

# Relaxometric study of manganese complexes based on a pyclen structure as MRI contrast agents

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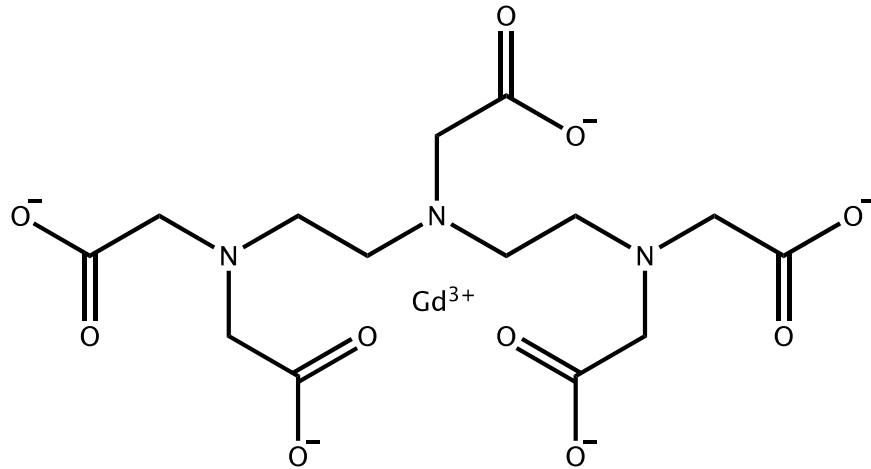
<sup>4</sup>Center for microscopy and molecular imaging (CMMI), 81 rue Adrienne Bolland, 6041 Charleroi, Belgium

COST – 16<sup>th</sup> March 2021

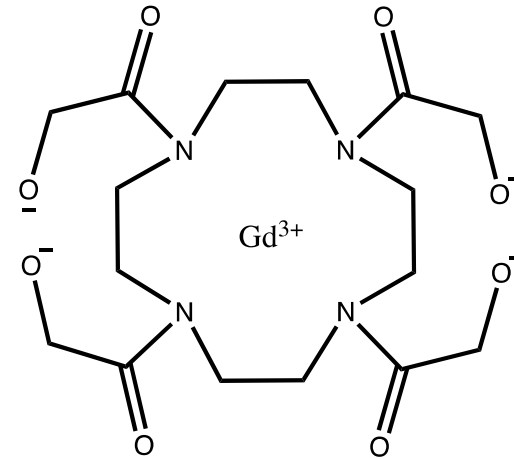


# Introduction

## Gadolinium complexes



Gd-DTPA



Gd-DOTA

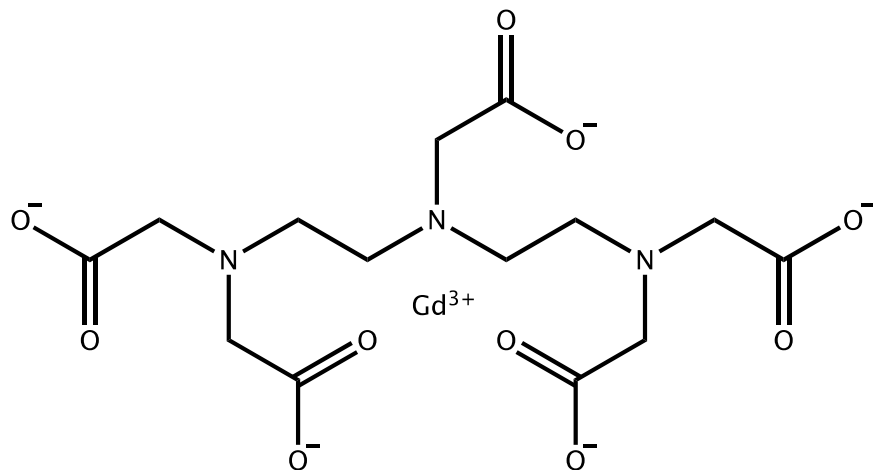
- ➔ Nephrogenic systemic fibrosis (NSF)<sup>1</sup>
- ➔ Retention in the brain<sup>2</sup>

<sup>1</sup>Beam, A. S., *et al*, *Radiol. Technol.* **88**, 583–589 (2017)

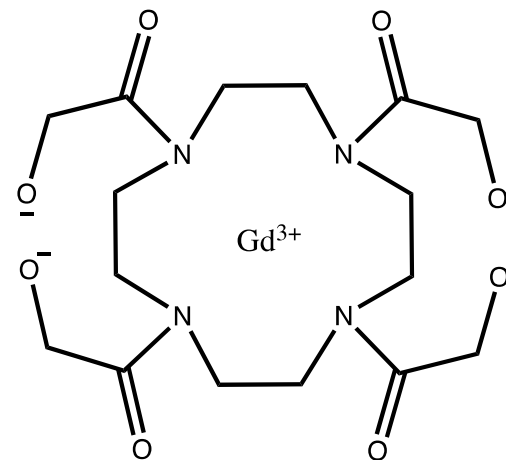
<sup>2</sup>Gianolio, E., *et la*, *Eur. J. Inorg. Chem.* **2019**, 137–151 (2019)

# Introduction

## Gadolinium complexes



Gd-DTPA



Gd-DOTA

➔ Nephrogenic systemic fibrosis (NSF)<sup>1</sup>

➔ Retention in the brain<sup>2</sup>

Alternative ?



