Molecular Factors that Determine Curie Spin Relaxation in Dy-Chelates

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Introduction

The alignment of paramagnetic ions increases with field strength and inverse temperature according to Curie's law. This so called "Curie spin" (1) can enhance T2 relaxation and becomes important at high fields for metal ions having a high magnetic moment and a very short electronic relaxation time, as in the case of dysprosium(III). At high fields Dy chelates are expected to shorten the T2 of solvent protons with little effect on T1. It has recently been shown that transverse Curie spin relaxation effects increase with the square of the magnetic field and have a strong temperature dependence, and that this effect may be further enhanced by its complexation to macromolecules (e.g. dendrimers) (2). For small, rapidly tumbling molecules (single chelates), the water residency time, τ_m, is the correlation time which determines relaxation (3,4).

In order to better understand the relaxation mechanism(s) governing Curie spin relaxation, two synthetically matched chelates, designated as **Dy-L1** and **Dy-L2**, were studied. These complexes differ primarily in that **Dy-L1** contains a coordinated water molecule (q=1), whereas **Dy-L2** does not (q=0); this allows a separation of the inner- and outer-sphere effects. Both complexes contain moieties which enable them to bind non-covalently to human serum albumin (HSA). Addition of **Dy-L1** to HSA has the effect of dramatically lengthening the molecule's rotational correlation time, τ_R, without having a large influence of τ_m (5), thereby probing the effect of slow rotation on relaxation.

Methods

NMRD profiles were recorded with a custom designed variable field relaxometer at 3, 10, 23, and 37 ^oC over the frequency range 2–63 MHz in 0.01 M phosphate buffered saline (PBS). T2 was measured using a CPMG pulse sequence and T1 by saturation recovery. In addition, T1 and T2 measurements were made at 300 MHz with and without the addition of 4.5% HSA. ^{17}O relaxation measurements were made at 40.7 MHz. All Dy concentrations were verified by ICP analysis. The Curie spin contribution to relaxivity was obtained by subtracting the relaxivity in the low field limit, and the data were fit to known equations (6).

Results

Fig. 1 shows that Curie spin relaxation is predominantly an inner-sphere effect. For **Dy-L1**, T2 relaxivity, R2 (filled symbols) increases with increasing field and decreasing temperature as expected, whereas R1 (open symbols) shows no field dependence. ^1H R2 values were fit by varying the hyperfine coupling constant, A/h, using τ_m values obtained from ^{17}O NMR. In the absence of HSA, R2 (^1H) can be solely accounted for by τ_m. Calculated parameters for **Dy-L1** are shown in Table 1. The NMRD profile of **Dy-L2** shows that R1 and R2 are approximately equal, and that R2 is not increasing with the square of the magnetic field (verified at 300 MHz). However, while having little influence on their relaxation rates, **Dy-L2** produces a large chemical shift of both ^{17}O and ^1H nuclei. This outer-sphere chemical shift represents about 40% of the observed ^{17}O shift for **Dy-L1** and is much larger for ^1H. This must be accounted for in the analysis to determine τ_m for **Dy-L1** otherwise the calculated τ_m will be too short. Addition of **Dy-L1** to a 4.5% HSA solution (Fig. 2) has a dramatic effect on 1/T2 relative to the same sample in PBS, whereas 1/T1 remains unchanged. The 1/T2 vs [Dy] plot is nonlinear for the HSA sample and is typical of protein binding. It is evident that R2 is increased by as much as 6 times upon **Dy-L1** binding to HSA.

Fig.1

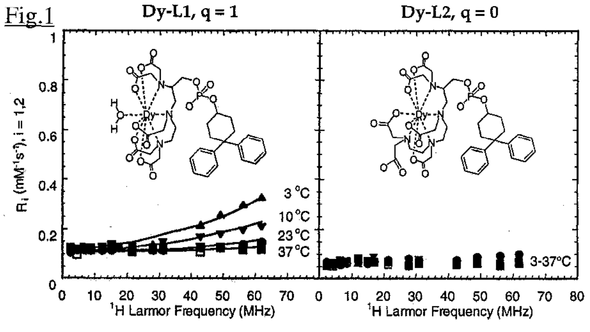

Fig. 2

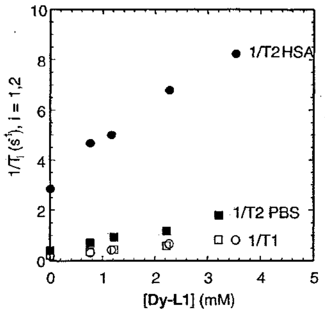

Table 1

τ_m^{298}	51 ns	T_{1e}	0.5 ps
$\Delta H^‡$	+38.9 kJ mol^{-1}	*A/h* (^1H)	+0.88 MHz
$\Delta S^‡$	+28.3 J K^{-1}mol^{-1}	*A/h* (^{17}O)	-0.75 MHz

Conclusions

Curie spin relaxation is predominantly an inner-sphere effect, and is dominated by the water residency time τ_m. For rapidly tumbling complexes (single chelates), the transverse relaxivity can be improved at least 6-fold by slowing of the molecular rotation, e.g. by complexation with HSA.

References

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