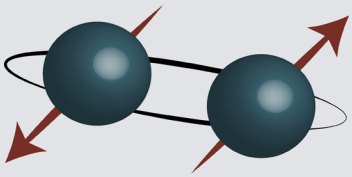
PERM 2020 Program

The Inaugural Parahydrogen Enhanced Resonance Meeting

PERM 2020



July 27-29

Virtual via Zoom

Parahydrogen Enhanced Resonance Meeting

Advancing next-generation hyperpolarization.

Welcome to the inaugural Parahydrogen Enhanced Resonance Meeting!

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Willkommen 欢迎 Добро Пожаловать! Welkom
Velkommen Üdvözöljük chào mừng 어서 오십시오 ようこそ

Dear Parahydrogen Community,

We are excited to offer the inaugural Parahydrogen Enhanced Resonance Meeting 2020 as an opportunity to promote parahydrogen-based research around the world. In this difficult year we remember and honor all those who have been affected by COVID-19. Recognizing that in this period global cooperation and collaboration is necessary more than ever, this meeting will provide an opportunity to foster both long-term scientific and social relationships. With registered attendees from 15 countries and talks from across 4 continents, PERM is truly a next-generation global conference showcasing how science can unite across any boundary.

While most of us have been sidelined from research for a significant period this year, PERM seeks to provide a spark of innovation and science in the parahydrogen community. The meeting includes a wealth of educational and invited talks from leaders in the field of parahydrogen-enhanced resonance and includes an exciting lineup of promoted talks showcasing innovative new work. As a fully virtual conference, PERM promotes attendance not only to the scheduled periods, but also provides open access to content outside of the conference boundaries on YouTube.

We hope PERM helps to lay the technical foundation for new cooperation and progress in the parahydrogen community and we look forward to your support in maintaining this effort in the years to come.

Best Regards,

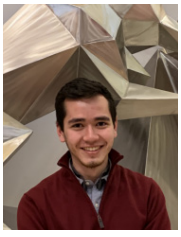
PERM Organizing Committee

Prof. Thomas Theis
Assistant Professor
NC State University

Prof. Eduard Chekmenev
Associate Professor
Wayne State University

Dr. Sören Lehmkuhl
Postdoctoral Associate
NC State University

Prof. Boyd Goodson
Distinguished Professor
Southern Illinois University



Mr. Patrick TomHon
Graduate Student
NC State University

Prof. Matthew Rosen
Assistant Professor
MGH/Martinos Center
Harvard Medical School

PERM Technical Guidelines

We are excited to host the inaugural PERM as full virtual event, utilizing a multi-platform approach across Zoom, Slack, and YouTube to enable active engagement around the world and at any time of day. As part of this effort we provide a set of details and guidelines to help the conference run smoothly.

Slack participation is encouraged on the workspace perm-conference.slack.com. Registered attendees will receive an invitation to the workspace one week before the conference to become familiarized with the interface and ask any questions about participation. A few basic guidelines in Slack:

1. Please maintain civil discourse in all Slack channels. The PERM organizing committee will serve as moderators for the workspace.
2. The three primary public channels for the workspace are: **#general**, **#help**, and **#presentation-breakout**. New channels will be created as needed by moderators, with suggestions welcome from attendees.
    a. **#general** is the "main hall" for the conference, serving as a general scientific discussion area for any attendee.
    b. **#help** will serve as a central notification hub for both technical assistance in Slack, but also across any other platform during the conference.
    c. **#presentation-breakout** will serve as a breakout room specifically dedicated to continuing question/answer discussion periods or follow-up discussions from previous talks.

If you feel uncomfortable using a new platform, we encourage you to use tutorial resources available online.

Zoom will be the central component of live conference activity, with talks broadcast around the world. Zoom links for the conference sessions will be provided via email and on Slack to registered attendees.

Zoom Guidelines for Attendees:

1. Video and audio permissions disallowed for all participants
2. Questions queued in chat to hosts during presentation OR asked by raised hand
    a. Written questions asked by the hosts/moderators
    b. Raised hands will be unmuted by hosts/moderators to ask their question
    c. Extended question periods can move to Slack @ **#presentation-breakout** (see above)

Zoom Guidelines for Speakers:

1. Each speaker will be promoted to co-host for their presentation, then demoted following the Q/A session. We encourage speakers to enable video during their presentation.
2. Speakers will receive a one-minute verbal warning before the end of their allotted period.
3. If the speaker runs over their allotted time limit the discussion/question section will be shortened to ensure the conference stays on schedule. We encourage further discussions on Slack @ **#presentation-breakout** (see above).

Monday, July 27, 2020

1100 – 1110 UTC: Introduction

PERM Introductory Remarks

Prof. Thomas Theis (North Carolina State University), PERM Organizing Committee Chair

1110 – 1405 UTC: Educational Session

1110 – 1140 UTC: **How to Get and How to Use Parahydrogen**

Dr. Andrey Pravdivtsev (Universitätsklinikum Schleswig-Holstein) and Dr. Andreas Schmidt (Universitätsklinikum Freiburg)

1140 – 1210 UTC: **Signal Amplification by Reversible Exchange (SABRE)**

Prof. Simon Duckett (University of York)

Coffee Break

1225 – 1255 UTC: **SABRE-SHEATH: SABRE in Shield Enable Alignment Transfer to Heteronuclei**

Prof. Ed Chekmenev (Wayne State University) and Prof. Thomas Theis (North Carolina State University)

1255 – 1325 UTC: **Spin order of molecular hydrogen in PHIP and SABRE experiments**

Prof. Konstantin L. Ivanov (International Tomography Center)

1325 – 1355 UTC: **Spin-lock Induced Crossing and NMR in the Strong-Coupling Regime**

Dr. Stephen DeVience (Scalar Magnetics, LLC.)

Coffee Break

1405 – 1440 UTC: Keynote Session

Fifty years of ups and downs...

Prof. Alex Pines (University of California, Berkeley)

1440 – 1530 UTC: Lunch/Dinner Break

1530 – 1740 UTC: Invited Session 1

1530 – 1600 UTC: **The Virtuous Triangle: Parahydrogen, Long-Lived States, and Hyperpolarization**

Prof. Malcolm Levitt (University of Southampton)

1600 – 1630 UTC: **Reaction monitoring using SABRE-enhanced low-field NMR spectroscopy**

Dr. Meghan Halse (University of York)

1630 – 1700 UTC: **Parahydrogen-Induced Polarisation in Microfludic Lab-on-a-Chip Devices**

Prof. Marcel Utz (University of Southampton)

1700 – 1730 UTC: **Chemical Kinetics of Hyperpolarized Species: Estimating the Influence of Chemical Parameters in PHIP/SABRE Experiments**

Dr. Danila Barskiy (University of California, Berkeley)

Coffee Break

1740 – 1920 UTC: Promoted Session 1

1740 – 1805 UTC: **Parahydrogen-polarized [1-^{13}C]fumarate – a path to in vivo application**

Dr. James Eills (Johannes Gutenberg Universität Mainz)

1805 – 1830 UTC: **GemPHIP: accumulation of the singlet-order on methylene proton pairs**

Dr. Laurynas Dagys (University of Southampton)

1830 – 1855 UTC: **Parahydrogen discriminated signals used as a detection block with improved resolution**

Mr. Santiago Bussandri (Universidad Nacional de Cordoba, Argentina)

1855 – 1920 UTC: **Highly Polarized and Long-Lived Metronidazole $^{15}NO_2$ Spin-Relays over Six Chemical Bonds using SABRE-SHEATH**

Dr. Jonathan Birchall (Wayne State University)

Tuesday, July 28, 2020

1100 – 1130 UTC: Kirill Kovtunov Memorial Lecture

Bridging the gap: from homogeneous to heterogeneous PHIP and beyond

Prof. Igor Koptyug (International Tomography Center)

1135 – 1440 UTC: Promoted Session 2

1135 – 1200 UTC: **Hyperpolarized 13C MRI of Fumarate Using Selective trans-Alkenylation Catalyst with Parahydrogen**

Prof. Shingo Matsumoto (Hokkaido University)

1200 – 1225 UTC: **Tuning Pd–Au Bimetallic Catalysts for Heterogeneous Parahydrogen-Induced Polarization**

Dr. Weiyu Wang (Innovation Academy of Precision Measurement Science and Technology)

1225 – 1250 UTC: **Hyperpolarization of 15N nuclei in nimorazole and dalfampridine drugs using SABRE at microtesla magnetic fields**

Dr. Oleg G. Salnikov (International Tomography Center)

Coffee Break

1300 – 1325 UTC: **Spatially resolved NMR spectroscopy of heterogeneous gas phase hydrogenation with parahydrogen**

Ms. Alexandra Svyatova (International Tomography Center)

1325 – 1350 UTC: **3D operando visualization of complex heterogeneous catalytic system using parahydrogen**

Ms. Elizaveta Kononenko (International Tomography Center)

1350 – 1415 UTC: **NMR Signal Enhancement in Hydrogenation Reactions over Differently Prepared Heterogeneous Rh/TiO2 Catalysts**

Ms. Ekaterina Pokochueva (International Tomography Center)

1415 – 1440 UTC: **Metal-Free Parahydrogen-Induced Polarization**

Prof. Vladimir V. Zhivonitko (University of Oulu)

1440 – 1530 UTC: Lunch/Dinner Break

1530 – 1810 UTC: Invited Session 2

1530 – 1600 UTC: **Hyperpolarization from Parahydrogen Utilizing Intermetallic Nanoparticles**

Prof. Russ Bowers (University of Florida)

1600 – 1630 UTC: **Long-lived nuclear spin order: theory and applications**

Dr. Giuseppe Pileio (University of Southampton)

1630 – 1700 UTC: **Cobalt-Catalyzed Parahydrogen Induced Polarization**

Prof. Alison Fout (University of Illinois at Urbana-Champaign)

1700 – 1730 UTC: **SABRE-enhanced NMR spectroscopy using quantum defects in diamond**

Dr. Nithya Arunkumar (Harvard University)

1730 – 1800 UTC: **Exploring New Spin Physics for High and Low Field SABRE**

Mr. Jacob R. Lindale (Duke University)

Coffee Break

1810 – 1925 UTC: Promoted Session 3

1810 – 1835 UTC: **Hyperpolarized Magnetic Resonance of Exchangeable Protons Using Parahydrogen and Aminosilane**

Mr. Ewoud Vaneeckhaute (KU Leuven)

1835 – 1900 UTC: **Multi-Physics Modelling of PHIP on a Microfluidic Chip**

Ms. Sylwia J Ostrowska (University of Southampton)

1900 – 1925 UTC: **Long-Lived Spin States of HP hydrocarbon gases**

Ms. Nuwandi Ariyasingha (Wayne State University)

Wednesday, July 29, 2020

1030 – 1100 UTC: Early Morning Session

Clinical translation of hyperpolarization – PHIP and dDNP

Prof. Jan Henrik Ardenkjær-Larsen (Technical University of Denmark)

1105 – 1315 UTC: Lightning Talk and Poster Session

1105 – 1210 UTC: Lightning Talks

SQUID-based ultralow field MRI of hyperpolarized material by using SABRE

Prof. Keunhong Jeong (Korea Military Academy)

Practical Aspects of RASER with the Parahydrogen-Induced Polarization Technique

Dr. Baptiste Joalland (Wayne State University)

In-situ characterisation of SABRE catalyst activation via T1 measurements in the Earth's Magnetic field

Dr. Fraser Hill-Casey (University of York)

Synthesis of 15N-labeled contrast agents for 15N hyperpolarization by SABRE

Dr. Nikita V. Chukanov (International Tomography Center)

Zero- to ultralow- field NMR spectroscopy of azobenzene hyperpolarized by SABRE

Dr. Kirill Sheberstov (Helmholtz-Institut Mainz)

Parahydrogen-induced polarization enables chemical reaction monitoring at zero magnetic field

Ms. Dudari B. Burueva (International Tomography Center)

Exploring SABRE Polarisation Transfer using in situ Earth's field NMR

Mr. Matheus Rossetto (University of York)

Quantifying the Effects of Quadrupolar Sink via ^{15}N Relaxation Dynamics in Metronidazoles Hyperpolarized via SABRE-SHEATH

Mr. Mohammad S. H. Kabir (Wayne State University)

Optimising the SABRE hyperpolarisation of amines using in-situ Earth's Field NMR

Ms. Aminata Sakho (University of York)

Validating Quantitative Hyperpolarised Reaction Monitoring on a Benchtop NMR Spectrometer

Mr. Alastair D. Robinson (University of York)

Cobalt-catalyzed Hyperpolarization of Olefins via SABRE

Ms. Safiyah R. Muhammad (University of Illinois at Urbana-Champaign)

Virtual Reality Understanding of Catalytic Mechanisms in SABRE

Mr. Kailai Lin (Duke University)

Chemical Kinetic Aspects of Hyperpolarization Buildup and Decay Revealed via Side-Arm Para-Hydrogenation of Vinylated Fatty Acid Precursors

Mr. Erik Van Dyke (University of California, Berkeley)

1210 – 1315 UTC: Open Poster Session Rooms

1320 – 1435 UTC: Promoted Session 4

1320 – 1345 UTC: **Applications of SABRE hyperpolarised NMR**

Dr. Ben. J. Tickner (University of York)

1345 – 1410 UTC: **Polarizing Poison: Signal Amplification By Reversible Exchange (SABRE) of Fentanyl Derivatives**

Dr. Ryan E. Mewis (Manchester Metropolitan University)

1410 – 1435 UTC: **Beyond NMR – applications of parahydrogen in exploring new exotic magnetic effects in molecules**

Dr. Petr Štěpánek (University of Oulu)

1435 – 1505 UTC: Lunch/Dinner Break

1505 – 1910 UTC: Closing Session

1505 – 1530 UTC: **Singlet-Contrast Magnetic Resonance Imaging**

Dr. James Eills (Johannes Gutenberg Universität Mainz)

1530 – 1555 UTC: **Investigating tumor metabolism using ParaHydrogen hyperpolarized [1-^{13}C]pyruvate**

Dr. Eleonora Cavallari (University of Torino)

1555 – 1620 UTC: **Continuous Flow Tube-in-tube PHIP Membrane Reactor**

Mr. Patrick TomHon (North Carolina State University)

Coffee Break

1630 – 1700 UTC: **The SABRE pumped single-mode RASER**

Prof. Stephan Appelt (RWTH Aachen and FZ Jülich)

1700 – 1730 UTC: **Bio-translation and clinical translation of PHIP in cells and in vivo**

Prof. Francesca Reineri (University of Torino)

1730 – 1800 UTC: **Zero to earth's field NMR: relaxometry and spectroscopy via atomic sensing**

Dr. Michael Tayler (The Barcelona Institute of Science and Technology)

1800 – 1830 UTC: **Parahydrogen-induced Polarization in Searches for New Physics**

Dr. John Blanchard (Helmholtz-Institut Mainz)

1830 – 1900 UTC: **On Parahydrogen Induced Magnetism of Jovian Planets**

Prof. Ed Chekmenev (Wayne State University)

PERM Closing Remarks

Prof. Thomas Theis (North Carolina State University), PERM Organizing Committee Chair

Abstract Table of Contents

Educational Speakers' Abstracts

The SABRE pumped single-mode RASER

Stephan Appelt[a,b]*, Simon Fleischer[b], Sören Lehmkuhl[c], Thomas Theis[c]

[a] Central Institute for Engineering, Electronics and Analytics – Electronic Systems (ZEA-2), Forschungszentrum Jülich GmbH, 52425 Jülich, Germany

[b] Institut für Technische und Makromolekulare Chemie, RWTH Aachen University, 52056 Aachen, Germany

[c] Department of Chemistry, North Carolina State University Raleigh, NC 27695-8204 (USA)

Recently the para-hydrogen (p-H_2) pumped RASER (Radiofrequency Amplification by Stimulated Emission of Radiation) was discovered [1]. The RASER is a quantum sensor not limited by the transverse spin-relaxation time. In this lecture, I will discuss the dynamical features of the SABRE (Signal Amplification By Reversible Exchange) pumped RASER operating in the low field regime (~1-4mT). The first example of a ^{1}H-SABRE-pumped single-mode RASER using 3-picoline as the target molecule will be presented [2]. Only one ^{1}H RASER mode can be observed, although the simulated ^{1}H-NMR spectrum at low field shows a fine splitting into several lines due to the strong coupling regime. The observed single mode is caused by a collapse phenomenon, which occurs mainly at low fields. A truely pure single-mode RASER, in which all protons are chemically and magnetically equivalent, is realized by SABRE-pumped pyrazine molecules in free solution. I will report about recent experiments, showing the exact non-linear RASER dynamics of pyrazine under different pumping conditions. Long after switching off the p-H_2 supply, several RASER bursts with decreasing amplitude and increasing width are observed [3,4]. These revivals are unrelated to spin-echoes and instead form due to the presence of a long-lived singlet reservoir in solution, which keeps the protons of pyrazine in a RASER-active state.

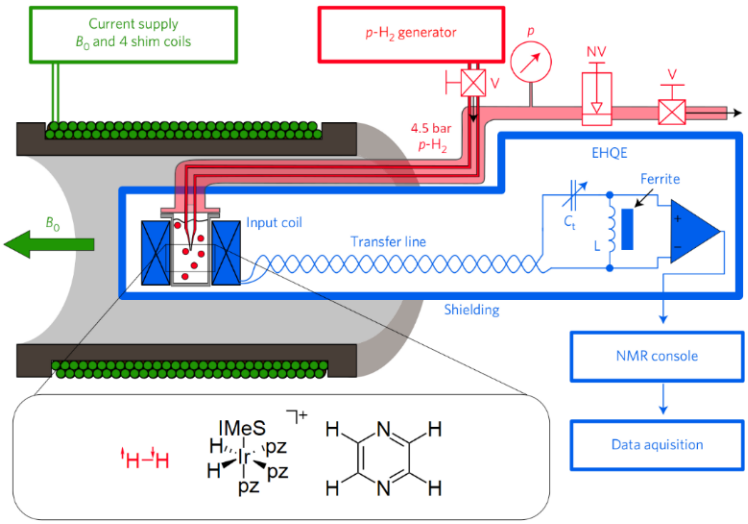


Figure 1: The pure single-mode ^{1}H RASER realized at B_0 = 3.9 mT (166 kHz ^{1}H-resonance) and pumped by the SABRE hyperpolarization method. Pyrazine molecules are pumped into a highly polarized state in the presence of an Ir-IMeS catalyst and by applying a continuous flow of p-H_2 gas bubbles. The protons of pyrazine are RASER active provided the RASER threshold condition is fulfilled.

[1] M. Süfke, S. Lehmkuhl, A. Liebisch, B. Blümich and S. Appelt, Para-hydrogen raser delivers sub-millihertz resolution in nuclear magnetic resonance, Nature Physics 6 (2017) 568-572.

[2] S. Appelt, A. Kentner, S. Lehmkuhl, B. Blümich, From LASER physics to the para-hydrogen pumped RASER, Progress in Nuclear Magnetic Resonance Spectroscopy 114-115 (2019), 1-32.

[3] S. Fleischer, SABRE- and RASER NMR spectroscopy of organic molecules. Bachelors Thesis, RWTH Aachen (2020).

[4] S. Appelt, S. Fleischer, S. Lehmkuhl, T. Theis, B. Joalland, N. M. Ariyasingha, E.Y. Chekmenev, SABRE and PHIP pumped RASER and the route to chaos, Perpectives in JMR (2020), to be published.

Clinical translation of hyperpolarization – PHIP and dDNP

Jan Henrik Ardenkjaer-Larsen

Technical University of Denmark, Kgs Lyngby Denmark. GE Healthcare, Brøndby, Denmark

Hyperpolarized magnetic resonance (MR) grew out of the vision that MR has excellent properties for measuring biochemistry, *in vivo* and non-invasively. The MR spectrum provides both identification and quantification of metabolites, and can characterize disease for early diagnosis, staging and monitoring of response to treatment. However, MR Spectroscopy suffers from several limitations: poor sensitivity, leading to long scan-times and poor spatial resolution, and limited spectral resolution due to a crowded spectrum. The long scan time means that only steady-state concentrations or slow dynamic changes can be measured.

