Solvent effects of hyperpolarization 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: Hyperpolarization can provide improved sensitivity for NMR, recently enabling the real-time monitoring of metabolism in vivo in animals and patients.[1] The use of parahydrogen for polarization experiments has the advantages of easy implementation and fast polarization. Among the parahydrogen polarization techniques, the signal amplification by reversible exchange (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. Traditionally, methanol-d_4 was used as a solvent, which is not suitable for injection in vivo. We therefore investigated the possibility of SABRE polarization in solvents more compatible with in vivo applications, namely DMSO, ethanol and water. In this work, we investigated the possibility to use SABRE to polarize several substrates such as 3-amino-1,2,4-triazine and some drugs used daily in the clinic for treating tuberculosis, pyrazinamide and isoniazid. Conditions such as polarizing magnetic field strength and temperature as well as the hydrogen bubbling intensity and time were optimized for each solvent.

Methods: The samples contained 0.40 mM of the catalyst precursor [Ir(COD)(IMes)Cl] [COD = cyclooctadiene, IMes =1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene] and 4.0 mM of substrate in either methanol-d_4, methanol, ethanol or dimethyl sulfoxide (DMSO). Water samples were prepared by bubbling hydrogen through a methanol sample for at least 2 hours, then adding water and evaporating methanol under vacuum, since the catalyst is not soluble in water[4]. The polarization was achieved using a Bruker parahydrogen polarizer. The temperature of the sample was controlled by a home-built water bath system. The polarizing magnetic field was controlled by a small electromagnetic coil surrounding the sample, which was tuneable up to ±145 G. Polarization was achieved by bubbling 92.5% parahydrogen through the sample for about 30s. The sample was then pneumatically transferred to the flow cell in a Bruker 700 MHz or 750 MHz spectrometer. This process took about 2 s. Once the sample was in the NMR probe, spectra were acquired immediately. After data acquisition, the sample was returned to the mixing chamber for repolarization.

Results and Discussion: For the pyrazinamide and isoniazid, all the protons gained a maximum absolute enhancement at 65 G. In all solvents, the enhancements increased dramatically at higher temperature, before levelling off at about 37.5–46.1 °C. Generally, the enhancements in methanol-d_4 were best, followed by methanol and ethanol (Table 1). In DMSO, the enhancements were an order of magnitude smaller. Unfortunately, no polarization was observed for these two compounds in water currently. For 3-amino-1,2,4-triazine, on the other hand, enhancements of up to 65 times were found at 54.4 °C. According to SABRE theory, best enhancements occur at optimal *J* coupling networks for polarization transfer, appropriate

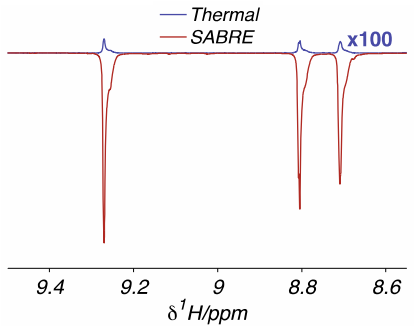

Fig 1: Enhancment of a pyrazinamide

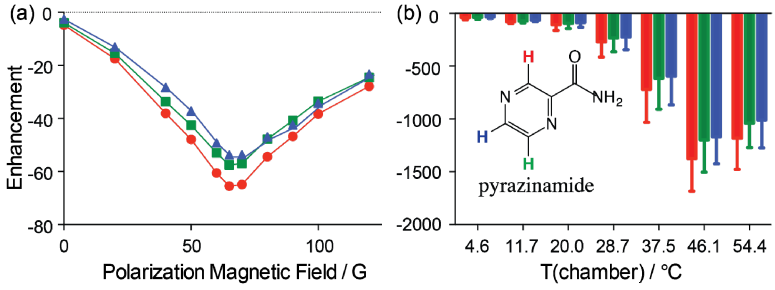

Fig. 2: Enhancement of pyrazinamide protons dependence on (a) polarization magnetic field strength; (b) polarization temperature in methanol-d_4.

binding kinetics and minimum spin relaxation. Pyrazinamide reflects a better spin system than isoniazid. Generally, at higher temperature, the binding kinetics is faster and the spin relaxation rates are smaller for small molecules. Faster binding kinetics and slower relaxation led to higher enhancements, in most cases, the best enhancement found at 37.5–46.1 °C. The enhancements were also negatively correlated with the viscosity of the solvents (methanol < ethanol < DMSO). In the fast tumbling range, the spin relaxation rates for protons in the substrate-metal complex are faster in more viscous solvents, causing polarization loss and a concomitant lower SABRE enhancement. By replacing the protons with deuterons, the spin relaxation in methanol-d_4 is the slowest, therefore showing the best enhancement (Fig. 2).

Conclusion: 3-amino-1,2,4-triazine, isoniazid and pyrazinamide are polarized using SABRE. In methanol-d_4, up to -1400 times enhancement was obtained for pyrazinamide, corresponding to 8% polarization, which is comparable to that of DNP. In water, up to -65 times enhancement was obtained for 3-amino-1,2,4-triazine.

	methanol-d_4	methanol	ethanol	DMSO
pyrazinamide	-1376	-906	-335	-42
isoniazid	-216	-165	-120	-39

Table 1: Enhancments of pyrazinamide and isoniazid

References: 1. Kurhanewicz J et al. Neoplasia, 2011;13:81; Viali A. & Aime S. 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; 4. Jan Falk Frederik, Ph.D. thesis.