New Hyperpolarized Agents from Para-Hydrogenation of ^{13}C-labelled Butynoic Acid and Methylbutynoate

A. Viale[1], D. Santelia[1], F. Reineri[1], R. Napolitano[1], R. Gobetto[1], and S. Aime[1]
[1]Chimica IFM, University of Torino, Torino, TO, Italy

Purpose

To develop new ^{13}C-hyperpolarized probes based on the para-hydrogenation of unsaturated substrates to be used in innovative MRI applications.

Introduction

^{13}C-Hyperpolarized agents are expected to have a large impact in MRI. Two main approaches to ^{13}C-hyperpolarized species have been proposed, namely DNP and para-hydrogenation of unsaturated ^{13}C-labelled substrates.[1] The latter route is simple and cheap but it is limited in terms of the number of available substrates that may be used. In fact several requisites have to be satisfied in order to develop the para-hydrogenation-based approach to a ^{13}C-hyperpolarized agent, namely: i) fast hydrogenation, ii) efficient separation of the hydrogenation product from the catalyst and the organic solvent used in the hydrogenation step, iii) good aqueous solubility of the hydrogenated ^{13}C-labelled product, iv) long T_1 of the ^{13}C nucleus, v) matching of the biodistribution/metabolism/relaxation characteristics of the agent with the MRI acquisition protocol. Till now few systems have been reported and even less tested by MRI. Here we report the study of the para-hydrogenation of two novel water-soluble substrates, suitable as potential ^{13}C-MRI contrast agents.

Methods

The substrates of choice are ^{13}C-carbonyl labelled butynoic acid (1) and its methyl ester (2) . Para-hydrogenation reactions (p-H_2=50%) were carried out in a NMR tube equipped with a Young valve, in acetone-d_6 solutions. Both protonated and perdeuterated derivatives have been considered. Single scan ^{13}C spectra were recorded at 14.1 T. Field cycling (μ-metal shield) has been used in order to obtain an in-phase enhanced ^{13}C signal useful for MR image acquisition. After para-hydrogenation of the deuterated methyl ester of butynoic acid, the catalyst [Rh(COD)(dppb)][BF_4] was removed by means of ion exchange on DOWEX-50WX2-400 resin, and ^{13}C-RARE images were obtained at 7.0 T.

Results and Discussion

Para-hydrogenation of butynoic acid leads to isocrotonic acid in low yield due to the presence of the carboxylate group on the substrate that de-activates the catalyst. Part of the polarization is spread out to the methyl group protons. In fact, the per-deuterated derivative shows an increased polarization transfer at the ^{13}C-carbonyl moiety.

Better results have been obtained with the methylester of butynoic acid. Its hydrogenation reaction is markedly more efficient (85% yield) and gives rise almost quantitatively to the trans-isomer (although in the PHIP spectrum there is evidence for the intermediacy of the cis form). The obtained product is well soluble in water (ca.300mM) and the presence of the methyl ester group contributes to lengthen the relaxation process. Figure 1 shows the ^{1}H and ^{13}C spectra of the para-hydrogenated ^{13}C-enriched per-deuterated butynoic methyl ester recorded after elimination of the Rh catalyst (^{13}C enhancement: 670). Images of this ^{13}C signal have been obtained at 7.0 T by using the single shot RARE sequence.

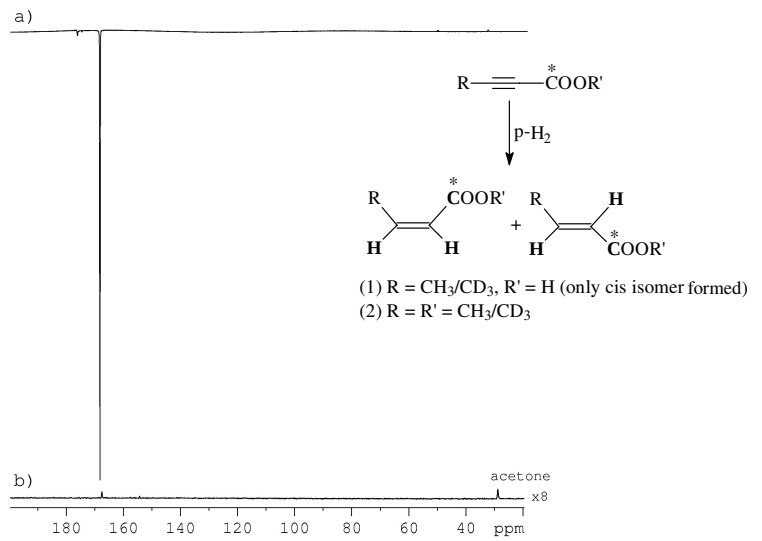

Fig. 1: ^{13}C NMR single scan spectra of hyperpolarized deuterated ^{13}C-labelled methyl 2-butenoate obtained by para-hydrogenation of deuterated methyl 2-butynoate (2) (RT, 14.1 T), recorded a) immediately after para-hydrogenation, field cycling application and catalyst elimination, and b) after relaxation (trace multiplied x8)

References

[1] a) K. Golman, L.E. Olsson, O. Axelsson, S. Månsson, M. Karlsson, J.S. Petersson, *Br. J. Radiol.*, **2003**, 76, S118; b) Mansson S., Johansson E., Magnusson, P., Chai C.M., Hansson G., Petersson J.S., Stahlberg F., Golman K., *Europ. Radiol.* June **2005**, E-pub. ahead of print