The prospect of sensitivity gains by many orders of magnitude triggered the invention of several methods for enhancing the nuclear spin polarization. The theoretical potential for more than 10,000-fold enhancement of nuclear spin polarization at room temperature and typical magnetic field strengths, would enhance the sensitivity and compensate for the low metabolite concentrations in tissue, and would enable non-invasive, real-time metabolic imaging of hyperpolarized agents.

Hyperpolarization can be based on several principles, of which, three have successfully been applied to molecules in solution: ParaHydrogen Induced Polarization (PHIP), brute force polarization, and dissolution Dynamic Nuclear Polarization (dDNP). Optical pumping effectively polarizes noble gasses for lung imaging. The dDNP method has been particularly successful in making solutions of biologically interesting molecules with highly polarized nuclear spins. Clinical imaging is now a reality with hyperpolarized ^{13}C-pyruvate [1,2]. We will give an overview of the clinical translation of the method and make parallels to PHIP, an alternative method with significant advantages.

[1] S.J. Nelson, J. Kurhanewicz, D.B. Vigneron, P.E.Z. Larson, A.L. Harzstark, M. Ferrone, M. Van Criekinge, J.W. Chang, R. Bok, I. Park, G. Reed, L. Carvajal, E.J. Small, P. Munster, V.K. Weinberg, J.H. Ardenkjaer-Larsen, A.P. Chen, R.E. Hurd, L.-I. Odegardstuen, F.J. Robb, J. Tropp, J.A. Murray, , Metabolic imaging of patients with prostate cancer using hyperpolarized [1-^{13}C]pyruvate., Sci. Transl. Med. 5 (2013) 198ra108. https://doi.org/10.1126/scitranslmed.3006070.

[2] J. Kurhanewicz, D.B. Vigneron, J.H. Ardenkjaer-Larsen, J.A. Bankson, K. Brindle, C.H. Cunningham, F.A. Gallagher, K.R. Keshari, A. Kjaer, C. Laustsen, D.A. Mankoff, M.E. Merritt, S.J. Nelson, J.M. Pauly, P. Lee, S. Ronen, D.J. Tyler, S.S. Rajan, D.M. Spielman, L. Wald, X. Zhang, C.R. Malloy, R. Rizi, Hyperpolarized 13C MRI: Path to Clinical Translation in Oncology, Neoplasia. 21 (2019) 1–16. https://doi.org/10.1016/J.NEO.2018.09.006.

SABRE in Shield Enables Alignment Transfer to Heteronuclei

Thomas Theis[1,2] and Eduard Y. Chekmenev[3,4]

[1] Departments of Chemistry and Physics, North Carolina State University, Raleigh, NC, USA

[2] Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, Chapel Hill & Raleigh, NC, USA

[3] Department of Chemistry, Karmanos Cancer Institute (KCI), Integrative Biosciences (Ibio), Wayne State University, Detroit, Michigan, USA

[4] Russian Academy of Sciences, Moscow, Russia

Signal Amplification By Reversible Exchange (SABRE) is a relatively simple hyperpolarization technique, established in 2009, which has significantly broadened the substrate scope of parahydrogen induced polarization (PHIP) techniques.[1] Already in the original demonstration it was shown that SABRE can spontaneously hyperpolarize protons as well as heteronuclei such as ^{15}N or ^{13}C. However, only for protons, the ideal magnetic field was identified, enabling most efficient hyperpolarization transfer in the few milli-Tesla regime.[1, 2] In contrast, for heteronuclei (any other nucleus than proton), most importantly ^{15}N, the ideal polarization transfer field is in the sub-micro-Tesla regime, which typically requires magnetic shielding of the Earth's field. First indication of this effect were described in 2012 in the context of SABRE enhanced zero-field NMR.[3] In these original experiments it was not beneficial to perform hyperpolarization at ~6 mT and larger zero-field NMR signals were obtained, simply by dispersing parahydrogen gas through the SABRE solution at zero-field. However, it was not until 2015 that the ideal magnetic field in the sub-micro-Tesla regime was clearly identified in the Chekmenev lab.[4, 5] History, development and theory of the method coined "SABRE in Shield Enables Alignment Transfer to Heteronuclei" (SABRE-SHEATH) will be detailed.

In current and future applications, the appeal of SABRE-SHEATH stems from its relative experimental simplicity. All that is needed is bubbling or mixing of parahydrogen through a solution of substrate and SABRE polarization transfer catalyst in a magnetically shielded environment. Accordingly, it was possible to explore a wide range of substrates in a relatively short period of time.[6] More recently it also enabled efficient hyperpolarization of ^{13}C-pyruvate as first shown in the Duckett lab[7] and ^{13}C-acetate as shown in the Goodson lab.[8] Because of the large range of substrates and its relative ease, SABRE-SHEATH is expected to be of central relevance in future applications using hyperpolarized heteronuclei as will be discussed.

Acknowledgements: EYC would like to thank NSF CHE-1904780, NIH 1R21CA220137, and DOD CDMRP under W81XWH-12-1-0159/BC112431 for funding support. TT acknowledges funding from NIH NIBIB under R21EB025313, from the North Carolina Biotechnology Center Translational Research Grant, and from the Mallinckrodt Foundation.

References:

1. R. W. Adams, J. A. Aguilar, K. D. Atkinson, M. J. Cowley, P. I. Elliott, S. B. Duckett, G. G. Green, I. G. Khazal, J. Lopez-Serrano and D. C. Williamson, *Science*, 2009, **323**, 1708.
2. R. W. Adams, S. B. Duckett, R. A. Green, D. C. Williamson and G. G. Green, *J. Chem. Phys.*, 2009, **131**, 194505.
3. T. Theis, M. P. Ledbetter, G. Kervern, J. W. Blanchard, P. J. Ganssle, M. C. Butler, H. D. Shin, D. Budker and A. Pines, *J. Am. Chem. Soc.*, 2012, **134**, 3987.
4. T. Theis, M. L. Truong, A. M. Coffey, R. V. Shchepin, K. W. Waddell, F. Shi, B. M. Goodson, W. S. Warren and E. Y. Chekmenev, *J. Am. Chem. Soc.*, 2015, **137**, 1404.
5. M. L. Truong, T. Theis, A. M. Coffey, R. V. Shchepin, K. W. Waddell, F. Shi, B. M. Goodson, W. S. Warren and E. Y. Chekmenev, *J. Phys. Chem. C*, 2015, **119**, 8786.
6. J. F. P. Colell, A. W. J. Logan, Z. Zhou, R. V. Shchepin, D. A. Barskiy, G. X. Ortiz, Q. Wang, S. J. Malcolmson, E. Y. Chekmenev, W. S. Warren and T. Theis, *J. Phys. Chem. C*, 2017, **121**, 6626.
7. W. Iali, S. S. Roy, B. J. Tickner, F. Ahwal, A. J. Kennerley and S. B. Duckett, *Angew. Chem. Int. Ed.*, 2019, **58**, 10271.
8. M. E. Gemeinhardt, M. N. Limbach, T. R. Gebhardt, C. W. Eriksson, S. L. Eriksson, J. R. Lindale, E. A. Goodson, W. S. Warren, E. Y. Chekmenev and B. M. Goodson, *Angew. Chem. Int. Ed.*, 2020, **59**, 418.

SPIN-LOCK INDUCED CROSSING AND NMR IN THE STRONG-COUPLING REGIME

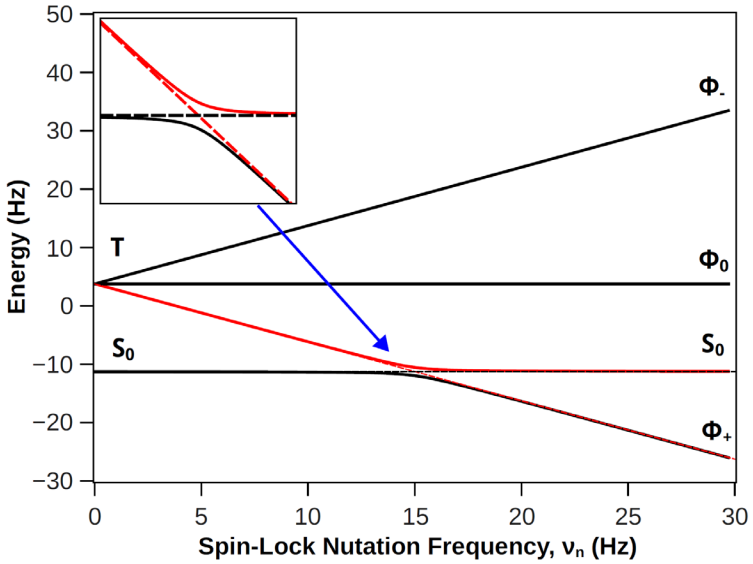
Stephen DeVience, PhD

1. Scalar Magnetics, LLC
2. Case Western Reserve University, Dept. of Biomedical Engineering

The long-lived singlet state is one example of “dressed” eigenstates that appear in the strong-coupling regime, where spin-spin coupling is much larger than chemical shifts. This situation predominates at low magnetic fields but can also occur at high fields in the case of nearly-equivalent spins or in the presence of strong resonant RF fields. Historically, spectroscopic information in this regime has been considered “lost,” because for most molecules the conventional NMR spectrum only exhibits a single line.

In actuality, the information is often not lost but only hidden, and it can be recovered using appropriate pulse sequences to manipulate the dressed states. These include magnetization-to-singlet (M2S), spin-lock induced crossing (SLIC), and adiabatic passage spin-order conversion (APSOC). These were initially designed to create singlet order from magnetization and vice versa, and they have become particularly useful during hyperpolarization via PHIP and SABRE, where they are used to move polarization from parahydrogen to the desired substrate nuclei. However, the sensitivity of these sequences to couplings and chemical shifts means they have much more to offer. They actually provide a way to perform NMR spectroscopy in the strong-coupling regime even for complex molecules with more than just singlet and triplet states.

In this educational talk, I will demonstrate how and when to work in the dressed state basis, how SLIC and related sequences can be used to detect and manipulate dressed states, and how they can be applied to situations in PHIP, SABRE, low-field, and high-field spectroscopy.



Signal Amplification by Reversible Exchange (SABRE)

Simon B. Duckett

Centre for Hyperpolarisation in Magnetic Resonance (ChyM), University of York, York, United Kingdom.

Hyperpolarisation techniques, where the Boltzmann spin state population is disturbed from its equilibrium position are used to increase MRI and NMR sensitivity by several orders of magnitude.[1] A number of methods for hyperpolarisation have been developed, and they are now beginning to find use in clinical diagnosis. Hyperpolarisation approaches that utilize *para*hydrogen as a polarization feedstock are known as PHIP (*para*hydrogen induced polarization) processes. In the original form of PHIP, as pioneered by Weitekamp, the molecular probe incorporated atoms that were previously found in *para*hydrogen. The variant, signal amplification by reversible exchange (SABRE), is a rapidly emerging and inexpensive method for hyperpolarising materials that does not change the chemical identify of the molecule it hyperpolarises.[2] Instead, it achieves hyperpolarisation by the transfer of the latent polarization of *para*hydrogen into a target via a metal complex scaffold, without changing the material's chemical identity. This PHIP approach has developed substantially from the early starting points of Weitekamp,[3, 4] Eisenberg[5, 6] and Bargon.[7, 8] This educational talk will illustrate some of the developments associated with SABRE.

1. J. H. Ardenkjær-Larsen, et al., *Increase in signal-to-noise ratio of > 10,000 times in liquid-state NMR*, Proc. Nat. Acad. Sci., 10158-10163, 2003.
2. R. W. Adams, et al., *Reversible Interactions with para-Hydrogen Enhance NMR Sensitivity by Polarization Transfer*, Science, 1708-1711, 2009.
3. C. R. Bowers, et al., *Parahydrogen and synthesis allow dramatically enhanced nuclear alignment*, J. Am. Chem. Soc., 5541-5542, 1987.
4. M. G. Pravica, et al., *Net NMR alignment by adiabatic transport of para-hydrogen addition-products to high magnetic-field*, Chem. Phys. Lett., 255-258, 1988.
5. T. C. Eisenschmid, et al., *Para hydrogen induced polarization in hydrogenation reactions*, J. Am. Chem. Soc., 8089-8091, 1987.
6. S. B. Duckett, et al., *Observation of new intermediates in hydrogenation catalyzed by Wilkinsons catalyst using parahydrogen-induced polarization*, J. Am. Chem. Soc., 10548-10556, 1994.
7. J. Barkemeyer, et al., *Hetero-nmr enhancement via parahydrogen labeling*, J. Am. Chem. Soc., 2927-2928, 1995.
8. J. Bargon, et al., *Nuclear-magnetic-resonance studies of homogeneous catalysis using parahydrogen - analysis of nuclear singlet triplet mixing as a diagnostic-tool to characterize intermediates*, J. Chem. Phys., 6150-6153, 1993.

Bridging the gap: from homogeneous to heterogeneous PHIP and beyond

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Nuclear spin polarization stemming from the spin order of parahydrogen has been demonstrated initially in a liquid phase upon homogeneous hydrogenation of an unsaturated substrate molecule over a dissolved transition metal complex.[1] Over the years, this initial demonstration evolved into a powerful technique for producing hyperpolarized substances for a range of potential applications, including metabolic studies in vivo. The chemistry that overcomes the NMR-silent nature of p-H_2 is the oxidative addition of an H_2 molecule to the catalytically active center, which often results in the formation of a metal dihydride complex as a reaction intermediate. Already in the very first studies it was clearly shown that the singlet spin order of p-H_2 can be transformed into spin hyperpolarization as soon as p-H_2 molecule is chemically activated. This can cause a dramatic enhancement of the NMR signals of short-lived reaction intermediates, providing an unprecedented access to key mechanistic details of the catalytic process. This opportunity was widely explored in the context of H_2 activation by transition metal complexes in homogeneous solution.[2]

In contrast, the studies of heterogeneous catalytic processes are a lot more challenging, but may have a much stronger impact on both fundamental knowledge and industrial practice. Almost all industrial-scale catalysis is heterogeneous, largely because heterogeneous catalysts are much easier to remove and recycle. Therefore, the development of the heterogeneous version of PHIP (HET-PHIP) is a highly valuable extension of the technique.

Originally considered impossible, HET-PHIP was first demonstrated[3] by using a known bridge between homogeneous and heterogeneous catalysis, by chemically linking PHIP-active transition metal complexes to a porous solid support. This was soon followed by the first observation of HET-PHIP with catalysts comprising supported metal nanoparticles.[4] These findings demonstrated unambiguously that pairwise addition of H_2 by industrial-type heterogeneous catalysts is feasible, and thus the technique is potentially applicable to study them. Since then, the studies were successfully extended[5] to a very broad range of heterogeneous catalysts and conditions, demonstrating that HET-PHIP is a rather general phenomenon. There is also a major potential for further progress. In particular, efforts to extend the approach to nuclear spin isomers of molecules other than H_2 may result in a major advance in this field.

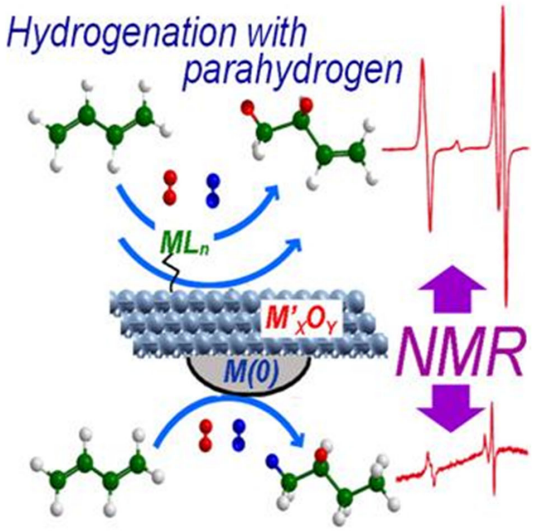

Figure 1. HET-PHIP effects are now observed with immobilized metal complexes, metal nanoparticles, metal oxides and several other types of heterogeneous hydrogenation catalysts.

[†]This presentation is the dedication to the memory of Dr. Kirill V. Kovtunov, a close friend and a valued partner in research, whose contribution to this field is essential and vast.

REFERENCES: (1) Bowers, C.R.; et al. *J. Am. Chem. Soc.* **1987**, *109*, 5541-5542. (2) Duckett, S.B.; et al. *Coord. Chem. Rev.* **2008**, *252*, 2278-2291. (3) Koptyug, I.V.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 5580-5586. (4) Kovtunov, K.V.; et al. *Angew. Chem. Int. Ed.* **2008,** *47*, 1492-1495. (5) Kovtunov, K.V.; et al. *Topics in Catalysis* **2016**, *59*, 1686-1699.

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HOW TO GET AND HOW TO USE PARAHYDROGEN

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Almost 90 years ago Werner Heisenberg was awarded the Nobel prize in physics (1932): *"for the creation of quantum mechanics, … which has, inter alia, led to the discovery of the allotropic forms of hydrogen."*

Now we know, that the molecular hydrogen (H_2) has four nuclear spin eigenstates: three triplet states, referred to as *ortho*hydrogen (oH_2), and one singlet state, referred to as *para*hydrogen (pH_2). At thermal equilibrium at room temperature, these four states are almost equally populated, giving a fraction of 25 % for pH_2. However, the singlet state is a lower energy state and can be enriched to, for instance, ≈50 % at 77 K (boiling point of nitrogen) or almost 100 % at 20 K (boiling point of H_2, **Fig. 1a**). The *para*-to-*ortho* transitions are symmetry forbidden, hence, the pH_2-enrichment is technically achieved by bringing H_2 gas in contact with a catalyst (for instance iron oxide) at low temperatures. In the absence of the catalyst and at room temperature the lifetime of pH_2 is very long (days-weeks).

Spin alignment of pH_2 can be utilized to boost the intrinsically low equilibrium magnetization of nuclear spins at room temperature and magnetic fields of modern NMR/MRI systems. Hyperpolarization through pairwise hydrogenation (PHIP, **Fig. 1b**) and temporal association (SABRE, **Fig. 1c**) are only some examples of pH_2 applications. Advancement of pH_2 hyperpolarization made possible hyperpolarization of metabolites with more than 10% polarization of ^{1}H, ^{13}C, ^{15}N using various RF pulse-sequences at high magnetic fields or via magnetic field cycling at low and ultra-low fields.

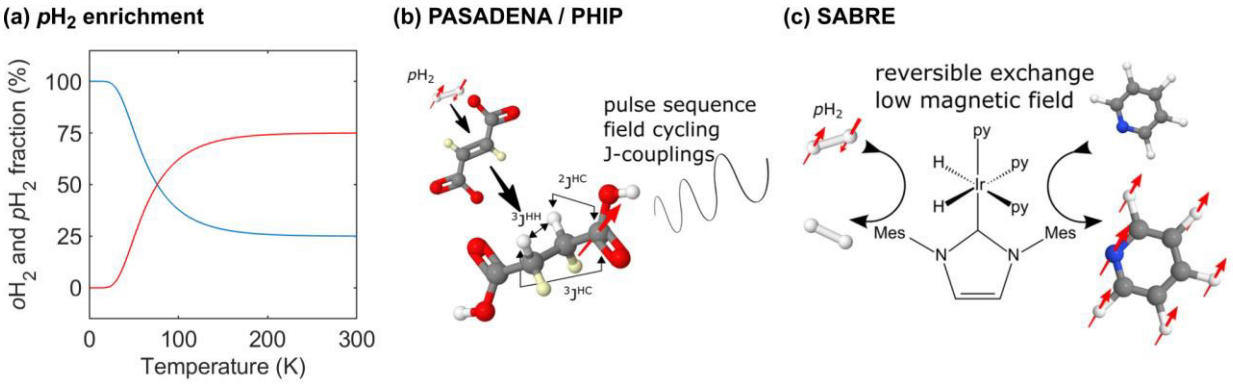

Figure 1. Fractions of pH_2 (blue) and oH_2 (red) as a function of temperature (a); hydrogenating PHIP (b) and non-hydrogenating PHIP (SABRE) (c).

