

### 369 Smart contrast agents: Synthesis and characterization of a new pH sensitive structure

S. Laurent (Mons/BELGIUM), L. Vander Elst (Mons/BELGIUM), F. Botteman (Mons/BELGIUM), R. N. Muller (Mons/BELGIUM)

#### The Abstract

**Introduction:** The residence time of the coordinated water molecule  $\tau_M$  of gadolinium derivatives of DTPA is known to depend on functionalization of the ligand (1). In this study, Gd-DTPA-BHydroxA, a bisamide derivative of Gd-DTPA is synthesized and characterized at various pH. (Figure 1)

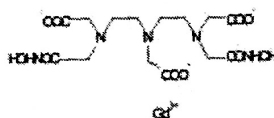


Figure 1 : structure of Gd-DTPA-BHydroxA

**Material and Methods:** The ligand DTPA-BHydroxA was obtained by reaction of hydroxylamine and DTPA-Bisethylthioester. Relaxation rates at 0.47 T were obtained on a Bruker Minispec P-120. Variable temperature  $^{17}\text{O}$  NMR measurements were recorded as already described on a AMX-300 spectrometer (Bruker, Karlsruhe, Germany) (1).

**Results and Discussion:** The temperature dependence of the proton relaxivity of the complex at 0.47 T (20 MHz) as well as the evolution of the transverse relaxation rate of  $^{17}\text{O}$  at pH 6.0 or 9.0 show a pH sensitive behavior (figures 2 and 3). At pH 6, the water residence time of the neutral complex is approximately 10 times larger ( $\tau_M^{310} = 824 \pm 41$  ns) than at basic pH ( $\tau_M^{310} = 78 \pm 8$  ns) where the complex is negatively charged.

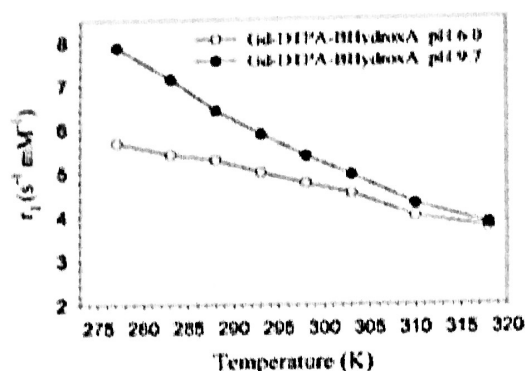


Figure 2 : Proton relaxivity versus temperature of Gd-DTPA-BHydroxA at pH 6.0 and 9.7 ( $B_0 = 0.47$  T)

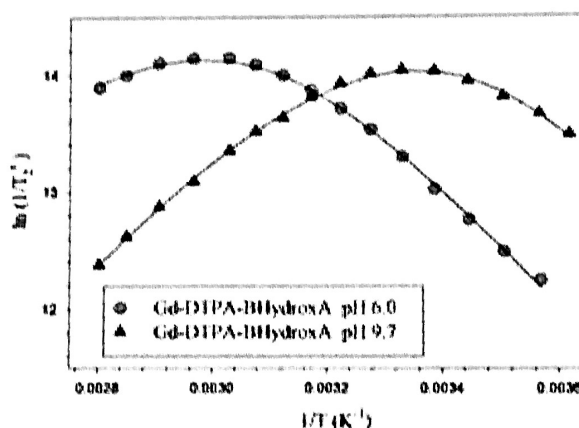


Figure 3 : Reduced transverse relaxation rate of water oxygen-17 ( $1/T_2^r$ ) as a function of the temperature for aqueous solutions of Gd-DTPA-BHydroxA.

At pH 9.7, the water exchange rate does not limit the proton relaxivity whereas at pH 6, a limitation at low temperatures is observed. This difference could be attributed either to a prototropic exchange at high pH or to a faster exchange of the whole water molecule.

The analysis of the transverse relaxation rate of  $^{17}\text{O}$  shows that the negative charges favour the expulsion of the water molecule and therefore confirms the second hypothesis. Above pH 9.7, the deprotonation of the hydroxamic group located near the coordination sphere and the subsequent faster water exchange thus explains the higher proton relaxivity at low temperatures.

**Conclusions:** The study of the Gd-DTPA-BHydroxA clearly shows that anionic groups have a positive influence on the water exchange rate. For this complex, a faster water exchange is favored at basic pH by ionization of the hydroxamic group. Such a structure could be the basis of a new smart pH sensitive contrast agents.

**References:**

(1) Botteman F., Nicolle G., Vander Elst L., Laurent S., Merbach A.E., Muller R.N. [2002] Eur. J. Inorg. Chem., 2686-2693