NMR and MRI sensitivity enhancement by Parahydrogen Induced Polarization (PHIP)

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COST Annual Meeting, June 27th 2014, Zurich, Switzerland
1. Introduction
   Applications, Historical Background

2. Theory and Setup
   Parahydrogen, Homogeneous Hydrogenation,
   Polarization Transfer, SABRE

3. Applications
   Investigation of catalytic mechanisms, PHIP with
   heterogeneous catalysis, MRI of gases, molecular
   imaging, $^{1}$H MRI contrast, continuous polarization via
   membranes, polarization storage

4. Conclusions and Outlook
Introduction

- Method to obtain hyperpolarized molecules via a chemical route
- Homogeneous hydrogenation with p-H₂
  - Symmetry reduction of the p-H₂
  - Protons become non-equivalent
  - Polarization above Boltzmann
- Enhanced NMR signals of the products

**Signal increase ≈ 465**
Introduction

Applications of PHIP

- **In chemistry:**
  - Characterization of short-lived reaction intermediates
  - Investigation of catalytic mechanisms
  - Determination of kinetics

- **In medicine:**
  - Boosting the sensitivity of medical diagnosis
  - Magnetic labeling of active contrast agents
  - Examination of the metabolisms of physiological relevant substances
  - Tumor diagnosis
Introduction

Historical Background

• First observed at UC Berkeley (1980) by Bryndza & Bergman, “The Monday Phenomenon”

• Theoretically postulated and early experiments, at CALTECH (1986 & 1987) by Bowers & Weitekamp, “PASADENA Effect”

• Additional chemical applications at Rochester, NY & Bonn, Germany (1987) by Eisenberg, Bargon, et. al.

• Lowfield experiments at CALTECH (1988) by Pravica & Weitekamp, “ALTADENA Effect”
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3. Experimental part
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4. Conclusions and Outlook
The Nuclear Spin of H$_2$

\[ \Psi_{\text{total}} = \Psi_{\text{Translation}} \ast \Psi_{\text{Vibration}} \ast \Psi_{\text{Electron}} \ast \Psi_{\text{Rotation}} \ast \Psi_{\text{Nuclear spin}} \]

antisymmetric in exchange of the nuclei

even rot. states are symmetric and lower in energy

Parahydrogen is the low energy spin isomer

Orthohydrogen
Magnetic, I=1

Parahydrogen
Non-magnetic, I=0
Parahydrogen Enrichment

\( \text{n-H}_2 \) consists of 75% o-H\(_2\) and 25% p-H\(_2\) (at room temperature)

Enrichment strategy → Cooling (catalyst)

liquid nitrogen

helium (cryostat)

77 K: 50% p-H\(_2\)

30 K: >95% p-H\(_2\)
Theory and Setup

Para-H₂ generator from Bruker

Output: 93% enriched p-H₂ at maximum pressure of 10 bar
A continuous-flow, high-throughput, high-pressure parahydrogen converter for hyperpolarization in a clinical setting

The apparatus produces a continuous flow of four standard liters per minute of 98% enriched pH₂ at a pressure maximum of 50 bar.

Theory and Setup

Homogeneous Hydrogenation

R-C=CH₂ + p-H₂ → Catalyst system → Hydrogenation → RHC - CH₂ → Polarization transfer → RH - ^13C^*_H - CH₂

PASADENA → *H_a H_b → Relaxation → RHC - CH₂

ALTADENA → H_a H_b
**Theory and Setup**

Population Model: Level scheme for a two spin system

Boltzmann population after regular hydrogenation or relaxation
PASADENA

Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment

Energy levels

**Theory and Setup**

Hydrogenation within the NMR spectrometer at high magnetic field
**ALTADENA**

Adiabatic Longitudinal Transport After Dissociation Engenders Net Alignment

Theory and Setup

Energy levels

NMR-Spectrum

Hydrogenation outside the NMR spectrometer at low magnetic field

Resonance 1 in absorption

Resonance 2 in emission

2 singlets 'antiphase'

\[ \text{RHC—CH}_2 \]

\[ \text{H}_a \quad \text{H}_b \]

\[ \alpha \beta \]

\[ \beta \alpha \]

\[ \beta \beta \]

\[ \alpha \alpha \]

\[ \text{E} \]

\[ \text{ppm} \]

\[ \text{6 bar} \]

\[ \text{p-H}_2 \text{ (Singlet state)} \]

- Catalyst
- Substrate
- Solvent

Place in NMR spectrometer (field \( B_0 \))