Acknowledgements:

ANP acknowledges the support of the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (01ZX1915C). ABS thanks the the German Consortium for Translational Cancer Research (DKTK) for funding support.

Bio-translation and clinical translation of PHIP in cells and in vivo

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This educational session will provide an introduction to the applicability of parahydrogen polarized substrates to biological studies in cells and in vivo.

Hydrogenative PHIP is an affordable and easy to handle tool that can provide hyperpolarized molecules in few seconds.

Main hurdles to the use of PHIP in biological systems are associated to the presence of the hydrogenation catalyst and of organic solvents, as well as to the limited number of bio-molecules that can be obtained from addition of a hydrogen molecule to an unsaturated precursor. An overview of the biologically most relevant molecules that have been polarized using PHIP will be presented together with the methods that have been developed in order to achieve aqueous solutions of the hyperpolarized substrates ready for the injection in cells and living systems.

Till now, the biological investigations of PHIP-generated substrates rely on the detection of ^{13}C hyperpolarized signals because of its relatively long polarization lifetime and of its null background signal. Therefore, the parahydrogen spin order must be converted into ^{13}C polarization in order to have the molecule suitable for the intended biological study. This task can be achieved using different modalities either based on RF pulses or magnetic field sweeps, whose choice is basically related to the characteristics of the parahydrogenation products and to their peculiar scalar coupling patterns.

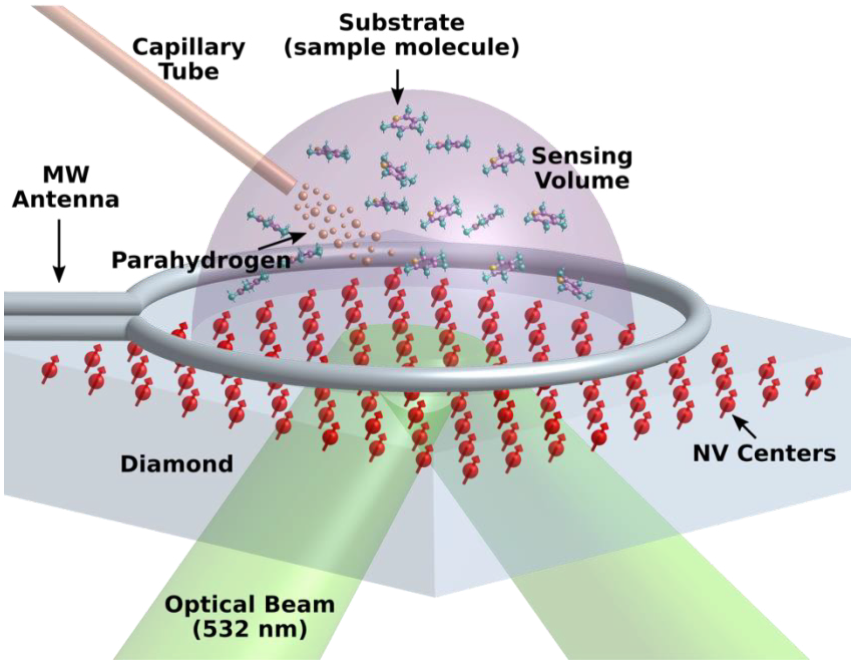
Finally, a few examples of the application of PHIP polarized molecules to biological investigations will be shown and the main issues that need to be tackled toward the clinical translation will be discussed.

Invited Speakers' Abstracts

SABRE-enhanced NMR spectroscopy using quantum defects in diamond

Nithya Arunkumar

Harvard University
University of Maryland



NV-NMR sensor integrated with signal amplification by reversible exchange (SABRE)

Optically-probed nitrogen-vacancy (NV) quantum defects in diamond can detect nuclear magnetic resonance (NMR) signals with high-spectral resolution from micron-scale sample volumes of about 10 picoliters [1, 2]. However, a key challenge for NV-NMR is detecting samples at millimolar concentrations. In this talk, I will discuss our recent experiments where we demonstrate an improvement in NV-NMR proton concentration sensitivity of about 10^5 over thermal polarization by hyperpolarizing sample proton spins through signal amplification by reversible exchange (SABRE). Thus, enabling micron-scale NMR of small molecule sample concentrations as low as 1 millimolar in picoliter volumes [3]. The SABRE-enhanced NV-NMR technique may facilitate detection and chemical analysis of low concentration molecules and their dynamics in complex micron-scale systems such as single-cells.

[1] D. R. Glenn, D. B. Bucher, J. Lee, M. D. Lukin, H. Park, and R. L. Walsworth, Nature 555, 351 (2018).

[2] D. B. Bucher, D. R. Glenn, H. Park, M. D. Lukin, and R. L. Walsworth, Phys. Rev. X 10, 021053 (2020).

[3] N. Arunkumar, et al., arXiv: 2006.03910 (2020).

Chemical Kinetics of Hyperpolarized Species:
Estimating the Influence of Chemical Parameters in PHIP/SABRE Experiments

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Recent advances in simulating nuclear spin dynamics in PHIP and SABRE experiments made it possible to predict the magnetic field dependence of pH$_2$-derived polarization transfer for various substrates [1-2]. However, not only the details of the magnetic field dependence are of the interest for pH$_2$-oriented NMR researchers; one also needs to predict the influence of chemical parameters of the system (i.e., the concentrations of chemical components and the kinetic rates of underlying reactions) on the magnitude of hyperpolarization effects. To analyze PHIP/SABRE in such a context, a phenomenological physicochemical approach was developed that treats the imbalance of nuclear spin states of molecules as fictitious hyperpolarized chemical species [3-4].

In this educational presentation, I introduce the concept of hyperpolarized species and justify its applicability for describing PHIP/SABRE processes. I show analytical expressions for deriving maximal achievable polarization for exemplary magnetization transfer processes. Applications of this phenomenological approach for the analysis of more general cases, such as SABRE-relay, are discussed as well (Figure 1) [5].

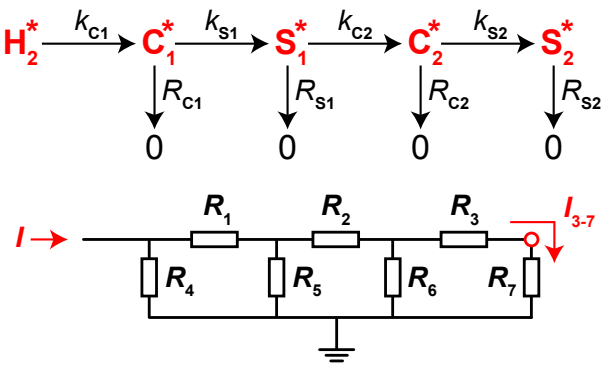

Figure 1: Interconversion of hyperpolarized species is governed by corresponding relaxation and reaction rates. Top – hyperpolarized species for the general SABRE-relay scheme. Bottom – circuit diagram describing the equivalent electric process.

References: [1] A. Pravdivtsev et al. *ChemPhysChem.*, **2013**. [2] K. Ivanov et al. *Prog. Nucl. Magn. Reson. Spectrosc.,* **2014**. [3] D. Barskiy, A. Pravdivtsev, K. Ivanov, K. Kovtunov, I. Koptyug. *Phys. Chem. Chem. Phys.,* **2016**. [4] D. Barskiy, S. Knecht, A. Yurkovskaya, K. Ivanov, *Prog. Nucl. Magn. Reson. Spectrosc.,* **2019**. [5] *In preparation*.

PARAHYDROGEN-INDUCED POLARIZATION IN SEARCHES FOR NEW PHYSICS

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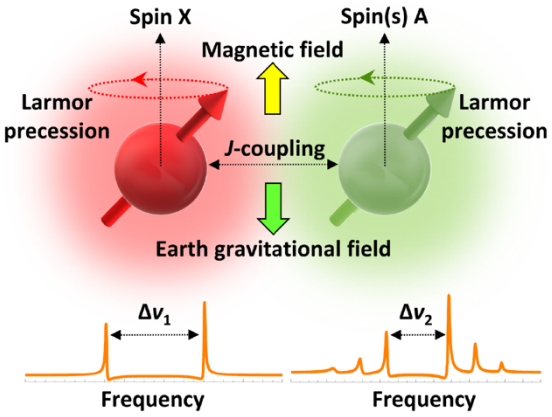
The Standard Model of particle physics is a triumph of modern science, bolstered in 2012 by the discovery of the Higgs boson. Detection of all fundamental particles predicted by the Standard Model does not, however, mean that the study of fundamental physics is *done* – many questions still remain, including:

- "What is the nature of the dark matter that makes up the majority of the matter in the universe?"
- "Are there additional fundamental forces beyond electromagnetism, gravity, and the weak and strong nuclear interactions?"

In principle, dark matter fields or new forces may couple to nuclear spins, in which case nuclear magnetic resonance (NMR) techniques can be used to search for the resulting effects. Regarding dark matter, a wide variety of theories predict new spin-0 bosons such as axions [1] and axion-like particles (ALPs) as well as spin-1 bosons such as dark photons [2]. Such fields would couple to nuclear spins, resulting dark-matter-driven spin precession, as searched for by the Cosmic Axion Spin Precession Experiment (CASPEr) [3]. Alternatively, if a new field behaves as an additional component of gravity, for example, there would be coupling of spins to gravitational fields, causing particles to acquire a gravitational dipole moment (GDM) that would add to the magnetic dipole moment, changing the Larmor frequency depending on the projection of the magnetic field on the local gravitational field.



Concept of single-species comagnetometer based on SABRE-polarized acetonitrile for GDM search.

In NMR-based fundamental-physics searches, sensitivity is limited in part by nuclear spin magnetization and, therefore, by nuclear spin polarization. Existing experiments using thermally pre-polarized nuclear spins have been able to set limits [4,5], but increasing spin polarization can immediately improve such limits by several orders of magnitude. I will discuss ongoing efforts in our labs using parahydrogen-derived spin order to enhance nuclear spin polarization in searches for ultralight bosonic dark matter and nuclear gravitational dipole moments.

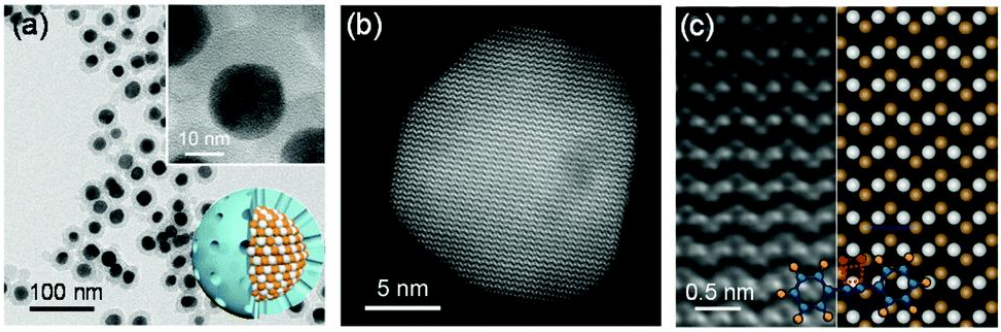
[1] R. D. Peccei and H. R. Quinn, *Phys. Rev. Lett.* **38**, 1440 (1977).
[2] L. Ackerman, M. R. Buckley, S. M. Carroll, and M. Kamionkowski, *Phys. Rev. D* **79**, 023519 (2009).
[3] D. Budker, et al., *Phys. Rev. X* **4**, 021030 (2014).
[4] T. Wu, et al., *Phys. Rev. Lett.* **122**, 191302 (2019).
[5] A. Garcon, et al., *Sci. Adv.* **5** (10), eaax4539 (2019).

HYPERPOLARIZATION FROM PARAHYDROGEN UTILIZING INTERMETALLIC NANOPARTICLES

Yong Du,[1] Tommy Y. Zhao,[1] Minda Chen,[2] Ranjan Bahera,[2] Wenyu Huang,[2,4] and Russ Bowers[1,3]

[1]University of Florida, Department of Chemistry, Gainesville; [2]Iowa State University, Department of Chemistry, Ames, [3]National High Magnetic Field Lab, Florida; [4]Ames Lab, Ames, Iowa

Intermetallic nanoparticles (iNPs) have atomic-level homogeneity and high surface stability, differentiating them from random alloys prepared by conventional methods. PtSn iNPs are specially designed to be encapsulated in a mesoporous silica shell that endows PtSn iNPs with accurate structures after synthesis while allowing reactants to access the PtSn intermetallic surface during catalysis. We recently reported selective hydrogenations using parahydrogen that illustrate the correlation of the structure of these PtSn iNPs to catalytic behaviors.[1-3] We also observed a novel type of spin transfer catalysis using Pt_3Sn iNPs and other bimetallic compositions, referred to as the SWAMP effect.[3] This presentation will highlight some of the more intriguing results with an emphasis on the molecular level understanding. Not only is the mechanism of hyperpolarization induced at the surface of these iNP catalysts fundamentally interesting, the substantially higher pairwise efficiency and solvent hyperpolarization could have promising applications to sensitivity enhanced NMR spectroscopy and imaging with all the well-established advantages of heterogeneous catalysis.



(a) TEM image of PtSn iNPs encapsulated in mesoporous silica at lower magnification showing clear core–shell structure, with its model illustration. Inset: TEM image of a PtSn iNP at higher magnification and a model structure of PtSn iNP encapsulated in a mesoporous silica shell. (b) Atomic resolution aberration-corrected STEM image of a PtSn iNP displaying the PtSn(110) facet. (c) Aberration-corrected STEM image of PtSn(110) facet placed beside the theoretical model of PtSn(110) with an adsorbed alkyne. Pearl (yellow) dots represent Pt (Sn) atoms. Blue (orange) dots represent carbon(hydrogen) atoms in alkyne, and red dots represent H2 undergoing pairwise-hydrogenation.

References:

1. Y. Pei et al., Nanoscale, 2020, DOI: 10.1039/D0NR00920B
2. Y. Du et al., JPCC, 2020, DOI: 10.1021/acs.jpcc.0c02493
3. E. W. Zhao et al., ACIE, 2017, DOI: 10.1002/anie.201701314
4. E.W. Zhao et al., Chem, 2018, DOI: 10.1016/j.chempr.2018.03.004

Financial support was received from NSF grant CHE-1808239 (C.R.B. and W.H.) and the National High Magnetic Field Laboratory's User Collaborative Grant Program, which is supported by the National Science Foundation Cooperative Agreement No. DMR-1644779* and the State of Florida.

On Parahydrogen Induced Magnetism of Jovian Planets

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Russian Academy of Sciences, Moscow, Russia

All Jovian planets, *i.e.*, Jupiter and other gas giants in our Solar system, exhibit planetary magnetism—there is no exception from this rule. Historically, the magnetism of Jupiter was hypothesized based on the planetary radio emission. This "suspicion" was confirmed in 1973 during Pioneer 10's mission.

The strength of the planetary magnetism of Jovian planets is astonishing: for example, Uranus has stronger regional magnetic fields than those seen on our planet, yet Uranus is composed of H_2 (83±3%), He (15±3%), methane (2.3%) and other hydrogen containing compounds, which are known to be electrically nonconductive. Various theories have been proposed to explain planetary magnetism of Jovian planets including most prominently the metallic hydrogen core theory. The latter theory may explain the magnetism of heavier Jupiter and Saturn, but fails short to theoretically explain the magnetic field of lighter Uranus and Neptune. The formation of "ocean of diamonds" have been proposed to explain the magnetism of these two planets. Both theories face a number of other challenges: the multi-polar nature of planetary magnetism of Jovian planets, etc.

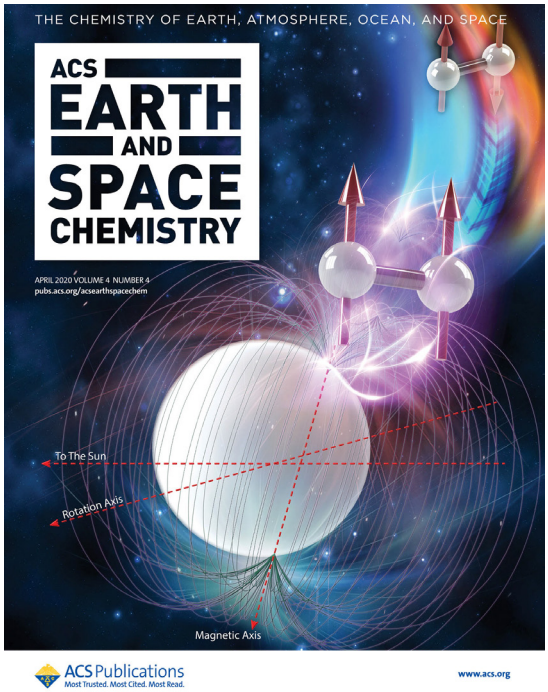

Figure 1. Rapid orthohydrogen ↔parahydrogen interconversion in cold aerosol-rich clouds of Jovian planets may lead to hyperpolarization of orthohydrogen and consequently induce or contribute to planetary magnetization. The graphics is used with permission from ACS.

The phenomenon of parahydrogen induced polarization and by extension magnetization has been demonstrated later in the 1980s (1). In 2009, this technique has been expanded to signal amplification by reversible exchange (SABRE), which relies on parahydrogen exchange (2). In 2014, we have demonstrated the formation of hyperpolarized orthohydrogen after utilization of parahydrogen to prepare hyperpolarized substrates via SABRE (3). Based on this work, it is hypothesized that the production of hyperpolarized orthohydrogen may in fact endow or significantly modulate the magnetism of all Jovian planets in our Universe (4). Unlike other theories of planetary magnetism of Jovian planets relying on deep electrically conductive layers, the proposed parahydrogen-based theory relying on the magnetism in the upper planetary layers can be potentially experimentally validated during future flyby missions.

REFERENCES: (1) Bowers, C. R.; Weitekamp, D. P. *Phys. Rev. Lett.* **1986**, *57*, 2645. (2) Adams, R. W.; Aguilar, J. A.; Atkinson, K. D.; Cowley, M. J.; Elliott, P. I. P.; Duckett, S. B.; Green, G. G. R.; Khazal, I. G.; Lopez-Serrano, J.; Williamson, D. C. *Science* **2009**, *323*, 1708. (3) Barskiy, D. A.; Kovtunov, K. V.; Koptyug, I. V.; He, P.; Groome, K. A.; Best, Q. A.; Shi, F.; Goodson, B. M.; Shchepin, R. V.; Coffey, A. M.; Waddell, K. W.; Chekmenev, E. Y. *J. Am. Chem. Soc.* **2014**, *136*, 3322. (4) Chekmenev, E. Y. *ACS Earth and Space Chem.* **2020**, *4*, 495.

ACKNOWLEDGMENTS: This work was supported by NSF CHE-1904780, NIH 1R21CA220137, DOD CDMRP under W81XWH-12-1-0159/BC112431 and W81XWH-15-1-0271.

Cobalt-Catalyzed Parahydrogen Induced Polarization

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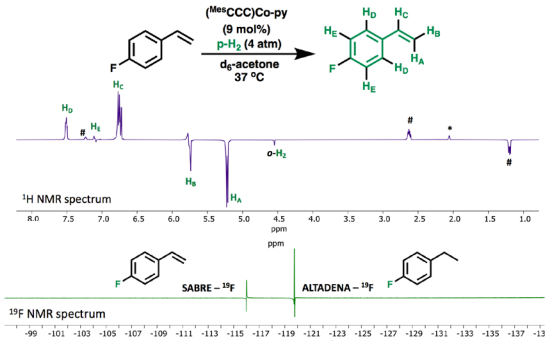

Figure 1. Single transient ^{1}H (top) and ^{19}F NMR (bottom) spectra of the hyperpolarization of a 65 mM solution of 4-fluorostyrene in d_6-acetone. # mark ALTADENA product.

The use of sustainable first-row transition metal catalysts for parahydrogen induced polarization (PHIP) is of significant interest. Here we discuss the use of the cobalt complex (^{Mes}CCC)Co-py [^{Mes}CCC = bis(2,4,6-trimethylphenyl-enzimidazol-2-ylidene)phenyl), py = pyridine], for the hydrogenation of olefins, alkynes, and nitriles.[1-3] Interestingly, the *para*hydrogenation of ethyl acrylate produced hyperpolarized ethyl propionate in both the ^{1}H and ^{13}C nuclei.[1] Furthermore, the (^{Mes}CCC)Co-py catalyst is also capable of the non-hydrogenative hyperpolarization of olefins. A variety of olefinic substrates have been demonstrated for hyperpolarization in the ^{1}H channel and the transfer of polarization to ^{13}C and ^{19}F nuclei for 4-fluorostyrene (Figure 1) will be presented.

