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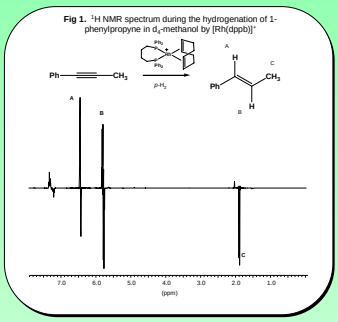
Application of the *para*-Hydrogen Phenomenon to Magnetic Resonance Imaging

Introduction

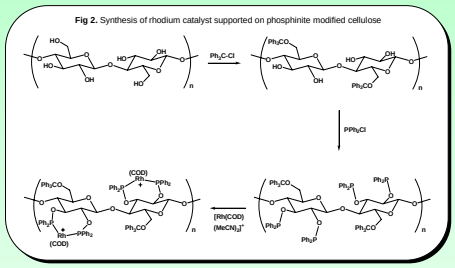
Para-hydrogen derived signal enhancements can be observed in the products of catalytic hydrogenations of unsaturated organic substrates, provided the hydrogen atoms are transferred pair-wise from the metal dihydride, that they are inequivalent and that the rate of hydrogenation is faster than the rate of spin relaxation.[1] This provides the potential for the *in situ* preparation of *para*-hydrogen enhanced organics for use in magnetic resonance imaging (MRI).

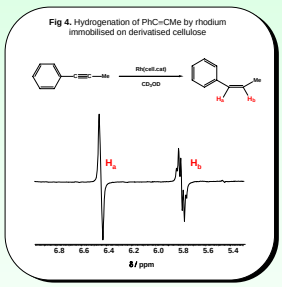
Catalyst Development



The cationic rhodium complexes of the type, $[Rh(COD)(PPh_2(CH_2)_nPPh_2)]^+$ (n = 2,3,4, COD = 1,5-cyclooctadiene), are effective catalysts for the hydrogenation of a wide variety of substrates and also yield polarised hydrogenation products. On testing the model substrate, PhC≡CMe, enhanced signals for the product, *trans*-PhHC=CHMe, were observed (Fig 1). An interesting observation in this system is the polarisation in the methyl group and the *trans* arrangement of the product. This suggests the involvement of an η^3-allyl intermediate allowing scrambling of the *p*-H_2 protons in the product.

We aim to produce sterile and pure materials suitable for human imaging. In order to separate polarised product from the catalyst, an immobilised catalyst is needed. Cellulose was treated with trityl chloride to protect the pendant 6-OH group, and then treated with PPh_2Cl to give a solid state phosphinite (based on ref. 2) on which a rhodium catalyst can be immobilised (Fig 2).





The cellulose derived heterogenised catalyst is observed to heterogeneously catalyse the rapid gas phase hydrogenation of ethene to ethane by gas phase NMR.

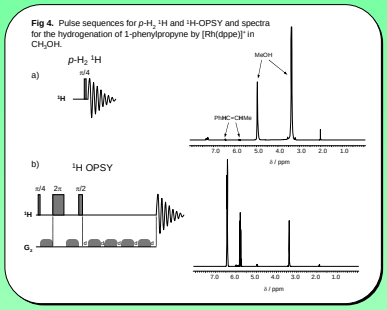
When used as a suspension on d_4-methanol in the presence of PhC≡CMe and *para*-hydrogen, signal for PHIP enhanced *trans*-PhCH=CHMe can be observed. Work is currently ongoing to utilise this catalyst and develop methodologies for *in situ* generation of PHIP enhanced products using a flow reactor concept.

Development of Spectroscopic Methods

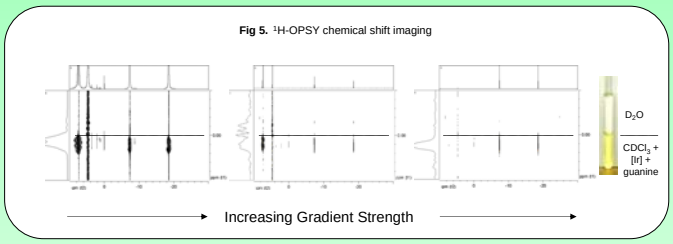
An important aspect of our research is the development of spectroscopic methods relating to *para*-hydrogen. *Para*-hydrogen adapted experiments have been recently developed for TOCSY, DOSY, HMBC, ROESY and WATERGATE.

With regard to imaging, we have developed a new technique called Only *Para*-hydrogen Spectroscopy (OPSY) (Fig 4b). This experiment is designed to observe PHIP enhanced signals with selective filtering of those derived from Boltzmann populated spin states (a similar but less effective technique has been proposed by Bargon[3]). An accurate calibration of the π/2 pulse is important in this experiment. The first part of the sequence (π/4-gradient-2π-gradient) is a gradient echo that refocuses *para*-hydrogen signals whilst defocusing most of the thermal signals. Thermal signals that are left are efficiently defocused in the second part of the sequence involving a π/2 pulse followed by a sequence of delays and four gradients. The sequence can be simplified merging the last four gradients into a single gradient four times the strength, however, this slightly decreases the effectiveness of thermal signal suppression.

Fig 4a shows the ^{1}H NMR spectrum of a sample of $[Rh(COD)(dppe)]^+$ and 1-phenylpropyne in proteo-methanol. The spectrum is dominated by solvent signals but small anti-phase PHIP enhanced peaks can be seen for the polarised product. Application of the ^{1}H-OPSY pulse sequence (Fig 4b) results in near total solvent signal suppression and easy observation of PHIP peaks. This sequence can be used in place of the normal π/4 read pulse in *para*-hydrogen adapted COSY, HMBC, HMQC, HMQC-COSY and DOSY experiments.



The OPSY sequence has been used in *z*-axis chemical shift imaging experiments. Variation of the gradient strength allows PHIP enhanced signals to be observed with selective filtering of normal Boltzmann signals (Fig 5, [Ir] = $[Ir(CO)Cl(P\{o\text{-tolyl}\}_3)_2]$)



Current Work

Ongoing work includes:

- Developing techniques for *in situ* PHIP enhanced product formation and design of prototype flow reactor.
- Adapting spectroscopic methods developed for conventional NMR spectroscopy to MRI in collaboration with the York Neuro-Imaging Centre (YNIC, Fig 6)
- Further development of spectroscopic techniques, e.g. reverse-INEPT for ^{1}H detection of materials after ALTADENA PHIP transfer to heteronuclei.

Fig 6. MRI at YNIC, York

Conclusions

Good potential catalytic systems have been identified for the generation of PHIP enhanced organic and have lead to the design of a heterogenised catalyst. Development of new spectroscopic methods such as OPSY allows the efficient filtering of thermal signals for selective observation of PHIP enhanced resonances and this is now being applied to MRI.

Acknowledgements

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