Single scan multi-nuclear NMR at earth magnetic field using para-hydrogen induced polarization (PHIP-EF-NMR)

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Introduction

Lack of sensitivity is the hallmark problem in MR (NMR, MRI and MRS). To increase MR sensitivity commonly the main magnetic field strength $B_0$ is increased leading to a more favorable Boltzmann distribution and corresponding sensitivity increase. Alternatively hyperpolarization as a tool to enhance MR sensitivity, especially DNP, has attracted an increasing interest over the last years. In principle, hyperpolarization methods can increase nuclear polarization to the order of unity, which corresponds to a sensitivity enhancement of several orders of magnitude with respect to standard MR techniques based on thermal polarization. In contrast to other hyperpolarization methods like DNP, PHIP can provide high degrees of polarization within seconds at moderate experimental conditions and at a relatively low cost per sample. The aim of this study was to develop a novel application of PHIP: the acquisition of single shot multi nuclear NMR spectra in the earth field of compounds at millimolar concentration.

Material and methods

As test compound we used 4,4,4-trifluoro but-2ynoate (I), which was dissolved in deuterated acetone and degassed. A separate stock solution was made with [Rh-(cyclooctadiene)dyphenylphosphanylbutane][BF₄] catalyst also in degassed deuterated acetone. After activation and subsequent degassing of the catalyst the substrate and catalyst solutions were mixed resulting in a total volume of 310 µl containing 9 mM of the substrate and 15 mM of the catalyst. This substrate-catalyst solution was inserted in the isocentre of a homebuilt earth field (EF) NMR setup, where it was hydrogenated (reaction 1) under 2 bar 80% enriched para-hydrogen to form 4,4,4-trifluoro but-2enoate (II). The NMR setup allowed for the external earth field to be compensated or enhanced during the field cycling experiment. The $B_0$ coil is encompassed by a Helmholtz pair exactly perpendicular to the earth magnetic field (ca. 67°) used for $B_0$ compensation or enhancement. The hydrogenation was performed at an enhanced magnetic field of 150 µT after which the field was instantaneously (<500 µs) reduced to a strength of 2 µT by reversing the current through the Helmholtz pair. The field was then adiabatically restored to earth magnetic field (50 µT) by lowering the current through the Helmholtz pair to 0 A. This was immediately followed by a single non-selective RF pulse. This field cycling was performed in a different field as described earlier.

Results

After 6 seconds the hydrogenation reaction was ended by releasing the pH₂ gas from the reactor. This resulted in close to full conversion (95%) of the substrate into the product as was established by conventional high-field $^1$H NMR following the EF-NMR experiment. The small frequency separation between $^1$H and $^{19}$F resonances, ca. 120 Hz at 50 µT allows them to be detected simultaneously (Fig. 1).

The multiplet structure of $^1$H and $^{19}$F signals results from H-F heteronuclear couplings ($J_{HF} = 8.4$ Hz, $J_{HF} = 0.8$ Hz). The SNR was estimated to be at least 100:1 (RMSD noise of the spectrum was ca. 0.03 µV / kHz). A reference spectrum of 3.9 ml H₂O was acquired using a repetitive ($n = 32$) 5 second 15 mT pre-polarization of the sample. By comparing the integrals of the $^1$H multiplets of II with the singlet of the water reference the polarization of II following para-hydrogenation and diabatic-adiabatic field cycling was estimated to be approximately 3% (8-9 orders of magnitude times Boltzmann at earth field, still 2-3 orders of magnitude times Boltzmann at 14 T).

Discussion

Numerical simulations of the diabatic-adiabatic field cycling experiment on molecule II indicate a maximum attainable $^{19}$F and $^1$H polarization of ca. 60%. Optimization of the described method (e.g. shielding of the EF-NMR equipment, optimization of the coil fill factor) should provide a further 1-2 orders of magnitude increase in MR sensitivity.

Conclusion

The polarization enhancement obtained using para-hydrogenation with subsequent diabatic-adiabatic field cycling allows for single scan acquisition of a multi nuclear NMR spectrum in the earth field of a sub-millilitre (310 µl) sample at millimolar (9 mM) concentration. This illustrates the enormous sensitivity gain achievable by this technique. At the polarization levels obtained with this method fast high resolution earth field MR imaging should be technically feasible.

References