REFERENCES: (1)Tokmic, K.; Greer, R. B.; Zhu, L.; Fout, A. R. ^{13}C NMR Signal Enhancement Using Parahydrogen-Induced Polarization Mediated by a Cobalt Hydrogenation Catalyst. *J. Am. Chem. Soc.* **2018**, *140*, 14844–14850. (2)Tokmic, K.; Markus, C. R.; Zhu, L.; Fout, A. R. Well-Defined Cobalt(I) Dihydrogen Catalyst: Experimental Evidence for a Co(I)/Co(III) Redox Process in Olefin Hydrogenation. *J. Am. Chem. Soc.* **2016**, *138*, 11907–11913. (3)Tokmic, K.; Fout, A. R. Alkyne Semihydrogenation with a Well-Defined Nonclassical Co-H_2 Catalyst: A H_2 Spin on Isomerization and E-Selectivity. *J. Am. Chem. Soc.* **2016**, *138*, 13700–13705.

Reaction monitoring using SABRE-enhanced low-field NMR spectroscopy

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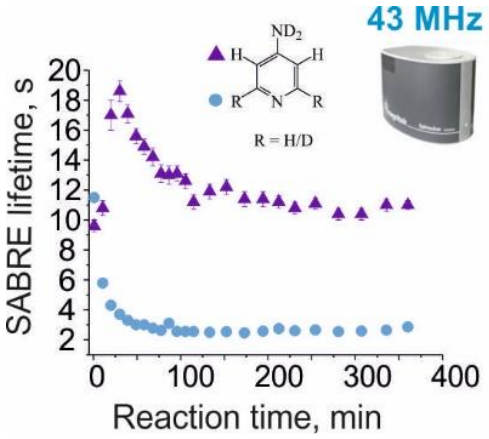

Figure 1. ^{1}H SABRE hyperpolarisation lifetimes of 4-aminopyridine, measured on a 1 T (43 MHz) benchtop NMR spectrometer as a function of reaction time with *p*-H_2, provide insight into the reactivity of the SABRE-active catalyst. [2]

Hyperpolarisation holds great promise for integration with compact NMR spectrometers, whose relatively low magnetic fields (≤ 2 T) limit both sensitivity and chemical shift dispersion. Signal amplification by reversible exchange (SABRE), [1] which catalytically transfers spin order from the nuclear singlet isomer of H_2, *para*hydrogen (*p*-H_2) to a target analyte, is particularly attractive for compact NMR applications because it generates polarisation quickly (in tens of seconds) and the level of polarisation is independent of the detection field. In addition, the SABRE process is fully reversible and so polarisation can be renewed upon supply of fresh *p*-H_2.

In this work we demonstrate the use of SABRE hyperpolarisation and low-field NMR detection for reaction monitoring. We focus, in particular, on the reactivity associated with the SABRE catalyst, i.e. the formation of the activate species through reaction of a pre-catalyst with *p*-H_2 and the target substrate, and hydrogen isotope exchange on the substrate mediated by the active SABRE complex. Changes in the observed ^{1}H SABRE-enhanced signals and single-shot measurements of the ^{1}H SABRE hyperpolarisation lifetimes are used to monitor the reactivity and to differentiate between the different chemical processes (Figure 1). [2] The use of a benchtop (1 T) NMR spectrometer for signal detection is compared to a fully *in situ* approach, where signal detection is achieved in the Earth's magnetic field. [3]

REFERENCES: (1) Adams R.W. *et al*., *Science,* **2009**, 323, 1708-11. (2) Semenova *et al*., *Analytical Chemistry*, **2019**, 91, 6695-6701. (3) Hill-Casey *et al*., *Molecules*, **2019**, 24, 4162.

Spin order of molecular hydrogen in PHIP and SABRE experiments

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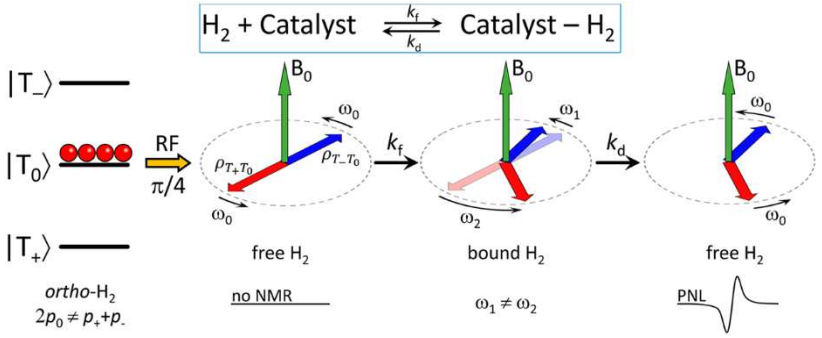

The NMR signal of dissolved molecular hydrogen enriched in parahydrogen (p-H_2) exhibits in the presence of an organometallic hydrogenation catalyst an unusual, Partially Negative Line (PNL) shape. It results from a strongly enhanced antiphase two-spin order $I_{1z}I_{2z}$ connected to the population of the T_0 level of orthohydrogen (o-H_2). This two-spin order is made visible by a slow asymmetric exchange process between free hydrogen and a transient catalyst-hydrogen complex. By Only Parahydrogen Spectroscopy (OPSY) it is possible to selectively detect the two-spin order and suppress the signal from the thermal o-H_2. The intensity of the PNL can be strongly affected by the PArtially NEgative Line (PANEL) experiment, which irradiates a long narrow-band RF pulse. When the RF field is in resonance with the chemical shift values of the hydrogen bound to the elusive catalyst or of the free hydrogen, a strong intensity reduction of the PNL is observed. Numerical simulations of the experiments show that the indirect detection has at least 3 orders of magnitude higher sensitivity than the normal NMR experiment. A theoretical model, including reversible binding and S-T_0 evolution, is developed, which reproduces the NMR line shape, the nutation angle dependence and the dependence on the frequency of the irradiation field of the PNL and permits the determination of the proton chemical shift values and the sign of the scalar coupling in the transient NMR invisible complex where singlet-triplet conversion take place. Additionally, we have determined the rate of the singlet-triplet conversion in H_2 at variable magnetic field and measured the field dependence of the PNL intensity: these results allow one to estimate the efficiency of S-T_0 conversion in PHIP/SABRE systems.

Singlet-triplet conversion in molecular hydrogen has important consequences for PHIP/SABRE experiments. Specifically, NMR methods used for transferring spin order of H_2 to other nuclei need to be modified. Here we demonstrate that methods proposed for the initial singlet order may not work for the $I_{1z}I_{2z}$ order; however, a simple modification using an RF-pulse on the proton channel makes them efficient again. Measurements of the dependence of the signal enhancement on the RF-pulse duration give a reliable estimate of the relative contribution of the antiphase spin order and singlet spin order.

THE VIRTOUS TRIANGLE: PARAHYDROGEN, LONG-LIVED STATES, AND HYPERPOLARIZATION

Malcolm H. Levitt

University of Southampton, UK

Para-enriched hydrogen is in a state of enhanced nuclear singlet order, which is one example of a long-lived spin-state with a frequently extended relaxation time compared to ordinary nuclear spin magnetization. Hence it is not surprising that there is a great deal of synergy between parahydrogen-enhanced NMR methodology and that of long-lived states. I will explore some of that synergy in my talk. Possible topics include:

- The mathematical constraints on unitary spin evolution, with and without symmetry
- The symmetry theory of long-lived states
- Singlet-to-magnetization conversion methodology and applications to PHIP

In addition I hope to touch on some new tweaks to parahydrogen-induced polarization, including:

- trans-vicinal hydrogenation and the hyperpolarization of fumarate
- geminal-PHIP and singlet-hyperpolarized CH_2 groups.

Exploring New Spin Physics for High and Low Field SABRE

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Signal Amplification By Reversible Exchange, or SABRE[1], is an exciting hyperpolarization method that has attracted much attention in the last decade. While SABRE has come far in this time, there is still much work to do to push the limits of achievable hyperpolarization from SABRE as well as broaden its accessibility to the scientific community. Recently[2], we introduced a new master equation for exchange that accounts for all moments of the exchange interaction without any additional computational cost over traditional master equation methods. Performing simulations within this framework allows for significantly accelerated exploration of the SABRE phase space than would be permitted by experiments. Even simple "pulse-delay" type sequences, where ^{15}N SABRE targets are polarized in a coherent SABRE-SHEATH[3] mode and then allowed to exchange during a holding field, generate highly structured hyperpolarization dynamics in unexpected regions of phase space (Figure 1). For any appreciable delay length (on the order of ligand exchange), these structures are exquisitely sensitive to inhomogeneities, and thus quickly become unobservable in experiments. However, this has spurred new insights into practical pulse sequence design and optimization, which aim to both increase achievable polarization and expand experimental regimes where SABRE is possible. Our progress on the development on a collection of new SABRE pulse sequences and experimental results will be presented.

References

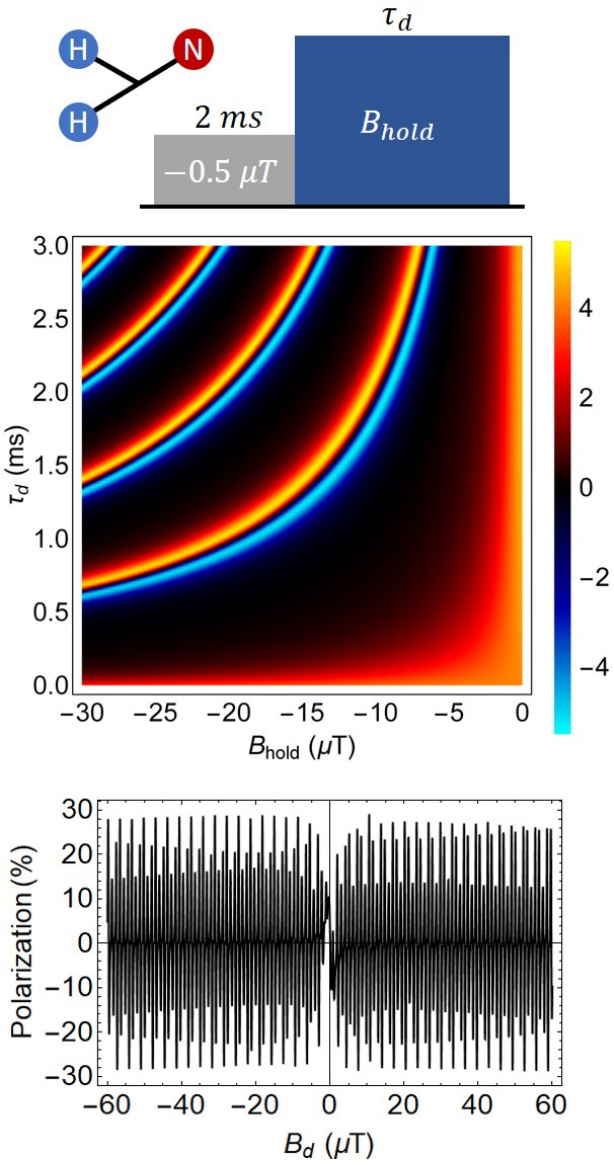
1 Adams, R. W. *et al.* Reversible interactions with para-hydrogen enhance NMR sensitivity by polarization transfer. *Science* **323**, 1708-1711, doi:10.1126/science.1168877 (2009).

2 Lindale, J. R., Eriksson, S. L., Tanner, C. P. N. & Warren, W. S. Infinite-order perturbative treatment for quantum evolution with exchange. *ArXiV* **2003.02342** (2020).

3 Theis, T. *et al.* Microtesla SABRE Enables 10% Nitrogen-15 Nuclear Spin Polarization. *J. Am. Chem. Soc.* **137**, 1404-1407, doi:10.1021/ja512242d (2015).

Acknowledgments

This work was supported by the National Science Foundation grant CHE-1665090.



Unexpected hyperpolarization dynamics using short delay lengths in coherent SABRE-SHEATH. Even on simple SABRE (AA'B) systems, the combination of small flip angle ($-0.5\,\mu T, 2\,ms$) and short ($\tau_d < 4\,ms$) delays generates highly structured hyperpolarization dynamics. This indicates the ability to generate on the order of 2% spin polarization in 60 ms of experiment. For longer delay lengths (bottom), this produces incredibly structured field dependences that are not experimentally accessible.

Long-lived nuclear spin order: theory and applications

G. Pileio

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Although the existence of singlet states has been known for many decades in magnetic resonance, the way to manipulate these and the exploitation of their features has only started in 2004 after the publication of the first paper on the subject by the Levitt's group. From early 2005, I had the privilege to work on this topic firstly as the subject of my postdoctoral researches and, more recently, as one of the interests of my own research group. In 2019, upon invitation by the Royal Society of Chemistry UK, I edited the first book on the subject containing contributions from a number of well-respected colleagues that share with me a deep interest on the topic and have so far contributed with brilliant ideas and applications of this form of spin order.

In this talk I will resume the content of the book by briefly introducing the basics of singlet order NMR and then highlighting a few (for the sake of time) of the applications described in the book. The subject of long-lived singlet order is of clear interest to the parahydrogen-enhanced NMR community with the book containing explicit examples of combinations of singlet order with the PHIP and SABRE techniques.

I will finally describe a new technique developed in my group to measure the lifetime of long-lived spin order in a single shot which may enable important new possibilities when combined with parahydrogen and other hyperpolarisation techniques.

Zero to earth's field NMR: relaxometry and spectroscopy via atomic sensing

Michael CD Tayler

Institute of Photonic Sciences, The Barcelona Institute of Science and Technology (Spain)

Nuclear spin systems often behave interestingly as a function of magnetic field. The SABRE method of parahydrogen-induced hyperpolarization, as an example, relies upon spin-eigenstate level anticrossings occurring at specific magnetic fields. A detailed study of these field-dependent effects usually demands switchable magnet apparatus and/or shuttling of samples from one magnetic location to another, to access a range of magnetic fields anywhere from a few nanotesla to several tens of tesla. The choice of apparatus is based primarily upon available field range, spectroscopic resolution and sensitivity depending on timing, power consumption, cost and size constraints.

This talk will discuss principles, merits and challenges of such field-cycling NMR experiments performed in the range 1 nT to 20 mT, inside magnetically shielded enclosures. Current experimental demonstrations focus on liquid-state systems where chemical shifts do not need to be resolved: (1) ultralow-field homonuclear T_1 and T_2 relaxation times to characterize surface motion effects in pore-confined liquids, including an example of T_1/T_2 convergence below 100 Hz Larmor frequency; (2) heteronuclear-J-coupled systems. I will discuss fast-field-cycling NMR across the Hz to MHz ^{1}H Larmor frequency range, coupled with NMR detection at arbitrary Larmor frequency from Hz to several kHz using a DC-field-tunable atomic magnetometer (see Figure 1).

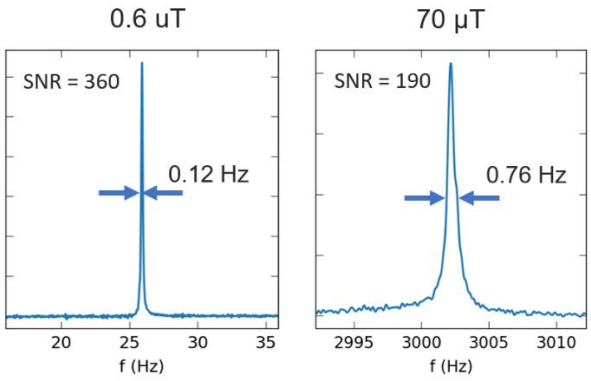
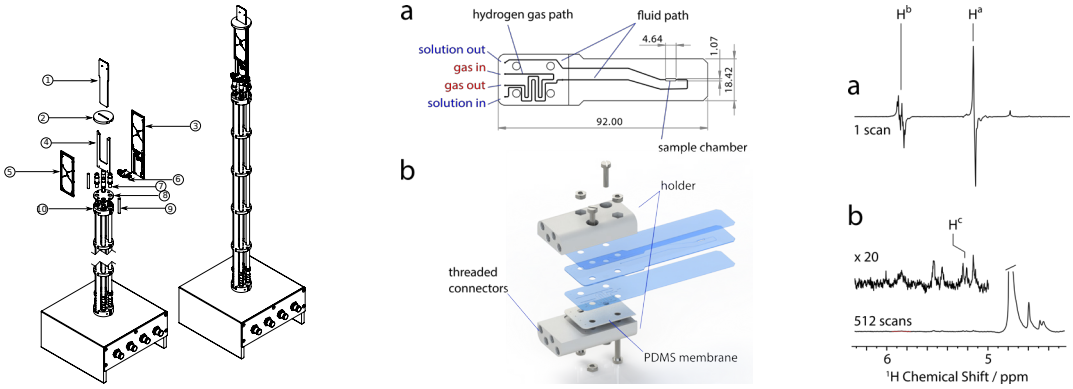


Figure 1: Optical magnetometry techniques enable tunable and high-resolution NMR detection from zero field to above the geomagnetic field range without major variation in sensitivity. The above spectra were recorded using the same instrument, for a test sample of H2O (0.1 mL, initial spin polarization ~1 ppm, single scan).

Marcel Utz, Sylwia Ostrowska, and Manvendra Sharma
School of Chemistry, University of Southampton, UK

Microfluidic lab-on-a-chip (LoC) devices are increasingly used in medical diagnostics, but also in chemistry and life science research. They provide detailed control over experimental conditions, which is of particular importance for cultures of cells, tissues, and small organisms, and offer advantages of experimental throughput, cost, and scaling. Information readout is not typically done by NMR, but by fluorescence-based assays. By contrast, NMR is rarely used, mostly due to its limited sensitivity, which is exacerbated by the small sample volumes. At the same time, NMR spectroscopy is an ideal tool to investigate live processes, due to its non-invasive nature, the ability to resolve complex mixtures and analyse them quantitatively. Over the past few years, we have developed an integrated NMR LoC platform based on a transmission line probe design [1], which accommodates generic planar microfluidic devices of nearly arbitrary design and complexity. This system allows high-resolution NMR spectra to be obtained from sample volumes around 1 µL with an absolute limit of detection of 1 nmol$\sqrt{s}$, corresponding to 1 mM$\sqrt{s}$ in terms of sample concentration.

Microfluidic systems offer the additional opportunity to integrate some of the chemical and spin manipulations necessary for hyperpolarisation into the same LoC platform. We have recently shown that parahydrogen-induced polarisation can be implemented on a microfluidic platform [2], resulting in an increase in a ^{1}H sensitivity in the pmol$\sqrt{s}$ range. However, the yield of hyperpolarised substrate in this system needs to be increased significantly for practical applications. In this presentation, we will discuss efforts at improving performance through kinetic modelling of the hydrogenation process, as well as strategies for onward conversion of the hyperpolarised substrate to biologically meaningful metabolites.



References

1. Sharma, M. & Utz, M. Modular Transmission Line Probes for Microfluidic Nuclear Magnetic Resonance Spectroscopy and Imaging. *Journal of Magnetic Resonance* **303,** 75–81 (2019).
2. Eills, J., Hale, W., Sharma, M., Rossetto, M., Levitt, M. H. & Utz, M. High-Resolution Nuclear Magnetic Resonance Spectroscopy with Picomole Sensitivity by Hyperpolarization on a Chip. *J. Am. Chem. Soc.* **141,** 9955–9963 (2019).

Promoted Speakers' Abstracts

Long-Lived Spin States of HP hydrocarbon gases

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In this work, we report the presence of long lived spin states (LLSS) in hyperpolarized (HP) molecules prepared via Parahydrogen Induced Polarization (PHIP) experiments [1,4,5] and spin-Lock Induced Crossing (SLIC) [2]. LLSS created by HP propane and HP diethyllether (DE) will be discussed.

