T_2-Selective MRI Contrast-Reagents: Revisiting the Inner-Sphere Curie-Spin Relaxation Mechanism of Dysprosium (III) Chelates

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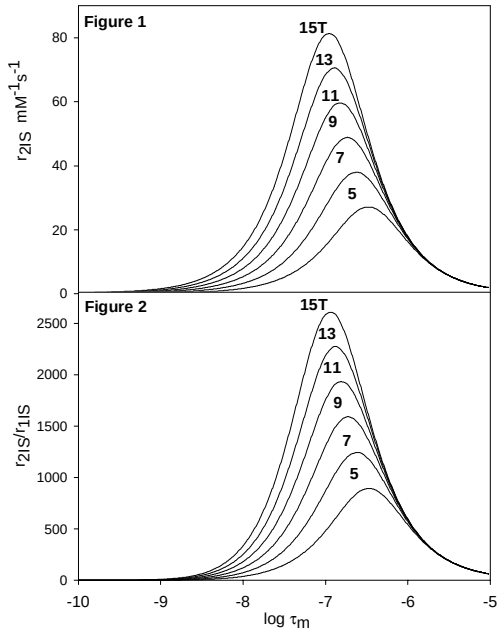
Synopsis: Whereas the hyperfine inner-sphere (IS) relaxivity of gadolinium(III)-based contrast reagents (CRs) decreases with increasing magnetic field strength (B_0), that of dysprosium(III)-based CRs (Dy-CRs), having larger magnetic moments, increases quadratically because of the contribution of the Curie-Spin relaxation mechanism. Furthermore, Dy-CRs display very high T_2-selectivity and strong temperature dependence (α T^{-6}); thus, they could be used to restrict catalysis of ^1H_2O relaxation to the transverse plane and/or to measure small tissue temperature variations. The purpose of this study is to estimate the maximum attainable transverse (r_{2IS}) and longitudinal (r_{1IS}) IS relaxivities, as well as the T_2-selectivity, for monomeric, single water site (q = 1) Dy-CRs, while also investigating the effects of the mean CR water lifetime, τ_m, on ^1H_2O relaxation.

Introduction: In the early 1950's, NMR allowed new experiments involving systems in dynamic equilibrium because NMR signals that emanate from spins in distinct electromagnetic environments usually have different properties. The local electromagnetic field that water proton spins (^1H_2O) experience can be systematically perturbed with a paramagnetic dopant whose unpaired electron dipolar field catalyzes transverse and longitudinal relaxation. Coincident with the 1970's advent of MRI was the debut of paramagnetic species used for the enhancement of anatomic image contrast. Although CRs are typically gadolinium(III)-based, Dy-CRs could alternatively restrict CR-dependent relaxation acceleration to the transverse plane whenever a T_2-selective CR (T_2-CR) is desired. The "Curie-spin" (CS), or "molecular susceptibility," mechanism underlies this Dy-CR property, having little or no effect on longitudinal ^1H_2O relaxation, depending on the B_0 and τ_m values. The Solomon-Bloembergen-Morgan (SBM) equations neglect the effect of Boltzmann electronic polarization on the coupled proton spins. In the mid 1970's, Vega, Fiat, and Gueron realized that the dipolar field arising from a thermally averaged Boltzmann electronic polarization could also enhance the relaxation of coupled proton magnetization (1,2). They named this the CS mechanism because it can be described with the Curie Law. It becomes pronounced in paramagnetic species with rapid electronic relaxation [like Dy (III)], with long rotational reorientation times (τ_r), and at high B_0: it increases quadratically with B_0. Here, the effect of CR-water exchange on the CS-dominated transverse IS relaxivity of T_2-selective Dy-CRs is characterized. Furthermore, upper-limit r_{1IS} and r_{2IS} values, as well as the T_2-selectivity, are calculated; last, the limitations and conditions under which a Dy-based T_2-CR becomes viable are predicted by the τ_m (under present conditions, τ_m approaches the CS correlation time, τ_{CS}) and B_0-dependences of calculated relaxivities presented herein.

