

Paramagnetic CEST Agents: Theory versus Experiment

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Synopsis

Theoretical simulations of experimental Z-spectra for a series of LnDOTAM³⁺ (where Ln³⁺ is a trivalent lanthanide cation and DOTAM is 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylamide) complexes were carried out by using the modified Bloch equations for a three-pool (Ln³⁺-bound water, amide protons and bulk water) exchange model. Such simulations provide valuable insights into the influence of chemical shifts, water exchange rates, relaxation rates, applied B₁ fields and saturation duration times on the observed CEST effect. This has proven valuable in the design of paramagnetic CEST agents with optimal efficiencies.

Introduction

Balaban *et al.*¹ were first to report a new class of diamagnetic MRI contrast agents based on chemical exchange saturation transfer (CEST) between biomolecules and bulk water. More recently, Van Zijl *et al.*² have shown that the effect can be amplified by using exogenous macromolecules with large numbers of exchanging sites or endogenous proteins/peptides. This idea was further extended to paramagnetic systems.^{3,4} Recently, a theoretical framework based on the modified Bloch equations had been formulated to fit the experimental Z-spectra.⁵ Here we present a numerical analysis of experimental Z-spectra for series of LnDOTAM³⁺ complexes (Ln³⁺ = Ce³⁺ to Yb³⁺, except for Pm³⁺ and Gd³⁺).

Results and Discussion

DOTAM is a simple macrocyclic tetraamide ligand that forms kinetically stable complexes with lanthanide ions. One unique feature of such complexes is that they all have one inner-sphere water molecule (2 exchanging protons) and four amide groups (8 exchangeable protons) all in intermediate to slow exchange with bulk water. The Ln³⁺-bound water protons have chemical shifts ranging from +500 ppm (Tm) to -800 ppm (Dy), while amide protons have chemical shifts ranging up to 80 ppm (Dy). These features are useful in serving as a prototype three-pool paramagnetic CEST agent.

Although the Ln³⁺-bound water molecule exchanges too rapidly in these complexes to directly observe a bound-water ¹H resonance, the Z-spectra of such complexes do reveal the exchangeable sites (Figure 1). The experimental CEST spectra and best fit simulated curves for EuDOTAM³⁺ and DyDOTAM³⁺ are illustrated below. These two complexes differ dramatically in the chemical shift separation between the complex and bulk water resonances and the simulations show that water exchange also differs substantially in these two complexes ($\tau_M = 95 \mu s$ for Eu³⁺ and $22 \mu s$ for Dy³⁺). These data show that 1) the experimental Z-spectra can be fully simulated by using the modified Bloch equations, 2) the chemical exchange parameters (lifetime and chemical shift differences) can be estimated from Z-spectral simulations and 3) paramagnetic complexes with very large hyperfine shifts (such as Dy³⁺ and Tb³⁺) may serve as useful paramagnetic CEST agents at concentrations similar to those used for typical T₁ relaxation agents.

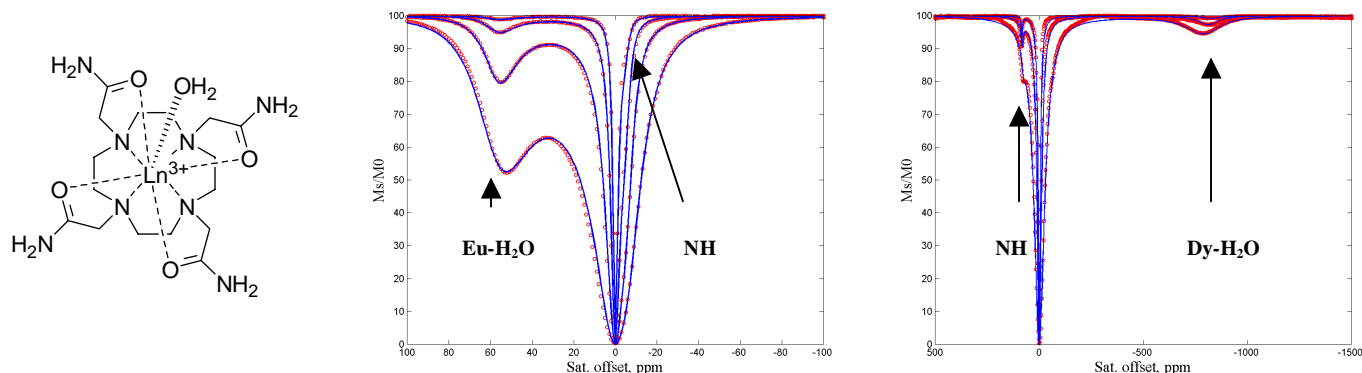


Figure 1. Z-spectral data (individual points) and best fit simulations to Bloch theory (solid lines) for **10 mM** EuDOTAM³⁺ at B₁ values of 109, 229, 505, and 1020 Hz (left, in descending order in the graph) and **1 mM** DyDOTAM³⁺ at B₁ values of 505, 1020 and 2000 Hz (right).

Conclusions

In summary, theoretical simulations of the experimental Z-spectra of the entire series of LnDOTAM³⁺ complexes were carried out by using the modified Bloch equations for a three-pool model. These data show that lanthanide ions with large hyperfine-shifted bound water resonances should be considered in the design of more efficient paramagnetic CEST agents.

Acknowledgments

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