HP DE. We report low-cost high-throughput preparation of HP DE which can potentially be applied as a HP contrast agent on pulmonary imaging using clinically available MRI scanners. High proton polarization levels (8%) and near complete chemical conversion within seconds have been observed for HP DE prepared by pairwise addition of parahydrogen (pH_2) to ethyl vinyl ether (Figure 1). Although gas-phase T_1 relaxation of hyperpolarized diethyl ether (p=0.5 bar) is very efficient with T_1 of 1.2 s, we demonstrate that at low magnetic fields, the use of LLSS created via pairwise parahydrogen addition extends the relaxation decay by approximately 3-fold, paving the way to bioimaging applications and beyond.

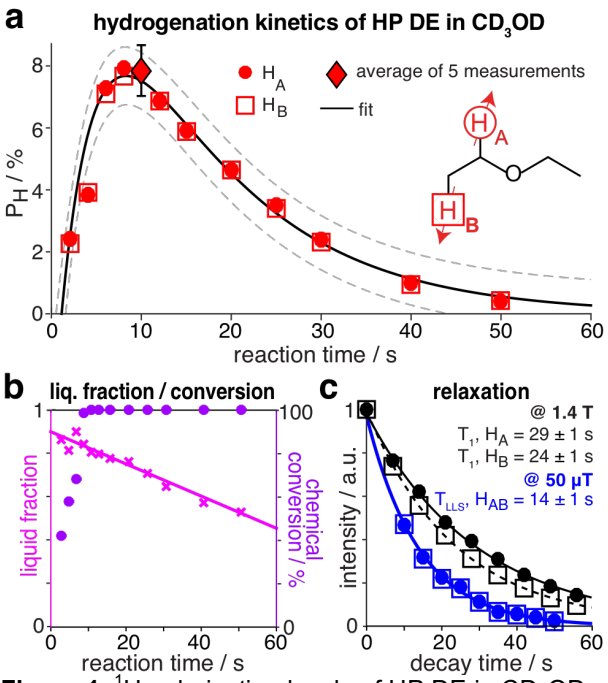

Figure 1. ^{1}H polarization levels of HP DE in CD_3OD as a function of reaction time in the Earth's magnetic field (50 μT). b) DE liquid fraction and chemical conversion of EVE to DE. c) Exponential decays of HP DE NMR signals at 1.4 T and the Earth's field.

HP Propane A systematic study of relaxation dynamics of propane and propane-d_6 prepared by heterogeneous pairwise pH_2 addition to propylene and propylene-d_6 was performed. Transformation of LLSS of HP propane into observable magnetization was accomplished by SLIC pulses. T_{LLSS} of HP propane is about three times longer than the corresponding T_1 value at clinically relevant conditions of 1 atm (~3 s vs. ~1 s). Propylene deuteration results in shorter T_{LLSS} values. However, another study conducted on propylene and cyclopropane deuteration reveals the presence of additional reaction pathways resulting in some symmetric isotopologues (which are NMR invisible when using parahydrogen). These more symmetric propane products may potentially have even longer proton polarization relaxation constants. Moreover, the presence of additional "NMR" invisible pathways suggests that the previously reported proton polarization values are likely several times greater (exceeding 6%) [3].

REFEERNCES: (1) Ariyasingha, N.M., Salnikov, O.G. *et al, JPCC* **2019**, *123*, 11734. (2) DeVience, S.J.; Walsworth, R.L.; Rosen, M.S. *Phys. Rev. Lett.* **2013,** *111*, 173002. (3) Salnikov, O.G. *et al,* ChemPhysChem **2018**, 19, 2621– 2626. (4) Kovtunov, K. V.; Truong, M. L.; Barskiy, D. A.; Koptyug, I. V.; Coffey, A. M.; Waddell, K. W.; Chekmenev, E. Y. *Chem. Eur. J.* **2014,** *20* (45), 14629–14632. (5) Barskiy, D. A.; Salnikov, O. G.; Romanov, A. S.; Feldman, M. A.; Coffey, A. M.; Kovtunov, K. V.; Koptyug, I. V.; Chekmenev, E. Y. *J. Magn. Reson.* **2017,** *276*, 78-85.

ACKNOWLEDGEMENTS: NSF CHE-1904780, DOD CDMRP W81XWH-15-1-0271 and W81XWH-15-1-0272.

Highly Polarized and Long-Lived Metronidazole $^{15}NO_2$ Spin-Relays over Six Chemical Bonds using SABRE-SHEATH

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Hyperpolarization of ^{15}N-labelled sites enables metabolic magnetic resonance spectroscopy (MRS) and MRS imaging (MRSI) of a variety of biomolecules, with significant translational application to the detection of abnormal metabolic processes in cancer and other diseases. Signal Amplification by Reversible Exchange (SABRE) is a relatively simple and inexpensive technology utilizing simultaneous chemical exchange between a parahydrogen (pH_2) polarization source and to-be-hyperpolarized (HP) biomolecules in the presence of a catalyst and a micro-tesla (μT) magnetic field (SABRE in SHield Enables Alignment Transfer to Heteronuclei, SABRE-SHEATH).[1] This process facilitates rapid increases in ^{15}N nuclear spin polarization, P_{15N}, up to 30% on timescales <1 minute,[2,3] and with long lifetimes >10 minutes,[4] presenting significant advantages over alternative spectroscopic techniques such as ^{13}C dissolution dynamic nuclear polarization (d-DNP).

Previous studies of ^{15}N hyperpolarization using SABRE-SHEATH have reported on direct or close proximal contact between ^{15}N-labelled sites and the Ir-IMes polarization transfer catalyst (PTC). Two-bond ^{1}H-^{15}N spin-spin couplings are appreciably strong, resulting in fast and efficient (*e.g.* high P_{15N}) polarization transfer from parahydrogen-derived hydrides to the ^{15}N nucleus that binds to the SABRE catalyst.[1] However, recent demonstrations have shown that a network of *J*-coupled spin *I*=½ nuclei (*e.g.* ^{15}N-^{15}N as demonstrated here) has the potential to transmit polarization over significantly greater intra-molecular distances. This facilitates efficient polarization of a wide range of compounds relevant to biomedicine, including uniformly ^{15}N-labelled metronidazole (MNZ-$^{15}N_3$), an FDA-approved antibiotic.

In this study, we demonstrate hyperpolarization of each of the three ^{15}N sites in 20-40 mM MNZ-$^{15}N_3$ to P_{15N} >16% (a >300,000-fold enhancement relative to thermal ^{15}N polarization of ^{15}N-pyridine at 1.4 T) in ~1 minute using SABRE-SHEATH at 0.4 μT. Spin-relayed polarization transfer via the network of two-bond ^{15}N-^{15}N spin-spin couplings is evident from our study (four and six chemical bond separation with respect to the hydride, respectively). The HP $^{15}NO_2$ site in particular exhibits a long *in vitro* lifetime, with exponential decay constant T_1 = 9.7±1.0 mins at 1.4 T, showing promise for potential *in vivo* biosensing applications in the future.

ACKNOWLEDGMENTS: NSF under CHE- NSF CHE-1904780, DOD CDMRP BRP W81XWH-12-1-0159/BC112431, DOD PRMRP awards W81XWH-15-1-0271, W81XWH-15-1-0272 and R01CA16700. Russian Science Foundation (grant #17-73-20030), Russian Ministry of Science and Higher Education (project AAAA-A16-116121510087-5).

REFERENCES: **(1)** Theis, T., Truong, M.L., Coffey, A.M., *et al.*, J. Am. Chem. Soc. 2015, **137**, 1404-1407. **(2)** Kidd, B.E., Gesiorski, J.L., Gemeinhardt, M.E., *et al.*, J. Phys. Chem. C, 2018, **122**, 16848–16852. **(3)** Barskiy, D.A., Shchepin, R.V., Coffey, A.M., *et al.*, J. Am. Chem. Soc. 2016, **138**, 8080–8083. **(4)** Shchepin, R.V., Birchall, J.R., Chukanov, N.V., *et al.*, Chem. Eur. J. 2019, **25**, 8829-8836.

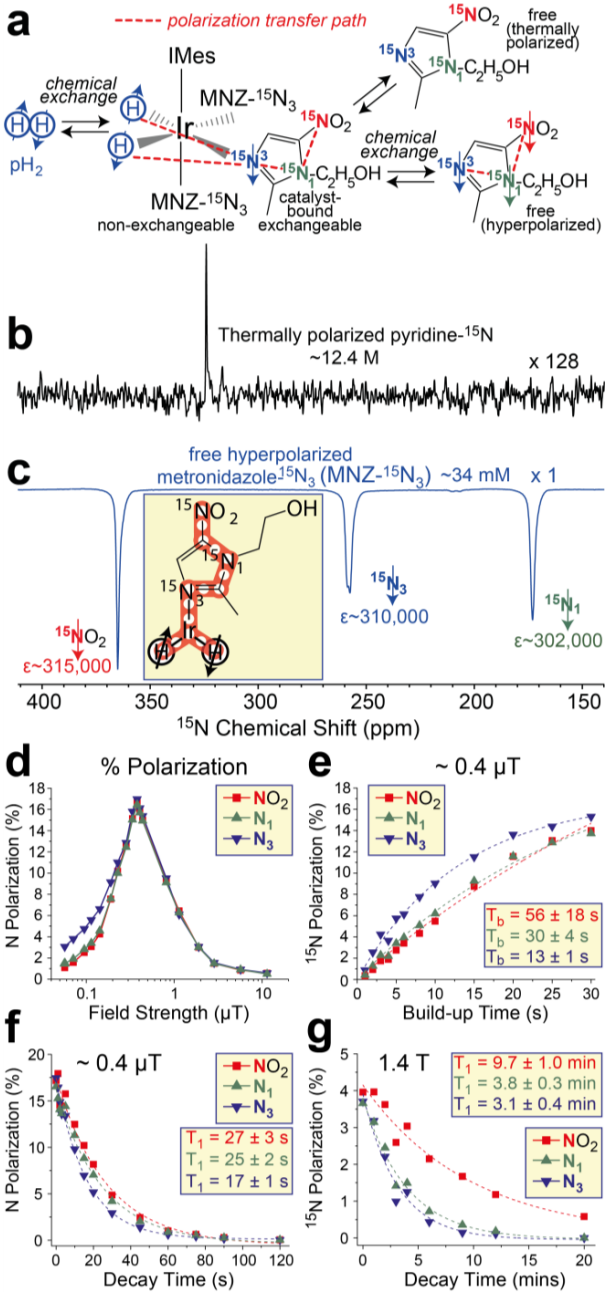

Figure 1. a) Schematic of SABRE hyperpolarization of MNZ-$^{15}N_3$. b) ^{15}N NMR spectrum of thermally polarized ^{15}N-pyridine signal reference. c) Corresponding ^{15}N NMR spectrum of HP MNZ-$^{15}N_3$. d) Dependence of ^{15}N polarization of HP MNZ-$^{15}N_3$ on magnetic field strength. e) ^{15}N polarization build-up of MNZ-$^{15}N_3$ at ~0.4 μT. f, g) ^{15}N polarization decay of HP MNZ-$^{15}N_3$ at ~0.4 μT and 1.4 T, respectively.

Parahydrogen discriminated signals used as a detection block with improved resolution

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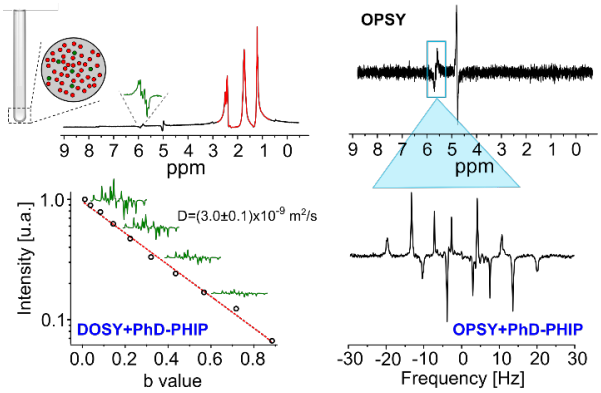

Highly diluted hyperpolarized hexyne (top left) thermal signals may be removed by using OPSY and spectral enhancement obtained by using OPSY+PhD-PHIP. (bottom left) shows a new DOSY+PhD-PHIP sequence

The signal enhancement in PHIP experiments if often reduced by a number of factors, being the most common ones line broadening due to B_0 inhomogeneities and spectral superposition with signals originated from thermally polarized molecules. We have proposed a solution to these topics by introducing the idea of acquiring PHIP signals during a train of refocusing pulses with specic phases, namely Parahydrogen Discriminated PHIP (PhD-PHIP) [1,2]. The different evolution of thermal and PHIP induced signals during this CPMG-like pulse sequence results in a large spectral separation upon Fast Fourier Transformation, enabling the clear identification of PHIP signals. In this way, partial *J*-spectra with information only concerning hyperpolarized molecules is obtained with improved resolution and sensitivity. Furthermore, the method can be easily implemented at low field equipment with very low magnetic field homogeneity for monitoring chemical reactions [3]. In the case of highly diluted samples, however, sensitivity still may pose a problem. In PhD-PHIP thermal signals are not removed but rather shifted to an entirely different part of the *J*-spectrum, still imposing a limitation in the settings of the receiver gain. This issue was tackled by the combination of OPSY (Only Parahydrogen SpectroscopY) as an encoding block and PhD-PHIP as a detection block, resuting in clear spectra as showin in the above figure [4]. In this presentation we will focus on the working principles of PhD-PHIP and explore the potential of combinig different pulse sequences for signal encoding. In particular we show results using a set of hollow Teflon membranes for parahydrogen dissolution on a target sample, which renders highly reproducible signals that enable the acquisition of 2D data sets. We will show a successful implementation of DOSY+PhD-PHIP where a double encoded pulsed field gradient was used to account for convexion.

[1] L. Buljubasich, I. Prina, M.B. Franzoni, K. Münnemann, H.W. Spiess, and R.H. Acosta. High resolution para-hydrogen induced polarization in inhomogeneous magnetic fields. *Journal of Magnetic Resonance*, 230:155-159, 2013.
[2] I. Prina, L. Buljubasich, and R. H. Acosta. High-Resolution Hyperpolarized *J*-Spectra with Parahydrogen Discrimination. *J. Phys. Chem. Lett.*, 4(22):3924-3928, 2013.
[3] I. Prina, L. Buljubasich, and R.H. Acosta. Parahydrogen discriminated PHIP at low magnetic fields. *Journal of Magnetic Resonance*, 251:1-7, 2015.
[4] S. Bussandri, L. Buljubasich, and R.H. Acosta. Combination of OPSY and PhD-PHIP results in enhanced sensitivity in PHIP. *Journal of Magnetic Resonance*, 299:28-32, 2019.

Investigating tumor metabolism using ParaHydrogen hyperpolarized [1-^{13}C]pyruvate

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An up-regulated conversion of pyruvate into lactate is a common feature of cancer cells and the use of hyperpolarized [1-^{13}C]pyruvate allows the detection of metabolic alterations both in cells and in vivo.

The PHIP-SAH strategy (PHIP by means of Side Arm Hydrogenation),[1] allowed to hyperpolarize pyruvate that, previously, could be obtained only by d-DNP.

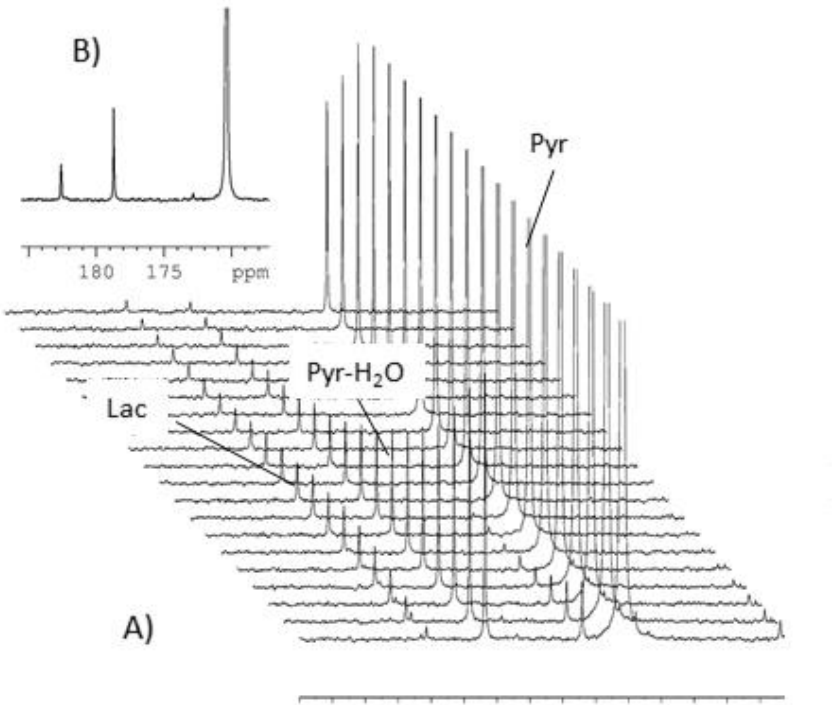

Figure 1 A) series of ^{13}C-NMR spectra acquired after the perfusion of a cells suspension (PC3 cells, 10M) with the aqueous solution HP-[1-^{13}C]pyruvate; B) expanded ^{13}C-NMR spectrum at maximum intensity of the lactate signal.

PHIP-SAH polarized [1- ^{13}C] pyruvate was added to cells suspensions (at the concentration of 5.0 ± 0.2 mM) in a 5 mm-NMR tube and series of ^{13}C-NMR spectra were acquired using a 14.1T NMR spectrometer. Different cancer cells lines were compared, characterized by a different degree of aggressiveness and ability to induce metastasis (Breast cancer cells: 4T1-168FARN, Prostate cancer cells: LnCap, DU145 and PC3).[2,3] The ^{13}C label exchange rate between pyruvate and lactate appeared higher in the more aggressive cell lines, for both breast and prostate cancer.

In vivo ^{13}C-MR dynamic studies were performed in a 1T or a 3T MR scanners, in order to assess the metabolic build-up of lactate. Space-selective ^{13}C-MR spectra were acquired on voxels centered on the tissue of interest and series of ^{13}C-MR spectra were acquired, using small flip angle pulses. Kinetic analysis of the metabolic exchange of the ^{13}C label between [1-^{13}C]pyruvate and [1-^{13}C]lactate were carried out by monitoring the time courses of their hyperpolarized signals.

In summary these studies have shown that *in vitro* and *in vivo* investigations of cancer metabolism, based on the administration of a dose of HP [1- ^{13}C]pyruvate obtained from the PHIP-SAH procedure, are well feasible.

REFERENCES: [1] Reineri F. et al. *Nat. Commun.* **2015** doi:10.1038/ncomms6858; [2] Cavallari E. et al. *Chem. Phys. Chem*. **2019**, 20, 318–325; [3] Cavallari E. et al, *Frontiers in Oncol.* **2020**, 10, 497.

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GemPHIP: accumulation of the singlet-order on methylene proton pairs

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Hyperpolarization using PHIP can be effectively achieved using a ruthenium-based *trans*-hydrogenation catalyst in contrast to typical *cis*-hydrogenation reactions [1,2]. This led to a development towards hyperpolarized metabolites such as fumarate, using pairwise trans-hydrogenation of an unsaturated precursor [3]. In addition to the main product, the ruthenium-based catalyst also forms a geminal hydrogenation (gem-hydrogenation) product [4], where the reaction with parahydrogen populates the singlet state of the methylene pair of protons. The singlet-order lifetime in methylene protons is often much longer than the T_1 relaxation time providing that singlet-triplet mixing is inhibited by a resonant RF field [5]. In this study we explore the geminal PHIP (gemPHIP) accumulation of hyperpolarized singlet order in the presence of a spin-locking field. PHIP measurements were conducted using *trans*-hydrogenation reaction of disodium acetylenedicarboxylate in D_2O with $[RuCp^*(MeCN)_3]PF_6$ as the catalyst. Experiments were carried-out utilizing spin locking at an elevated temperature of 333 K under a moderate pressure of 4 bar. Results indicated that the singlet state between geminal protons in our system is indeed long-lived. We interpreted our results by using a kinetic model involving nuclear spin dynamics as well as chemical kinetics. We find that suppressing singlet-triplet mixing by spin locking is an effective method to accumulate long-lived and hyperpolarized singlet order on methylene protons.

