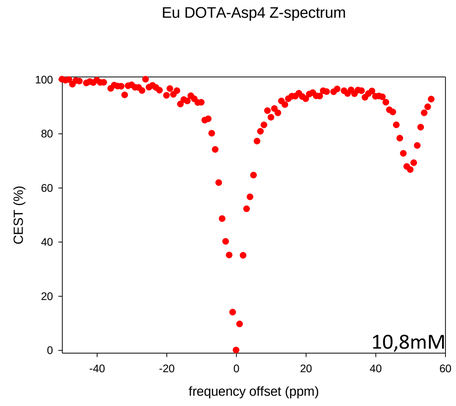


All Z-Spectra were recorded at 600MHz, 37°C and pH 7.4, using a saturation pulse of 659Hz. The exchange rates were measured using the omega-plot method [2].



K_{ex}=19230 s^{-1} [2]

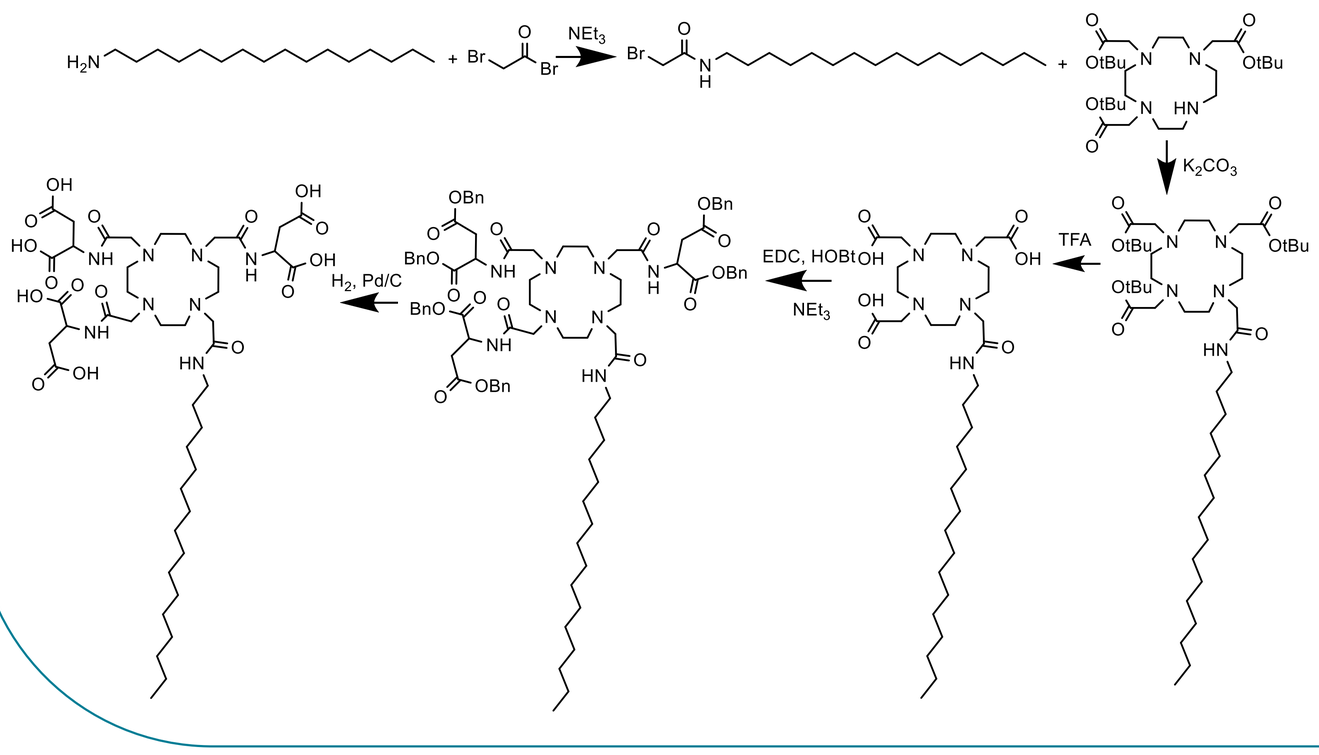




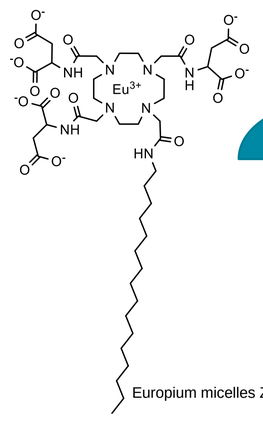
K_{ex}= 8095 s^{-1}

The introduction of carboxylate slows down the exchange rate, Eu-DOTA-Asp_4 is a great improvement compared to the commonly used Eu-DOTA-Gly_4.
The Eu-DOTA-Gly_4 data was obtained in the literature [2].

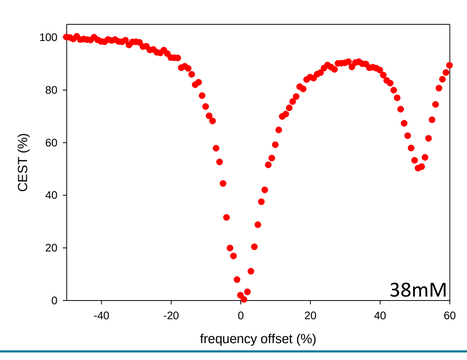
Amphiphilic complex synthesis



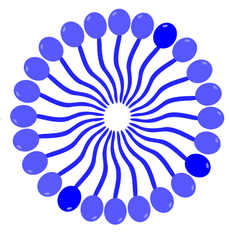
Micelle preparation and characterization

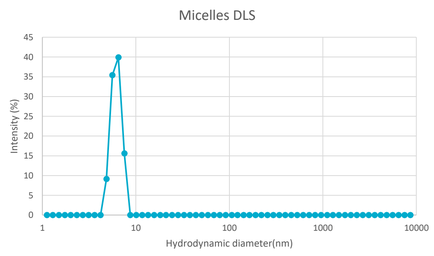


Europium micelles Z-Spectrum



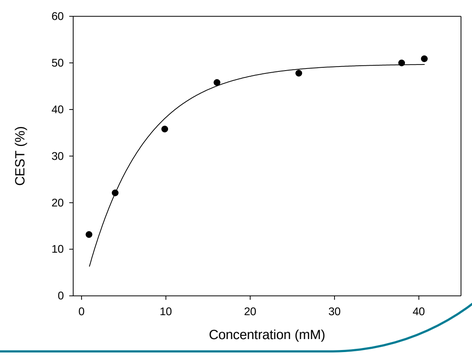
Tween 80





K_{ex}= 9506 s^{-1}

Influence of the complex concentration on the contrast



Conclusion

This study demonstrated the importance of the number of carboxylic acids on the innersphere water molecule exchange rate kinetics. The carboxylate functions interact with it by hydrogen bonding, slowing down the exchange rate and increasing the generated contrast. The aspartate derivatives are hence an interesting alternative to the well-known Eu-DOTA-Gly_4.
Finally, micelles were prepared. They generate a strong decease of the water peak intensity, up to 50%. The maximum contrast is obtained at around 18mM.

Acknowledgements

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References

[1]: Subha Viswanathan et al, Angew. Chem. Int. Ed. 2009, 48, 9330 –9333
[2]: Dixon W.T. et al, Magn. Reson. Med., 2010, 63, 625-632