

Only *para*-hydrogen spectroscopy (OPSY), a technique for the selective observation of *para*-hydrogen enhanced NMR signals

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An NMR method is reported for the efficient removal of signals derived from nuclei with thermally equilibrated spin state populations whilst leaving, intact, signals derived from *para*-hydrogen induced polarisation (PHIP) through gradient assisted coherence selection.

The detection and characterisation of intermediates in transition metal catalysed reactions is an important area for modern NMR spectroscopy. This is hard to achieve in practice because of the limited sensitivity of the NMR technique, the short-lived nature of these species and the fact that they are present in low concentration. These limitations have been overcome in some instances through the use of high-pressure NMR spectroscopy^{1,2} and *in situ* photolysis,^{3,4} techniques that enable the generation of higher concentrations of reactive intermediates than normal and the extension of their lifetime by generating them at low temperature.

Over the past 20 years the expanding field of *para*-hydrogen induced polarisation (PHIP) enhanced NMR spectroscopy has contributed to this area by allowing the characterisation and subsequent study of the reactivity of such transient species.^{5,6} *Para*-hydrogen (*p*-H₂) corresponds to dihydrogen with the anti-symmetric $\alpha\beta$ - $\beta\alpha$ nuclear spin arrangement. Chemical reactions involving *para*-enriched H₂ lead to the generation of non-equilibrium spin distributions in the H₂ addition products for *p*-H₂ derived protons. It is this non-Boltzmann spin population that gives rise to the signal enhancements seen in NMR observations and thereby facilitates the detection of species present at low concentration. For example, studies of the photochemical generation of [Ru(H)₂(CO)₂(dpae)] (dpae = 1,2-bis(diphenylarsino)ethane) from [Ru(CO)₃(dpae)] in the presence of *p*-H₂ have revealed that the hydride ligand signal enhancements approach 31 200 corresponding to formation of a 100% pure spin state at 400 MHz.^{4†}

This approach has been particularly successful in the examination of catalytic reactions that involve molecular hydrogen.^{7,8} Notably, the observation of one-proton-PHIP by Eisenberg and Permin,⁹ the detection of a number of alkyl complexes of palladium,¹⁰ and the detection of the cobalt acyl complex [Co(CO)₃(PPh₃)(COCH₂CH₂CH₃)] in model hydroformylation systems¹¹ has expanded the potential applications of this method beyond the detection of metal dihydrides in recent years.

Even with the dramatically high levels of signal amplification it is, however, by no means certain that reaction intermediates can be detected. Clearly, if a catalyst is examined with a typical 100-fold excess of substrate and the corresponding intermediates are formed

at sub 1% levels then the contrast between the *p*-H₂ derived enhanced signals and those of the substrate is, at best, only of the order of 1 : 1.5. In certain cases, thermal signals will therefore still obscure polarised peaks of interest. The dynamic range associated with the detector also exacerbates this contrast problem. It is therefore desirable to separate the polarised signals from those of their thermal counterparts. We have successfully overcome these problems in the past by deuterating the substrate but here we describe a less expensive and time consuming approach using *para*-hydrogen and readily available reagents. Bargon *et al.* have previously demonstrated that thermal signals can be attenuated or even suppressed by a method that has been applied to the study of CIDNP (chemically induced dynamic nuclear polarisation) where the results of spectra recorded using phase precise 45_{-y}^o and 135_y^o excitation pulses are summed.^{12,13} The success of this method is however limited by the fact that the intensity of the thermal signals must be constant in the two sub-spectra, a situation not generally applicable in *para*-hydrogen enriched samples where the rapid acquisition cycle means that the thermal signals are not always at spin-equilibrium, the chemical nature of the system evolves with reaction time, and the temperature and field homogeneity often fluctuate at early reaction times where the PHIP signals are largest. In addition, while this method can be applied to two-dimensional experiments it normally increases the time necessary for complete phase cycling by a factor of two and hence potentially halves the final resolution.