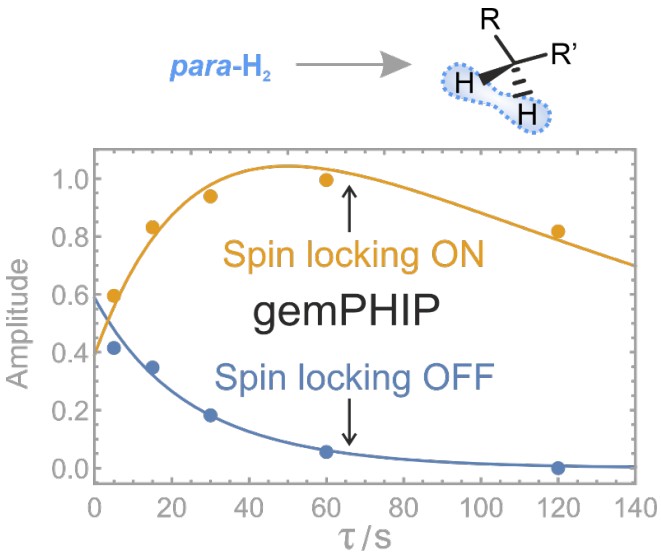

Figure 1. Accumulation of hyperpolarized spin order between geminal proton pairs during spin locking.

REFERENCES: [1] D. Schleyer et al., New J. Chem., 25, 3 (2001). [2] K. Radkowski et al., Angew. Chem, 52, 1 (2013). [3] B. Ripka et al, Chem. Commun., 54, 12246 (2018). [4] M. Leutzsch et al, Angew. Chem., 54, 42 (2015). [5] M. Carravetta, and M.H. Levitt, J. Am. Chem. Soc., 126, 6228 (2004).

Singlet-Contrast Magnetic Resonance Imaging

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For a number of reasons, ^{1}H would be the ideal nucleus for hyperpolarized MRI: ^{1}H-detection is highly sensitive, ^{1}H probes are readily available in commercial MRI scanners, protons are at ~100% natural abundance, and greater response to magnetic field gradients means higher spatial resolution can be obtained than for lower-γ nuclei. However, there are some significant drawbacks: protons typically relax relatively rapidly, and there is a large background signal in the body from water and fat.

PHIP-polarized fumarate opens a path to overcome these drawbacks. An unsaturated precursor molecule can be *trans*-hydrogenated to form fumarate [1], and the parahydrogen protons remain in a nonmagnetic singlet state since they are chemically and magnetically equivalent. This state is immune to certain relaxation mechanisms, meaning it can have a lifetime of over 1 minute [2]. This state is also unaffected by radiofrequency (rf) pulses, meaning the background ^{1}H NMR signals from water and fat in the body can be suppressed with rf pulse techniques, while the singlet state remains unperturbed. After enzymatic conversion to malate, the proton singlet state is broken, and hyperpolarized NMR signals are released.

The conversion of fumarate to malate is a step of the citric acid cycle observed in hyperpolarized ^{13}C-imaging experiments to detect cell necrosis *in vivo* [3]. In this work we demonstrate hyperpolarized ^{1}H imaging of the same process in D_2O. An out-of-phase echo (OPE) pulse sequence is continuously applied during the enzymatic conversion to suppress the background ^{1}H signals and convert the hyperpolarized malate PASADENA signals into in-phase magnetization for imaging, with 20% ^{1}H polarization achieved in this way.

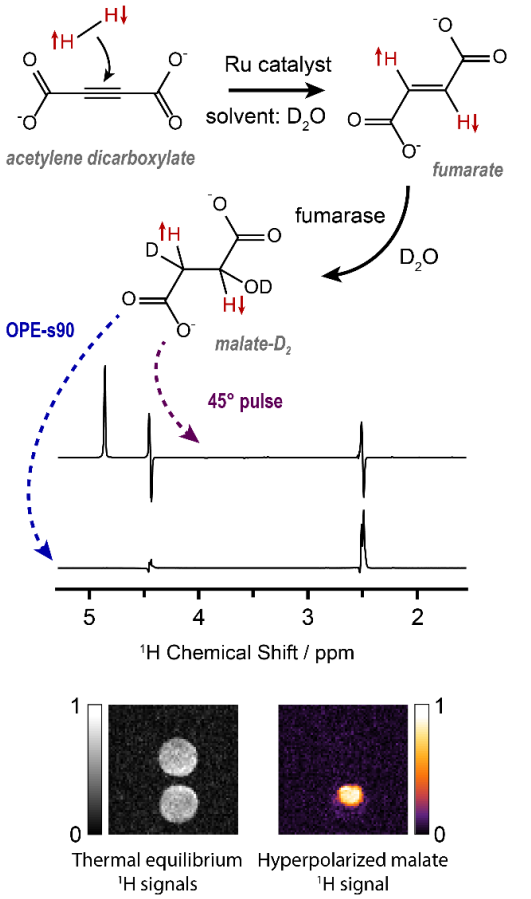

Figure 1: An OPE pulse sequence generates in-phase magnetization on the malate protons and supresses the water background. The images show two phantoms containing D_2O and fumarase, and hyperpolarized fumarate was injected into the lower one for singlet-contrast imaging.

REFERENCES: (1) J. Eills et al., *J. Am. Chem. Soc.* **2019**, 141, 51, 20209–20214. (2) A. Bornet et al., *Chem.–Eur. J.* **2014**, *20* (51), 17113–17118. (3) F. A. Gallagher et al., *Proc. Natl. Acad. Sci.* **2009**, 106 (47), 19801-6

Parahydrogen-polarized [1-^{13}C]fumarate – a path to in vivo application

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Fumarate is a biomolecule which is converted to malate by the enzyme fumarase in the citric acid cycle. This change in chemical identity provides a sensitive probe of cell necrosis, and can be observed via carbon-13 magnetic resonance imaging after in vivo injection of hyperpolarized fumarate. Fumarate transport through a cell membrane is a slow process: in regions of healthy cells the conversion to malate is slow and generally unobservable; however, if the cell membrane is ruptured, the enzyme fumarase leaks into the surrounding tissue, and the rate of malate formation is dramatically enhanced. ^{13}C imaging of fumarate-to-malate conversion has been used to detect tumour cell necrosis in mice [1], measure tumour response to therapy [2], and study acute kidney injury [3]. The technique is currently being assessed for application in clinical trials.

Until recently, it has only been possible to produce ^{13}C-hyperpolarized fumarate via dissolution dynamic nuclear polarization. We have shown that fumarate can also be hyperpolarized using parahydrogen, which is achieved by *trans*-hydrogenation of a precursor molecule [4]. In this work we show that parahydrogen-polarized [1-^{13}C]fumarate can be rapidly formed at a concentration of 45 mM (>90% yield) in less than 10 s, with the biomolecule succinate being the major side-product. A magnetic field sweep is applied to transform the proton singlet order into ^{13}C magnetization, with ~30% ^{13}C polarization readily achieved. The hyperpolarized fumarate is then injected into cell suspensions, and we observe the enzymatic conversion to malate [5]. We additionally show advances in the achievable concentration of [1-^{13}C]fumarate, and a method to purify the solution of the catalyst precursor.

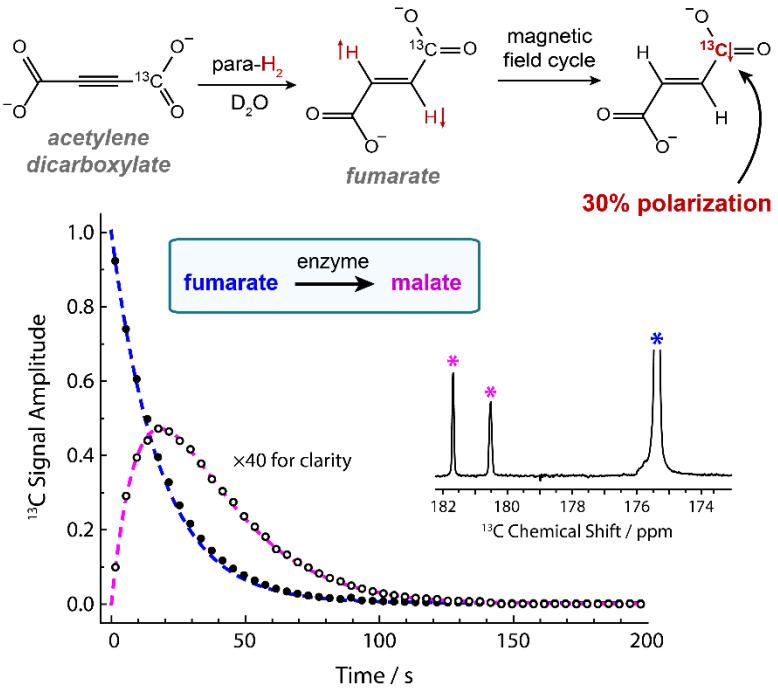

Figure 1: Top: the chemical reaction used to form fumarate via *trans*-hydrogenation, followed by a magnetic field cycle to polarize the ^{13}C nucleus. Bottom: conversion to malate after injecting the hyperpolarized [1-^{13}C]fumarate into a suspension of lysed cells.

REFERENCES: [1] F. A. Gallagher et al., *Proc. Natl. Acad. Sci.* **2009**, 106 (47), 19801-6. [2] F. A. Gallagher et al., *Prog. Nuc. Magn. Reson.* **2009**, 4 (55), 285-295. [3] M. R. Clatworthy et al., *Proc. Natl. Acad. Sci.* **2012**, 109 (33), 13374-13379. [4] B. Ripka et al., *Chem. Commun.* **2018**, 54, 12246-12249. [5] J. Eills et al., *J. Am. Chem. Soc.* **2019**, 141, 51, 20209–20214

3D *operando* visualization of complex heterogeneous catalytic system using parahydrogen

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Magnetic resonance imaging (MRI) can be used to investigate heterogeneous catalytic reactions under *operando* conditions. However, MRI has several limitations, especially during the studies of gas phase, where the spin density of the reagents and products is much lower comparing with the spin density in the liquid phase. In addition, inhomogeneities of magnetic field caused by the catalytic reactor further complicates the study. Hyperpolarization techniques help to overcome these limitations. In particular, parahydrogen-induced polarization (PHIP) allows one to enhance the NMR signal by several orders of magnitude and makes possible MRI visualization of hydrogenation processes in the gas phase.

This work continues the previous studies of 1,3-butadiene hydrogenation[1] and demonstrates the possibility of selective MRI in the complex catalytic system containing 3 different catalyst coatings (Pd/SiO_2, Rh/SiO_2, Pt/SiO_2) distributed along the axis of a glass tube. Selective MR imaging was done using true-FISP pulse sequence in a pseudo-3D mode. Eight 2D slices with 3 mm thickness were registered one after another, then they were converted into a 3D model using MATLAB (Figure 1), the resulted spatial resolution is 0.625×0.625×3 mm^3/pixel. For each reagent and product, ^1H MRI was done with parahydrogen (pH_2) and normal hydrogen (nH_2) to analyze areas of preferred formation of hyperpolarized products.

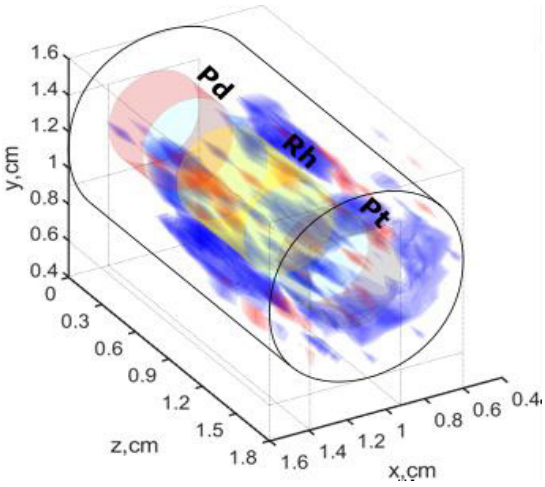

Figure 1. ^1H selective MRI of hyperpolarized gas without contribution of thermally polarized gas. The selective imaging was done using CH_2 group of 1-butene obtained during heterogeneous hydrogenation of 1,3-butadiene with pH_2 or nH_2. The reaction condidtions are following: 1,3-butadiene : pH_2 (or nH_2) ratio = 1 : 2, 1.9 mL s^{-1} flow rate, 70 °C. Three areas with the catalyst Pd/SiO_2, Rh/SiO_2, Pt/SiO_2 are labelled. The blue volume around the reactor indicates the formation regions, the red color indicates the consumption regions of 1-butene.

As a result, the mechanistic insights into hydrogenation processes were obtained. It was shown that the main part of 1-butene is formed near the reactor surface with Rh nanoparticles. The formation of the hyperpolarized 2-butene was preferably observed in regions where Rh and Pd were located. As for the hyperpolarized butane, it was preferably formed on the Pd/SiO_2 catalyst and to a lesser extent on the Pt/SiO_2 catalyst. These results demonstrate the possibility to use MRI as a highly sensitive *operando* method for detailed studies of the catalytic processes in heterogeneous systems.

REFERENCES: (1) Svyatova, A.; et. al. *Catal. Sci. Technol.* **2020**, *10*, 99–104.

ACKNOWLEDGMENTS: This work was supported by the Russian Science Foundation (grant # 19-13-00047).

Hyperpolarized ^{13}C MRI of Fumarate Using Selective *trans*-Alkenylation Catalyst with Parahydrogen.

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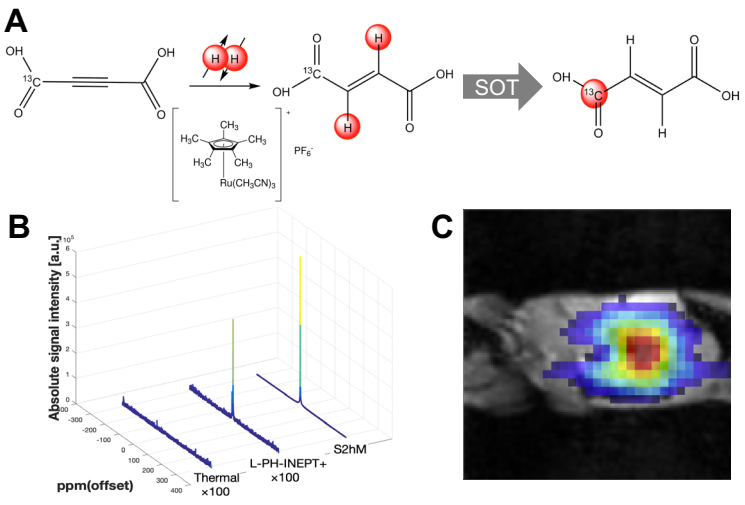

Figure 1. A) Preparation of hyperpolarized [1-^{13}C]fumarate by *trans*-alkenylation with parahydrogen. B) ^{13}C NMR of hyperpolarized fumarate using different spin order transfer methods. C) CSI of hyperpolarized ^{13}C fumarate in mouse.

Cell death is commonly observed in various diseases including inflammation, cardiac infarction, stroke, cancer treatment etc. Metabolic flux of exogenously administered hyperpolarized ^{13}C fumarate into malate can serve as a non-invasive imaging biomarker for necrotic cell death[1]. Although typical parahydrogenation of alkynes result in *cis*-alykenes as reaction products, a novel *trans*-selective ruthenium-based catalyst has recently been shown to demonstrate hyperpolarized [1-^{13}C]fumarate by parahydrogen addition to [1-^{13}C]acetylene dicarboxylate[2,3]. In this study, we at first established a cost-effective synthetic route for high yield of the fumarate precursor [1-^{13}C]acetylene dicarboxylate from ^{13}C sodium acetate as a starting material. Of note, one side ^{13}C labeling is mandatory for PHIP, instead of doubly-labeled [1,4-^{13}C]fumarate widely used in DNP studies. Several different ^{1}H-to-^{13}C spin order transfer methods including a magnetic field cycling (MFC) and INEPT-type pulse sequences L-PH-INEPT+ and S2hM[4] were compared. More than 12% ^{13}C polarization at the time of MRI scan was achieved by MFC and S2hM with $Cp^*Ru(MeCN)_3PF_6$ as a *trans*-selective hydrogenation catalyst. Mixing hyperpolarized [1-^{13}C]fumarate with tumor homogenate showed time dependent generation of [1-^{13}C]malate peak. Non-invasive chemical shift imaging of hyperpolarized [1-^{13}C]fumarate was feasible in mice using a 1.5T $^{1}H/^{13}C$ MRI scanner. Although the resulting fumarate concentration was relatively low (~10mM after 30 sec parahydrogen bobbling), these results show promise toward the feasibility of non-invasive cell death imaging with hyperpolarized ^{13}C fumarate by the parahydrogen induced hyperpolarization techniques.

REFERENCES: (1) Gallagher, F.A.; et al. *PNAS*. 2009, 106, 19801-6 (2) Ripka, B.; et al. *Chem. Commun.* 2018, 54, 12246-9. (3) Ellis, J. et al. *J. Am. Chem. Soc.* 2019, 141, 20209–14 (4) Stevanato, G.; et al. *J. Magn. Reson*. 2017. 277, 169-178.

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Polarizing Poison: Signal Amplification By Reversible Exchange (SABRE) of Fentanyl Derivatives

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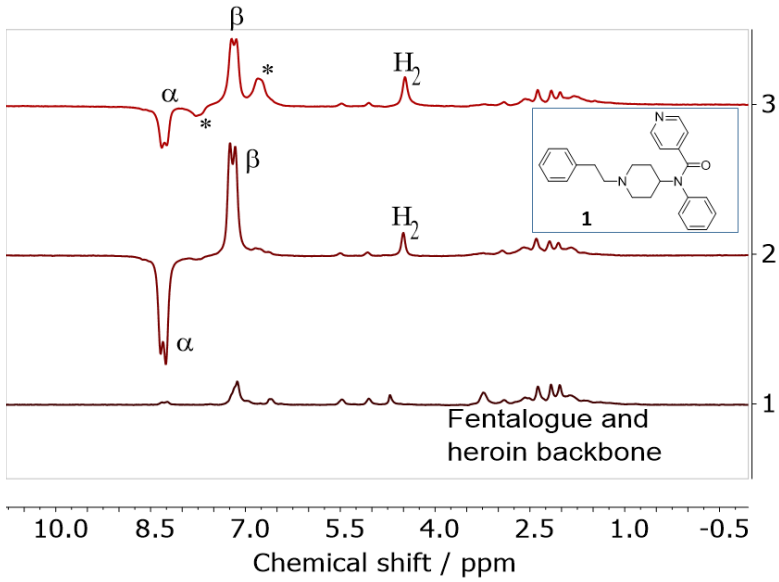

Figure 1. ^{1}H NMR spectra of **1**, heroin (3:97 **1**:heroin), and [Ir(IMes)(COD)Cl] in the ratio of 4:1 (relative to **1**) in the presence of *para*hydrogen in CD_3OD. Spectrum 1 is the thermal spectrum whereas spectra 2 and 3 are hyperpolarized following polarization transfer in earth's magnetic field, with 3 being collected subsequent to 2. Spectra collected at 60 MHz. α and β refer to the ortho- and meta-pyridyl protons respectively of 5. * indicates bound **1** of $[Ir(IMes)(\mathbf{1})_3(H)_2]^+$.

Signal Amplification By Reversible Exchange (SABRE), first reported in 2009,[1] allows for the creation of a hyperpolarized state in solution without chemical manipulation of the substrate. For example, World Health Organization essential medicines have been polarized without chemical modification.[2]

Despite also being a World Health Organization essential medicine, fentanyl has recently become a drug of abuse with an estimated potency of ~500 times that of morphine. This poses a serious threat to public health with quantities as low as ~2 milligrams enough to induce overdose. In particular, the lacing of heroin samples with fentanyl for increased potency and decreased production cost has been a major contributing factor to thousands of deaths per year in the US and an increasing number across Europe.

A range of fentanyl analogues (fentalogues), some of which are more potent than fentanyl, have recently appeared on the international drugs market however, due to the small quantities typically present, existing detection technology struggles to rapidly detect low concentrations of fentanyl or fentalogues.

