

# Computational Study of Structural Modifications to a Novel Class of Paramagnetic Chemical Exchange Saturation Transfer Agents

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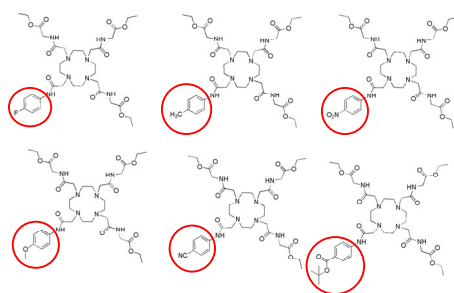
## Abstract

Magnetic Resonance Imaging (MRI) is a non-invasive tool used by the medical community to diagnose disease. Imaging agents, usually chelates, are used to enhance MRI signals. Our study focuses on the physical basis of MRI signal enhancement induced by structural modifications of a novel class of Paramagnetic Chemical Exchange Saturation Transfer (PARACEST) agents. With these agents, the MR image is modified by magnetization transfer between the H<sub>2</sub>O molecule bound to the Eu(III)(DOTA) chelate and bulk water, which is inversely proportional to the rate of H<sub>2</sub>O exchange between the bound and bulk H<sub>2</sub>O. The water exchange rate depends on the size, the coordination geometry of the lanthanide ion and the electronic properties of the groups attached to the coordinating pendant arm. We present here a computational study of the effect of chemical modifications of the *para*-substituents in the coordinating pendant arms on the CEST signal. The effect of simple electron-withdrawing (e.g. nitro) and electron-donating (e.g. methyl) substituents chemically attached to the chelate arms is quantified by correlating the experimental CEST signal with charge transfer interactions in the coordinated water-chelate system computed from quantum mechanics. This study analyzes the origin of the substituent effect on the CEST signal and the electronic structure of the complex.

## Approach

The goal of this study is to understand the electronic structure effect of the electron withdrawing or donating nature of the 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) pendant arms and the interactions between the central Ln(III) ion and exchangeable water molecules.

In order to compare the interactions across the complexes with different pendant arms, we examined DOTA structures without substituents, and with 6 substituents ranging from electron donating to electron withdrawing ones (*p*-CH<sub>3</sub>, *p*-OCH<sub>3</sub>, *p*-COOtBu, *p*-F, *p*-CN, *p*-NO<sub>2</sub>).



## Experimental Findings

CEST spectra\* of the six one-pendant arm complexes show an increase in the intensity of magnetization transfer at the bound water peak in the following order:

*para*-methyl > *para*-methoxyl > *para*-hydrogen > *para*-fluoro > *para*-nitro

\*Spectra obtained by S. J. Ratnakar, M. Woods, Z. Kovacs, A. D. Sherry, The University of Texas Southwestern Medical Center and University of Texas at Dallas

## Methods

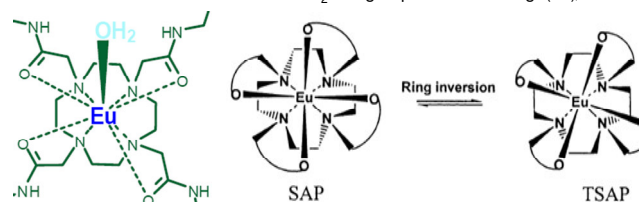
The starting geometry was obtained by substituting Eu(III) by Y(III) in the X-ray structure of the Eu(DOTA) complex (1). Y(III) has the same size, charge and coordination as Eu(III), and is considered a pseudo-lanthanide.

The geometry was optimized using Density Functional Theory (DFT), at the B3LYP(2,3) level. Basis sets used are: LanL2DZ(4-6) for Y, D95V(7) for other atoms.

Analysis of results was performed using Natural Bond Orbital (NBO) Theory(8,9). Calculations were carried out by Gaussian03(10) and NBO 4(11) software packages.

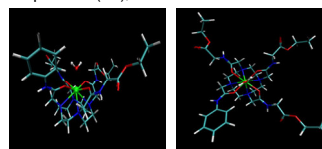
## Structure of Eu(DOTA) Complex

There are two conformations: square anti-prism (SAP) and twisted square anti-prism (TSAP), interconvertible either by rotation of the acetate arms or via the conformational interconversion of the CH<sub>2</sub>CH<sub>2</sub> groups within the ring. (12)



## Optimized Structure of Y(DOTA) Complex

The structures of seven complexes with one pendant arm were optimized, both with coordinated water and without it. The optimized structure in all cases is TSAP conformation, agreeing with experimentally derived geometries of related Y complexes. (13)



Left: side view, right: top view. For clarity, complex structure shown in stick model, exchangeable water in ball-and-stick model. Green: yttrium; red: oxygen; blue: carbon; white: hydrogen; dark blue: nitrogen.

