

Homogeneous Hydrogenation Yielding a Hyperpolarized Form of the Inhalation Narcotic Diethyl Ether

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Introduction

Due to low density and magnetic moment, heteronuclear MRI benefits greatly from signal enhancement, even at high field strength. One approach has been to use methods such as spin-exchange optical pumping of ³He and ¹²⁹Xe. Another approach, suitable for many bioactive molecules, is the transfer of spin order from parahydrogen^[1] into ¹³C polarization. Previous results with hyperpolarized ¹²⁹Xe^[2] have demonstrated the utility of measurements of blood uptake and brain deposition. Due to its similar magnet moment and safety profile, much larger blood/gas partition coefficient (> 100 times that of Xe), expected longer blood T₁, and relatively large anesthetic dose (blood concentration approximately 4 times that of Xe required for anesthesia), we anticipate that both ¹³C- and ¹H-hyperpolarized diethyl ether may offer considerably more signal in the dissolved phase.

Methods

The use of PHIP techniques in animal imaging has been demonstrated in a series of preliminary angiography MRI experiments by Axelsson, et al.^[3]. For lung imaging, however, this system is not appropriate because of its lower blood solubility and toxicity concerns. To demonstrate initial feasibility of using diethyl ether, we mixed an unsaturated precursor (ethyl vinyl ether) with a cationic hydrogenation catalyst in simple alcohols and acetone.

The samples were hydrogenated by shaking in 1 bar of 97% parahydrogen at earth's field. Subsequent insertion into a 200 MHz NMR spectrometer gives the spectra shown below (in this example, 5 mg of Rh(I)dppb BF₄⁻ catalyst was mixed with 0.75 ml of diethyl ether in acetone-d₆ and hydrogenation reaction time was 20 seconds).

Results and Discussion

Figure 1 shows the ¹H- (200 MHz, right) and corresponding ¹³C- (50 MHz, below) NMR spectra. Nuclear polarization, corresponding to an enhancement factor of more than 100, is transferred to the ¹³C nuclei. This is evident from the emission and enhanced absorption lines in both spectra. In the ¹H-PHIP-NMR spectrum net polarization is observed for both the CH₃ - (emission) and the CH₂-protons (absorption). In the ¹³C-PHIP-NMR spectrum, both resonances display antiphase multiplets, since the magnetic field has not yet been optimized.

The presence of enhancement, however, is unequivocal evidence for a homogeneous hydrogenation process, and the large enhancement, despite the low concentration of parahydrogen, is suggestive that it is the dominant hydrogenation pathway.

Conclusion

This work demonstrates that hyperpolarization of inhalation narcotics is feasible using known catalysts. In order to extend this result to practical imaging uses, we are currently focusing on optimizing catalysis speed and hydrogenation conditions as well as pulse sequences for efficient polarization transfer. We also evaluate alternate aerosol delivery mechanisms to suppress the short gas phase spin-lattice relaxation.

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