We present results for the hyperpolarization of known biologically active fentalogues and unknown fentalogues produced through the systematic derivatization of fentanyl. The successful SABRE hyperpolarization of fentalogues is discussed in relation to concentrations commensurate with the lethal dose.

The application of SABRE to a more realistic sample of fentalogue spiked heroin was tested and in a fentanyl/heroin mixture with 3% fentalogue, hyperpolarization is observed.[3] It is envisaged the application of SABRE could enable fentalogue detection on a benchtop instrument in a single scan, increasing the accessibility, and rapidity, of detection with a view towards a forensic application.

REFERENCES: (1) Adams, R. W.; et al. *Science*, **2009**, *323*, 1708-1711, 2009. (2) Olaru, A. M.et al.; *ChemistryOpen*, **2018**, *7*, 97-105. (3) Robertson, T. B. R.; et al. *ChemistryOpen*, **2019**, *8*, 1375-1382.

ACKNOWLEDGEMENTS: Manchester Metropolitan University is thanked for a Vice Chancellor studentship for TBRR. The Natural Sciences and Engineering Research Council of Canada (396154510) and Fonds de Recherche du Québec - Nature et Technologie (206375) are thanked for funding for NG.

Multi-Physics Modelling of PHIP on a Microfluidic Chip

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Microfluidic lab-on-a-chip (LoC) devices can combine synthesis, separation and analytical steps onto a single platform. It has recently been shown that integrating parahydrogen-induced polarization (PHIP) on a LoC device, in combination with optimized micro-NMR probes, can provide a continuous stream of hyperpolarized material. Mass sensitivities of the order of 2 $\mathrm{pmol}\sqrt{s}$ have been achieved in this way [1]. However, for practical applications, the efficiency and yield of this system must be improved. This requires quantitative understanding of the interplay between chemical reactions, transport processes, and spin dynamic in the fluid flowing in the LoC system.

In this work we demonstrate a spatially resolved kinetic model of a hydrogenation reaction (fig 1a) in a LOC device. The finite element simulation domain consisted of a PDMS membrane and a fluid channel with a sample chamber as shown in fig 1b. The simulation combines three separate finite element domains, which are coupled to the full model. The flow pattern in the channel is found by solving the Navier-Stokes equation. The resulting velocity distribution is used in a reaction-diffusion-convection simulation of the hydrogenation reaction in the channel. Finally, the uptake of parahydrogen through a PDMS membrane is modelled in a separate finite element domain, which is coupled to the flowing liquid through an appropriate boundary condition. Reaction rates were obtained from fitting of independently measured experimental data.

The finite element model predicts the concentration of species involved in the reaction as a function of flow rate. Fig 1c shows the change in concentration of allyl acetate and fig 1d in hydrogen. Understanding the concentration changes and species distribution throughout the device will aid design of more optimized devices.

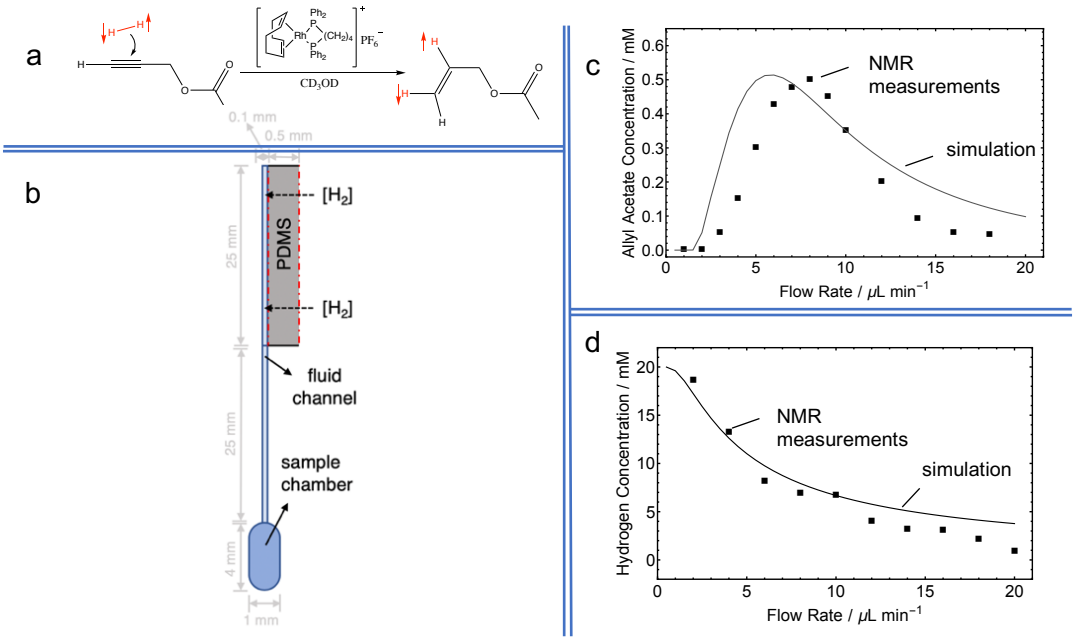

Figure 1 a) scheme of the hydrogenation reaction b) geometry of the simulation domain c) allyl acetate concentration in the sample chamber as a function of flow rate d) hydrogen concentration in the sample chamber as a function of flow rate.

References

[1] Eills, J.; et al. *J. Am. Chem. Soc.* **2019**, 141, 25, 9955–9963

NMR Signal Enhancement in Hydrogenation Reactions over Differently Prepared Heterogeneous Rh/TiO_2 Catalysts

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Parahydrogen-induced polarization (PHIP) is one of the hyperpolarization techniques, used for increasing the inherently low sensitivity of NMR spectroscopy. PHIP is based on the conversion of correlated spin order of parahydrogen (p-H_2) into polarization of a target molecule via catalytic hydrogenation. For a successful observation of PHIP effects in NMR spectra of hydrogenation products, two atoms from the same p-H_2 molecule should be added to the same substrate molecule – *i.e.* hydrogenation process should occur via pairwise addition of the hydrogen atoms. Among heterogeneous catalysts, the most promising results have been shown by Rh/TiO_2 which demonstrated high catalytic activity and stability in combination with substantial for this type of catalysts percentages of pairwise hydrogen addition of ~1%.[1]

In this work we investigated the influence of the preparation procedure on the performance of Rh/TiO_2 catalysts in hydrogenations of unsaturated hydrocarbons with p-H_2.[2] It was shown that the nature of the unsaturated substrate and the calcination temperature used during the catalysts preparation can significantly affect the observed catalytic behavior. The use of rhodium nitrate as a precursor provided very active catalysts in terms of both pairwise selectivity and overall conversion of 1,3-butadiene and propene. Calcination of such catalysts at 600 °C led to significant increase in the catalyst selectivity toward the pairwise H_2 addition route. This can be explained by the emergence of strong metal-support interaction between the support and the active metal which leads to the decoration of rhodium nanoparticles with titania, as confirmed by TEM, XPS, and CO chemisorption. We have found the optimal catalysts for the hydrogenation of 1,3-butadiene and propene with parahydrogen which are able to provide remarkable selectivity toward the pairwise addition route of 4.5 and 7%.

REFERENCES: (1) Kovtunov, K. V.; et al. *Chem. Eur. J.* **2014**, *20*, 11636–11639. (2) Pokochueva, E. V.; et al. *Faraday. Discuss.* **2020**, DOI: 10.1039/C9FD00138G.

ACKNOWLEDGMENTS: This work was supported by the Russian Foundation for Basic Research (grant #19-29-10003).

Hyperpolarization of ^{15}N nuclei in nimorazole and dalfampridine drugs using SABRE at microtesla magnetic fields

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[2]International Tomography Center SB RAS, Novosibirsk, Russia
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SABRE technique boosts nuclear spin polarization for a wide range of compounds without their chemical modification. Performing SABRE experiments at microtesla magnetic fields (SABRE-SHEATH approach[1]) enables hyperpolarization of heteronuclei that persists significantly longer than that of protons.

Nimorazole is a 5-nitroimidazole-based antibiotic drug which is now in Phase 3 clinical trial in Europe for potential use as a hypoxia radiosensitizer for treatment of head and neck cancers. We found that all three ^{15}N nuclei of isotopically labeled [$^{15}N_3$]nimorazole can be hyperpolarized using SABRE-SHEATH approach with polarization levels (P_{15N}) reaching 3.7% for the $^{15}NO_2$ group, and 1.9% and 2.8% for sp^2- and sp^3-hybridized nitrogens in imidazole ring, respectively.[2] Importantly, P_{15N} maximizes at ~54 °C, being an order of magnitude greater than that at ~20 °C. Dependences of P_{15N} vs. polarization transfer field for the three ^{15}N sites showed the maxima at ~0.4 μT. At this magnetic field, polarizations build up and decay with similar characteristic exponential times of 23–33 s. At the clinically relevant field of 1.4 T, polarization of $^{15}NO_2$ site relaxes with long T_1 of 5.9 min. The feasibility of ^{15}N MRI visualization of hyperpolarized [$^{15}N_3$]nimorazole was demonstrated with high spatial and temporal resolution (Figure 1). Therefore, we envision the use of [$^{15}N_3$]nimorazole as a theragnostic hypoxia contrast agent that can be potentially deployed in the next-generation MRI-LINAC systems.

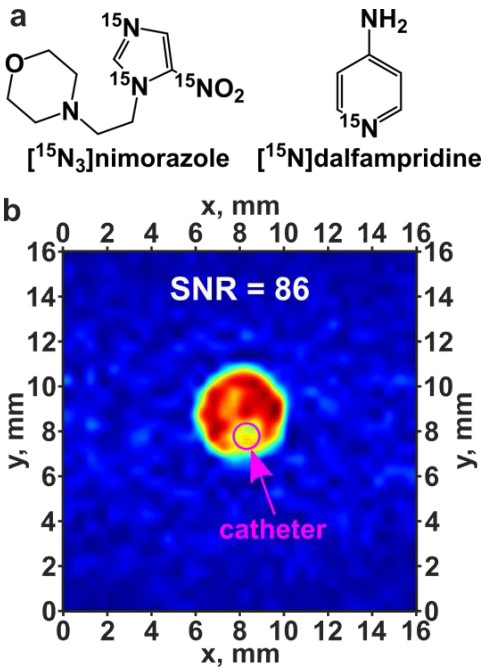

Figure 1. (a) Structures of compounds employed in this study. (b) ^{15}N TrueFISP MRI of hyperpolarized [$^{15}N_3$]nimorazole (~0.11 M) in a 5 mm NMR tube at 9.4 T (axial projection). Repetition time = 356 ms, matrix size = 32×32 (zero-filled to 512×512), spatial resolution = 0.5×0.5 mm^2/pixel.

Dalfampridine (4-aminopyridine) is a drug employed to reduce the symptoms of multiple sclerosis. Previously, we demonstrated that P_{15N} of ~8% can be obtained for this compound at natural abundance of ^{15}N nuclei using SLIC-SABRE.[3] SABRE-SHEATH approach for [^{15}N]dalfampridine provided similar P_{15N} of 6.8% which decays with T_1 of 33.5 s at 1.4 T. Dependences of P_{15N} on polarization transfer field, gas flow rate, pressure and temperature were also investigated, as well as polarization dynamics at microtesla magnetic field.

REFERENCES: (1) Theis, T.; et al. *J. Am. Chem. Soc.* **2015**, *137*, 1404–1407. (2) Salnikov O. G.; et al. *Angew. Chem. Int. Ed.*, **2020**, *under review*. (3) Skovpin, I. V.; et al. *Chem. Eur. J.* **2019**, *25*, 12694–12697. (4) Salnikov O. G.; et al. *manuscript in preparation*.

ACKNOWLEDGMENTS: This work was supported by the Russian Science Foundation (grant #17-73-20030), NSF CHE-1904780 and NIH 1R21CA220137. O.G.S. also thanks the Russian Foundation for Basic Research (grant #19-33-60045).

Beyond NMR – applications of parahydrogen in exploring new exotic magnetic effects in molecules

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Parahydrogen induced hyperpolarization is a popular technique in NMR due to its ability to increase the signal intensity by several orders of magnitude compared to thermal polarization. This enhancement of nuclear magnetization can be exploited also in other fields of molecular sciences beyond NMR. In this contribution, we will discuss the application of Signal amplification by reversible exchange (SABRE) in investigating nuclear magneto-optic (NMO) effects.

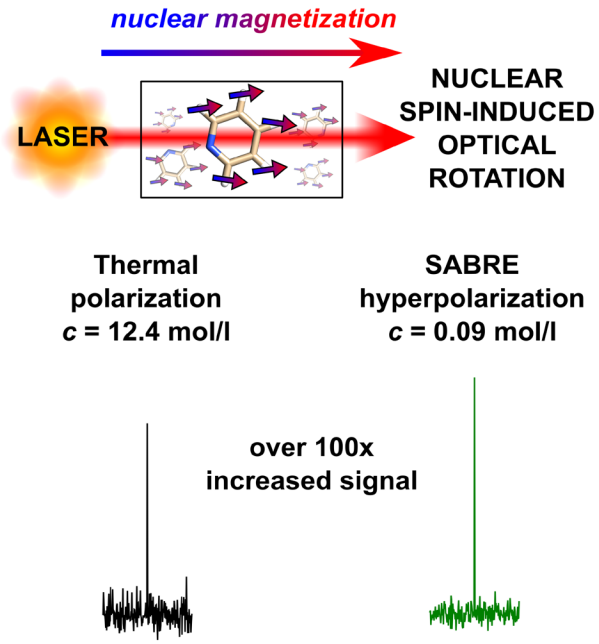

Figure 1: The continuous SABRE polarizer allows measurements of nuclear spin-induced optical effects in much lower concentrations than possible before.

The NMO effects are optical phenomena in molecules, which manifest as changes in polarization of light caused by aligned nuclear spins. They are related to NMR, but offer interesting new possibilities for studying radically different molecular properties inaccessible to NMR. To facilitate new measurements of NMO effects, we have recently developed a continuous SABRE polarizer well-suited for application in this field (1). Using this combination of approaches, we were able to enhance the NMO signal by over two orders of magnitude, making possible measurements of substrates in solution at previously unfeasible concentrations (2). In this presentation we describe the polarizer and its implementation with the NMO experimental setup. The applications of the NMO effects in molecular studies are also discussed.

REFERENCES: (1) Štěpánek P., et. al., *J. Magn. Res.* **2019**, *300*, 8-17. (2) Štěpánek P., Kantola A. M., *J. Phys. Chem. Lett.* **2019**, *10*, 5458-5462.

ACKNOWLEDGEMENT: European Union's Horizon 2020 MSCA (grant agreement No. 654967), European Research Council (ERC) (H2020/2018-2022/ERC grant agreement No. 772110), Academy of Finland (grant Nos. 316180, 289649 and 294027) and Magnus Ehrnrooth Foundation.

Spatially resolved NMR spectroscopy of heterogeneous gas phase hydrogenation with parahydrogen

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Selective heterogeneous hydrogenation of alkynes and dienes is a process of industrial importance. Spatially resolved NMR spectroscopy and imaging enable deeper understanding of an operating catalytic reactor performance. However, NMR studies of heterogeneous gas phase reactions are complicated because of the low spin density and magnetic field inhomogeneities. Parahydrogen-induced polarization (PHIP) technique allows to increase the sensitivity in NMR studies of hydrogenation reactions. In the previous study,[1] it was shown that model glass tube catalytic reactor minimizes magnetic field inhomogeneities and thus allows *operando* MRI studies. Therefore, in this work, 16 glass tube reactors containing Pd, Pt, Rh or Ir nanoparticles dispersed on a thin layer of TiO_2, CeO_2, SiO_2 or Al_2O_3 were tested for the hydrogenation of 1,3-butadiene using parahydrogen (pH_2).[2]

Gas phase ^1H NMR spectra were acquired for each reactor. The catalytic coatings of Ir and Rh gave hydrogenation products with the highest nuclear spin polarization while the coatings with Pd are the most selective ones for the semihydrogenation of 1,3-butadiene to 1- and 2-butenes. Consequently, spatially resolved ^1H NMR spectroscopy along the reactor axis with Ir/SiO_2 and Rh/CeO_2 catalysts were done using spin-echo pulse sequence. In the experiments with Ir/SiO_2 catalyst, the reaction products were distributed along the whole reactor indicating high reaction rates. The resulted product distribution allowed to suggest that butane is the secondary reaction product. For Rh/CeO_2 catalyst, the concentration of butane is constant over the entire length of the reactor, while 1,3-butadiene is not detected indicating fast hydrogenation. The concentration of 1-butene decreased earlier than the concentration of 2-butene. It means that butane is formed slightly faster from 1-butene than that from 2-butene. MRI experiments were also performed using Ir/SiO_2 or Rh/CeO_2 and normal hydrogen. These experiments reproduced the same trends as the ones observed with pH_2.

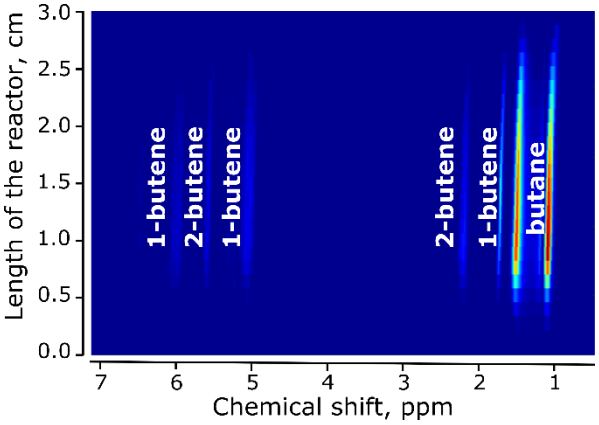

Figure 1. Distribution of ^1H NMR signal intensities in the working reactor along its Z-axis during 1,3-butadiene hydrogenation over Ir/SiO_2 catalyst with parahydrogen (1,3-butadiene:pH_2 ratio = 1:4, 5.1 mL·s^{-1} flow rate, 130 °C)

REFERENCES: (1) Kovtunov, K.V.; et al. *ChemCatChem* **2018**, *11*, 969-973. (2) Svyatova, A.; et al. *Catal. Sci. Technol.* **2020**, *10*, 99–104.

ACKNOWLEDGMENTS: This work was supported by the Russian Science Foundation (grant # 19-13-00047).

Applications of SABRE hyperpolarised NMR

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Magnetic Resonance (MR) techniques are insensitive as signal intensities are derived from small population differences across nuclear spin energy levels. Hyperpolarisation techniques can increase the number of spins that contribute to the MR signal. This has allowed metabolic imaging of prostate cancer in humans using pyruvate hyperpolarised using Dynamic Nuclear Polarisation (DNP).[1] Here, the cheaper Signal Amplification By Reversible Exchange (SABRE) is used to make biomolecules like pyruvate visible to MR in seconds.[2] SABRE catalytically transfers the latent polarisation of *para*-hydrogen (p-H_2), a spin isomer of hydrogen, to pyruvate using an iridium catalyst. This is possible due to the formation of novel [Ir(H)$_2$(carbene)(η^2-pyruvate)(*S*-sulfoxide)] polarisation transfer catalysts.[2] Pyruvate is hyperpolarised with ^{13}C signal enhancements of 2135-fold in methanol-d_4 using SABRE.[3] While these signal gains decrease in 70:30 D_2O:ethanol-d_6 mixtures they are sufficient to allow detection *in vitro* at 9.4 T.[2] For the first time we use SABRE to hyperpolarise pyruvate in a fast, cheap, and refreshable manner. While the NMR signal gains are not as high as those achieved using DNP, SABRE is reversible and provides time and cost advantages.

