Quantum Chemical Prediction and Experimental Validation of the Characteristics of diaCEST MRI Contrast Agents

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Introduction: Computational quantum chemistry methods are underutilized in the development of MRI contrast agents. Methods using Gauge Invariant Atomic Orbitals (GIAO) can accurately predict molecular magnetic properties and be employed to predict the physicochemical properties of MRI contrast agents to enhance image contrast. Density functional theory (DFT) provides the spin electron density in the presence of an external magnetic field, which can be used with the GIAO method.[1,2] Quantum theory of atoms in molecules (QTAIM) will be applied to characterize the electronic density of those molecules representing the highest potential for CEST.[3,4] Electron densities of the best CEST agents will show a Low Barrier Hydrogen Bond (LBHB) between donor and acceptor and have a large density at the bond critical point of the exchangeable proton with water. A library of diaCEST agents with large chemical shifts and fast exchange rates can be modeled with these methods to identify ideal agents for CEST MRI.

Computational Chemistry Methods: Full optimizations were performed for all compounds used in this study using *Gaussian09*.[5] Minima were assessed by frequency calculations. DFT level of theory was applied for optimizations and frequency calculations with the density functional B3LYP and the basis set 6-311+G (d,p).[5,6] NMR chemical shift calculations were obtained using the GIAO as implemented in *Gaussian09*.[1,5] Wavefunctions for QTAIM were obtained by requesting the word wfn in *Gaussian09*. The polarizable continuum model (PCM) was applied to model the behavior of water in the electronics of the desired structure.[7]

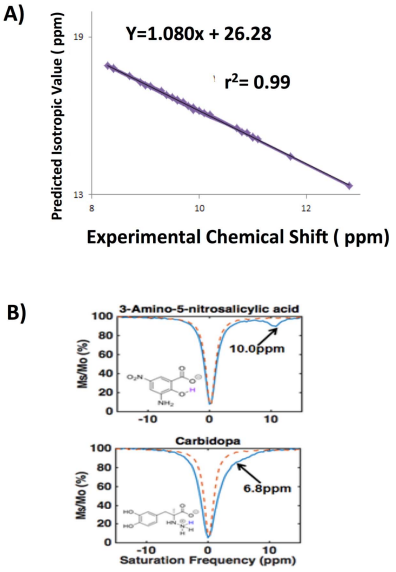
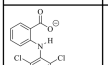
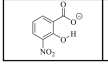


Figure 1. A) Correlation Between predicted and experimental chemical shifts. **B)** Experimental confirmation of two new agents predicted by DFT

Experimental Methods: A continuous wave saturation CEST-FISP[8] pulse sequence with 6 second saturation period consisting of 2.8 μT power, 90 Hz bandwidth and 54 saturation frequencies between +10 and -10 ppm was applied to obtain CEST spectrum results in 5.8 minutes on a 7T Bruker MRI scanner. A single function with a sum of three Lorentzian line shapes was fit to CEST spectra using Matlab and only CEST effects greater than 2√2*noise were retained.

Table 1. A) Prediction of CEST effect by Quantum Mechanics

Contrast Agent	R(O-H-O) or R(N-H-O) in A°	Density (a.u.)	∇²ρ (a.u)	H Charge	Bond angle	CEST predicted	CEST observed
	2.4995	0.07	1.54E-01	0.62	156.6°	yes	yes
	2.6275	0.04	1.38E-01	0.48	139.4°	no	no
	2.4376	0.10	1.42E-01	0.62	158.0°	yes	yes

Results: Figure 1. A set of salicylic acid analogues and anthranilic acid analogues were modeled using GIAO NMR method in *Gaussian09* to obtain isotropic values (absolute chemical shift). The theoretical and CEST frequencies were highly correlated (r^2 = 0.9992). Table **2.** Calculated QTAIM parameters to predict whether or not the contrast agent will show CEST. **Figure 2.** Experimental CEST spectra of predicted diaCEST agents by quantum chemistry.

Discussion: These results demonstrate that diaCEST contrast agents can be predicted by computational quantum chemistry methods before being tested in preclinical or clinical MRI scanners. Overall, we hypothesize that CEST agents with intramolecular LBHB hydrogen bonds, and large electron density at the hydrogen bond critical point will often have high chemical shifts and good exchange rates for CEST MRI.

References: 1. Ditchfield, R. Molecular Physics. 1974, 27, 789-807. 2. Friedrich, K.; et al. Phys D. 1990, 17, 45-46. 3. Bader R.F.W. Atoms in Molecules. A Quantum Theory; Clarendon: Oxford, 1990. 4. Bader, R.F.W. Chem. Rev. 1991, 91, 893-926. 5. Gaussian 09, Revision D.01, M. J. Frisch et al.,Gaussian, Inc., Wallingford CT, 2009. 6. Miertus, S.; et al. Chem. Phys. 1981, 55, 117-129. 8. Shah, et al., Magn. Reson. Med. 2011, 65, 432-437. 7. Yang, X.; et al. Angew. Chem. Int. Ed. 2013, 52, 8116-8119. 10. Song, X.; et al. Contrast Media Mol. Imaging. 2014. 8. Yang, X.; et al. Chem. Eur. J. 2014, 20, 1-10.