Construction and Use of a Cryostat for Hyperpolarization Based on a 15 cm, 4.6 T Magnet

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Introduction

A wide variety of hyperpolarized ^{13}C-enriched molecules can be produced conveniently using dynamic nuclear polarization (DNP) (1). Multiple variables including the polarizing field, temperature, radical and other conditions influence the level of polarization (2,3). With the production of large volumes of highly polarized imaging agents set as the goal, a flexible polarizer was constructed based on a cryostat (Kadel, USA) inside a conventional 4.6 T/150 mm bore magnet, operating at an ESR frequency of 129 GHz. Unlike other designs with a sample cryostat separate from the magnet cryostat (2), the 15 cm bore allows routing of the microwaves such that the waveguide does not have to be removed before dissolution. The extra space was also used to build a sample cup that is 1.2 cm wide and 1.8 cm tall, allowing volumes as large as 600 ul to be polarized. The high field allows relatively high polarizations to be achieved using radicals other than the trityl radical for samples of sodium [1-^{13}C]pyruvate. Using the preparation detailed below, 13.5 ml of 80 mM [1-^{13}C]pyruvate can be prepared from a sodium pyruvate target.

Methods

A temperature of 1.15 K as estimated by the helium pressure in the cryostat was achieved using a 451 m^3/hr vacuum pump/roots blower. Samples were prepared using a sodium [1-^{13}C]pyruvate concentration of 0.8 M and matrices of 50/50 D_2O/[d_8]glycerol with 33 mM [d_{16},^{15}N]tempone (Sigma Aldrich, Isotec). Samples were polarized at ~100 mW using a microwave source supplied by Virginia Diodes, Inc (Charlottesville, VA). Total irradiation time was 3 hours. Dissolution of the sample was accomplished using a homebuilt wand filled with 4 mL of water heated to 200^o C at 10 bar. Enhancements were measured by observing the ^{13}C spectrum with a 1° pulse and subsequent normalization against a thermally-polarized spectrum acquired with a 90° pulse. C57/bl6 mice with an indwelling jugular catheter were anesthetized with isoflurane according to an IACUC-approved protocol. Mice were studied in a vertical bore 9.4 T microimaging system equipped with a Doty dual-tuned 25 mm ^{1}H-^{13}C probe. ^{1}H Images were acquired using a gradient echo multislice protocol to confirm that the animal was positioned with the liver in the middle of the ^{13}C observe coil. 300 µL of 80 mM [1-^{13}C]pyruvate was injected. A single unlocalized 90°pulse was applied at the end of the injection.

Results

A ^{13}C polarization of 7.4% in [1-^{13}C]pyruvate was achieved using the [d_{16},^{15}N]tempone radical after the 3-hour polarization. A ^{13}C NMR spectrum predominantly from the liver is shown in the Figure 1. The expected resonances from [1-^{13}C]]pyruvate, [1-^{13}C]]alanine and [1-^{13}C]lactate were observed as well as a peak assigned to [1-^{13}C]malate. The cryostat design uses a LN2 outer shield around an inner LHe bath that is surprisingly efficient. Only 10 L of LHe are needed to precool the system and ~10 L is used over a period of 12 hours during vacuum operation. Therefore, total consumption of LHe over 5 days of continuous operation is 60-70 L.

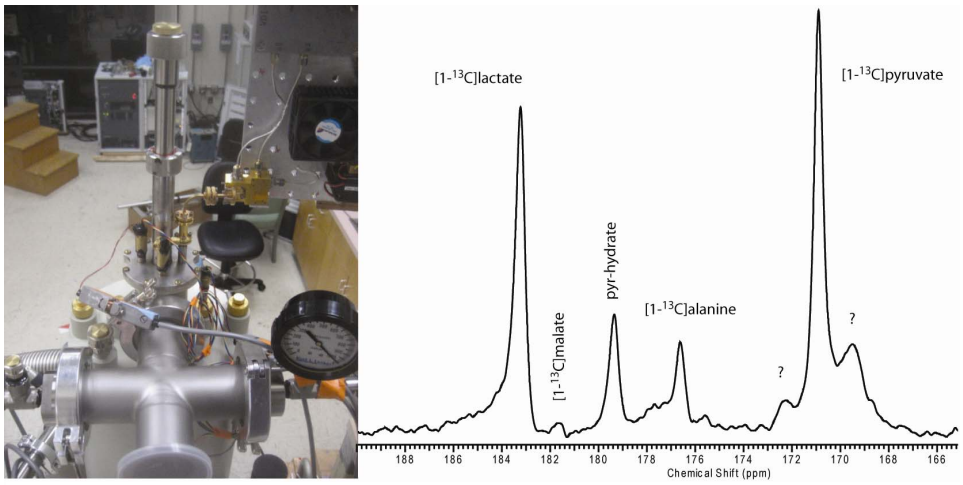

Figure 1. The left panel shows the top of the DNP cryostat with the 90 degree E-plane bend (adjacent to the sample insertion elevator) used for guiding the microwaves from the source to the target at the bottom of the cryostat. The right panel shows an unlocalized ^{13}C NMR spectrum predominantly from the liver of an anesthetized mouse following injection of hyperpolar-ized [1-^{13}C]pyruvate. No bicarbonate was observed in the spectra. The impurity peaks likely arise from di-pyruvate.

Conclusions

The use of a high field (4.6 T) and an isotopically modified tempone free radical allows production of samples with ^{13}C polarization sufficient for experiments in the living mouse. The total cost of the system, neglecting the magnet was less than $100,000 including the microwave source and the vacuum pump. Polarizations higher than those reported here can be expected once the dissolution process and sample delivery is optimized.

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