Molecular Mechanisms of Magnetization Transfer

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Introduction

Magnetization Transfer (MT) between water and immobilized tissue components such as proteins, lipids, or polysaccharides occurs in almost all tissues. The detailed molecular mechanisms of MT are thought to consist of exchange of protons and/or exchange of water molecules, though no conclusive experiments have been performed to disentangle these magnetically similar processes.

Methods

We conducted of MT experiments in two model systems, agarose (1.5%) and gelatin (15%). To examine the effect of pH on MT, two agarose samples were made at pH 3 and pH 6 and two gelatin samples were made at pH 5 and pH 8. To disentangle proton exchange from whole molecule exchange, a second set of samples were made in 80% D_2O, 10% water and 10% methanol. Methyl protons do not exchange and methanol MT with the immobilized matrix will reveal whole molecule exchange. MT was measured as a function of off-resonance frequency and a function of applied B1 field strength. T1 was measured by inversion recovery and T2 by CPMG sequences. MT parameters (Ra, Rt, Mb0, T2b) were estimated by standard MT theory (1).

Results

The results of the experiments shown in Figures 1-4 paint an unequivocal and somewhat unexpected picture of the interaction of water and methanol with agarose and gelatin. In agarose, Figs. 1 and 3 show that MT does not change with pH and that both water and methanol have a significant MT effect with agarose. From these data we conclude that MT in agarose is driven by whole molecule exchange. Agarose parameters estimated by MT theory are similar for pH 3 and 6 samples. Mb0 is 0.0046±0.0002, T2b is 13.0±0.3 microseconds, and Rt is 465±60 s^{-1}. In the water/methanol agarose samples, Rt is 52.5±4.12 s^{-1} for water and 8.43 ± 0.84 s^{-1} for methanol.

The picture in gelatin is entirely complementary to agarose. Fig. 2 shows a significant variation of MT with pH. Rt is found to be 43.5±4 s^{-1} at pH 5 and 116±12 s^{-1} at pH 8. The increased cross-relaxation rate with increased pH supports a base catalyzed proton exchange of water protons with the –OH and –NH groups in gelatin. Fig. 4 shows that there is only minimal methanol MT in gelatin and that whole molecule exchange is not an operative mechanism in this environment.

From these results we can say with some authority that MT in agarose is determined only by whole molecule water (or methanol) exchange and that MT in collagen is determined only by proton exchange.

Discussion

Previous structural and NMRD studies of agarose are consistent with the data presented here. X-ray diffraction studies reveal that agarose creates a double helical arrangement with water molecules likely intercalated and perhaps responsible for sustaining the structure (2). Chavez et al (3) find that NMRD profiles of agarose samples are explained by the exchange of the internal water molecules located in the central cavity of the agarose double helix with bulk water. In addition to a large MT effect, agarose creates a very short water proton T2 with minimal change on water proton T1. These findings are consistent with a small number of rigid water molecules in exchange with bulk water.

The results from gelatin are easier to comprehend. Gelatin is formed of collagen triple helices which provides no hydrophobic pockets for methanol binding. Therefore, the lack of a gelatin-methanol MT is not unexpected. Base catalyzed proton exchange is the operative mechanism of MT in gelatin.

These studies highlight the molecular nature of MT and start to form a coherent picture of MT in model systems. Future work will be directed to disentangling MT in more complicated tissue systems and in designing site-specific MT molecules that can be used as gadolinium-free, targeted contrast agents.

References

1) Henkelman et al. Magn Reson Med 1993; 29:759-766. 2) Arnontt et al J. Mol. Biol. 1974, 90, 269-284. 3) Chavez et al. JACS. 2006, 128, 4902-4910

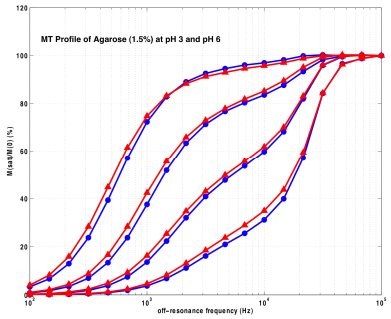

Figure 1. MT of water in agarose at pH 3 (blue) and pH 6 (red). Minimal difference is seen in the MT profile of water protons in agarose at different pH values.

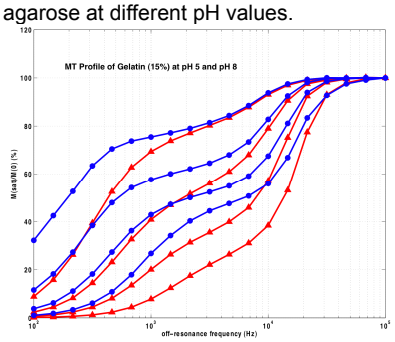

Figure 2. MT of water in gelatin at pH 5 (blue) and pH 8 (red). Significant MT changes occur in with pH in agarose.

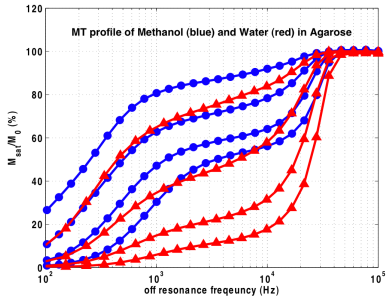

Figure 3. MT of methanol (blue) and water (red) in agarose. Both water and methanol have significant MT.

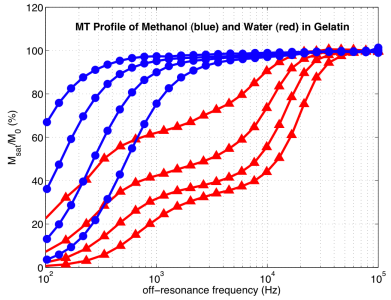

Figure 4. MT of methanol (blue) and water (red) in gelatin. No methanol-gelatin MT is observed. The methanol protons show only direct RF saturation.