

A Mobile DNP Polarizer for Clinical Applications

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Introduction

The application of ¹³C (or other low γ nuclei) NMR spectroscopy and imaging for clinical diagnosis has been constrained by the extremely long imaging and spectroscopy acquisition times that are required to obtain high SNR under physiological conditions (low natural abundance of ¹³C, low concentration of ¹³C-compounds, physiological temperature etc.). However, this obstacle could be overcome by in vitro hyperpolarization of a ¹³C containing molecule with long spin lattice relaxation time via DNP (dynamic nuclear polarization) or PHIP (parahydrogen induced polarization) and subsequent injection into the animal or patient of investigation. One major issue of this approach is the limited lifetime of the hyperpolarized state thereby restricting the in vivo application and detection of the hyperpolarized molecules to roughly 3 times T₁. This problem is even more pronounced if the hyperpolarization process could not take place in the vicinity of the used MR tomograph due to safety restrictions or space limitation like it is often the case in clinical MR facilities. Therefore, we propose the development of a mobile DNP polarizer based on a Halbach magnet operating at an intermediate field strength of 0.03-0.3 T. The use of a mobile permanent magnet design enables us to minimize the transport time from the hyperpolarization site to the MR tomograph resulting in an efficient use of the non-equilibrium magnetization regardless which scanner of the clinic has to be used. Moreover, the Overhauser effect at this intermediate field strength should be more efficient compared to high magnetic fields and also the penetration depth of microwave at this EPR frequencies (2-9 GHz) are sufficient to irradiate large sample volumes [1, 2].

Material and Methods

The employed Halbach magnet consists of three nested rings of permanent magnets in Halbach arrangement which can be rotated with respect to each other by the use of stepper motors thus enabling an accurate adjustment of the desired field strength [3]. The weight of the magnet is 90 kg including the stepper motors and control electronics and it can be transported on a table sized two-level carriage together with the microwave source (photograph in Fig. 1). For the DNP experiments the field strength of the magnet system was adjusted to 0.3 T, corresponding to electron and ¹H Larmor frequencies of 8.41 GHz and 12.77 MHz, respectively. For EPR irradiation and NMR detection a Bruker (Karlsruhe, Germany) probehead originally designed for Electron Nuclear Double Resonance (ENDOR) was used. Three different radicals were used for the DNP experiments: TAM (Tris{8-carboxyl-2,2,6,6-tetra[2-(1-hydroxyethyl)]-benzo(1,2-d:4,5-d)bis(1,3)dithiole-4-yl}methyl sodium salt), TEMPOL (4-Hydroxy-2,2,6,6-tetramethyl-piperidine-1-oxyl, Sigma, Germany) and a spin-labeled cationic polyelectrolyte poly(DADMAC) (a copolymer of poly(diallyldimethylammonium chloride) with 4% nitroxide radical-bearing monomers), which has an average molecular mass of M_w=490,000. Each of the radicals was dissolved in a 55:45 (volume %) glycerol:water (deionized) mixture to give a radical concentration of 2 mmol (TAM concentration: 15 mmol).

Results

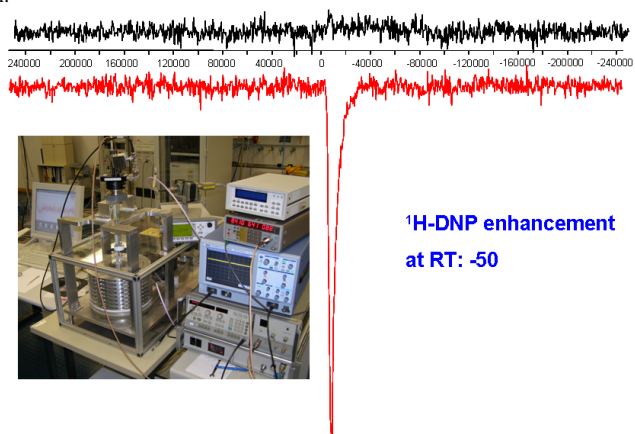
As an example for the performance of our mobile apparatus figure 1 shows the DNP ¹H NMR spectrum of poly(DADMAC) irradiated with 17 W microwave power, which is enhanced by a factor of ~50 compared to the reference. For the other radicals we measured lower enhancement factors, -36 (@ 17 W mw power) and -12 (@ 12 W mw power) for TEMPOL and TAM, respectively. To demonstrate the reliability of our experimental setup we measured the DNP enhancements for TAM and TEMPOL in dependence of the microwave irradiation frequency and found good agreement with the corresponding EPR spectra. In order to evaluate the maximum DNP enhancements which can be obtained with the different radicals at our experimental conditions, we measured the DNP enhancement factors for each radical at different microwave powers. By plotting the reciprocal Overhauser enhancement 1/(1-enhancement factor) against the reciprocal EPR power level 1/P the maximum achievable DNP enhancement factors can be extrapolated [2, 5]. Our data show the expected linear relation and the maximum enhancement factors obtained by this method are: -80 for Poly(DADMAC), -60 for TEMPOL and -27 for the TAM radical.

Fig. 1:

¹H-NMR spectra at room temperature of a 55:45 glycerol:water mixture doped with 2 mmol Tempol radicals which are covalently bound to a polyelectrolyte.

Black: reference spectrum without microwave irradiation. Red: DNP enhanced spectrum with 17 W CW microwave irradiation. The enhancement factor compared to the reference is -50.

The photograph shows the mobile polarizer which consists of the Halbach magnet, ENDOR probehead and microwave source with amplifier.



Discussion

Our results demonstrate that we are able to perform reliable DNP experiments in this mobile apparatus and to obtain reasonably high ¹H-DNP enhancements. One striking result concerning the choice of radicals is the fact that the use of solutions of nitroxide spin-labeled polyelectrolyte at incident microwave powers greater than 12W gives up to 1.5 times increased DNP enhancements as compared to free TEMPOL. This might be due to the broad range of intramolecular and intermolecular radical-radical distances and hence of dipolar couplings between electron spins that can be expected because of the statistical nature of the labeling and the manifold of conformations that a polyelectrolyte chain in solution may adopt [6]. In this respect, the spin-labeled poly(DADMAC) can be seen as a "broad-band" polarizing agent that might also be suitable for an efficient hyperpolarization of ¹³C. Although poly(DADMAC) itself has been shown to be toxic towards aquatic organisms [7] many natural water-soluble polyelectrolytes could be spin-labeled and used as non-toxic polarizing agents (e.g. polysaccharides, or chitosan derivatives) in our mobile DNP polarizer. Cooling of the sample will be the next step to significantly enhance the DNP efficiency.

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