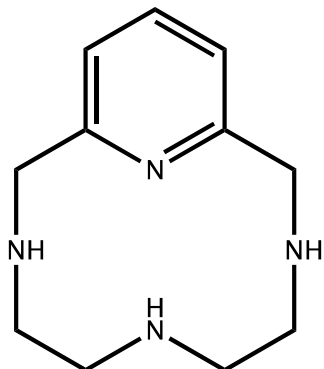
Manganese complexes

<sup>1</sup>Beam, A. S., *et al*, *Radiol. Technol.* **88**, 583–589 (2017)

<sup>2</sup>Gianolio, E., *et la*, *Eur. J. Inorg. Chem.* **2019**, 137–151 (2019)

# Introduction

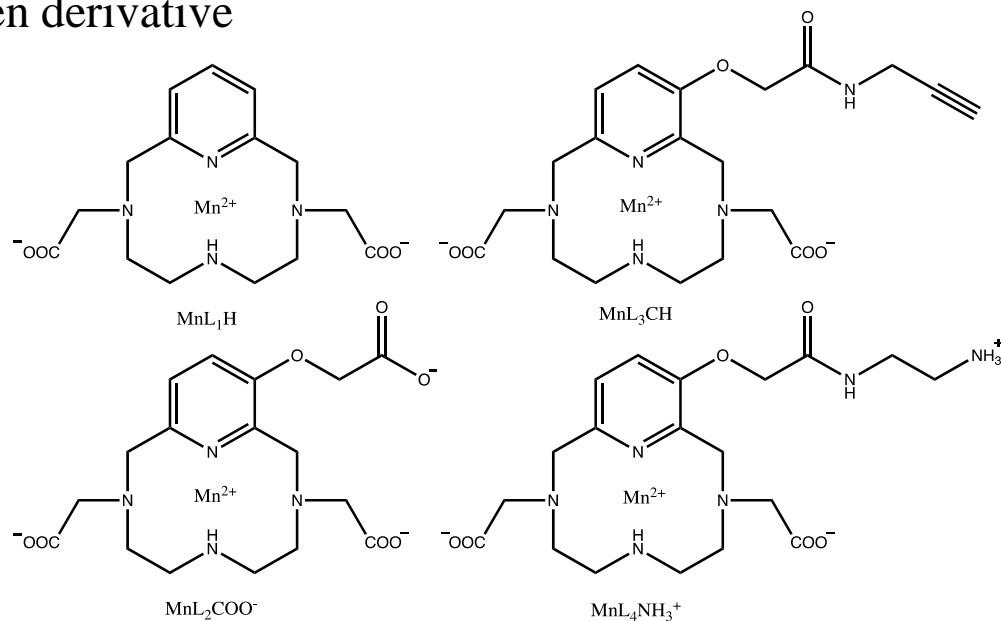
## Purpose of the work



Pyclyen structure

- Can be tuned to have one water molecule in the innersphere
- 7 coordination bond
- Increase the kinetic inertness
- Increase the thermodynamic stability
- Can play on the rotational correlations time to increase the relaxivity

# Synthesis of the pyclen derivative

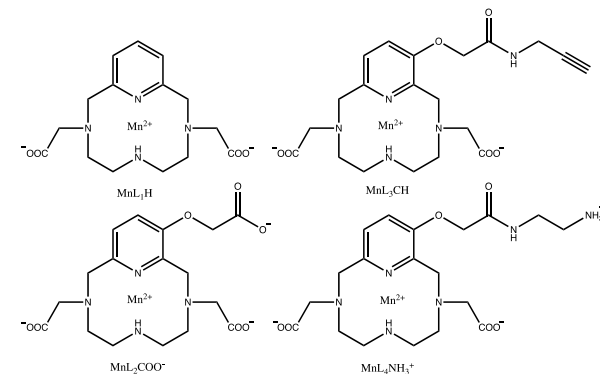
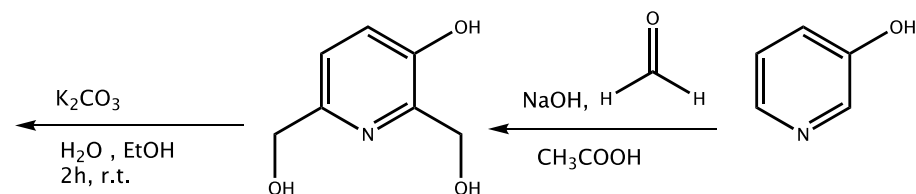
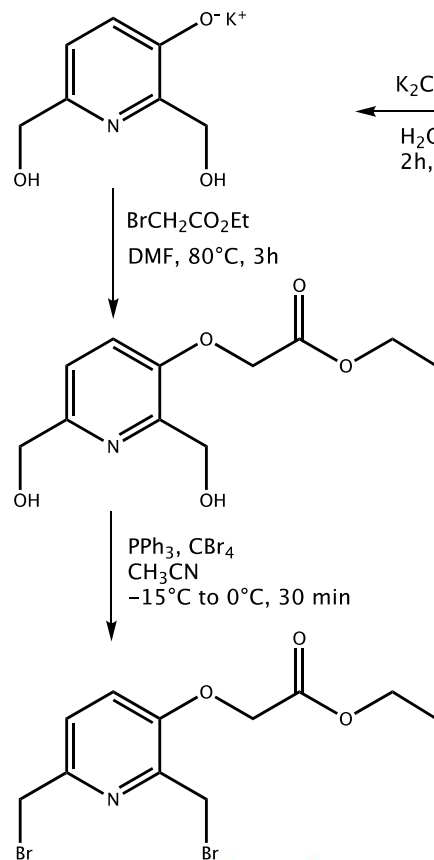
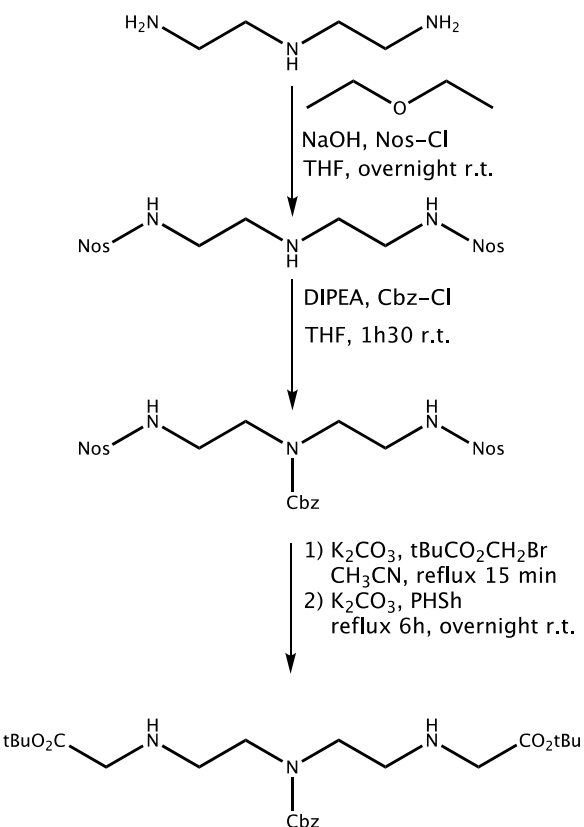


