Hyperpolarization of biologically relevant compounds which are important in the GABA metabolism

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Purpose

GABA is one of the most important inhibitory neurotransmitter in the central nervous system. Knowledge of changes in the GABA metabolism can help to understand different disease pattern. The ParaHydrogen Induced Polarisation (PHIP)[1] can be used to enhance MR signals for MRS and MRI examinations. The standard strategy to generate PHIP polarized substances is to transfer parahydrogen to an unsaturated precursor by a homogeneous hydrogenation. This demands the presence of a catalyst. A multitude of biological relevant molecules has free amino (-NH_2) and carboxyl groups (-COOH) which can interact with the catalytic center and inhibit the activity. Here, we described a new method to hydrogenate unsaturated organic amines in aqueous solution. Therefore, γ-acetylenic-GABA, trans-4-aminocrononic acid and D/L-propargylglycine were selected as precursor compounds to generate hyperpolarized vigabatrin GABA and allylglycine (Inhibitor of glutamate decarboxylase).

Methods

The hydrogenation of the unsaturated organic amins was realized with about 50 % enriched parahydrogen in vented, acidulated D_2O in presence of a water soluble Rh(I)-catalyst (fig.1). Therefore, two different Rh-catalysts (Chlorotris[(3,3′,3″-phosphinidynetris-(benzene-sulfonato)]-rhodium(I) nonasodium salt hydrate and [1,4-Bis(phenyl-3-propansulfonat)phosphino-butan](2,5-norborna-diene)-rhodium(I)tetrafluoroborate) were tested. Directly after hydrogenation the ^{1}H-NMR-spectrum was detected using a single pulse experiment with a 45°-excitation pulse on a Bruker WB300 spectrometer. The obtained signal enhancement (SE) of hyperpolarized substrate was calculated from signal-to-noise ratios of the thermal and the hyperpolarized spectra.

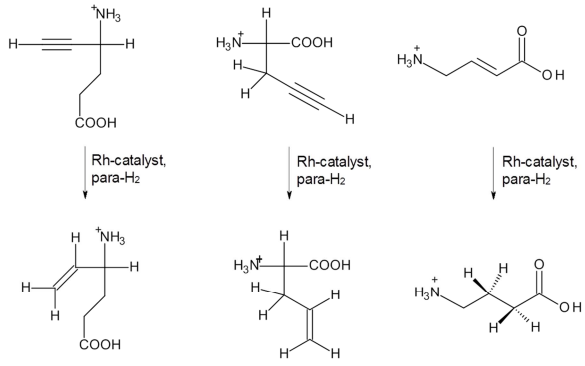

Figure 1: Illustration of the chosen substrates and the corresponding hyperpolarized products.

Results

Two water-soluble Rh-catalysts were tested for hydrogenation of three unsaturated amins: γ-acetylenic-GABA, trans-4-aminocrononic acid and D/L-propargylglycine in acidulated D_2O. Figure 2 shows as an example the ^{1}H-PHIP-NMR spectra of hyperpolarized GABA and D/L-allylglycine detected at 7T. The small antiphase signals prove the successful reaction. The desired target molecules can be simply deprotonated by neutralization of the reaction solution. Furthermore the study show that the factor of the signal enhancements depend on the pH-value (fig. 3) and the used catalyst.

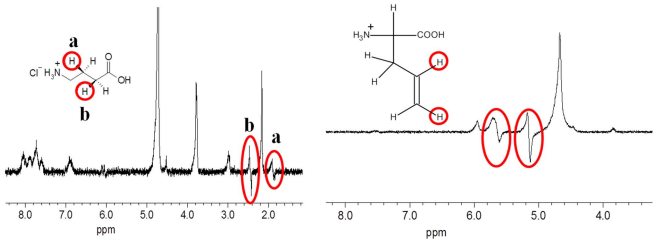

Figure 2: ^{1}H-NMR-spectra detected from hydrogenation of trans-aminocrotonic acid (left) and D/L-propargylglycine (right) in D_2O in the presence of HCl. The spectrum was acquired at 7Tesla in a single pulse experiment.

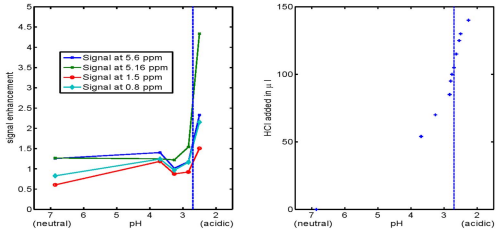

Figure 3: The optimum pH-value for hydrogenation was determined by titration.

Discussion

First hyperpolarization of amino carboxylic acids in aqueous solution via PHIP was presented in the ^{1}H-NMR spectra in fig.2. This was demonstrated for hyperpolarized GABA and two other biochemical relevant amines which play an important role in GABA metabolism. It was not necessary to use protecting groups. The signal enhancement can be improved by further optimization of reaction conditions. A subsequent transfer of hyperpolarization to ^{13}C would then provide an important reporter molecule for different MRI/MRS investigations. This new approach opens the way to hyperpolarize further biologically relevant molecules which were inaccessible to PHIP until now, like unprotected amino acids and peptides.

References

[1] Bowers CR, Weitekamp D, *Phys. Rev. Lett.* 57, 2645, **1986**; Natterer J, Bargon J, *Prog. Nucl. Mag. Res. Sp.* 31, 293-315, **1997**.