Parahydrogen Induced Polarization of Drug Compounds for MRI

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Introduction

Magnetic Resonance Imaging (MRI) is a modern technique that is of great importance for medical diagnostics. One drawback is the low NMR signal sensitivity, especially when monitoring tissue with low concentration of NMR sensitive nuclei. Besides the use of "passive" contrast agents, which will reduce the relaxation times of neighbor nuclei, one can use "active" contrast agents, which are physiologically relevant substances that have been hyperpolarized by the use of parahydrogen.

PHIP-NMR

The symmetry properties of hydrogen generate two spin isomers, para- and orthohydrogen. As the former is thermodynamically favored, it can be enriched in thermal hydrogen by cooling under the effect of a paramagnetic catalyst. Parahydrogen induced polarization (PHIP) makes use of the parahydrogen symmetry break during homogeneously catalyzed hydrogenation of unsaturated substrates (mostly with cationic Rhodium catalysts), creation of non-equivalent product protons and the deviation from Boltzmann distribution of the populated spin-states.[1-4]

This leads to absorption and emission signals (fig. 1) and a theoretical signal increase of up to 10^5, which is in practice limited by the relaxation time T_1 of the product.

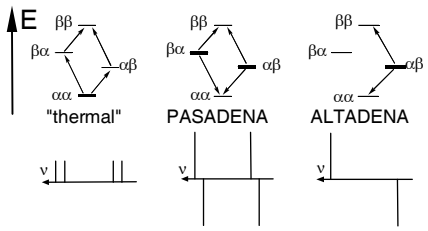

Fig. 1: Population of a 2-spin energy system and spectra in an AX-system (a) transfer of thermal H_2, (b) PASADENA (Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment), (c) ALTADENA (Adiabatic Longitudinal Transport After Dissociation Engenders Nuclear Alignment).

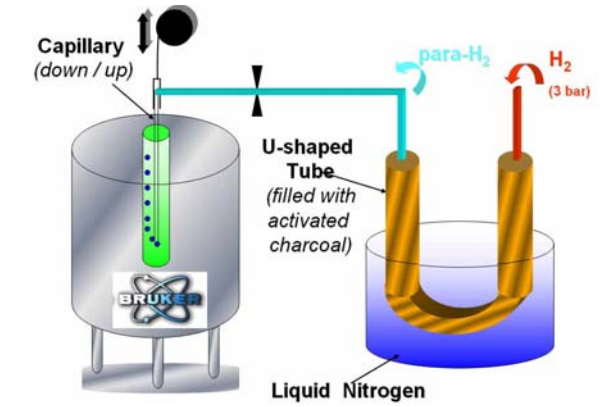

Fig. 2: Setup for NMR spectroscopy of PHIP experiments.

Fig. 2 shows the setup of parahydrogen enrichment, PHIP and NMR spectra measurement of the hyperpolarized product. We distinguish between polarization in high magnetic fields (in the spectrometer, PASADENA condition) and in low magnetic fields (outside the spectrometer, ALTADENA condition). Hydrogenation of hexynes as model compounds led to an increase of about 270 at non-optimized experimental conditions (fig. 3).

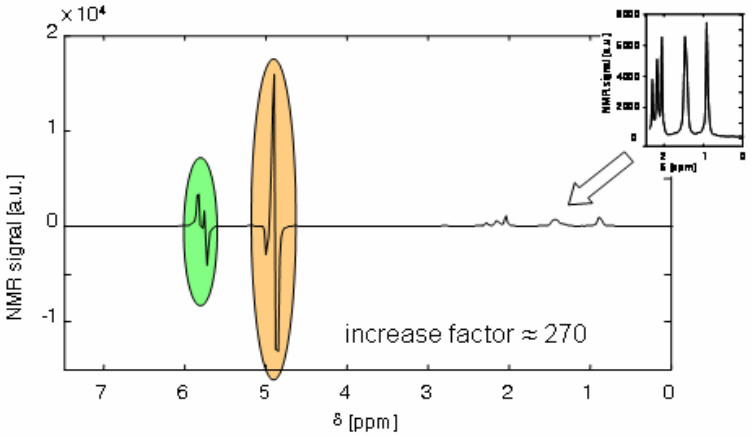

Fig. 3: PHIP-NMR spectrum of 1-hexyne (4 mins. hydrogenation, 1 pulse).

Physiologically active candidates for PHIP

Among the drugs used to treat epilepsy or for injection narcotics, barbiturates like methohexital or phenobarbital are attractive from the MRI and chemical point of view because of their long T_1, the central quaternary carbon atom and the straightforward synthesis of model structures from urea and malonic acid derivatives with unsaturated groups to introduce polarization (fig. 4).[5-7] Transfer of polarization in weak magnetic fields leads to hyperpolarization of hetero-nuclei (^{13}C, ^{15}N, ^{19}F, ^{31}P). Their signals are by 2-4 orders of magnitude more intense than in thermal equilibrium (by Boltzmann occupation numbers). To qualify for MRI purposes, the parahydrogenation has to be carried out at low or zero field to obtain net polarization. After synthesis of differently substituted barbiturates, we will attempt to study the speed of penetrating the blood-brain barrier by injecting the ^{1}H- and ^{13}C-hyperpolarized phenobarbitals into the blood stream.

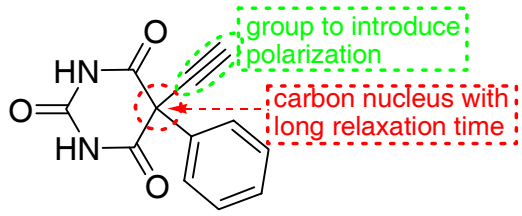

Fig. 4: Precursor for hyperpolarized phenobarbital.

Besides barbiturates, we are currently investigating the effect of hyperpolarization on and the relaxation behavior of hydrogenated phosphoenol pyruvate. Pyruvate is an important glycolysis metabolite.

Literature

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