Shake

Target substance
Theory and Setup

Theoretical signal increase

\[ S_{\text{enh}}(N_{\text{para}}) = \frac{\xi}{\epsilon} = \frac{(4N_{\text{para}} - 1)k_B T_{\text{exp}}}{3\gamma \hbar B_0} \]

\[ \begin{align*}
\xi & \equiv \frac{4N_{\text{para}} - 1}{3} \\
\epsilon & = \frac{\hbar \gamma B_0}{k_B T_{\text{exp}}} 
\end{align*} \]

- \( N_{\text{para}} \): \( p\text{H}_2^- \) fraction
- \( T_{\text{exp}} \): Temperature of NMR experiment
- \( k_B \): Boltzmann's constant
- \( \gamma \): gyromagnetic ratio
- \( B_0 \): external magnetic field strength
Theoretical signal increase for different field strength

\[ S_{\text{enh}} \]

- \( B_0 = 4.7 \, \text{T} \) (200 MHz)
- \( B_0 = 7 \, \text{T} \) (300 MHz)
- \( B_0 = 9.4 \, \text{T} \) (400 MHz)
- \( B_0 = 17.6 \, \text{T} \) (750 MHz)

\( T = 77 \, \text{K} \)

Enrichment temperature [K]
Experimental enhancement with different p-H$_2$ contents

a) 50% p-H$_2$

- $H_c = 1710$
- $H_b = 2665$

b) 95% p-H$_2$

- $H_c = 3360$
- $H_b = 5620$

$T_1$ (protons)
Spontaneous polarization transfer to $^{13}$C

Signal enhancement $C_3 \approx 5740$

75 MHz $^{13}$C NMR, Reference 174 scans

75 MHz $^{13}$C NMR, PHIP 1 scan

Polarization destroyed with rf pulse
Polarization transfer using rf pulses

PH-INEPT+ sequence

INEPT(+π/4) sequence

✓ PH-INEPT+ gives rise to selective polarization transfer under ALTADENA conditions yielding higher signal enhancements as spontaneous polarization transfer

Catalyst systems

**water-insoluble**

- High activity and low substrate specificity
- Embedding of stereo information possible
- Pairwise transfer of H₂ to the substrate molecule

**water-soluble**

- Problems: toxic, not in aqueous solution
- Problems: toxic, foaming

1,4-Bis(diphenylphosphino)butane] (1,5-cyclooctadiene)rhodium(I)tetrafluoroborate

1,4-Bis[sodium 3-(phenyl-3-propane sulfonate)phosphine] butane (2,5-norbornadiene) rhodium(I)tetrafluoroborate
Fig. 1. Schematic representation of the magnetization transfer process.
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   Parahydrogen, Homogeneous Hydrogenation, Population Model, Density Matrix, Polarization transfer

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   Investigation of catalytic mechanisms, PHIP with heterogeneous catalysis, MRI of gases, molecular imaging, $^1$H MRI contrast, continuous polarization via membranes, polarization storage

4. Conclusions and Outlook
Structure and dynamics in metal phosphine complexes using advanced NMR studies with PHIP

Standard pulse sequences for structure elucidation can be modified to give maximum PHIP signal.

Full hydrogenation mechanism of IrCl(CO)(PPh$_3$)$_2$ (Vaska’s complex)
PHIP employing heterogeneous catalysis

$^1$H NMR PASADENA spectra obtained during hydrogenation of propene with parahydrogen for Pt metal catalysts supported on different oxides.

K.V. Kovtunov, V.V. Zhivonitko, I.V. Skovpin, D.A. Barskiy, I.V. Koptyug, Top Curr Chem (2013) 338: 123–180

FLOW IN A REGULAR PHANTOM  FLOW IN POROUS MEDIUM

PROTON WATER IMAGE

Propene gas-phase image

Propene gas-phase image

ALTADENA image

ALTADENA image
Real-time metabolic imaging using PHIP

$^1$H MRI with PHIP

Para-hydrogenated Glucose Derivatives as Potential $^{13}$C-Hyperpolarized Probes for MRI

Para-hydrogenated Glucose Derivatives as Potential $^{13}$C-Hyperpolarized Probes for MRI

Single-scan 1H NMR spectrum (acetone-$d_6$/CD3OD 9:1, 298 K, 9.4 T) recorded immediately after para-hydrogenation of 4

Uptake of 100 mM $7a$ in human myelogenous leukemia cells.
Hyperpolarization: $T_1$ issue

- Creation of hyperpolarization in a continuous manner

- Use of singlet states (long-lived, slow relaxation, storage for polarization up to half an hour)


Meike Roth, Petra Kindervater, Hans-Peter Raich, Joachim Bargon, Hans-Wolfgang Spiess, Kerstin Münneemann:

