

PHIP hyperpolarization of linear and branched fluorinated alkanes as well as their interaction with cyclodextrins

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Purpose

The application of perfluorinated molecules as contrast agents for ¹⁹F MRI is a well studied field.^[1] In 2013, the first hyperpolarization of semifluorinated octene and octane derivatives was reported with some remarkable findings. It was demonstrated that the polarization, which had been generated by parahydrogen (PHIP)^[2], was transferred from protons over the chain to the end-standing CF₃-group. The achieved signal enhancement allowed ¹⁹F MRI.^[3] In the current study, on the one hand the generation of hyperpolarized 1H,1H,1H,2H,2H-perfluorohexane, 1H,1H,1H,2H,2H-perfluorooctane, 1H,1H,1H,2H,2H-perfluorodecane and perfluoro-(4-methylpentane) was compared and on the other hand the transfer of different linear and branched semifluorinated lipophilic substrates from organic phase to water, respectively D₂O, was investigated.

Methods

Four semifluorinated alkenes were chosen for hydrogenation reactions with 50 % enriched parahydrogen (6 bar pressure) in different vented solvents and in presence of Rh(I) based catalysts. The hyperpolarization of 1H,1H,1H,2H,2H-perfluorohexane, 1H,1H,1H,2H,2H-perfluorooctane, 1H,1H,1H,2H,2H-perfluorodecane and perfluoro-(4-methylpentane) was realized by hydrogenation in earth field (ALTADENA) and subsequent transport into high field (7T). ¹H NMR spectra were detected by using a single pulse experiment with a 45° excitation pulse on a Bruker wide bore 300 MHz spectrometer. In contrast to this, the ¹⁹F NMR spectra were measured under same reaction conditions, but using a 90° excitation pulse. The obtained signal enhancements (SEs) were calculated from signal-to-noise ratios of the thermal and the hyperpolarized spectra.

For transport of the named semifluorinated substrates and additionally (perfluorohexyl)-acetylene, α - respectively β -cyclodextrin was added to an aqueous solution. The building of a host-guest complex was studied by ¹H- and ¹⁹F- and NOE-NMR experiments. Followed hydrogenation investigations in D₂O were performed after complexation of the lipophilic fluorinated compounds with the used cyclodextrin derivative.

Results

The ¹H- and ¹⁹F-PHIP NMR spectra, measured directly after hydrogenation, in all cases show polarized signals. As it could be observed from the spectra in figure 1, the polarization was transferred from the protons, which arise from added parahydrogen, to the CF₃ groups in the molecules. The signal assignment was achieved from 2D ¹⁹F COSY spectra.

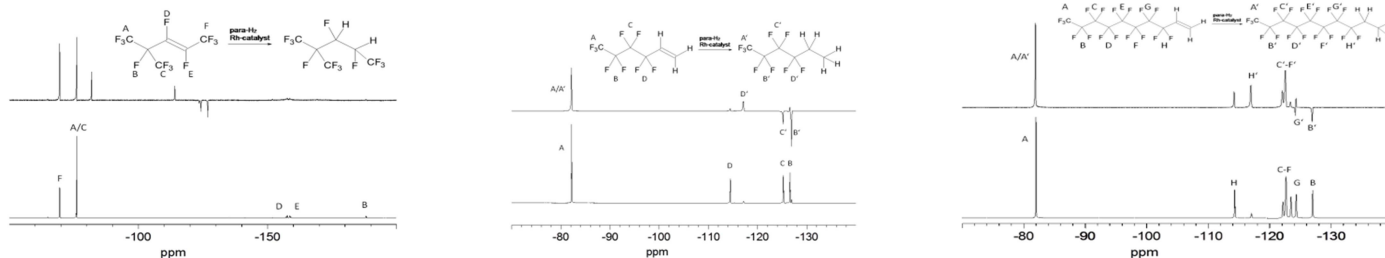


Figure 1: ¹⁹F NMR spectra measured directly after hydrogenation (using parahydrogen) (above) and the corresponding spectra in thermal equilibrium (below): (2E)-2-acetamido-3-(2,5-difluorophenyl)-acrylic acid (above), hyperpolarized fluorinated phenylalanine derivative (middle) and its spectrum in thermal equilibrium after hydrogenation (below).

The influence of the presence of a small amount of cyclodextrin concerning the chemical shifts can be observed in the here exemplarily shown ¹⁹F spectra in figure 2. ¹⁹F signals of the non-complexed (perfluorohexyl)-acetylene are originate from the insoluble phase on the bottom of the NMR tube (yellow phase in the scheme). After addition of cyclodextrin (here: β -cyclodextrin), smaller signals are observable (red arrows in the spectrum below).

By separation and measurement of the upper phase, the complex of semifluorinated substrate and cyclodextrin could be identified. This host-guest interaction enables a new way for hyperpolarization of lipophilic substrates in water as could be shown by hydrogenation reactions using water-soluble Rh(I) complexes.

Discussion

The hyperpolarization of different linear and branched fluorinated substrates has shown that the chain length has no important influence for the polarization transfer from protons to the end-standing CF₃ group. The measured ¹⁹F¹⁹F coupling constants will enable a theoretical description of this long distance polarization transfer. Additionally, the high sensitivity of the ¹⁹F chemical shifts enables a fast control of interaction with other substrates, like here described the building of a host-guest complex with cyclodextrin. This relatively strong intermolecular interaction allows the transport from the organic solvent to an aqueous solution and enabled the first hydrogenation of the lipophilic substrates in D₂O.

Conclusion

The presented measurements and results open a new way in the field of the hyperpolarization of lipophilic substrates for application in aqueous solution. These aspects are very important in analytical MR studies of biological systems.

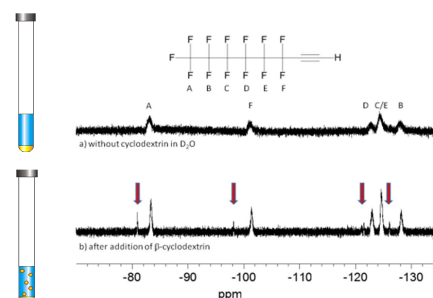


Figure 2: ¹⁹F NMR spectra measured in D₂O show the interaction between the fluorinated substrate and β -cyclodextrin, here, e.g., (perfluorohexyl)-acetylene.

References

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