Hyperpolarization of drugs using signal amplification by reversible exchange (SABRE)

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Target Audience: MRI physicists who are interested in hyperpolarization and imaging of drug distribution.

Purpose: By preparing nuclear spin polarization far beyond thermal equilibrium, hyperpolarization can provide improved sensitivity for NMR, recently enabling the real-time monitoring of metabolism in vivo.[1] The use of parahydrogen for polarization experiments has the advantages of easy implementation and fast polarization. Parahydrogen is a spin isomer of hydrogen with a pure spin state $|\alpha\beta - \beta\alpha\rangle$. Conventional parahydrogen induced polarization employs the strong signal of parahydrogen by observing the corresponding protons in the hydrogenation product of an unsaturated molecule. The SABRE approach[2] does not require chemical modification of the substrate to polarize. In this technique, the substrate and the parahydrogen bind to a catalyzing metal complex simultaneously,[2] during which polarization is transferred to the substrate through the scalar coupling networks. The polarized substrate is subsequently released and new substrate binds to the metal complex for polarization. Here we investigated the possibility to use SABRE to polarize several drugs used daily in the clinic. These are isoniazid and pyrazinamide used for treating tuberculosis (TB) and temozolomide for treating brain tumors.

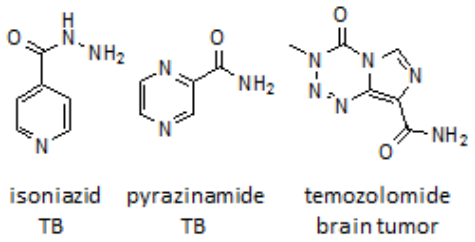

Fig 1: Structure of the drugs used in this study

Methods: 92.5% parahydrogen is generated by cooling down hydrogen gas to 36K in the presence of a catalyst for the conversion between the otho and para isomers of hydrogen. The polarization was achieved using a Bruker parahydrogen polarizer. First, a mixture of the iridium organic metal complex [IrCl(COD)(IMes)] (COD = 1,5-cyclooctadiene; IMes = 1,3-bis(2,4,6-trimethylphenyl) imidazole-2-ylidene)[3] and the substrate in methanol-d_4 solution was loaded into a mixing chamber in a small magnetic field underneath the NMR magnet. Polarization was achieved by bubbling parahydrogen through the sample. Then the sample was pneumatically transferred to the flow cell in a 700 MHz spectrometer. This process takes about 2 s. Once the sample was in the NMR probe, NMR spectra were acquired immediately. After NMR acquisition, the sample was returned to the mixing chamber for repolarization. Sample concentrations: isoniazid: 4 mM, Ir: 0.4 mM; pyrazinamide: 3.8 mM, Ir: 0.4 mM; temozolomide: 0.7 mM, Ir: 0.8 mM. To achieve high enhancement it is required that the differences in resonance frequency of the protons are of the same order as the scalar couplings and that the residence time of the substrate bound to the metal complex is appropriate. Therefore, the magnetic field and the temperature need to be optimized. The magnetic field in the mixing chamber equals the stray field of the NMR magnet plus the magnetic field generated by a small electromagnet outside the mixing chamber, which is tunable from -150 to 150 G. The temperature of the mixing chamber is controlled by a water bath. The time for the parahydrogen bubbling was experimentally determined by increasing the bubbling time until the enhancement stabilizes, usually 30s.

Results and Discussion: The NMR signal of the two protons of isoniazid was enhanced by 200 times at 36 G and 55 °C (Fig. 2). The enhancements depend on the polarization magnetic fields in a non-straightforward manner (Fig. 3a) and the optimal value can only be determined experimentally. This substrate prefers higher temperature with shorter residence time in the metal bound form. The NMR signal of pyrazinamide was enhanced by 30 times at 36 G and 0 °C, while temozolomide was enhanced by 200 times at 36 G and 0 °C.

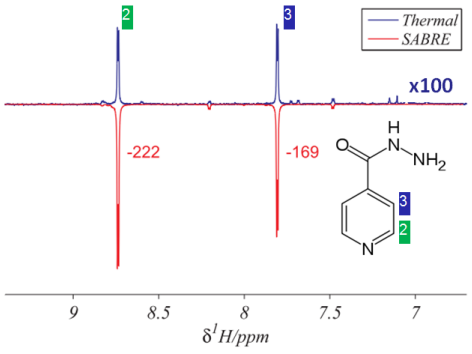

Fig 2: Enhancement of isoniazid using SABRE comparing to thermal polarization.

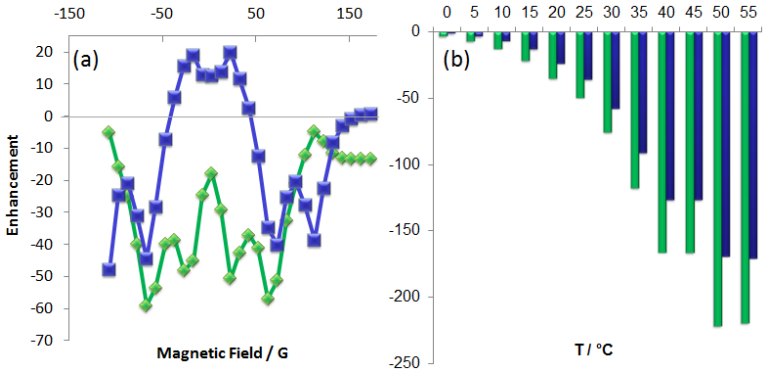

Fig 3: SABRE enhancements of isoniazid dependence on (a) the magnetic fields and (b) the temperature of water bath.

Conclusion: Isoniazid, pyrazinamide (drugs for TB) and temozolomide (drug for brain tumor treatment) are polarized using SABRE with enhancements up to 200 times at optimal polarization magnetic field and temperature.

References: 1. Alessandra V. and Silvio A. Curr. Opin. Chem. Biol. 2010;14:90; 2. Adams RW. et. al. Science 2009;323:1708; 3.Cowley M. et. al. J. Am. Chem. Soc. 2011;133:6134