## Steps :

- ➔ Functionalization of the upper and lower part
- ➔ Macrocyclization
- ➔ Selective deprotection
- ➔ Complexation

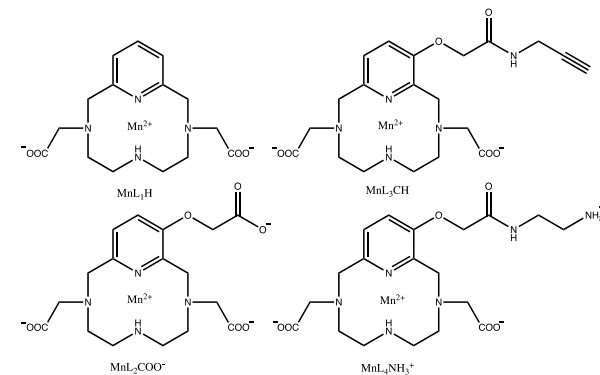
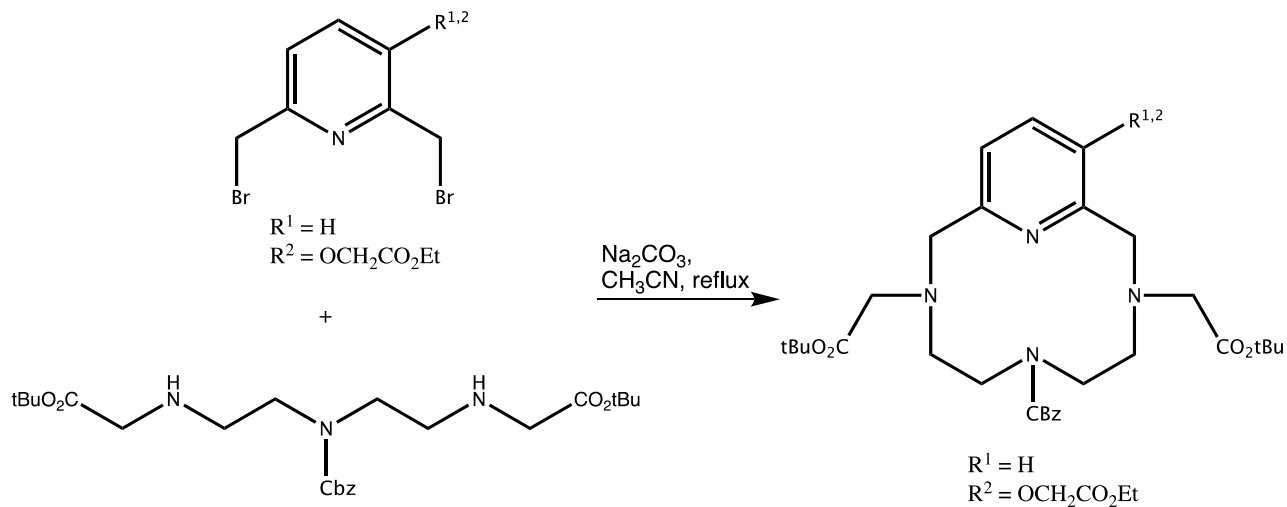
# Synthesis of the pycnen derivative

