A Simple, Low-Cost Device for Producing Hyperpolarized Heteronuclear Contrast Agents using Parahydrogen-Induced Polarization

S. Kadlecek[1], V. Vadhat[1], R. V. Cadman[1], K. Emami[1], J. M. Woodburn[1], R. A. Guyer[1], M. Ishii[1,2], J. Yu[1], H. H. Kim[3], W. Gefter[1], and R. R. Rizi[1]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Department of Otolaryngology, Johns Hopkins University, Baltimore, MD, United States, [3]Department of Chemistry, University of Pennsylvania, Philadelphia, PA, United States

Introduction: Hyperpolarization (super-thermal longitudinal alignment) of ^{13}C and other heteronuclei using the spin-order derived from parahydrogen is a promising tool for creating MRI contrast agents sensitive to metabolic activity. We present a simple, low-cost apparatus for generating these agents and our initial experience with a few target molecules.

Method: A device to utilize Parahydrogen-Induced Polarization (PHIP) must 1) heat and mix an unsaturated precursor solution with an appropriate hydrogenation catalyst, 2) dissolve parahydrogen in the solution in the presence of catalyst, and 3) apply a field cycling or RF pulse routine to transfer spin order from the para protons to a vicinal heteronucleus. The engineering solutions presented here borrow from extensive development work at GE Healthcare, Malmö, Sweden, but offer improved operation, simplicity and flexibility. The complete device is pictured in fig. 1. At the top, solutions are loaded under inert atmosphere into the pressurized glass tubes (1a). Although highly sensitive to O_2, we have found both catalyst and substrate solutions to be stable for weeks under these conditions. To begin the hyperpolarization process, valves 1b are opened, filling syringe pumps (1c) with liquid. Under computer control and using a National Instruments DAQ card, an polarization transfer NMR pulse sequence is begun (described in detail in another abstract) and a linear actuator (1d) injects the solutions through a mixing tee and into the reactor. The injection takes approximately 1 second per 2.5 ml solution. The polarization transfer sequence is calculated on the fly using previously measured ^1H-^1H and ^1H-heteronuclear scalar couplings for the selected substrate.

The path to the reactor consists of a copper rod (OD=0.75", length=40 cm, 1e) clamped around a copper EDM tube (ID=0.7 mm), which is heated to approximately 115C using kapton surface heaters. The liquid emerges from the tube in a hard stream at approximately 90C and 6.5 m/s. It then enters a reactor (PolyEtherEtherKetone thermoplastsic, 62 ml internal volume, pictured as 2f in the section view fig. 2) which was previously pressurized to 10 bar of parahydrogen and heated using a kapton surface heater to approximately 90C. Temperature control is implemented using solid state relays and the National Instruments DAQ board. We note that both heaters are turned off during the polarization transfer pulse sequence, and we have found no measurable permanent magnetism or RF shielding from either the heaters or the copper rod which might affect the sequence.

The reactor is mounted inside a B_1 (RF) coil (2g), which is surrounded by a B_0 coil (2h) and three layers of mu-metal shielding (2i). All coils have been designed for optimum homogeneity inside the shielding using a freeware numerical package (femm 4.0). B_0 is homogeneous to better than 1 part in 1000 and B_1 to 1 part in 100 over the reaction region. For ease of implementation with inexpensive DAQ hardware, the B_0 field is kept low enough that the ^1H frequency does not exceed 75 kHz. In this regime, we have found excellent linearity and reliability by using a low-cost monolithic, solid-state audio amplifier (2x LM4780, National Semiconductor, bipolar and in parallel) for the required ~2G B_1 field. After approximately 2 seconds of solution injection and 2 additional seconds for hydrogenation, the polarization transfer sequence executes in approximately 200 ms and the hyperpolarized solution is extracted by opening the reactor exhaust and output valves (1j) simultaneously. Residual H_2 pressure pushes the solution, optionally through a filter, into a stopped syringe. The output tube, like all other tubes in the device, is made from 1/32" ID PolyEtherEtherKetone, which does not measurably degrade the hyperpolarization.or introduce dead volume.

