Synthesis and Characterization of Novel MRI Contrast Agents Based on Pyclen-Derived Manganese Complexes

M. Brébart[a], C. Henoumont[a], G. Kadanuru Rajashekar[a], D. Stanicki[a], S. Laurent[a,b]

[a]*General, Organic and Biomedical Chemistry Unit, NMR and Molecular Imaging Laboratory, University of Mons (UMONS), Mons, Belgium*

[b]*Center for Microscopy and Molecular Imaging (CMMI), Gosselies, Belgium*

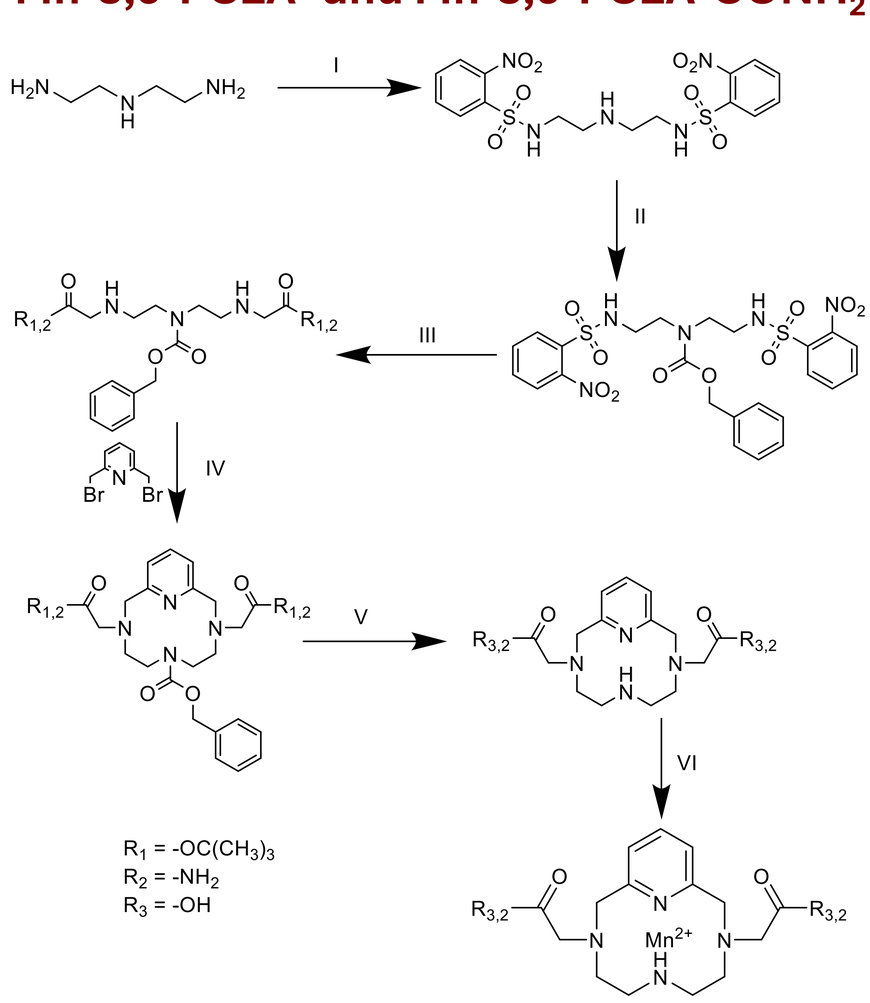
INTRODUCTION

Medical imaging techniques are widely used to detect pathologies and abnormalities in the human body. Among them, magnetic resonance imaging (MRI) is a powerful tool that provides cross-sectional images in a non-invasive manner. However, MRI suffers from low sensitivity and therefore requires the use of contrast agents to enhance image quality. Currently, most contrast agents are gadolinium-based (Gd^{3+}), but repeated administration may lead to toxicity[1]. To overcome this limitation, manganese(II) (Mn^{2+}) complexes have been investigated as potential alternatives.