## Functionalization of the upper and lower part



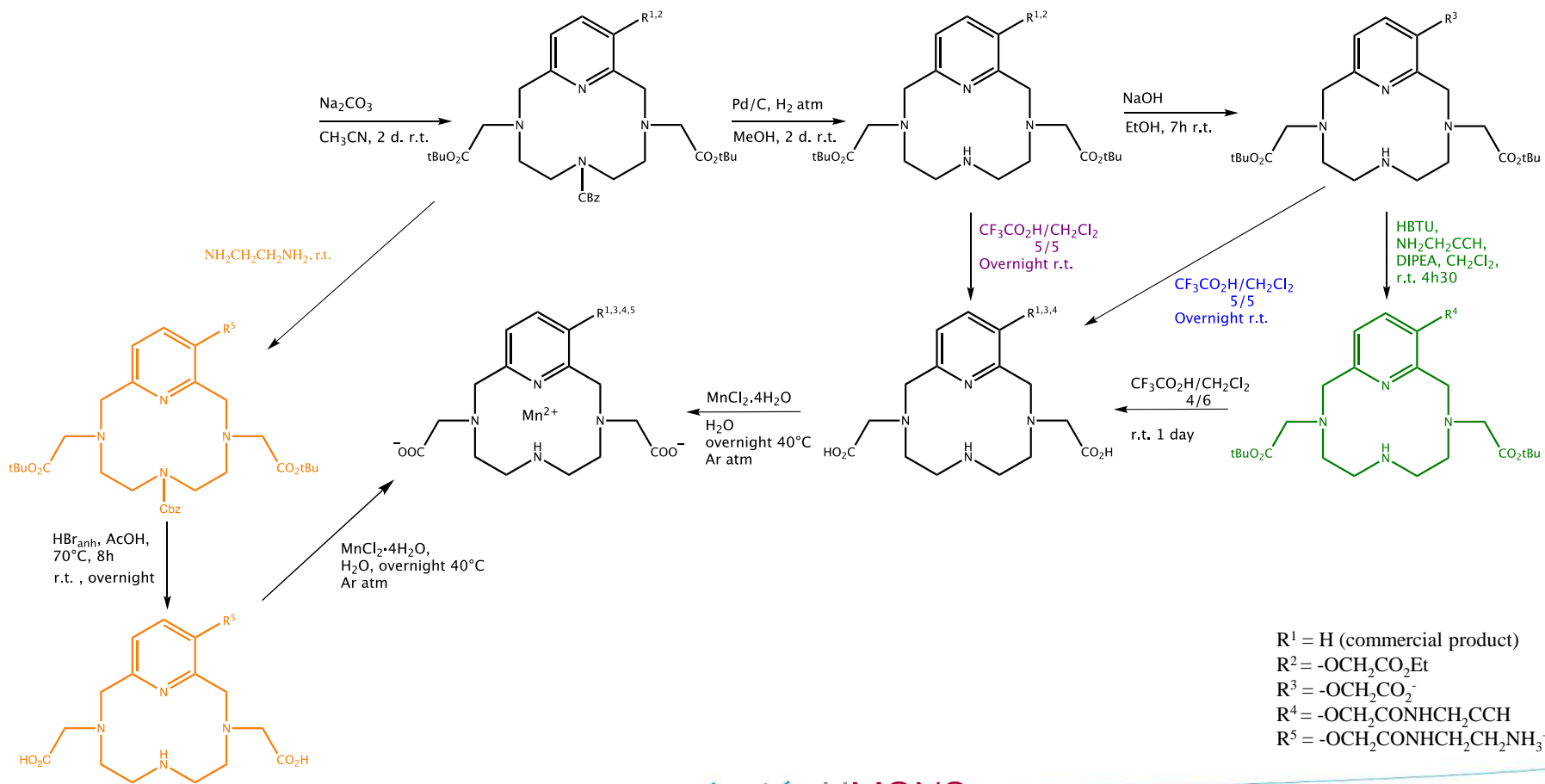
# Synthesis of the pyclen derivative

## Macrocyclisation step



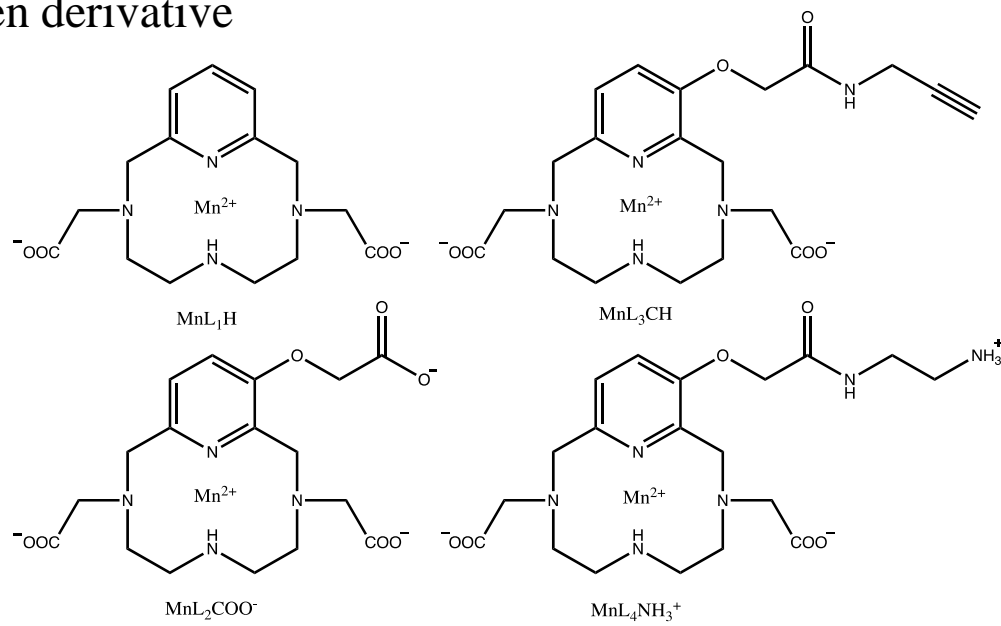
# Synthesis of the pycnen derivative

## Selective deprotection steps





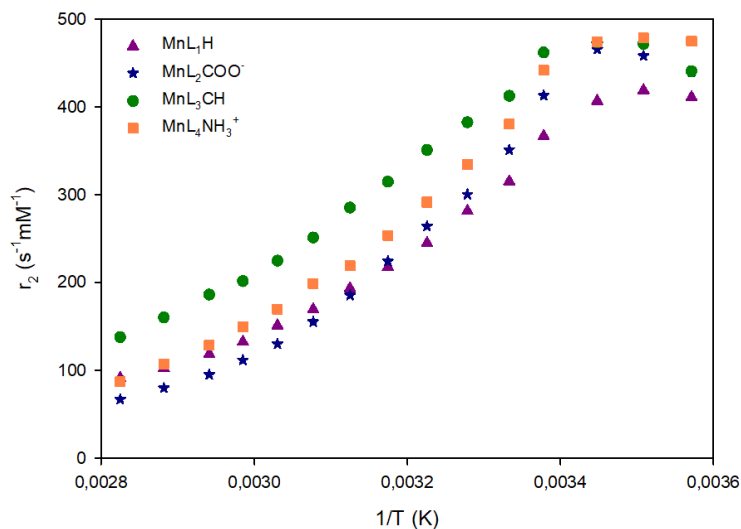
## Synthesis of the pycnen derivative



# Relaxometric characterization

## Determination of q

First technique by E. Gale *et al.*<sup>1</sup>: the <sup>17</sup>O water transverse relaxivity versus inverse of temperature, at 11.75 T



$$q = r_{2\max}^0 [\text{H}_2\text{O}] \left( \frac{2}{\sqrt{\frac{S(S+1)}{3} \frac{A_0}{\hbar}}} \right)$$

$$\approx \frac{r_{2\max}^0}{510}$$

	$r_{2\max}^0$ (s <sup>-1</sup> ·mM <sup>-1</sup> ) (67.8 MHz)	q (Eq. 1)
MnL <sub>1</sub> H	419.2	0.82 ± 0.2
MnL <sub>2</sub> COO <sup>-</sup>	458.4	0.90 ± 0.2
MnL <sub>3</sub> CH	473.4	0.93 ± 0.2
MnL <sub>4</sub> NH <sub>3</sub> <sup>+</sup>	478.6	0.94 ± 0.2

