Dy-complexes as High Field $T_2$ Contrast Agents: Influence of Water Exchange Rates

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Dy complexes can act as suitable negative ($T_2$) contrast agents for Magnetic Resonance Imaging (MRI). As clinical MRI moves toward higher fields, tuning of the exchange rate of coordinated water molecules will become necessary to optimize the $r_2$ relaxivity. For Dy complexes, this will require lengthening of the water residence time, a strategy opposite to that required to optimize the $r_1$ relaxivity of Gd complexes. However, very slow water exchange can be deleterious. This is illustrated here by a Dy complex that is characterized by a very slow water exchange. This complex, Dy-DOTA-4AmCE, is compared with several Dy-DTPA derivatives known for their efficacy as $T_2$ contrast agents at high magnetic fields.

Biomedical MR is moving toward higher magnetic fields (i.e. $B_0 > 4$ T) and is beginning to reach fields where standard clinical MRI gadolinium(III) contrast agents exhibit poor water relaxivity. Thus, new approaches are being examined that exploit theories and parameters that have been historically overlooked. Typical of this new and paradoxical trend is the interest in dysprosium complexes that exhibit slow water exchange. Theory indeed predicts that for such complexes, $r_2$ depends upon the magnetic field at which the measurement is taken and the residence time ($\tau_M$) of the water molecule(s) coordinated to the lanthanide ion(1). Experiments have confirmed that the transverse relaxivity ($r_2$) of complexes characterized by a relatively fast exchange rate of the coordinated water molecule increases with the square of the magnetic field and $\tau_M$ (2). If, however, water exchange is too slow, the transverse relaxivity can be limiting ($r_2 \propto \tau_M^{-1}$). Here, we report that such a condition occurs with Dy-DOTA-4AmCE, a macrocyclic complex characterized by a very long $\tau_M$ (Figure 1). The field dependence of $r_2$ is compared with the results obtained with five different Dy-DTPA derivatives that exhibit relatively fast water exchange (Dy-DTPA, Dy-DTPA-BA, Dy-DTPA-BEA, Dy-DTPA-BnBA, Dy-DTPA-BBMA) (Figure 1) (2).

**Rationale and Objectives:**

**Materials and Methods**

The synthesis of DOTA-4AmCE is outlined in Zhang et al.(3). The bisamide ligands were synthesized by reacting DTPA bis-anhydride with the corresponding amine (4−6). Dy(III) complexes were prepared by mixing equimolar amounts of hydrated LnCl$_3$ and the ligand, each dissolved in water. After complex formation, the pH was adjusted to 6.5−7. The absence of free Dy(III) was checked with arsenazo III indicator. The concentration of Dy(III) in stock solutions of the complexes was determined by atomic emission spectrometry (Jobin-Yvon 38+, Jobin-Yvon ISA, Longjumeau, France).

$^1$H $T_1$ and $T_2$ measurements were performed at 0.24, 0.47, 0.94, 1.41, 4.7, 7.05, 11.75, 14.1 and 18.8 T respectively.
tively on Minispec PC-10, Minispec PC-20, Minispec PC-40, Minispec MQ-60, Avance-200, AMX-300, AMX-500, AMX-600 and Avance 800 from Bruker. The outer sphere contribution was calculated according to Gillis et al. (7). The water exchange time $\tau_M$ of the Dy(III)-complex was separately obtained by analysis of the temperature dependence of the longitudinal and the transverse relaxation rates of $^{17}O$ at 7.05 T (AMX-300).

**RESULTS**

As predicted by the theory (8–10), the $r_1$ of a Dy-complex depends upon and is limited by the very fast electronic relaxation time of the Dy$^{3+}$ ion at low magnetic fields. At high magnetic fields, the Curie magnetization increases and the Curie contribution to $r_1$ becomes proportional to the square of the magnetic field and the rotational correlation time. Experimental data for the six complexes show that the proton $r_1$ increases from 0.08–0.1 s$^{-1}$mM$^{-1}$ at 0.47 T to 0.12–0.18 s$^{-1}$mM$^{-1}$ at 7.05 T and 0.43–0.48 s$^{-1}$mM$^{-1}$ at 18.8 T in good agreement with the theory. At 310 K, small values of $r_1$ (0.12–0.18 ps) are obtained by the theoretical fitting of the data (1,7), and depending on the size of the complexes, rotational correlation times range from 55 to 80 ps.

The field dependence of $r_2$ is shown in Figure 2. As predicted by the theory, the $r_2$ values at high field are significantly larger than $r_1$ and some differences are observed. The DTPA derivatives can be divided into three categories according to their high field behavior: Dy-DTPA has the smallest $r_2$, Dy-DTPA-BA and Dy-DTPA-BEA behave quite similarly and have the largest $r_2$ while Dy-DTPA-BnBA and Dy-DTPA-BBMA have intermedi-
relaxivity at high magnetic fields, a complex with a $\tau_M$ ranging between 0.1 and 1 $\mu$s is required. Thus, at intermediate magnetic fields (0.5 to 2.4 T), slow water exchange ($\tau_M > 1 \mu$s) is beneficial for the transverse proton relaxivity. Fine tuning of this parameter by the design of suitable molecular structure may thus lead to contrast agents of optimal relaxivities for high field murine imaging of the postgenomic era.

REFERENCES