

# Ln(III) chelates of (*bis*)-hydroxymethyl substituted N'-benzyl-DTTA: NMR and relaxometric characterization of the Gd(III) complex and *in vivo* study of the <sup>153</sup>Sm(III) labeled compound

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A new *bis*-hydroxymethyl-substituted DTTA chelator, L= N'-Bz-C<sub>4,4'</sub>-(CH<sub>2</sub>OH)<sub>2</sub>-DTTA (Fig.1) was synthesized and characterized. A variable temperature <sup>1</sup>H NMR spectroscopy study of the solution dynamics of diamagnetic (Ln(III) = La) and paramagnetic (Ln(III) = Sm, Eu) Ln(III) complexes of the ligand revealed that they are rigid when compared with analogous complexes containing the Ln(III)DTTA moiety unsubstituted at its backbone (1-3), as a result of their C<sub>4,4'</sub>-(CH<sub>2</sub>OH)<sub>2</sub> backbone substitution. The relaxometric characterization of the [GdL(H<sub>2</sub>O)<sub>2</sub>]<sup>-</sup> complex was performed using <sup>17</sup>O NMR and <sup>1</sup>H NMRD measurements, yielding the parameters that govern the relaxivity. The relaxometric behavior of this complex reflects the presence of two inner sphere water molecules and an accelerated water exchange, nearly optimal for achieving high relaxivities. The τ<sub>R</sub> value is characteristic of low molecular weight complexes, indicating that the complex does not self-associate in solution in the range of concentrations studied. <sup>1</sup>H relaxometry was also used to monitor the interaction of the [GdL(H<sub>2</sub>O)<sub>2</sub>]<sup>-</sup> complex with HSA, as well as with phosphate and lactate. The observed lack of formation of a ternary complex with lactate indicates that the two inner-sphere water molecules are not located in adjacent positions in the coordination sphere of the Gd(III) ion. The kinetics of transmetallation of [GdL(H<sub>2</sub>O)<sub>2</sub>]<sup>-</sup> was also studied, as well as the pharmacokinetics and biodistribution of the <sup>153</sup>Sm(III)-labeled ligand in Wistar rats. The compound described has a flexible synthetic procedure, allowing easy modification of the DTTA skeleton for the purposes of targeting and/or optimization of τ<sub>R</sub>. The *bis*-hydroxymethyl-substituted DTTA skeleton can be seen as a new potentially useful lead for the synthesis of high relaxivity contrast agents.

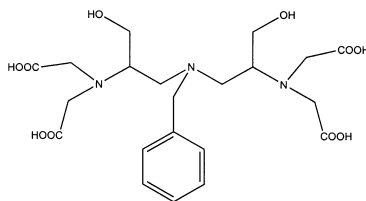


Fig. 1. N'- Bz- C<sub>4,4'</sub> - (CH<sub>2</sub>OH)- DTTA

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## References

- [1] J. Costa, É. Tóth, L.Helm, A.E. Merbach, *Inorg. Chem.*, **44** (2005) 4747
- [2] J. Costa, R. Ruloff, L. Burai, L.Helm, A.E. Merbach, *J. Am. Chem. Soc.*, **127** (2005) 5147
- [3] J.B. Livramento, A. Sour, A. Borel, A.E. Merbach, É. Tóth, *Chem. Eur. J.*, **12** (2006) 989