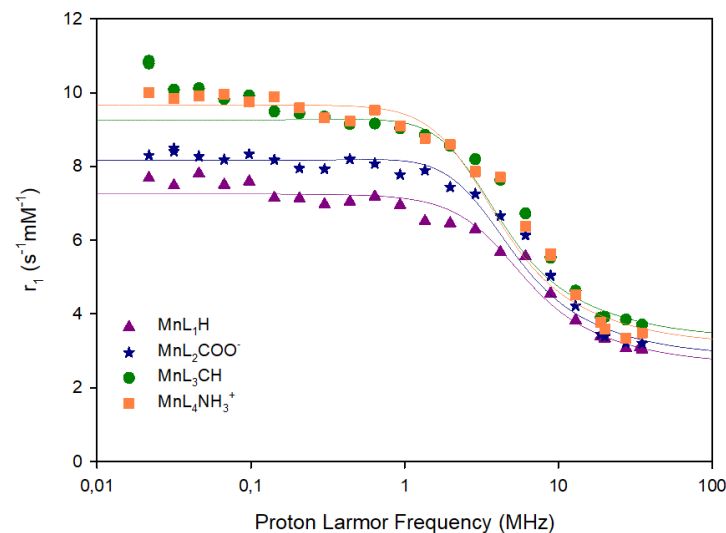
<sup>1</sup> Gale, E. M., *et al*, *J. Am. Chem. Soc.* 2013, 135, 18600–18608.

# Relaxometric characterization

## Determination of q

Second technique by J. Peters and C. Geraldes<sup>1</sup> : NMRD profiles at 25°C

$$q = \frac{r_{1p}}{9.16 \left\{ 1 - e^{(-2.97 \text{ FW } 10^{-3})} \right\}}$$



MnL <sub>1</sub> H
MnL <sub>2</sub> COO <sup>-</sup>
MnL <sub>3</sub> CH
MnL <sub>4</sub> NH <sub>3</sub> <sup>+</sup>

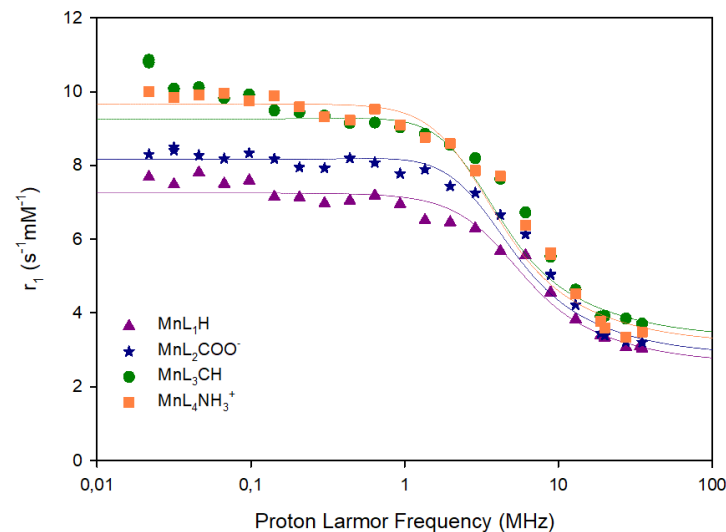
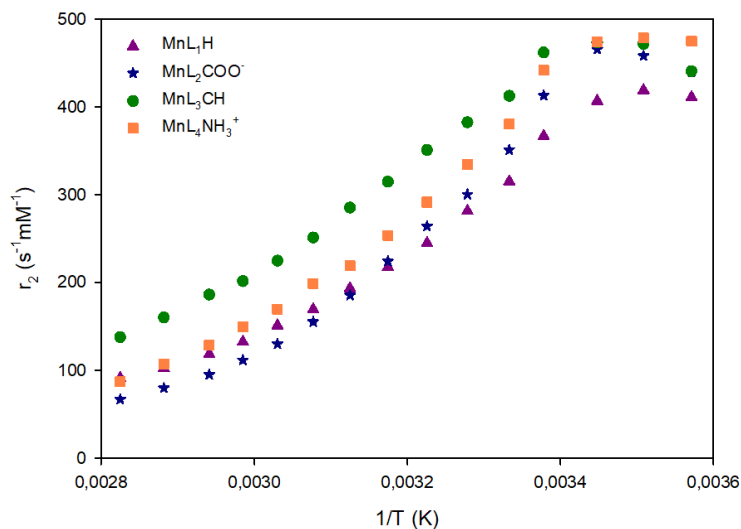
$r_{1p}$ (s <sup>-1</sup> ·mM <sup>-1</sup> ) (25°C and 0.02 MHz)	q (Eq. 2)
7.7	1.25 ± 0.4
8.3	1.30 ± 0.4
9.4	1.35 ± 0.4
10.0	1.42 ± 0.4

<sup>1</sup>Peters, J. A.; Geraldes, C. F. G. C., *Inorganics*, 2018, 6, 116.

