Direct Generation of 1H- and 13C-Hyperpolarized Molecules for MRI from Parahydrogen via Reversibly Functioning Catalysts

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Introduction

Parahydrogen-Induced Polarization (PHIP) yields strong nuclear spin polarization[1] of protons and heteronuclei including ^{13}C. Because of the relatively long T_1 relaxation times of quarternary carbons especially, ^{13}C-hyperpolarized molecules appear intrinsically more attractive as contrast reagents for MRI than their ^{1}H-hyperpolarized counterparts. Accordingly, ^{13}C-MRI angiography has already been successfully demonstrated for animals[2], whereas ^{1}H-MRI angiography seemed unlikely to be feasible, chiefly due to the short T_1-relaxation times of the protons in the ^{1}H-hyperpolarized molecular probes. Furthermore, since the signal intensity of ^{13}C-MRI – short of any type of hyperpolarization – is typically too weak to yield useful information, there is next to no background to interfere with ^{13}C-hyperpolarized contrast reagents in ^{13}C-MRI. However, a considerable drawback of parahydrogen-enhanced ^{13}C-MRI is the need for a chemically 'unsaturated' precursor for the active contrast reagent to be formed via hydrogenation using parahydrogenation, i.e., compounds containing a double or a triple bond. Frequently this requires custom chemical synthesis of sometimes hard to come by compounds. We have found that quite a few hydrogenation catalysts function reversibly, i.e., they operate both as hydrogenation and as dehydrogenation catalyst. Using them eliminates the need for the special chemically 'unsaturated' precursor compounds, since the catalyst form them *in situ* from the regular target molecules to be hyperpolarized. To demonstrate the principle thereof and the feasibility to hyperpolarize the starting material of a hydrogenation procedure using parahydrogen we have chosen the system styrene / ethylbenzene. One may enter this reversible hydrogenation / dehydrogenation either from styrene or from ethylbenzene (the latter is common in the chemical industry to produce styrene from ethylbenzene on a large scale).

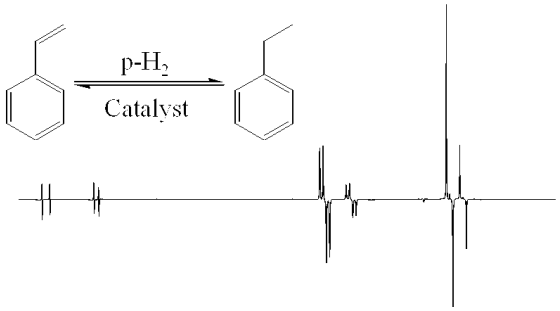

Figure: ^{1}H-PHIP NMR spectrum recorded during the para-hydrogenation of styrene using a reversibly functioning Rh-catalyst. Note that the hydrogenation product ethylbenzene as well as the starting material styrene both exhibit ^{1}H-polarization. As an intermediate of this reaction the catalyst is attached to the hydrogenation product, which causes the 'satellite resonances' of ethylbenzene shifted upfield.

Results

As is evident from the figure, both the starting material and the hydrogenation product display ^{1}H-hyperpolarization. When conducting the reaction at low magnetic fields ^{13}C-hyperpolarization is likewise obtained in both compounds. Quite a few catalysts qualify for this purpose, namely those containing either Rh or Ru as the transition metal. Their cationic nature allows for their subsequent removal using ion exchange resins. The Ru-containing catalyst has been found to dissolve and function in supercritical CO_2, rendering its removal and that of the solvent particularly attractive and easy.

Discussion and Conclusions

We have shown that a variety of hydrogenation catalysts qualify for the reversible hydrogenation / dehydrogenation of a variety of substrates, especially of those containing aromatic moieties, i.e., phenyl groups like in the system styrene / ethylbenzene as outlined here. Quite a few physiologically important molecules contain phenyl groups, e.g. amino acids, drugs, etc. They may conveniently be hyperpolarized using parahydrogen in combination with the appropriate reversible catalyst, which renders the method of parahydrogen-enhanced MRI much more convenient to apply. Furthermore, using orthodeuterium instead of parahydrogen, partially deuterated derivatives of the starting material can conveniently be obtained, in which both the T_1-relaxation times of the remaining protons as well as those of the ^{13}C-nuclei are longer than normally, due to the lower magnetic moment of the deuterons *versus* the protons. The quadrupole moment of the deuterons causes relatively short T_1-times of the deuterons themselves, but that does not interfere with the longer T_1-times of the protons. The energetically favored spin isomer of D_2, orthodeuterium (o-D_2), is accessible via electrolysis of D_2O followed by cooling to cryotemperatures below 77K.

References

[1] Natterer et al. Parahydrogen induced polarization, Prog Nucl Mag Res 1997; 31**:** 293-315

[2] Golman et al. Parahydrogen-induced polarization in imaging: Subsecond C-13 angiography, Mag. Res. Med. 2001; 46: 1-5