Continuous $^1$H and $^{13}$C signal enhancement in NMR and MRI using parahydrogen and hollow fiber membranes Angew. Chem. Int. Ed. 2010, 49, 8358 –8362.
Original idea: Xe dissolution

⇒ Hollow fibers for loading liquid with HP $^{129}$Xe
⇒ Continuous delivery
⇒ No bubbling, foaming or destruction of polarization


Membrane technique

**Membrane setup:**

- **NMR coil**
- **p-H₂ inlet**

**Chemical structure**

\[
\begin{align*}
\text{C}_2 &= 2090 \\
\text{C}_1 &= 2070 \\
\end{align*}
\]

**PASADENA using membranes**

<table>
<thead>
<tr>
<th>+</th>
<th>-</th>
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<tbody>
<tr>
<td>hyperpolarized peaks</td>
<td>only in aqueous solution</td>
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<tr>
<td>possibility to work under pressure</td>
<td></td>
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<tr>
<td>high conversion rates</td>
<td></td>
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<td>real PASADENA conditions</td>
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<tr>
<td>constant conversion rate over time</td>
<td></td>
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<tr>
<td>high spectral resolution</td>
<td></td>
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<td>continuous flow measurements</td>
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**Chemical structure**

\[
\begin{align*}
\text{C}_2 &= 1510 \\
\text{C}_1 &= 1770 \\
\end{align*}
\]

**ALTADENA**
PASADENA using membranes

- Constant hyperpolarization with high spectral resolution
- Possibility to examine a reaction in real time

Signal enhancement > 2000
PHIP $^1$H-$^1$H COSY, 1 scan, 7 min 18 s

thermal $^1$H-$^1$H COSY, 8 Scans, 57 min 45 s

- Constant hyperpolarization with high spectral resolution
- Rigorous test for constant hyperpolarization → 2D spectra
- Possibility to examine an ongoing reaction in real time
- Performance of more complicated experiments with hyperpolarization

PASADENA using membranes
Polarization transfer using membranes

- Constant hyperpolarization of hetero nuclei
- Possibility to perform more complicated $^{13}$C NMR experiments with hyperpolarization

Reference 64 scans

signal enhancement > 5000

- ✓ Constant hyperpolarization of hetero nuclei
- ✓ Possibility to perform more complicated $^{13}$C NMR experiments with hyperpolarization
MRI using membranes

Sample: 8 mm tube (6mm ID), projection, 20 mmBirdcage, TE=4.3 ms, BW: 625 Hz, TR=50 ms, matrix: 128x64
**T<sub>1</sub> issue**

- Use of singlet states (long-lived, slow relaxation, requires a strongly coupled two-spin system)

### Inequivalent pair

\[ \Delta \omega_z \gg J \]

- **Weakly Coupled System**, Redfield-Abragam theory.
- Intra-pair dipolar coupling

### Chemically Equivalent Pair

\[ \Delta \omega_z = 0 \]

- **Strongly Coupled System**
  - singlet state is an exact eigenstate.
  - immune to dipolar coupling, which dominate \( T_1 \).
  - singlet states are long lived.
  - but: NMR silent!!!
- pH$_2$ possesses singlet symmetry
- Introduction of pH$_2$ into a symmetry breaking magnetic environment mixes the singlet state with the triplet state.
- But: the pH$_2$ singlet state is preserved if the symmetry is not broken

**Symmetrical Molecule!!!**

Acetylene dicarboxilic acid dimethylester  
Maleic acid dimethylester

The pH$_2$ remains chemically equivalent and strongly coupled *for every field*
Long lived states on protons

Long lived states on protons

- $^1$H long lived states accessed by rf irradiation
- MRI of long lived states

$T_s \sim 4 \text{ min}$

$T_1 = 15 \text{ s}$

Conclusions and Outlook

• Dramatic signal enhancement

• Polarization transfer to carbon nuclei randomly and via appropriate pulse sequences (e.g. PH-INEPT+)

• continuous generation of hyperpolarization or lifetime prolongation by the use of singlet states can (partially) overcome the \( T_1 \) issue

• examination of reaction mechanism of hydrogenation reactions

• Monitor metabolism of physiologically active hyperpolarized substrates at the target tissue
Many thanks to:

- Dr. B. Franzoni
- Dr. D. Graafen
- Dr. F. Dechent
- Dr. L. Buljubasich
- Dr. P. Blümler
- Prof. H. W. Spiess
- B. Piechalska
- M. Braun

funding by the German Federal Ministry of Education and Research (VIP0327) and by the EU (COST TD1103)

and you for your attention!