# Relaxometric characterization

## Determination of q

Comparison of the two techniques : 1 water molecule in the innersphere

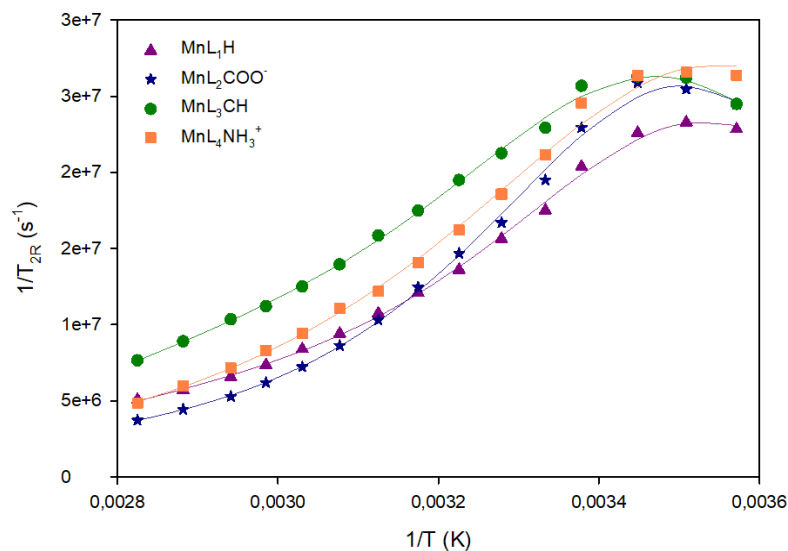


	$r_{2\max}^0$ ( $\text{s}^{-1} \cdot \text{mM}^{-1}$ ) (67.8 MHz)	q (Eq. 1)	$r_{1p}$ ( $\text{s}^{-1} \cdot \text{mM}^{-1}$ ) (25°C and 0.02 MHz)	q (Eq. 2)
MnL <sub>1</sub> H	419.2	$0.82 \pm 0.2$	7.7	$1.25 \pm 0.4$
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MnL <sub>4</sub> NH <sub>3</sub> <sup>+</sup>	478.6	$0.94 \pm 0.2$	10.0	$1.42 \pm 0.4$

# Relaxometric characterization

## Determination of $\tau_M$

Measurement of the  $^{17}\text{O}$  water transverse relaxation rate as a function of the inverse of temperature, at 11.75 T<sup>1</sup>



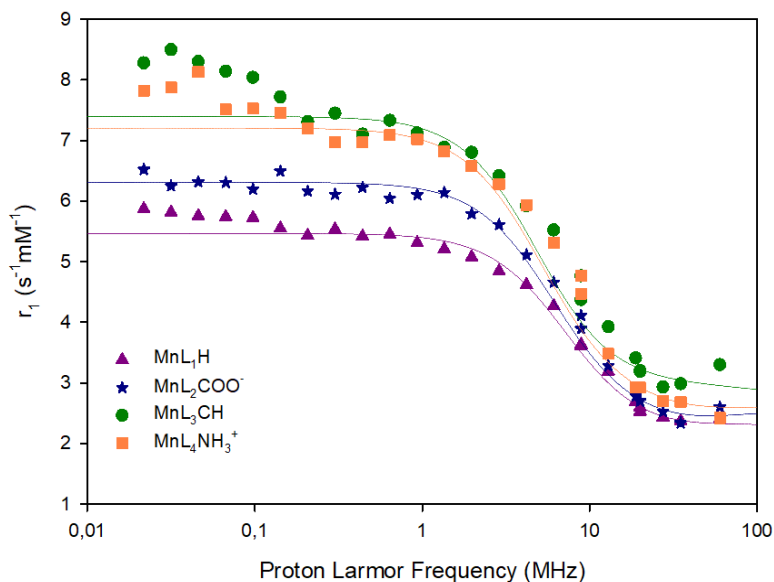
	$\tau_M$ (ns)
MnL <sub>1</sub> H	6.5 ± 0.4
MnL <sub>2</sub> COO <sup>-</sup>	6.1 ± 0.7
MnL <sub>3</sub> CH	8.4 ± 0.9
MnL <sub>4</sub> NH <sub>3</sub> <sup>+</sup>	6.35 ± 0.7

Fast exchange between the water molecule in the innersphere and the water molecules of the bulk

<sup>1</sup> Swift, T. J.; Connick, R. E., *J. Chem. Phys.*, 1962, 37, 307.

# Relaxometric characterization

## NMRD profiles at 37°C



the theoretical fitting of  $^1\text{H}$  NMRD profiles at 37°C with Bloembergen and Solomon's theory using the MINUIT minimization software.<sup>1,2,3</sup>

	$\tau_R$ (ps)	$\tau_{SO}$ (ps)	$\tau_v$ (ps)
$\text{MnL}_1\text{H}$	$48.7 \pm 3.8$	$119 \pm 19.2$	7.7
$\text{MnL}_2\text{COO}^-$	$57 \pm 5.2$	$155 \pm 29.5$	8.3
$\text{MnL}_3\text{CH}$	$65.6 \pm 0.85$	$224 \pm 31.6$	9.4
$\text{MnL}_4\text{NH}_3^+$	$59 \pm 0.6$	$272 \pm 6760.0$	10.0



Increase with the presence of the arm on the pyridine

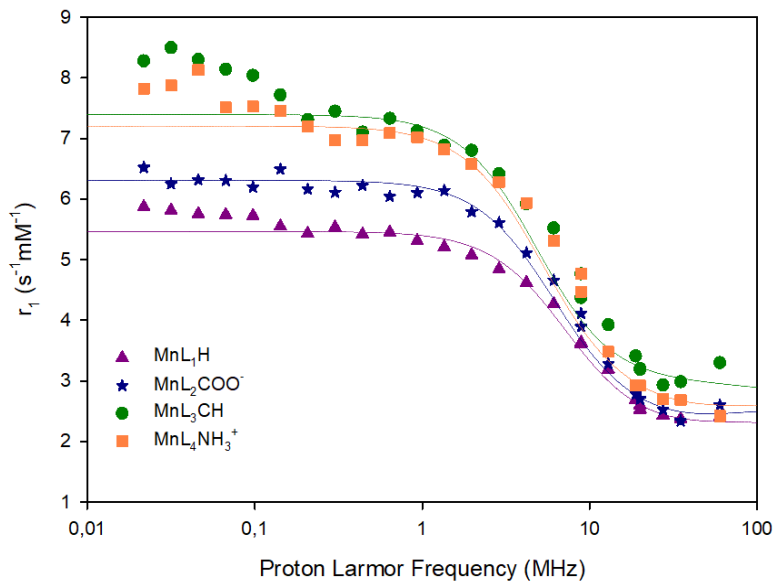
<sup>1</sup>Solomon, I., *Phys. Rev.*, 1955, 99, 559–565.