In a previous PhD project[2], the Mn-3,9-PC2A complex was synthesized and characterized. Although promising, it displayed limited stability toward transmetallation reactions with zinc ions (Zn^{2+}). To improve its kinetic inertness, structural modifications were introduced by replacing the carboxylate arms with amide functional groups. In this study, the stability of the two complexes is compared, with a particular focus on their behavior toward transmetallation reactions.

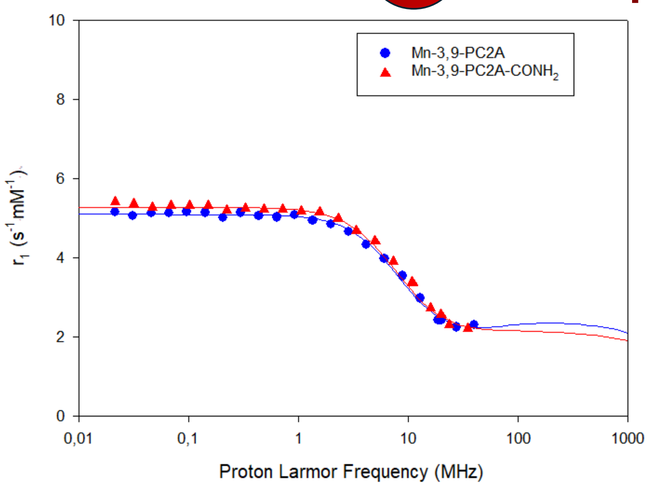
RESULTS

1 Scheme of the synthetic pathway of contrast agents Mn-3,9-PC2A[2] and Mn-3,9-PC2A-$CONH_2$



I: NaOH, Nos-Cl, THF, Et_2O, O.N.; **II**: DIPEA, Cbz-Cl, THF, 24h r.t.; **III**: 1) K_2CO_3, $BrCH_2CO_2R_{1,2}$, CH_3CN, reflux 4h; 2) K_2CO_3, PHSh, reflux O.N.; **IV**: Na_2CO_3, CH_3CN, 48h r.t.; **V**: CH_2Cl_2, CH_3COOH, HBr/CH_3COOH, reflux, 7h; **VI**: $MnCl_2.4H_2O$, pH 5-6, 40°C, O.N.

2 NMRD profiles



	Mn-3,9-PC2A	Mn-3,9-PC2A-$CONH_2$
d_{NMR} (nm)	0,36	0,36
D (m^2s^{-1})	3,3 x 10^{-5}	3,3 x 10^{-5}
r (nm)	0,28	0,28
τ_R (ps)	52 ± 9	43,7 ± 0,9
τ_M (ns)	6,5	16,3
τ_{SO} (ps)	85,3 ± 19	127 ± 32
τ_v (ps)	4,17 ± 0,9	5,1 ± 2,5
q	1	1

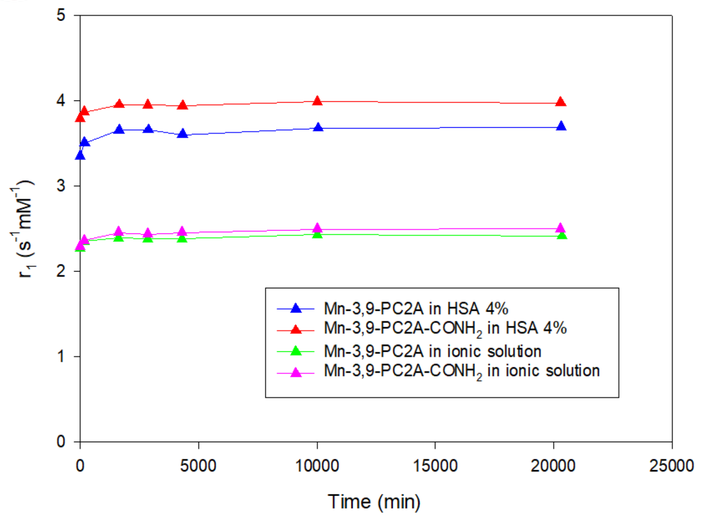
d_{NMR}, D, and r were fixed according to literature values[1].
q and τ_M were determined by ^{17}O NMR.
Both complexes exhibit **very similar NMRD profiles**.

