^{19}F-MRI using Hyperpolarized Substrates and Field Cycling

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INTRODUCTION

Standard MRI contrast agents usually contain paramagnetic substances such as gadolinium complexes. Therefore, the image intensity is modified passively by decreased relaxation times. Another approach is the development of active contrast agents that generate the signal by themselves. To acquire a background-free signal, MR-sensitive nuclei apart from protons can be used assumed that the biological abundance is very low. As the MR-sensitivity is reduced proportional to γ^3 as compared to ^{1}H-experiments the high sensitivity of ^{19}F (83% of ^{1}H) and the marginal abundance (4µM) in body tissues qualifies fluorinated substrates as one of the major candidates as reporter molecules for MRI and MRS investigations. Additionally, many pharmaceuticals contain ^{19}F allowing to monitor their pharmacokinetics and metabolism as well as to depict anatomy and physiology [1] However, due to the limited in vivo substrate concentration and the resulting small spin densities ^{19}F signals often remain weak. Increasing the signal-to-noise ratio (SNR) using higher B_0 fields has almost reached technical limits. Here, hyperpolarization techniques provide alternative ways for signal enhancement apart from thermal polarization. We applied the ParaHydrogen Induced Polarization method (PHIP) [2] and transferred spin polarization from para-hydrogen to ^{19}F, which is documented for a class of closely related aromatic systems [3]. The efficiency of the polarization transfer was further improved by field cycling (FC) procedure [4] leading to ^{19}F MRI with reliable SNR. This enabled hyperpolarized ^{19}F MRI as the pre-requisite to monitor spatially resolved high-sensitivity biomarkers.

THEORY

One technique to create non-Boltzmann hyperpolarization is the PHIP-effect [2]. Parahydrogen represents the nuclear singlet state of H_2 with an antisymmetric spin configuration. As this spin isomer is transferred into an AX spin system only spin states with corresponding symmetry are populated provided that spin correlation is conserved during this process. This process is initialized by a homogeneous hydrogenation of an unsaturated substrate using an appropriate catalyst. The achieved selective population of product states causes a strong deviation from Boltzmann statistics and leads to enhanced anti-phase signal patterns in the NMR spectrum. This generated hyperpolarization can also be transferred to other NMR active nuclei in the same substrate such as other ^{1}H and or to hetero nuclei such as ^{13}C or ^{19}F [3].

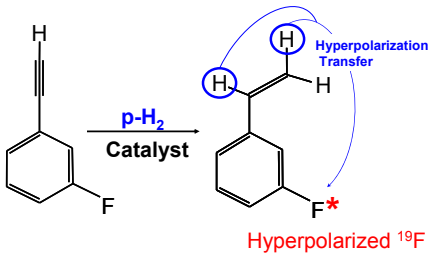

Fig. 1: Hydrogenation reaction to hyperpolarized product and polarization transfer to ^{19}F.

METHODS

We choose 3-fluorostyrene (I) generated from 3-fluorophenylacetylene as an exploratory target because a considerable signal enhancement was already reported [3]. Pressurized (p = 3 bar) *in situ* parahydrogenation of 3-fluorophenylacetylene (1.5 mmol) dissolved in 2.5 ml acetone-d6 introduces the required hyperpolarization into the hydrogenation product (fig. 1). Reaction is driven by shaking for 10 s followed by spectra or image detection after delay of 10 seconds with or without FC. FC is realized by a sudden drop from the initial field (earth field) to a very low field (0.7 µT) followed by an adiabatic re-magnetization step. Data were acquired using a 4.7 T animal system (Bruker BioSpec) with a Tx/Rx coil (LP, Doty Scientific DSI-1139). Spectra were detected after single pulse excitation (sinc-shaped pulse, BW 24.4 kHz dur. 0.82 ms, FA 90°). Images were acquired with a FLASH sequence (FA 5°, TR/TE 10/3.8 ms, 1.25x1.25x15 mm^3, 10 averages).

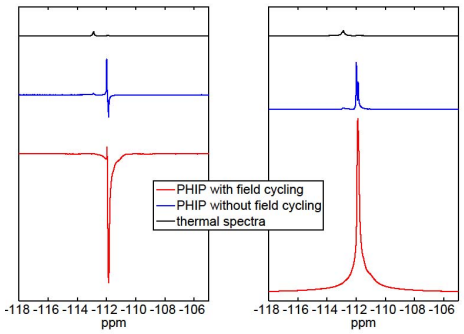

Fig. 2: Signal enhancement by PHIP an FC. Left: absorption; right: magnitude.

RESULTS

Figure 2 shows the effect of FC in comparison to the standard PHIP-experiment. The reference for enhancement calculation is the thermal spectrum (black). The PHIP spectrum of the product (blue) shows antiphase patterns and a signal enhancement of about 24, determined from the magnitude spectra. The spectrum obtained with field cycling (fig. 2, red), shows an enhancement of 61 clearly demonstrating the benefit of applying FC. After hydrogenation the population of the resulting eigenstates is determined by the scalar couplings of the spin-system. At 0.7 µT the transferred protons and the examined ^{19}F nucleus become strongly coupled and thus hyperpolarization can be transferred more efficient. Due to the additional enhancement and the inphase resonances, faster imaging with sufficient SNR is feasible (fig. 3).

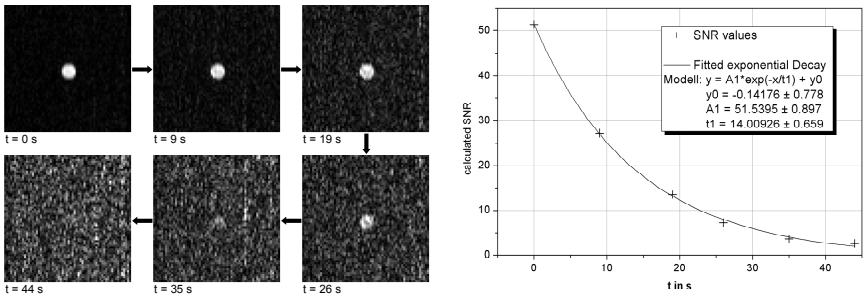

Fig. 3: 19F-Imaging with field cycling: SNR over delay time t shows the temporal decay of hyperpolarization with an exponential character.

DISCUSSION & CONCLUSION

The smaller enhancement factors compared to [3] result from wider stray field of the animal scanner, which is passed before detection. Therefore, the parahydrogenation partly continues under higher field conditions leading to more PASADENA-like signal patterns and reduced enhancement factors. Additional the use of coil-adapted larger probe volumes leads to decreased reaction rates. Nevertheless, the improvement due to FC is clearly demonstrated within this consistent series. Altogether the MR-images and spectra prove that new highly-sensitive contrast agents and biomarkers based on ^{19}F can be generated via PHIP. Beside a strong signal enhancement hyperpolarization should allow imaging at even lower magnetic field strength as this non-thermal polarization is not a result of Zeeman-splitting. This offers the opportunity for an application of this method using all kinds of clinical MR-scanners even the less modern systems.

REFERENCES

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