

# Fluorinated paramagnetic contrast agents – Study of the paramagnetic effect from diverse lanthanide ions ( $\text{Gd}^{3+}$ , $\text{Dy}^{3+}$ , $\text{Tb}^{3+}$ , $\text{Eu}^{3+}$ ) on fluorine relaxation times.

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## Introduction

Medical imaging is a dynamic area of researches whose one of the goal is the elaboration of more efficient contrast agents (CA). Those agents need to be improved to optimize the detection of affected tissues such as cancers or tumours while decreasing the injected quantity of agents. The paramagnetic contrast agents containing fluorine atoms can be used both on proton and fluorine MRI. This research field is therefore promising thanks to the ability to map the anatomy by  $^1\text{H}$  MRI and locate exactly the agents by  $^{19}\text{F}$  MRI.

## Methods

One of the challenges in this domain is to synthesize a molecule containing several chemically equivalent fluorine atoms with short relaxation times to allow the record of  $^{19}\text{F}$  MR images in good conditions. In that aim, we propose to synthesize a CA containing a paramagnetic ion and nine chemically equivalent fluorine atoms by a cycloaddition reaction between two previously synthesized molecules. Initially, a derivative of DOTA-GA macrocyclic ligand has been synthesized through a multistep synthesis. Diverse lanthanide ions have then been complexed in order to evaluate the more efficient to decrease the fluorine atoms relaxation time  $T_1$ . Finally, a nonafluorinated compound has been synthesized and grafted on the DOTAGA derivative in order to obtain the final fluorinated complexes (figure 1).

## Results

The structure of the fluorinated paramagnetic contrast agents ( $\text{Gd}^{3+}$ ,  $\text{Dy}^{3+}$ ,  $\text{Tb}^{3+}$ ,  $\text{Eu}^{3+}$  complexes) were confirmed by mass spectrometry. Those fluorinated contrast agents were then characterized by  $^{19}\text{F}$  NMR where differences were observed on the fluorine relaxation times  $T_1$  and  $T_2$  depending on the lanthanide ion:  $\text{Gd}^{3+}$  induced a strong decrease of the relaxation times  $T_1$  and  $T_2$  whereas  $\text{Eu}^{3+}$  is nearly inefficient. On the other hand,  $\text{Tb}^{3+}$  and  $\text{Dy}^{3+}$  induced a moderate and appropriate decrease of each  $T_1$  and  $T_2$ . Moreover, no concentration dependence of relaxation times was observed in this range of concentration for all the tested lanthanide ions, proving that only the internal effect is present.

Molecular dynamic simulations have been performed in order to understand the folding of the molecule. These simulations showed that strong interactions force the molecule to fold, inducing a decrease of the distance between the paramagnetic ion and fluorines.

## Conclusions

This study has shown the paramagnetic influence of several lanthanide ions on fluorine atoms situated close to them. Although the gadolinium ion has the highest paramagnetic effect, its influence can sometimes be too strong and decreases the relaxation times in a too significant way. An alternative can then be envisaged by the use of the dysprosium and terbium ions which allow to obtain appropriate relaxation times for clinical use.