<sup>2</sup>Bloembergen, N., *J. Chem. Phys.*, 1957, 27, 572–573.

<sup>3</sup>Bloembergen, N.; Morgan, L. O., *J. Chem. Phys.*, 1961, 34, 842.

# Relaxometric characterization

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the theoretical fitting of  $^1\text{H}$  NMRD profiles at 37°C with Bloembergen and Salomon's theory using the MINUIT minimization software.<sup>1,2,3</sup>

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Slightly lower values for  $\text{MnL}_1\text{H}$  and  $\text{MnL}_2\text{COO}^-$

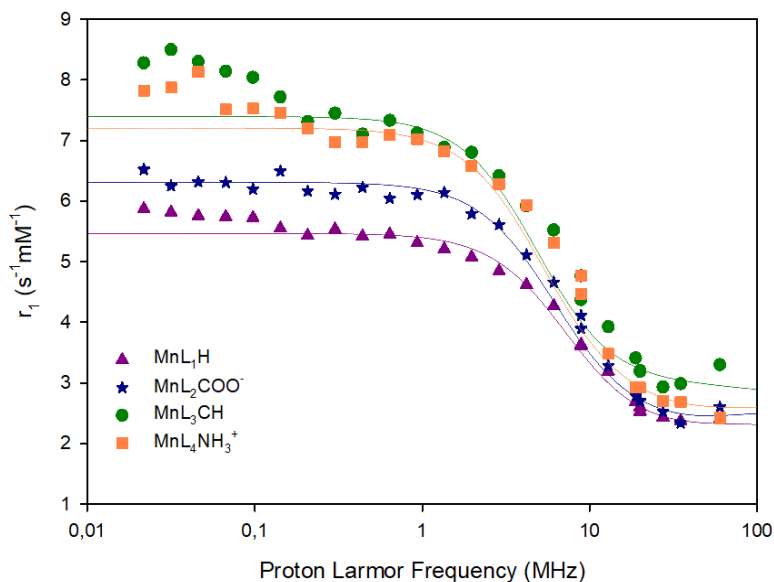
<sup>1</sup>Solomon, I., *Phys. Rev.*, 1955, 99, 559–565.

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	$r_1$ at 20MHz ( $\text{s}^{-1} \cdot \text{mmol}^{-1} \cdot \text{L}$ )*	$r_1$ at 60MHz ( $\text{s}^{-1} \cdot \text{mmol}^{-1} \cdot \text{L}$ )*
$\text{MnL}_1\text{H}$	2.6	2.4
$\text{MnL}_2\text{COO}^-$	2.7	2.6
$\text{MnL}_3\text{CH}$	3.2	3.3
$\text{MnL}_4\text{NH}_3^+$	2.9	2.4

37°C in water\*

<sup>1</sup>Solomon, I., *Phys. Rev.*, 1955, 99, 559–565.

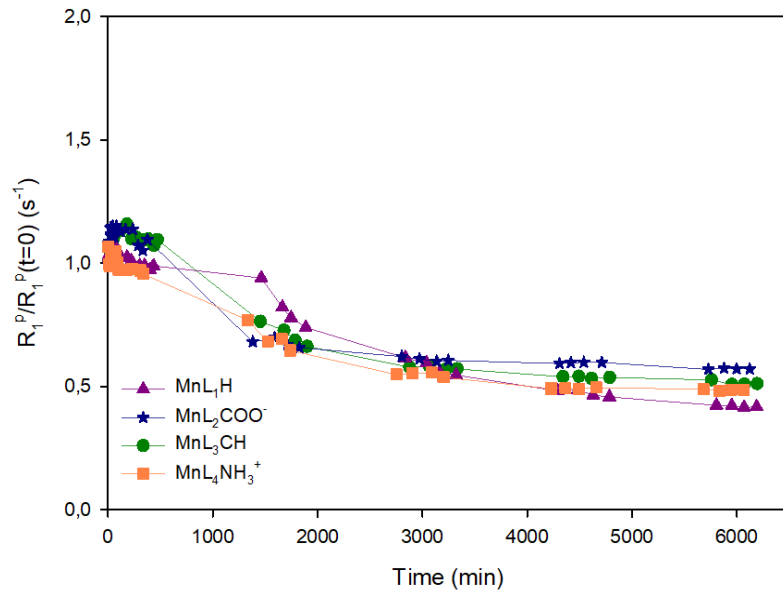
<sup>2</sup>Bloembergen, N., *J. Chem. Phys.*, 1957, 27, 572–573.

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## Transmetallation evaluation

Evolution of the normalized paramagnetic longitudinal relaxation rate in order to evaluate the transmetallation kinetic between manganese and zinc ions