Simulations: The calculated IS relaxivities and T_2-selectivity are confined to the limiting case where $\tau_r >> \tau_m$, thus $\tau_{CS} \approx \tau_m$: as τ_r approaches infinity, τ_{CS} approaches τ_m. Bulk magnetic susceptibility (BMS) and outer-sphere (OS) contributions to relaxation will be treated in future investigation. For relevance to human physiology, present simulations hold T = 310 K. The B_0 and τ_m dependences of the Dy-CR r_{1IS} and r_{2IS} values are calculated using the published CS (1,2) and Swift-Connik equations for the 5 T < B_0 < 15 T range. [At low B_0 values, the CS relaxation channel closes; B_0 > 15 T is unlikely to soon become available for human MRI because of magnet design and RF excitation pulse issues.] A broad τ_m range, $10^{-12} < \tau_m < 10^{-4}$ s, is employed because the optimum τ_m is B_0-dependent and different for r_{1IS} and r_{2IS}. The parameters (in their usual notations) used in the simulations are: q = 1, p_m = 1.8 x 10^{-5}, γ_I = 2.675197x10^8 rad s^{-1} T^{-1}, μ_0 = 4πx10^{-7} kg m s^{-1} A^{-2}, μ_B = 9.27410x10^{-24} JT^{-1}, k = 1.38062x10^{-23} JK^{-1}, r (Dy-H) = 3.111x10^{-10} m (3), $(\Delta\omega_m/\omega_I)^{iso}$ = 43 ppm (4), $(\Delta\omega_m/\omega_I)^{con}$ = 17 ppm (4), and μ_{eff} = 10.646. The sum of the scalar and dipolar SBM contributions to R_{1m} and R_{2m} (the rate constants [T_{1m}^{-1}, T_{2m}^{-1}] for CR-bound ^1H_2O), ΣR_{1m}^{SBM} = 1665.14 s^{-1} and ΣR_{2m}^{SBM} = 3027.76 s^{-1} (5), respectively, are essentially asymptotic for the B_0 range used: thus the corrections of Gillis et al (6) are not included. The τ_r value is set to infinity in order to isolate water exchange effects on the CS relaxivity contribution and to estimate its upper-limit for the chosen B_0 range. Alternatively, one could more realistically simulate the B_0- as well as τ_m-dependences of relaxivities at fixed τ_r values or any other combination of τ_r, τ_m, and B_0. In the same way, relaxivity dependences can be simulated for q > 1, and for polymeric Dy-CRs with minor parameter adjustments.



Results and Discussion: The B_0 and τ_m dependences of r_{2IS} and the T_2-selectivity (r_{2IS}/r_{2IS}) are plotted in **Figs. 1** and **2** respectively, assuming the limiting $\tau_r >> \tau_m$ case [therefore, $\tau_{CS} \approx \tau_m$]. The optimum τ_m shifts to smaller values as B_0 increases. The optimum τ_m for r_{1IS} (not shown) ranges from 5x10^{-10} to 2x10^{-10} s, and varies from 3x10^{-7} to 10^{-7} s for r_{2IS} and r_{2IS}/r_{2IS}, depending on B_0. The topological features of **Figs. 1** and **2** are easily intuited. If τ_m is too short, the protons will not effectively interact with the paramagnetic species; on the other extreme, however, if τ_m is excessively long, then the CR loses its catalytic effectiveness because it interacts with too few water molecules per unit time. As depicted in **Fig. 1**, r_{2IS} reaches its zenith at a value slightly below 85 $mM^{-1}s^{-1}$ (for B_0 = 15 T and $\tau_m \approx 10^{-7}$ s) and r_{1IS} (not shown) peaks at a value slightly below 0.35 $mM^{-1}s^{-1}$ (for B_0 = 15 T and $\tau_m \approx 2x10^{-10}$ s). This r_{1IS} increase corresponds to an ~ 7 fold enhancement whereas the r_{2IS} increase is ~ 1700 fold higher than IS relaxivities measured for Dy-CRs [r_{1IS} = 0.05 $mM^{-1}s^{-1}$, r_{2IS} = 0.05 $mM^{-1}s^{-1}$ at 310 K for varied B_0 (5)] when the overall correlation time is dominated by the, somewhat B_0-independent, electronic relaxation time constant [in other words, when the CS relaxation mechanism is ineffectual]. Selectivity is defined here as the ratio $\Delta R_{2IS}/\Delta R_{1IS}$; for any given [CR], this equates to r_{2IS}/r_{1IS}. This is plotted in **Fig. 2**, displaying a maximum r_{2IS}/r_{1IS} ~ 2600 (for B_0 = 15 T and $\tau_m \approx 10^{-7}$ s). Realistically speaking, τ_r is a finite number; therefore, the assumption that $\tau_{CS} \approx \tau_m$ will lead to a small error in τ_{CS} ($\leq$ 10 %), as long as τ_r is at least 10 τ_m.

Conclusion: The irrefutable benefits of high B_0 and the flourishing of targeted-CR developments in MRI research presage countless clinical promises. With the future prevalence of high field MRI scanners, close attention should be paid to the potential applications of the CS relaxation mechanism, since it increases quadratically with B_0. Dy-CRs might be effectively administered as T_2-CRs and/or as temperature indicators. Development of monomeric targeted-CRs, capable of binding large cellular assemblies such as erythrocytes and leukocytes, could henceforth yield another *avant-garde* T_2-selective blood-pool agent. The conditions for the optimum CS relaxation mechanism are somewhat confined; in order to maximize the CS effect on ^1H_2O transverse relaxation, T_2-CR design must also consider the modulatory effect of τ_m—particularly, τ_m on the order of 100 ns. Despite relatively small enhancement in the actual r_{2IS}value, the "Curie-Spin" contribution to transverse relaxation may also be maximized using polymeric and/or q > 1 Dy-CRs. Currently, the relative magnitudes of the combined IS plus OS CS and the BMS contributions to r_2 are under investigation. If the hyperfine r_2 (r_{2IS} + r_{2OS}) can become sufficiently large, it may be possible to minimize the non-analytical BMS relaxivity ($r_{2\chi}$) term, which becomes finite in the multicompartmental tissue situation, and which increases with B_0.

Support: NIH (RO1 EB-00422 and RO1 NS-40801) and DOE (DE-ACO2-98CH108).

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