## NBO Analysis of Y(DOTA) Complexes with One-pendant Arm

Within the NBO framework, we analyzed the charge transfer (CT) interactions between nearly empty Y(III) orbitals (4d) and the donating bond and lone pair NBOs of the carbonyl oxygen atom of the variable arm. The extent of CT depends on orbital orientations and overlaps. The ligands with electron withdrawing groups have a clearly reduced transfer of electron charge into the Y orbitals, causing Y ion to become more positive and more tightly bound to the water molecule, which in turn affects the exchange rate.

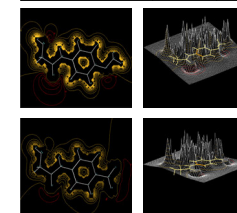
Interaction*	CH <sub>3</sub>	OCH <sub>3</sub>	COOtBu	F	CN	NO <sub>2</sub>
ligand C-O BD $\square$ Y LP(4)*	0.42	0.22	0.06	-0.06	-0.50	-0.85
ligand O LP(1) $\square$ Y LP(2)*	-0.26	-0.24	0.09	0.27	0.37	0.54
ligand O LP(1) $\square$ Y LP(3)*	-1.35	-0.46	-0.73	-0.70	0.83	1.52
ligand O LP(1) $\square$ Y LP(4)*	1.98	1.05	0.29	0.13	-1.81	-2.91
ligand O LP(2) $\square$ Y LP(3)*	-0.63	-0.14	-0.08	0.23	0.99	1.47
ligand O LP(2) $\square$ Y LP(4)*	0.66	0.16	0.40	0.27	-0.21	-0.55

Charge transfer energy changes (kcal/mol) in going from electron donating to electron withdrawing substituent in *para* position. Energies calculated relative to the structure with hydrogen in the *para* position

## Charge Analysis of Pendant Arms

We analyzed the charge, Mulliken (MK) and Electrostatic Potential (ESP) of the carbonyl oxygen atom which coordinates the metal in the center of the DOTA ligand. The charges presented were obtained using pendant arms extracted from the DOTA complex, capped at nitrogen with hydrogen atoms. The extent of the charge depends on the ability of the electron donating group (EDG), or the electron withdrawing group (EWG) to donate or pull away electron density from the coordinating oxygen.

Basis Set (MK)	MeO	CH <sub>3</sub>	H	F	COOtbutyl	CN	NO <sub>2</sub>
6-31G(d)	-0.495	-0.491	-0.488	-0.488	-0.451	-0.473	-0.469
6-31G(d,p)	-0.460	-0.461	-0.509	-0.457	-0.452	-0.449	-0.447
6-311++G(3df,2p)	-0.788	-0.789	-0.782	-0.782	-0.761	-0.761	-0.774
6-311++G(3df,2p)	-0.774	-0.777	-0.773	-0.773	-0.748	-0.764	-0.752
Basis Set (ESP)	MeO	CH <sub>3</sub>	H	F	COOtbutyl	CN	NO <sub>2</sub>
6-31G(d)	-0.490	-0.487	-0.487	-0.490	-0.464	-0.476	-0.477
6-31G(d,p)	-0.475	-0.475	-0.555	-0.470	-0.463	-0.458	-0.451
6-311++G(3df,2p)	-0.621	-0.622	-0.626	-0.619	-0.591	-0.613	-0.597
6-311++G(3df,2p)	-0.621	-0.622	-0.626	-0.619	-0.590	-0.613	-0.597



Above: Convergence study of Mulliken charges and electrostatic potential charges on the coordinating oxygen (4-6).

Left: contour plots with corresponding electrostatic potential plots of the *p*-methoxy pendant arm, and the *p*-nitro pendant arms.

## Future Plans

- Determine charges on metal coordinating atoms (N, O) of the DOTA ligand, with the metal absent and present, as well as with the coordinated water molecule absent and present.
- Further investigate charge transfer energy changes (kcal/mol) in going from electron donating to electron withdrawing substituent in *para* position.
- Investigate how pendant arm electron donating and withdrawing ability influences the equilibrium between SA and TSA conformations.
- Perform NBO analysis of two-pendant arm complexes and compare results to one-pendant arm complexes to assess the influence of the presence of the additional arm, and its location.
- Rationalize experimental findings, and propose structural changes to improve the design of PARACEST agents

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