Synthesis and physicochemical characterizations of a fluorinated paramagnetic contrast agent

E. Hequet [a], C. Henoumont [a], L. Vander Elst [a], R. N. Muller [a,b], S. Laurent [a,b]

a. NMR and Molecular Imaging Laboratory, University of Mons - UMONS, 19 Avenue Maistriau B-7000 Mons, Belgium
b. Center for Microscopy and Molecular Imaging, 8 Rue Adrienne Bolland, B-6041 Charleroi, Belgium

• Introduction

The elaboration of new contrast agents for medical imaging is an expanding field in chemistry. These new agents have to optimize the detection of affected tissues such as cancers or tumours while decreasing the injected quantity.

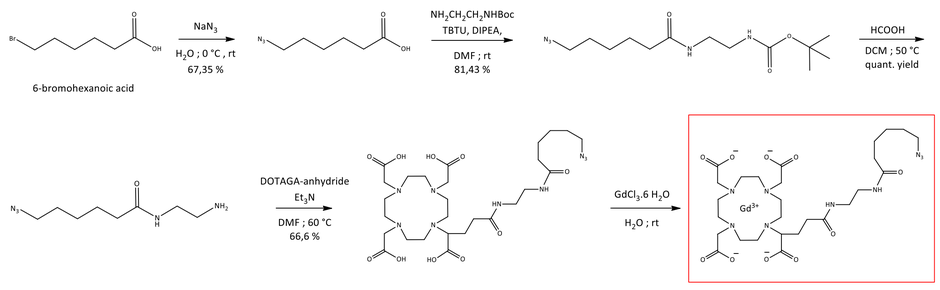
Paramagnetic contrast agents containing fluorine atoms can be used both on proton and fluorine MRI. This research field is therefore promising thanks to the ability to map the anatomy by ^{1}H MRI and locate exactly the agents by ^{19}F MRI.

These new complexes need to contain several chemically equivalent fluorine atoms characterized by a short relaxation time to allow the record of fluorine MR images in good conditions. Therefore, a compound containing a paramagnetic ion and fluorine atoms has been synthesized.

• Materials and methods

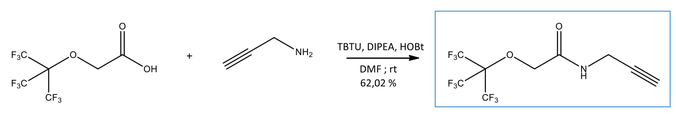
The fluorinated paramagnetic contrast agent has been obtained through a cycloaddition reaction between the previously synthesized compounds **A** and **B**. These reactions are described below :

1. DOTAGA derivative synthesis:



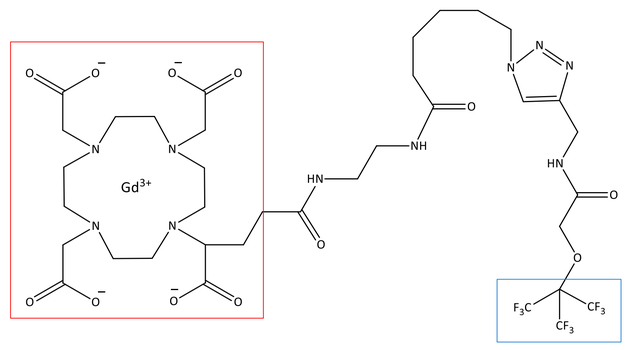
Compound A

2. Nonafluorinated compound synthesis:



Compound B

3. Fluorinated paramagnetic contrast agent synthesis: Click Chemistry



Click Chemistry : 0,8 eq. compound A, 1 eq. compound B, 0,2 eq. $Cu(OAc)_2$, 1 eq. sodium ascorbate, DIPEA ; H_2O, DMF ; MW : 80 °C, 20 min.

• Results et discussion

Mass spectrometry:

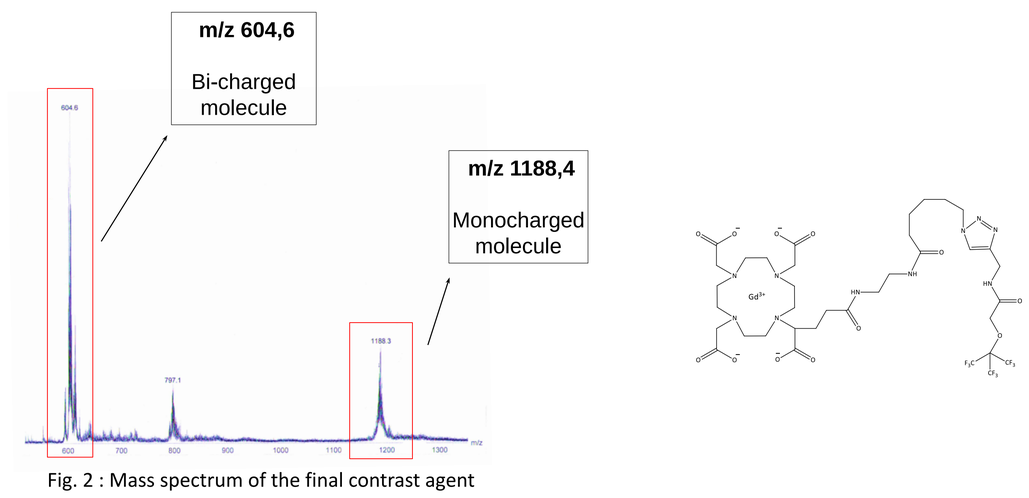


Fig. 2 : Mass spectrum of the final contrast agent

Mass spectrometry allows to confirm the structure of the expected fluorinated paramagnetic contrast agent.

