PHIP of valproic acid and related structures

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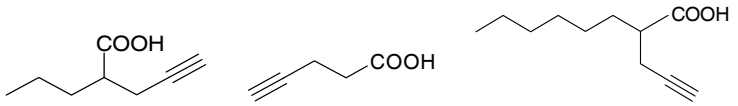
Purpose

Since the last few years Parahydrogen Induced Polarization (PHIP) is increasingly used as a promising tool for medical/biological applications in magnetic resonance as it can increase MR-sensitivity by orders of magnitude with low technical effort.[1] So far only a few number of molecules acting as metabolic sensors were already hyperpolarized with PHIP, but the direct hyperpolarization of drugs used in the treatment of neurological disorders was not achieved so far. In this study the feasibility of applying PHIP to valproate (VPA) and structurally related molecules with different side chains was examined. Although VPA's anticonvulsive activity is utilized in epilepsy treatment, the dose-effect-relation is not consistent.[2] Therefore, a MR-based monitoring of distribution or even metabolism in the brain enabled by hyperpolarized VPA would yield important therapeutic information.

Methods

2-propyl-4-pentynoic acid (PPA) was examined as a precursor, to achieve hyperpolarized VPA via hydrogenation with para-H_2 (twice). As this substrate only is available in very small amounts, two structurally related substances were investigated previously. All tested precursors possess the same basic structure of 4-pentynoic acid (PA) (figure 1). Here, the VPA precursor structurally ranges between PA and 2-hexyl-4-pentynoic acid (HPA), which only differ due to a side chain in α-position. Hydrogenations were performed using a Rh-catalyst under 6 bar para-H_2 (50%) by 10 s sample shaking. Spectra were recorded in a single scan (π/4-pulse) on a Bruker WB 300 (7T); images were acquired on a BioSpec 47/20 animal scanner (4.7T).



2-propyl-4-pentynoic acid 4-pentynoic acid 2-hexyl-4-pentynoic acid

Figure 1: Chemical structures of the precursors.

Results and Discussion

Figure 2 shows ^{1}H-spectra after parahydrogenation of a) PA to 4-pentenoic acid, c) HPA to and 2-hexyl-4-pentenoic acid, d) PPA to 2-propyl-4-pentenoic acid and the subsequent hydrogenation step to e) VPA. The PHIP spectra acquired by hydrogenation from triple to double bond show signal enhancements for the terminal added ^{1}H between 268 and 60 compared to the Boltzmann-spectra (below). The enhanced signal of 4-pentenoic acid was utilized in a ^{1}H-FLASH experiment (b) (α=15°, TR=10.5ms, t_{aq}=336ms, 0.625x0.625x5mm^3, zero filling 2, FOV=8x4 cm) resulting in increased image quality. The successful PHIP of VPA, which was the focus of this study, is proved by the typical signal patterns of multiplet polarizations (0.9ppm & 1.35ppm) in fig. 2e). Even if no remarkable enhancement was achieved, the polarization obviously was generated by transfer of p-H_2. The small signal enhancements are predominantly caused by a much smaller conversion rate of double to single bond which (concerning relaxation) leads to a decrease of the total polarization respectively. Optimized reaction conditions and catalysts or decoupling of singlet and triplet states during hydrogenation, etc. will boost the obtainable enhancements. Another beneficial approach is the transfer of polarization to ^{13}C, which usually possess longer relaxation times and a small natural background. According experiments as well as investigations with different solvents/catalysts were performed, but are not addressed in this abstract.[3]

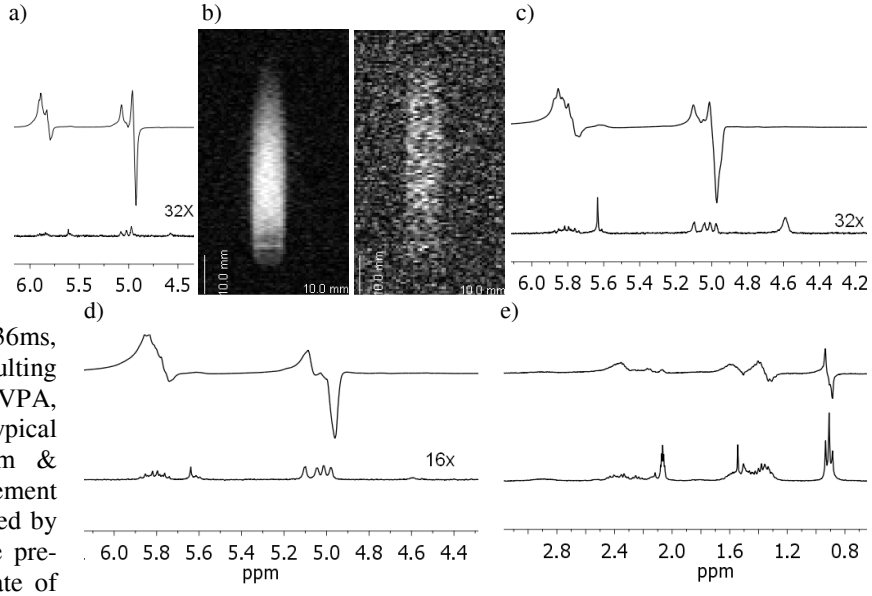


Figure 2: ^{1}H-MR-spectroscopy and imaging experiments

Conclusion

For the first time PHIP of VPA and related structures was demonstrated as well as the integration in preliminary imaging experiments. Concerning larger polarizations due to experimental optimization a wide potential of hyperpolarized VPA for pharmaceutical and medical applications and even for an understanding of the drug mechanism (dose-effect-relation) is predictable.

References: [1] Bhattacharya et al. (2011),*NMR Biomed* 24 (8),1023 [2] Wahabet al. (2012), *Epilepsia* 51(3),154 [3] Lego et al. (2013) submitted to *NMR Biomed*