$t_{1/2}$  half-life of approximately 1350 min

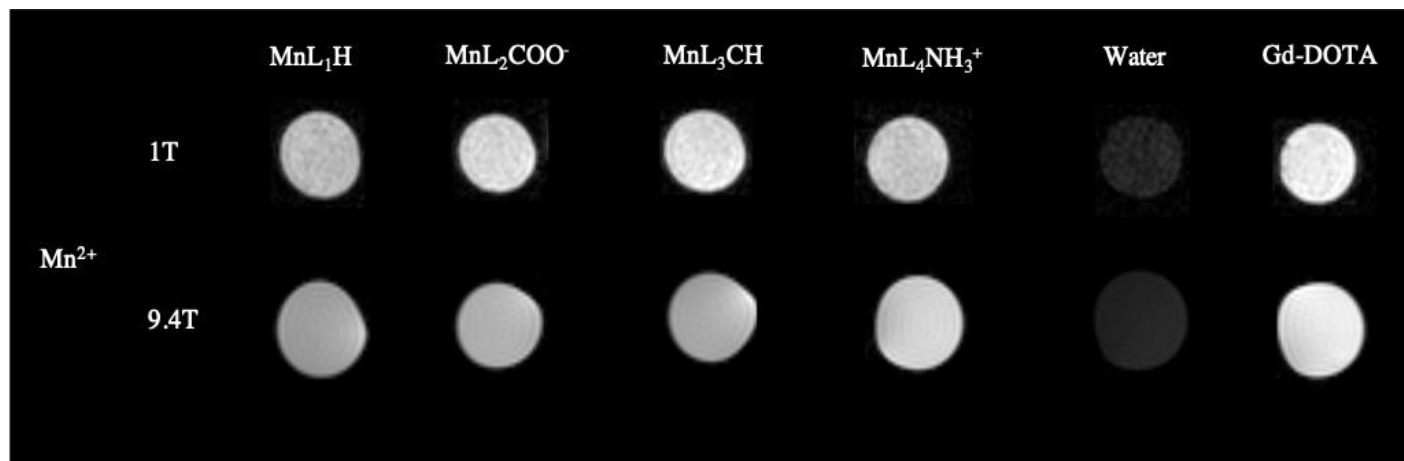
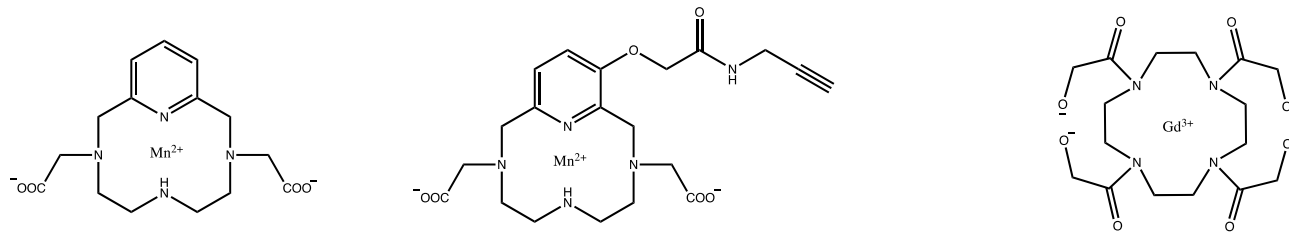
Experiment performed during 5 days in phosphate buffer at 20 MHz and 37°C. The concentration of Mn-complexes and of competing Zn(II) salt is 2.5 mM, which is much higher than its normal physiological level (~10 μM).<sup>1,2</sup>

<sup>1</sup> Laurent, S. *et al*, *Contrast Media Mol.*, Imaging 2010, 5, 305–308.

<sup>2</sup> Laurent, S. *et al*, *Invest. Radiol.*, 2001, 36, 115–122.

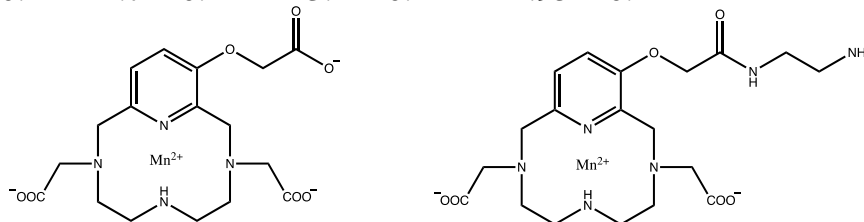
## Phantom images

Mn<sup>2+</sup>-complexes at a concentration of 0.5 mM compared with a commercial Gd-complex, Gd-DOTA, at the same concentration, and with pure water

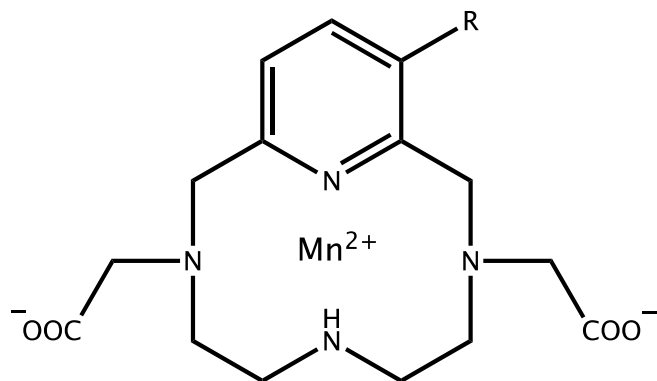


$r_1$  (s<sup>-1</sup>·mM<sup>-1</sup>)  
9.4T, 37°C

MnL <sub>1</sub> H	MnL <sub>2</sub> COO <sup>-</sup>	MnL <sub>3</sub> CH	MnL <sub>4</sub> NH <sub>3</sub> <sup>+</sup>	Water	Gd-DOTA
2.8 ± 0.1	2.7 ± 0.1	3.1 ± 0.1	2.95 ± 0.1		3.2 ± 0.1



## Conclusions



- ➔ Manganese complexes based on pycnen derivatives
- ➔ Functionalization of the arm on the pyridin
- ➔ Close to the Gd-DOTA efficacy

## Perspectives

- ➔ Increase of the relaxivity
- ➔ Thermodynamic stability

# Thank you for your attention

## Mn<sup>2+</sup> Complexes with Pyclyen-Based Derivatives as Contrast Agents for Magnetic Resonance Imaging: Synthesis and Relaxometry Characterization

Marie Devreux, Céline Henoumont, Fabienne Dioury, Sébastien Boutry, Olivier Vacher, Luce Vander Elst, Marc Port, Robert N. Muller, Olivier Sandre, and Sophie Laurent\*

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