Here we describe an efficient method for filtering thermal signals from ¹H NMR spectra whilst leaving those derived from PHIP intact. We have termed this approach Only *Para*-hydrogen Spectroscopy (OPSY). Fig. 1a shows the pulsed field gradient encoded NMR pulse sequence used. It should be noted that the OPSY experiment shares a similarity to the intermolecular multiple

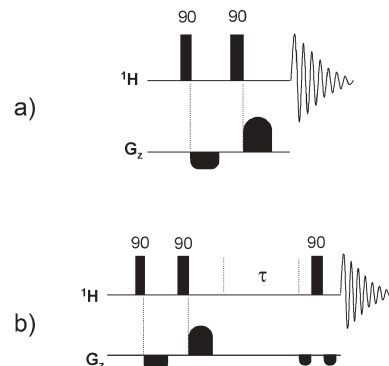


Fig. 1 Field gradient encoded pulse sequences for (a) ¹H OPSY and (b) ¹H-¹H OPSY-COSY experiments.

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quantum coherence (iMQC) spectroscopy experiment^{14,15} favoured in MRI, but the iMQC signals do not contribute to those observed here. The pulse sequence achieves its discrimination through the differential effects of the gradient on the double quantum (DQ) coherent term $2I_{1x}I_{2x}$ term produced for p -H₂ derived nuclei, and the single quantum (SQ) I_x terms generated for thermal magnetisation by the first 90° pulse. Precession during the gradient pulse generates a statistical distribution of the terms $I_{1x}I_{2y}$ and $I_{1y}I_{2x}$ (unimportant constants omitted). The application of the second 90° pulse and subsequent gradient pulse, which has twice the area of the first, converts these states into the observable $I_{1y}I_{2z}$ and $I_{1z}I_{2y}$ SQ terms. Because the p -H₂ derived signals dephased during the first gradient at twice the rate of the thermally based SQ terms, only this magnetisation is refocused by the second gradient and therefore only p -H₂ derived signals are observed.‡

The OPSY sequence was initially tested on the [Rh(COD)(dpe)]BF₄ (where dpe is bis(diphenylphosphino)ethane) catalysed hydrogenation of 1-phenylprop-1-yne in protio-methanol. Fig. 2a shows the organic region of the resulting ¹H spectrum that is produced using a 45° read pulse; it is clearly dominated by solvent signals. Close examination reveals extremely small signals for the enhanced olefinic protons of the hydrogenation product PhCH=CHMe at δ 6.4 and 5.8. Fig. 2b shows the corresponding NMR spectrum obtained using the OPSY sequence in magnitude form. The solvent signals are now almost totally suppressed and the dominant peaks are due to the PHIP enhanced protons of the product.

The OPSY filter can also be applied to two-dimensional experiments. Fig. 1b shows the pulse sequence for an OPSY adapted COSY experiment where the initial 90° pulse of the standard COSY sequence (or 45° pulse in the case of a p -H₂ adapted experiment) has been replaced by the OPSY sequence.

A sample containing 4-vinylcyclohexene and [Rh(COD)(dppb)]BF₄ (where dppb is bis(diphenylphosphino)butane) in CD₃OD was then examined under 3 bar of p -H₂. Fig. 3a shows a typical ¹H NMR spectrum produced during this reaction. A PHIP enhanced signal is observable for the methyl group of the hydrogenation product 4-ethylcyclohexene at δ 0.95, along with a smaller PHIP enhanced resonance at δ 1.21. Upon application of the OPSY filter (Fig. 3b) these peaks appear very easily, and two further resonances are observed at δ 1.76 and 1.32, which were

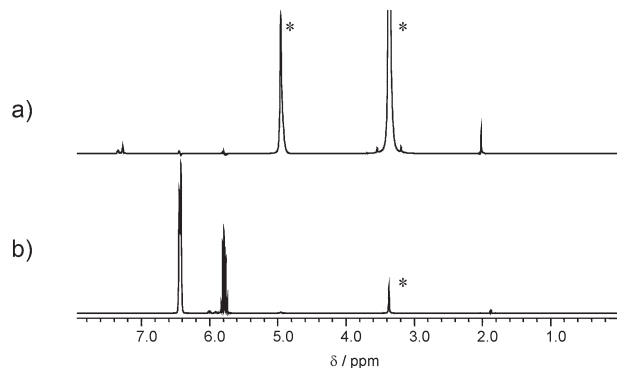


Fig. 2 (a) Magnification of the organic region of the ¹H NMR (45° pulse p -H₂ acquisition) spectrum for a sample charged with [Rh(COD)(dpe)]BF₄ (1 mg) and PhC≡CMe (10 μ L) in CH₃OH (500 μ L) (10 μ L of CD₃OD added to lock) under 3 bar p -H₂, (b) ¹H OPSY of the same sample (* = CH₃OH).

