Strategies to simplify and generalize hyperpolarization of heteronuclei invoking the cost-efficient SABRE method

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Purpose

Hyperpolarized magnetic Resonance (HP-MR) creates new avenues for interrogating disease states, their aggressiveness, progression, and response to treatment.[1] The current biomedical applications of HP-MR use dissolution dynamic nuclear polarization (d-DNP)[2] associated with large costs and complex experimental design. The presented research reduces cost and complexity of hyperpolarization, using "Signal amplification by reversible exchange" (SABRE) invoking parahydrogen (*para*-H_2) as alternate hyperpolarization source.[3] The current limitation of SABRE is that it primarily hyperpolarizes protons, which depolarize quickly (typically in seconds), precluding metabolic tracking on biologically relevant timescales; in addition, protons are associated with background signals from water. Heteronuclei such as ^{15}N are more attractive because they often have long polarization lifetimes and because they are not associated with competing background signals. Here we present two approaches to hyperpolarize ^{15}N: The first creates >10% ^{15}N polarization inside a magnetic shield, the second creates ^{15}N hyperpolarization directly inside the magnet both using the cost-efficient SABRE.

Methods

In the first approach, we conduct SABRE in a magnetic shield to demonstrate efficient hyperpolarization of ^{15}N-pyridine (Py). With the magnetic shield we reduce the Earth's magnetic field to ~0.5% of its original value establishing a field of ~0.2 μT. At this low field parahydrogen (p-H_2) is bubbled through a solution containing Py and a catalyst that reversibly binds the target (Py) and p-H_2. At this low field, the frequency difference between parahydrogen and the targeted ^{15}N resonates with the *J*-coupling network in the catalyst which drives hyperpolarization. The sample is subsequently transferred from the shield into a 9.4 T NMR spectrometer for detection. We name this method **SABRE-SHEATH** (**SABRE** in **SH**ield **E**nables **A**lignment **T**ransfer to **H**eteronuclei).

In our second approach, we demonstrate that low power RF-pulses can also create SABRE-^{15}N-hyperpolarization. By design of a specialized pulse sequence containing elements where the RF-amplitude (ω_1) matches the J-coupling network we demonstrate hyperpolarization directly inside the magnet avoiding the sample transfer process altogether.[4] We name this method **LIGHT-SABRE** (**L**ow **I**rradiation **G**enerates **H**igh **T**esla **SABRE**)

Results

Figure 1 summarizes the central achievements. 1) With the SABRE-SHEATH method we achieve close to ~30,000 fold signal enhancement corresponding to 10% ^{15}N-polarization. 2) With the LIGHT-SABRE method ~500 fold enhancements over thermal 9.4T signals are observed. This enhancement corresponds to 0.17% polarization, which is still significantly higher than the thermal polarization of 3.3 10^{-6}.

Discussion

With the SABRE-SHEATH method we create large degrees of hyperpolarization on heteronuclei at a fraction of the cost associated with d-DNP. With the LIGHT-SABRE method we retain the inexpensive nature of the hyperpolarization technique and simultaneously significantly reduce experimental complexity by creating the hyperpolarization directly in the magnet. The LIGHT-SABRE enhancements observed in these first proof of concept experiments are lower than those in the SABRE-SHEATH approach but we expect to increase the enhancements significantly by improving RF-coil design and LIGHT-SABRE pulse sequences.

Conclusion

The theoretical insights that led to SABRE-SHEATH and LIGHT-SABRE immediately extend to biologically significant molecules such as, nicotinamide, pyrazinamide, isoniazid which we are currently pursuing. At the same time, we expect that both methods will be developed into tools to hyperpolarize very general classes of molecules, not restricted to ^{15}N either, but we expect to be able to hyperpolarize ^{13}C and ^{31}P as well with both methods. The ability to efficiently, continuously and cost effectively hyperpolarize heteronuclei on a wide range of molecules has the potential to fundamentally alter the ways in which we conduct and disseminate HP-MR.

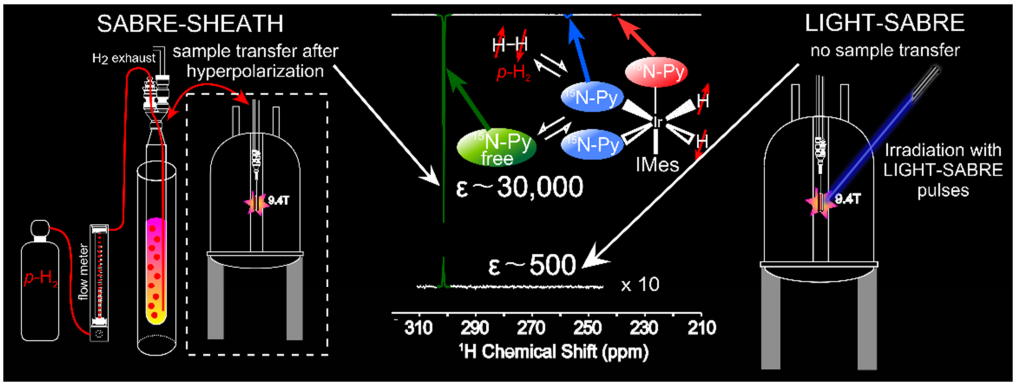

Fig. 1 The SABRE-SHEATH and the LIGHT-SABRE methods to create nitrogen-15 hyperpolarization derived from parahydrogen in reversible exchange. In the SABRE-SHEATH method, parahydrogen is bubbled through the solution creating the hyperpolarization when maintained at a low field provided by a magnetic shield. In the LIGHT-SABRE method hyperpolarization is created by simultaneously bubbling parahydrogen through the solution and applying the LIGHT-SABRE Pulse sequence. While larger enhancements are obtained using SABRE-SHEATH, the LIGHT-SABRE method circumvents the sample transfer step creating direct in magnet hyperpolarization.

References

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