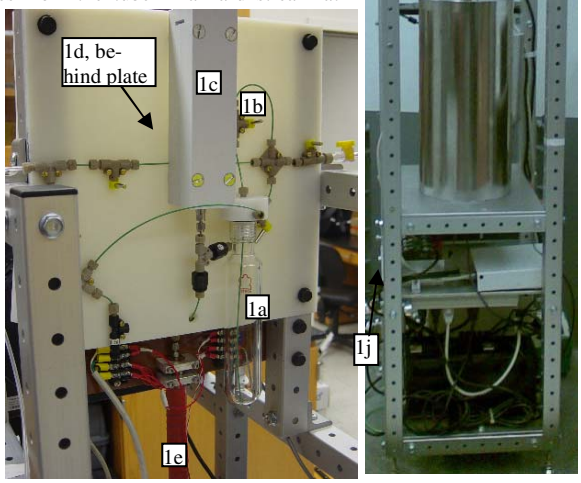

Figure 1: Photograph of PHIP hyperpolarization apparatus showing complete device (right) and blowup of injection region (left). Individual parts are described in the text.

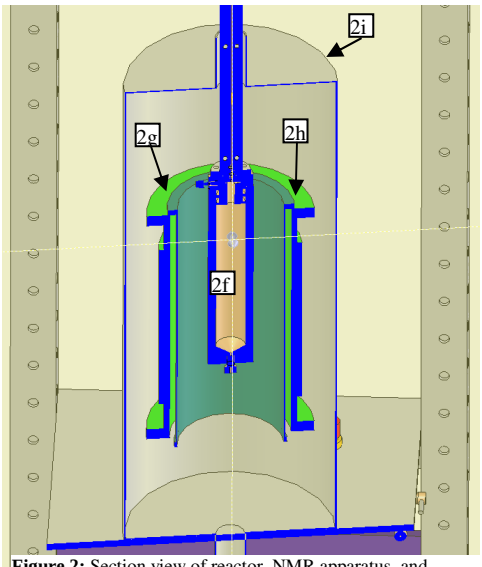

Figure 2: Section view of reactor, NMR apparatus, and magnetic shielding.

Results and Discussion: The achievable level of hyperpolarization using this device is limited by incomplete population of the para state, incomplete hydrogenation in the short time available, T_2-like relaxation during the pulse sequence (para-ortho conversion mediated by the catalyst, or other decay of coherences), imperfect RF pulses, and T_1 relaxation before measurement. Nonetheless, we have found sizeable polarizations in several small molecules (table 1). It is interesting to note that preliminary results suggest that carboxylic acid groups, although possessing favorable T_1 relaxation, may be subject to an unidentified T_2-like relaxation that has thus far limited our achievable polarization.

Hyperpolarized molecule	*Unsaturated precursor*	*P*
Hydroxyethyl propionate	2-hydroxyethyl propionate	32%
Methyl propionate	Methyl acrylate	13%
Methyl isobutyrate	Methyl methacrylate	< 1%
Sodium succinate	Sodium maleate, sodium fumarate, sodium acetylene dicarboxylate (ADC)	~1-2%
Dimethyl succinate	Dimethyl acetylene dicarboxylate	5%
Dimethyl maleate	Dimethyl acethyle dicarboxylate	4%
Sodium maleate	Sodium acetylene dicarboxylate	~1-2%

Table 1: Achieved levels of hyperpolarization (*P*) in several molecules using the device. Quoted values are the fraction of nuclei with respect to initial precursor concentration, and are not corrected for non-unity hydrogenation fraction,or post-hyperpolarization T_1 during the ~30 seconds required for measurement.

Conclusion: We have presented a description of a simple, low-cost device for preparing hyperpolarized samples using Parahydrogen-Induced Polarization.

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