

367 Synthesis and characterization of a new Gd-DTPA derivative with a Fast Water Exchange

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The Abstract

Introduction: The water residence time (τ_M) is a decisive parameter of the efficiency of MRI paramagnetic contrast agents but the effects of chemical modification on this factor are still controversial. In this study, a new Gd-DTPA derivative (GdL1) with an additional carboxylate group (Figure 1) was synthesized and characterized by multinuclear NMR.

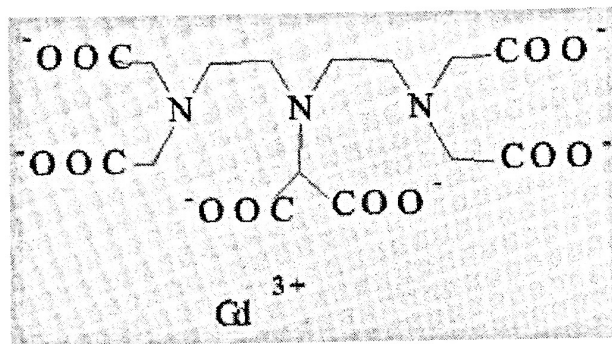


Figure 1: Structure of the Gd-complex GdL1

Materials and Methods: The ligand is obtained by acidic cleavage of the ester synthesized as reported by Amedio et al. (1). Proton relaxation rate and variable temperature ^{17}O NMR measurements were recorded as already described on a Bruker Minispec PC-120 and on a Bruker AMX-300 spectrometer (7.05T). (2) Proton NMRD profile was obtained on a Stellar relaxometer.

Results and Discussion: The analysis of the ^{17}O NMR data results in a water residence time of GdL1 almost 5 times smaller than that of the parent compound Gd-DTPA at pH=7.0 (table 1). The proton relaxivity of GdL1 at 20 MHz is 25 % larger than the Gd-DTPA one at 310 K (table 1) indicating that the additional COO^- is not coordinated to the Gd ion. Using the classical innersphere and outersphere theories, the theoretical adjustment of the proton NMRD profile needs a high value of the electronic relaxation time at low field (τ_{SO}) as well as a reduction of the distance between Gd^{3+} ion and the coordinated water hydrogens (table 1 and figure 2). Since the presence of the additional carboxylate group could be responsible for a second hydration sphere whose molecules are exchanging very fast with the bulk, second sphere water molecules were included in the theoretical model used above. The following parameters obtained are : $\tau_R=65$ ps, $\tau_{SO}=100$ ps, $\tau_V=8$ ps, 4 water molecules in the second sphere at a distance of 0.4 nm and a correlation time for these second sphere molecules equal to 29 ps.

Figure 2: proton NMRD profile of GdL1 and Gd-DTPA at 310 K
Table 1

Complexes	r_1 at 20 MHz ($\text{s}^{-1}\text{mM}^{-1}$)	τ_M^{310} (ns)	τ_R^{310} (ps)	τ_{SO}^{310} (ps)	τ_V^{310} (ps)	r (nm)
Gd-DTPA	3.8	143 ± 25	59	82	23	0.31
GdL1	4.8	32 ± 2	73	169	41	0.305

Conclusions: Thanks to its short water residence time, this new Gd-complex with a global -3 charge appears thus as a good candidate to a macromolecular coupling.

References:

- (1) Amedio J.C., Van Wagenen G., Zavlin G. [2000] Synthetic communications, **30**, 3755-3763
- (2) Botteman F., Nicolle G., Vander Elst L., Laurent S., Merbach A.E., Muller R.N. [2002] Eur. J. Inorg. Chem., 2686-2693

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