^{1}H relaxation times dependence on the concentration:

In some cases, when the concentration increases, molecules tend to agglomerate and form macromolecules like micelles.

The linear behavior of the ^{1}H relaxation times for increasing concentrations of gadolinium (fig.3) allow to confirm that the synthesized fluorinated paramagnetic contrast agent does not tend to agglomerate.

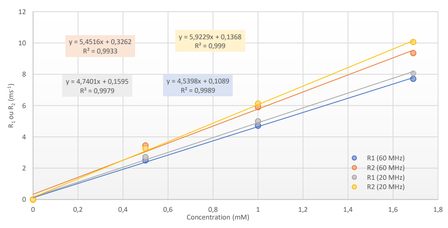


Fig.3 : ^{1}H relaxation times at different concentrations

Table 1 : ^{19}F relaxation times at different concentrations

	[ ] (mM)	^{19}F T_1	^{19}F T_2
B		2,058 s	1,797 s
Fluorinated paramagnetic contrast agent	0,5	13,84 ms	7,62 ms
	1	13,53 ms	8,35 ms
	1,69	13,24 ms	8,95 ms
	8,47	12,34 ms	8,74 ms

NMRD profiles:

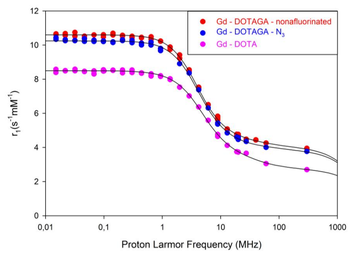


Table 2 : relaxivities of the different Gd-complexes

	r_1 ($s^{-1}mM^{-1}$) 20 MHz	r_1 ($s^{-1}mM^{-1}$) 60 MHz
Gd - DOTA	4,01	3,34
Gd - DOTAGA - N_3	4,57	4,01
Gd - DOTAGA - nonafluorinated	4,78	4,26

NMRD profiles (i. e. relaxivity measurements over a broad range of magnetic fields) were recorded for the fluorinated paramagnetic agent and its corresponding commercial compound, Gd-DOTA. The increase of the relaxivities reflects a better efficiency of the fluorinated paramagnetic contrast agent.

^{19}F NMR:

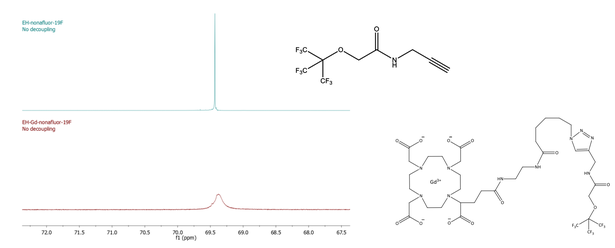


Fig.4 : comparison of ^{19}F NMR spectrum between the compound B and the final contrast agent

The ^{19}F NMR characterization of the synthesized contrast agent shows a huge broadening of the peak corresponding to the fluorine atoms. This broadening reflects the effect of the gadolinium ion on the fluorine relaxation times. This has been confirmed by the T_1 and T_2 relaxation time measurements of the fluorine atom (table 1).

Those measurements were performed at several concentrations of the compound in order to evaluate the mechanism of the gadolinium effect. It could indeed be expected an “internal” effect coming from a dipolar interaction between the gadolinium ion and the fluorine atoms of the same molecule, as well as an “external” effect coming from the diffusion of the fluorine atoms near the gadolinium center of other molecules.

The former effect being expected to be independent of the concentration, on the contrary of the latter effect, a study over a broad range of concentrations was performed and revealed nearly constant relaxation times for the different studied concentrations.

It seems thus that the gadolinium effect on the fluorine relaxation times is mainly “internal”.

This significant decrease of the fluorine relaxation times for the paramagnetic agent compared to the diamagnetic compound B is very promising for a future use in ^{19}F MRI.

• Conclusion and perspectives

The expected fluorinated paramagnetic contrast agent and all the intermediate products have been characterized by mass spectrometry, ^{1}H, ^{13}C, and ^{19}F NMR for the final product. These characterizations allow to confirm that the synthesized agent has promising properties for a future use in ^{19}F MRI.

However, stability tests and *in vitro* and *in vivo* ^{19}F MRI have to be performed in order to guarantee the potential diagnosis of the agent.

Furthermore, possible perspectives are envisaged in the future. A modification of the synthesis strategy could allow an active targeting of the compound via the grafting of a vector, or could also allow to increase the number of chemically equivalent fluorine atoms via a dendrimeric structure, which could be benefit to increase the sensitivity.

• Acknowledgements

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• References

[1] Janjic J.M., Ahrens E.T., *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2009 September 1; 1(5): 492 – 501

Contact: Emilie.HEQUET@umons.ac.be