3 Relaxivity measurements (r_1) in different media (at 37 °C and 20 MHz)

	Mn-3,9-PC2A	Mn-3,9-PC2A-$CONH_2$
Water	**2,40**	**2,38**
HSA 4%	3,35	3,79
Ionic solution	2,27	2,29

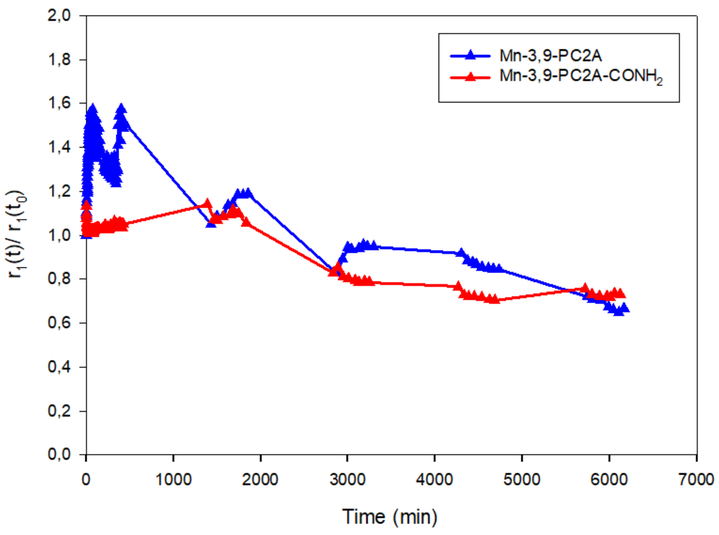
Ionic solution: Cl^-, lactate, citrate, carbonate, and phosphate ions.

4 Study of stability over time



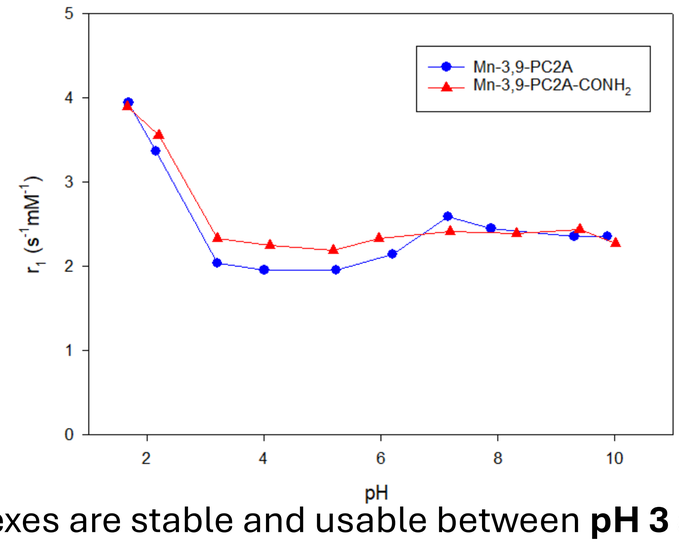
Relaxivity remained constant over time, indicating that the **complexes are stable** in the presence of HSA. No anions (chloride, lactate, citrate, carbonate, or phosphate) were able to displace the water molecule in the inner coordination sphere.

5 Transmetallation stability with Zn^{2+}



Both complexes undergo **transmetallation reactions**.

6 Relaxivity study as a function of pH



The complexes are stable and usable between **pH 3 and pH 10**.

CONCLUSION

The modification of the functional arms in Mn-3,9-PC2A had only a minor impact. Both complexes showed similar NMRD profiles and remained prone to transmetallation with Zn^{2+} ions. They are stable and usable over a broad pH range (3–10). Further *in vitro* and *in vivo* studies are required to assess their true potential as MRI contrast agents.

[1]T. Grobner and F. C. Prischl, *Kidney International*, 2007, **72**, 260–264.
[2]M. Devreux et al., *Inorg. Chem.*, 2021, **60**, 3604–3619.

Martin.BREBART@umons.ac.be