

Synthesis of hyperpolarized Ethanol via PHIP

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Introduction

In the last few years Parahydrogen Induced Polarization (PHIP) has been developed as a method for metabolic studies in Magnetic Resonance.[1] But until now, it was limited to unsaturated organic molecules, which have no hydroxyl group next to double or triple bonds because of keto-enol tautomerism. Our study presents the first time an approach to generate hyperpolarized ethanol which is probably the mostly used psychoactive drug. It is highly relevant because it acts on brain metabolism through multiple chemical interactions.

To avoid the keto-enol tautomerism between ethanal and acetaldehyde (fig. 1a), vinyl acetate was used as a precursor (fig. 1b). After hydrogenation of vinyl acetate with parahydrogen to ethyl acetate, a hydrolysis with sodium hydroxide leads to hyperpolarized ethanol and acetic acid (fig. 1b). It is the first time that PHIP is observed after hydrolysis in the second chemical reactions. The approach of using another reaction step for phase extraction of a hyperpolarized target molecule was recently proposed by Aime.[2]

Methods

The hydrogenation of vinyl acetate was realized with about 50 % enriched parahydrogen in vented D₂O in presence of the water soluble 1,4-bis-[(phenyl-3-propanesulfonate)phosphine]butane-(norbornadiene)-rhodium(I) tetrafluoroborate catalyst. Directly after hydrogenation, a sodium hydroxide solution was added and ¹H-NMR-spectra were detected using a single pulse experiment with a 45° excitation pulse on a Bruker WB300 spectrometer.

The obtained signal enhancement (SE) was calculated from signal-to-noise ratios of the thermal and the hyperpolarized spectra.

Results and Discussion

The typical antiphase pattern of CH₂-group at 3.8 ppm and the CH₃-group at 1.3 ppm of ethanol (fig. 2a) that appear directly after the hydrolysis step, demonstrate the successful polarization with the proposed method. For calculation of SE a thermal spectrum was recorded after equilibration (fig. 2b). Concerted with the slow experimental accomplishment of manual reactant injection, shaking, and transport into the detection field, the observed signal enhancement is rather low i.e. SE(CH₂) = 4 and SE(CH₃) = 1. The spectra also show a complete reaction. Both spectra show signals of ethanol, H₂O and acetic acid, but no signals of residual starting material or acetaldehyde. Considering signal reduction due to longitudinal relaxation during the several experimental steps allows for estimation of the minimum achievable SE. Here we obtained a value of SE ≈ 45 by back calculation using measured T₁ times of the compounds.

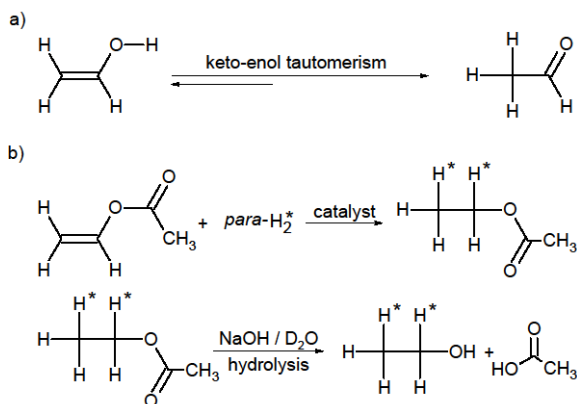


Fig. 1: a) Vinyl alcohol is tautomerized to stable acetaldehyde, which is not PHIP active b) PHIP hyperpolarization to ethanol is realized by intermediate reactions.

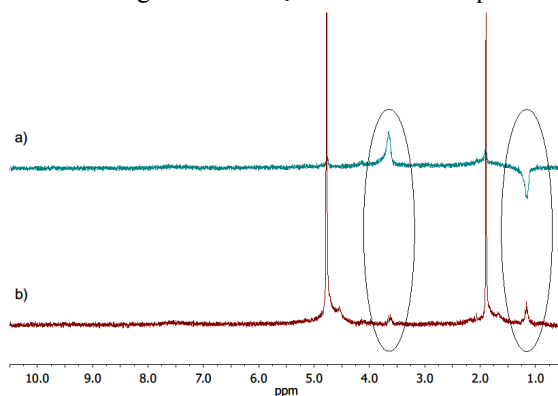


Fig. 2: a) ¹H-NMR-spectrum of PHIP hyperpolarized ethanol and b) thermal spectrum recorded after equilibration of the same sample.

Conclusion

This study shows first NMR-spectra of hyperpolarized ethanol. Additionally we presented a pathway to apply PHIP on formerly not accessible target molecules. The presented pathway shows an option to extend PHIP on biological relevant compounds, such as serine, malate, adrenaline, glucose, or related structures.

References

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- [2] F. Reineri et al., Angew Chem Int Ed Engl, **2011**, 50,7350-7353