Hyperpolarizing (1H and 13C) Naturally Occurring Amino Acids to Explore their Function via MRI

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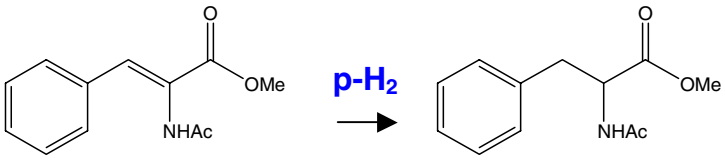
Introduction

L-Phenylalanine (PHE) is an essential amino acid, i.e., it cannot be synthesized within the human but has to be provided via food. The daily requirement is ~ 2.2 grams. Its main metabolic route is hydroxylation to L-tyrosine (TYR) by phenylalanine hydroxylase (PAH). Therefore, PHE is a component of artificial nutrition for parenteral administration (= introduced by way other than the intestines) in mixtures for infusions or injections. Accordingly, TYR is suitable for infusions and is approved for this purpose. Since TYR is thus formed within the body, it is a non-essential amino acid. A deficiency in PAH results in intolerance to the dietary intake of PHE and produces a spectrum of disorders including phenylketonuria (PKU). Without dietary restriction of PHE, most children with PKU develop profound and irreversible mental retardation. The diagnosis of PAH deficiency is based on the detection of an elevated [>120 µmol/l (2mg/dl)] plasma PHE concentration and evidence of normal BH_4 cofactor metabolism. Upon additional hydroxylation through the enzyme tyrosine-3-hydroxylase (tyrosine 3-monoxygenase or TH), PHE is eventually converted into the amino acid dihydroxyphenylalanine (L-DOPA), the starting material for the decarboxylated neurotransmitter L-dopamine (DA) as well as for the hormones L-noradrenaline and L-adrenalin.

Parkinson's Disease is caused by a shortage of DA that is produced in the brain. Without this chemical messenger the signals from the brain do not get through to the spinal chord - thence to the various muscles of the body - and muscular function is impaired. DA is synthesized within nerve cells. Chemically, TYR is converted to L-DOPA and then to DA in a two-step process. The first, rate limiting step is catalysed by TH. The second step is catalysed by aromatic L-DOPA decarboxylase. If in parts of the nervous system that release DA as a neuro-transmitter (dopaminergic neurons) no further metabolism occurs, DA is stored in vesicles in the presynaptic nerve terminals.

Results

We have generated PHE and other amino acids in ^{1}H- and ^{13}C-hyperpolarized form of appropriate precursors via Parahydrogen Induced Polarization (PHIP)[1]. The amino acids can be generated both in their true and false chiral form. This allows studying the different actions of the chiral isomers, which serve as a molecular probe in this case. This special feature renders PHIP-MRI unique among the imaging methods used in medical research.



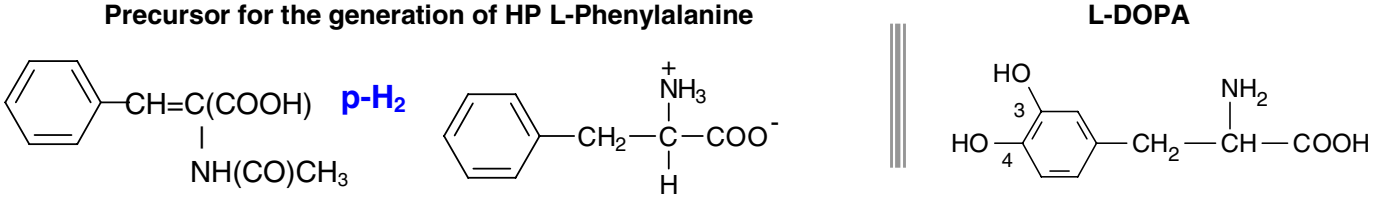
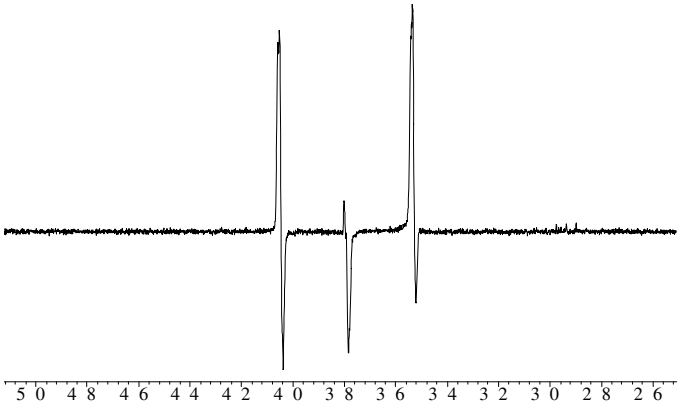


Figure 1: Asymmetric amino acids accessible in hyperpolarized form via PHIP-MRI



Discussion and Conclusions

PHIP is a very sensitive *in situ* method not only assisting to understand the reaction mechanisms of homogeneous hydrogenations, but it can directly provide the above listed drugs in both ^{1}H- and ^{13}C-hyperpolarized form, i.e., magnetically tagged, which will make it possible to follow their fate via MRI, here via PHIP-MRI, supplementing PET.

Figure 2: ^{13}C-PHIP spectrum of the γ-C atom of ^{13}C-hyperpolarized N-acetyl-phenylalanine recorded during the hydrogenation of ^{13}C-enriched 2-phenylacetamido acrylic acid methyl ester yielding a target molecule closely related to PHE and L-DOPA.

References

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