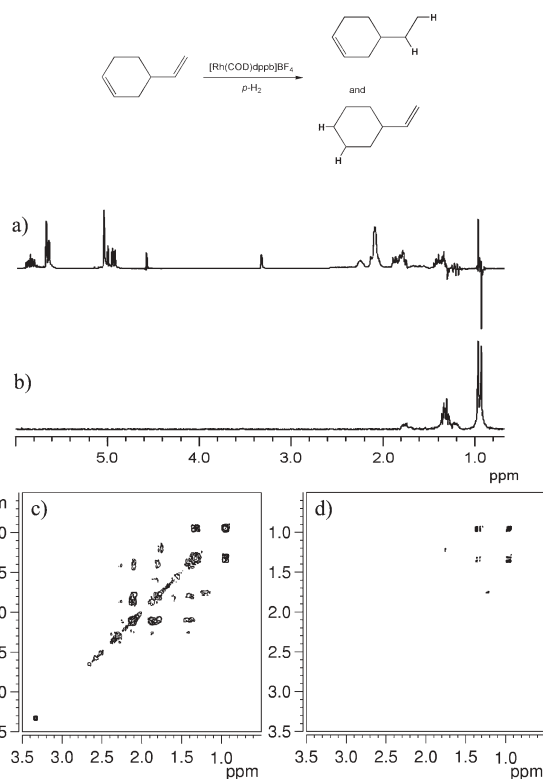


Fig. 3 NMR spectra for a sample charged with [Rh(COD)(dppb)]BF₄ (1 mg) and 4-vinylcyclohexene (10 μ L) in CD₃OD (500 μ L) under 3 bar p -H₂, (a) ¹H PHIP (45° pulse acquisition), (b) ¹H OPSY, (c) p -H₂ COSY, (d) OPSY-COSY.

previously obscured by thermal signals. The larger of these signals, at δ 1.32, corresponds to the methylene resonance of 4-ethylcyclohexene and the weaker PHIP signals, at δ 1.76 and 1.21, arise from the p -H₂ derived ring protons of the alternative hydrogenation product vinylcyclohexene. GC-MS data show no evidence for the double hydrogenation to ethylcyclohexane on the time scales of these experiments. These data therefore reflect the kinetic selectivity of the initial hydrogenation step.

Fig. 3c shows a COSY spectrum that was also recorded during this reaction. In contrast, Fig. 3d shows the corresponding OPSY-COSY spectrum where the thermally derived signals have been removed. The peaks that arise from the major hydrogenation product 4-ethylcyclohexene are now visible, in addition to weaker cross peaks for the minor hydrogenation product vinylcyclohexene.

These initial results demonstrate the power of the OPSY filter for the selective observation of PHIP enhanced signals that may otherwise not be observable due to other more intense thermally derived signals. Our recent results, detailing the detection of complexes through PHIP enhancements of acyl and alkyl protons, demonstrated a clear need for such a technique.^{10,11} Levitt and Carravetta recently showed that the singlet state for two coupled protons could have an increased longevity well beyond the T_1 limit measured for the individual nuclei.¹⁶ This was later demonstrated as being true with the singlet state generated in hydrogenation products derived from p -H₂.¹⁷ The OPSY filter might therefore be applied to the selective observation of PHIP enhanced materials in MRI, without the need to cross polarise a

heteronucleus.¹⁸ Singlet state terms similar to those derived through PHIP also exist in the density operators of non-equilibrium spin states of coupled nuclei generated by chemically induced dynamic nuclear polarisation (CIDNP)¹² and solid state DNP techniques.

OPSY thus provides an efficient means of selectively filtering thermal signals from PHIP enhanced NMR spectra. We wish to thank the Basic Technology programme and the BBSRC for funding this research.

Notes and references

† A selective 90° pulse on one PHIP signal was used in this experiment. ¹H PHIP spectra are normally collected using a hard 45° pulse and hence give a maximum enhancement of 15 100 at 400 MHz.

‡ Typical OPSY gradient strengths used are 5 G cm⁻¹ for 1 ms.

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