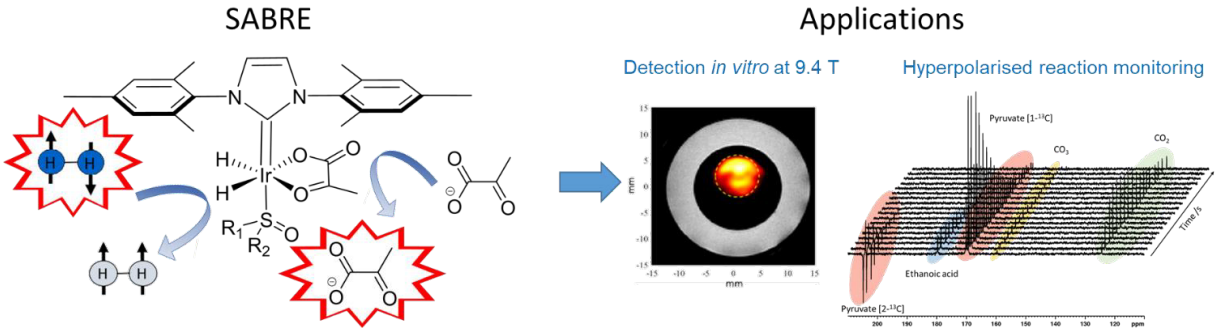

Figure 1: Pyruvate can be hyperpolarised reversibly using SABRE *via* formation of novel [Ir(H)$_2$(carbene)(η^2-pyruvate)(*S*-sulfoxide)] polarisation transfer catalysts (left). This can be used for applications such as *in vitro* MRI detection or hyperpolarised reaction monitoring.

We show applications of SABRE hyperpolarised NMR to monitor the reaction between pyruvate and H_2O_2 and can extract a reaction rate consistent with that determined from ^{1}H NMR and UV spectroscopy.[4] SABRE can be a useful tool for reaction monitoring as it can make the short lived 2-hydroperoxy-2-hydroxypropanoate intermediate visible to NMR in just a single scan ^{13}C NMR spectrum.[4]

We demonstrate extension of SABRE to hyperpolarise a wider range of non-ligating molecules *via* exchange of hyperpolarised protons in a technique termed SABRE-relay.[5] We also demonstrate the use of SABRE for detection of low concentration molecules in mixtures and coligand sensing applications.[6] We expect SABRE will provide unique opportunities for detecting molecules and monitoring chemical change by NMR.

REFERENCES:

[1] S. J. Nelson *et. al*., *Sci. Trans. Med*., 2013, **5**, 198, 198ra108
[2] W. Iali *et. al*., *Angew. Chem.*, 2019, **131**, 30, 10377-10381
[3] B. J. Tickner *et. al*., *Cat. Sci. Technol.,* 2020, **10**, 1343-1355
[4] B. J. Tickner *et. al*., *Anal. Chem.,* 2020, In Press
[5] P. J. Rayner *et. al*., *Chem. Sci*., 2019, **10**, 33, 7709-7717
[6] B. J. Tickner *et. al*., *Chem. Sci.,* 2019, **10**, 20, 5235-5245

ACKNOWLEDGEMENTS: Wellcome Trust (092506 and 098335); MRC (MR/M008991/1); EPSRC (G0025101 and EP/M020983/1).

Continuous Flow Tube-in-tube PHIP Membrane Reactor

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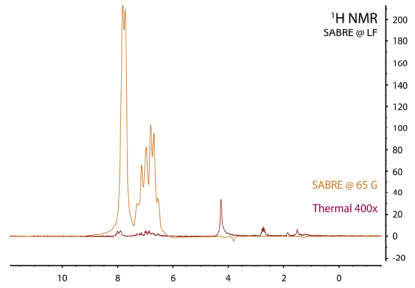
[1] These authors contributed equally to this work.

Parahydrogen-induced hyperpolarization [3] uses parahydrogen (*p*-H2) as a source of spin order to generate hyperpolarization in target substrates either through chemical addition or exchange reactions. Signal Amplification By Reversible Exchange (SABRE) is *p*-H_2 based method that uses an organometallic catalyst to transfer spin order from *p*-H_2 to target substrates [4,5]. SABRE relies on reversible exchange reactions of parahydrogen (*p*-H_2) and substrate with a polarization transfer complex (PTC). Hence, optimization of *p*-H_2 delivery in this biphasic reaction is crucial for maximization of SABRE hyperpolarization. Standard delivery methods included bubbling and shaking to mix gas and liquid phases, but these both suffer from low mass transfer of hydrogen into solution.



In gas-mediated reaction, mass transfer of gas into liquid phase is primarily determined by gas-liquid interfacial area. In conventional batch methods such as bubble column offers relatively low gas-liquid interfacial area (50-600 m^2/m^3) [6]. Due to poorly defined specific interfacial area, reaction often suffers mass-transfer limitation by low overall mass transfer coefficient of the reactor (0.005-0.25 s^{-1}) [7]. Therefore, the processing time of the reaction significantly increases, resulting many drawbacks in understanding fundamentals and optimization of the SABRE hyperpolarization. Utilizing AF-2400 tubing, significantly higher specific interfacial area of ~5000 m^2/m^3 was achieved, increasing mass transfer coefficient to 0.1-1 s^{-1}, [8] thereby accelerating the SABRE hyperpolarization process significantly. Herein, we present a new accelerated system (Figure 1) for parahydrogen hyperpolarization that maximizes parahydrogen delivery through a tube-in-tube design, accesses implementation in any applied magnetic field (from μT to mT), and can be utilized in both high and low-field magnets.

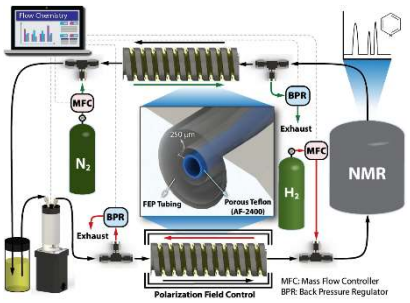


Fig 1 (A) SABRE hyperpolarization of pyridine at 1 T with 50% pH2. (B) Hyperpolarization reactor configuration.

[1] J. H. Ardenkjaer-Larsen, G. S. Boebinger, A. Comment, S. Duckett, A. S. Edison, F. Engelke, C. Griesinger, R. G. Griffin, C. Hilty, H. Maeda, et al., *Angew. Chemie - Int. Ed.* **2015**, *54*, 9162–9185. [2] J. B. Hövener, S. Bär, J. Leupold, K. Jenne, D. Leibfritz, J. Hennig, S. B. Duckett, D. Von Elverfeldt, *NMR Biomed.* **2013**, *26*, 124–131. [3] C. R. Bowers, D. P. Weitekamp, *Phys. Rev. Lett.* **1986**, *57*, 2645–2648. [4] R. W. Adams, J. A. Aguilar, K. D. Atkinson, M. J. Cowley, P. I. P. Elliott, S. B. Duckett, G. G. R. Green, I. G. Khazal, J. Lopez-Serrano, D. C. Williamson, *Science (80-.).* **2009**, *323*, 1708–1711. [5] P. J. Rayner, S. B. Duckett, *Angew. Chemie - Int. Ed.* **2018**, *57*, 6742–6753. [6] J. Yue, G. Chen, Q. Yuan, L. Luo, Y. Gonthier, *Chem. Eng. Sci.* **2007**, *62*, 2096–2108. [7] J.-C. Charpentier, in *Adv. Chem. Eng.* (Eds.: T.B. Drew, G.R. Cokelet, J.W. Hoopes, T. Vermeulen), Academic Press, **1981**, pp. 1–133. [8] L. Yang, K. F. Jensen, *Org. Process Res. Dev.* **2013**, *17*, 927–933.

Hyperpolarized Magnetic Resonance of Exchangeable Protons Using Parahydrogen and Aminosilane

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Efficient, room temperature hyperpolarization of exchangeable solvent protons combining parahydrogen (p-H_2), an aminosilane (aminopropyl-diethoxymethyl-silane, APDMS) and IrCl(COD)(IMes) to generate an active aminosilane-iridium complex, was successfully accomplished in methanol-d_4.[1] The use of aminosilanes for hyperpolarization is unique and widely anticipated since it offers excellent opportunity to graft spin hyperpolarization-catalysis onto solid-phase materials. Mechanistically, a primary pool of aminosilanes transfer its hyperpolarization to exchangeable protons and co-solutes with labile protons, partly overcoming the catalytic specificity of traditional SABRE spin-transfer catalysis. Low-field dependency of hyperpolarization, insights on proton exchange and properties of APDMS and IMes, the N-heterocyclic carbene ligand were exposed. Ir complexation by APDMS is revealed by studying the IMes resonances of the organometallic complex upon addition of APDMS, $(NH_4)_2CO_3$ and finally p-H_2. Bidentate amine and silicon binding to iridium [2] could contribute to the present potency of APDMS interaction with the Ir-precursor. Substitution of an aliphatic amine for APDMS dramatically reduced hydroxyl hyperpolarization, further supporting the importance of the full silane species with silicon. In summary, this research extends the arsenal of solvent hyperpolarisation methods, overcoming the target specificity of traditional p-H_2 based applications, and opens new routes heterogenising SABRE spin-catalyst for p-H_2 hyperpolarization.

[1] Vaneeckhaute, et al. *J. Phys. Chem. C.* **2020**, acs.jpcc.0c01149, Just Accepted. DOI: 10.1021/acs.jpcc.0c01149
[2] Komuro, T. et al. *Chem.Commun.* **2019**, 55, 957–960.

Tuning Pd−Au Bimetallic Catalysts for Heterogeneous Parahydrogen-Induced Polarization

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Heterogeneous parahydrogen-induced polarization (HET-PHIP) is particularly attractive for the study of catalytic mechanism and in vivo imaging application.[1-2] The hydrogenation process in HET-PHIP often follows the classic Horiuti-Polanyi mechanism – a non-pairwise addition process, which leads to a low polarization. The hydrogenation reaction over Pd−Au bimetallic catalysts was studied with parahydrogen-enhanced NMR spectroscopy with the aim to explore the potential of Pd based catalysts in HET-PHIP by producing high polarization levels. The composition and structure of Pd-Au/TiO_2 catalysts were correlated to the pairwise hydrogen addition. We showed that catalysts with high Au content and random alloy morphology catalyze high pairwise selectivity. This can be accounted for by the Pd ensembles effect.

As shown in Figure 1a, the signal enhancements increase with the Au content. The increasing Au component isolates the surface Pd component and leads to a smaller Pd ensemble surface, which restrict proton mobility on catalyst surface and result in a high pairwise selectivity. Random alloy morphology catalyst produces a higher pairwise selectivity (Figure 1b). This is due to the smaller Pd ensemble surface of random alloy morphology than that of other core-shell morphologies.

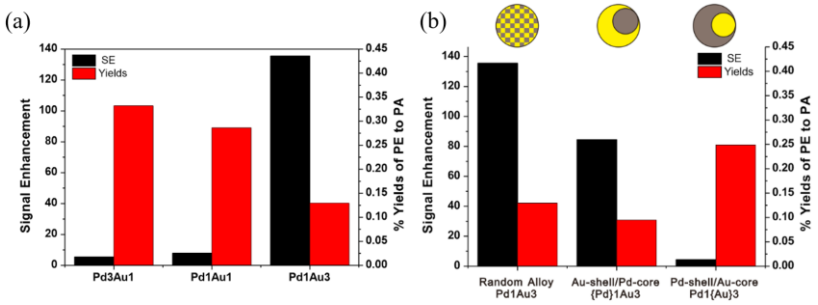

Figure 1. Signal enhancement and yields of propene (PE) to propane (PA) obtained on catalysts with Pd:Au nominal loading ratios as 3:1, 1:1 and 1:3 (a) and nanoparticle morphologies as random alloy, Au-shell/Pd-core, and Pd-shell/Au-core (b).

REFERENCES: (1) D. A. Barskiy; et al. *Chem-Eur J* **2017,** *23*, 725-751. (2) J. B. Hovener; et al. *Angew. Chem. Int. Ed.* **2018,** *57*, 11140-11162.

Metal-Free Parahydrogen-Induced Polarization

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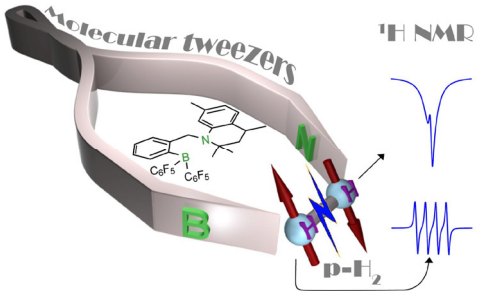

Figure 1. Metal-free activation of parahydrogen by QCAT *ansa*-aminoborane.

Chemical activation of parahydrogen molecules plays a key role in parahydrogen-based hyperpolarization techniques. Commonly, metal-containing activators/catalysts (complexes, nanoparticles, oxides) are employed to mediate such activations and produce hyperpolarization in parahydrogen-induced polarization (PHIP) as well as in signal amplification by reversible exchange (SABRE). Signal enhancements provided by the hyperpolarization in homogeneous and heterogeneous chemical processes has been used for boosting sensitivity in NMR, metabolic imaging and mechanistic studies of chemical reactions. At the same time, more biogenic main group chemical systems have been documented as promising metal-free activators for molecular hydrogen. Herein, an overview of current results about PHIP and SABRE with such metal-free systems is presented.[1-4]

We show that unimolecular pairs of sterically separated ('frustrated') Lewis acids and bases (FLPs) are promising metal-free parahydrogen activators that provide hyperpolarization of protons and heteronuclei in FLP-H_2 adducts (Figure 1), free FLP molecules and hydrogenation products. We present results on N-B based FLP systems and pnictogen biradicaloids.[1-4] Role of kinetic parameters, dihydrogen bonding and structural features are discussed in the context of hyperpolarization effects. We also discuss alternative P-B pairs based metal-free systems for PHIP and SABRE.

REFERENCES: (1) Zhivonitko, V. V.; et al. *J. Am. Chem. Soc.* **2014,** *136*, 598-601. (2) Zhivonitko, V. V.; et al. *Phys. Chem. Chem. Phys.* **2016,** *18*, 27784-27795. (3) Sorochkina, K.; et al. *J. Phys. Chem. Lett.* **2018,** *9*, 903-907. (4) Zhivonitko, V. V.; et al. *Phys. Chem. Chem. Phys.* **2019,** *21*, 5890-5893.

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Lightning Talk/Poster Abstracts

Parahydrogen-induced polarization enables chemical reaction monitoring at zero magnetic field

Dudari B. Burueva[1,2], James Eills[3,4], John W. Blanchard[3], Antoine Garcon[3,4], Román Picazo Frutos[3,4], Kirill V. Kovtunov[†1,2], Igor V. Koptyug[1,2], Dmitry Budker[3,4,5]

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[4]Johannes Gutenberg University, Mainz 55090, Germany
[5]University of California Berkeley, Berkeley 94720, U.S.A.

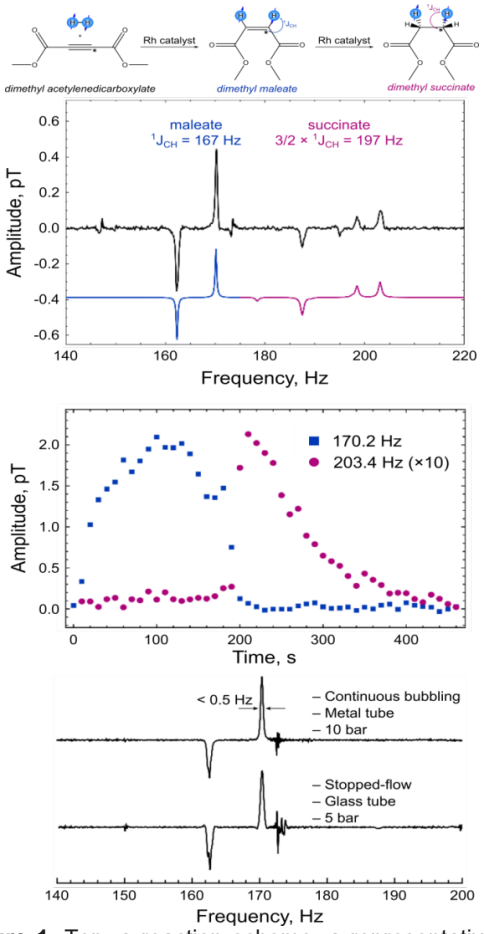

Figure 1. Top: a reaction scheme, a representative *J*-spectrum (black) acquired during the chemical reaction in a titanium tube and a simulated spectrum (shown beneath). Center: the time-dependence of NMR signals of products for the reaction carried out at 5 bar p-H_2 pressure in a titanium tube. Bottom: representative spectra showing that ZULF NMR is almost insensitive to sample heterogeneity.

Zero- to ultralow-field (ZULF) NMR is a promising technique for *in situ* chemical reaction monitoring under practical conditions. Unlike conventional NMR, ZULF NMR is performed in the absence of an applied magnetic field. In this regime, intramolecular spin interactions (e.g. electron-mediated indirect nuclear spin-spin couplings, *J*-couplings) dominate, and the Zeeman interaction can be treated as a perturbation on the "local" *J*-coupling and dipole-dipole interactions. Specifically, ZULF NMR is not suitable for chemical shift measurements, but chemical and structural information encoded in the *J*-couplings is preserved allowing for chemical fingerprinting and analysis.[1] Importantly, in ZULF NMR there is a negligible magnetic susceptibility broadening for heterogeneous samples and narrow resonance lines can be achieved. Moreover, since the low-frequency magnetic fields readily penetrate metals, reactions carried out in reactors made from conductive materials can be addressed by ZULF NMR under realistic conditions.

Herein, the kinetics of the two-step hydrogenation of dimethyl acetylenedicarboxylate with parahydrogen was studied by ZULF NMR (Figure 1) using a commercial atomic magnetometer.[2] The hydrogenation reaction was monitored by observing the NMR signals of the hydrogenated products (dimethyl maleate and dimethyl succinate) over time. The observed kinetics behavior is in line with the accepted mechanism of unsaturated substrate hydrogenation over cationic Rh catalysts used in this work.[3]

Also, the reaction was conducted in conventional glass NMR tubes, as well as in a titanium tube. It was shown that the sample heterogeneity induced by bubbling parahydrogen during signal acquisition practically does not affect the spectral resolution in ZULF NMR. Importantly, the reaction can be monitored even when it is carried out in a metal container (Figure 1, central panel).

REFERENCES:

1 R. McDermott, A. H. Trabesinger, M. Mück, E. L. Hahn, A. Pines and J. Clarke, *Science*, 2002, **295**, 2247–2249.
2 J. W. Blanchard, T. Wu, J. Eills, Y. Hu and D. Budker, *J. Magn. Reson.*, 2020, **314**, 106723.
3 R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, 1976, **98**, 2134–2143.

ACKNOWLEDGEMENTS: DBB and IVK thank RFBR (#19-29-10003) and RSF (#19-13-00047) for financial support.

Synthesis of ^{15}N-labeled contrast agents for ^{15}N hyperpolarization by SABRE

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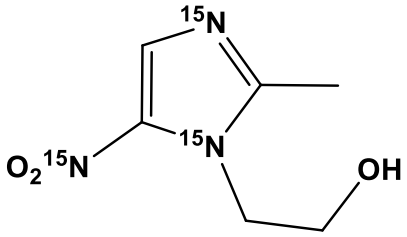
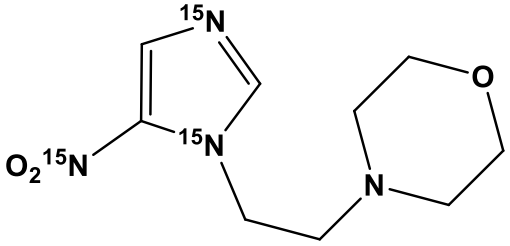
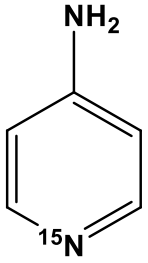


[$^{15}N_3$]metronidazole



[$^{15}N_3$]nimorazole



[^{15}N]4-aminopyridine

Various hyperpolarization strategies may be employed to increase nuclear spin polarization and, hence, NMR sensitivity. One such technique is Signal Amplification by Reversible Exchange (SABRE) which utilizes simultaneous reversible chemical exchange of parahydrogen and substrate molecules at a metal center. Bioactive N-heterocycles are promising substrates in this case since they usually undergo the required exchange process and can be utilized as theragnostic MRI contrast agents.

Metronidazole is an antibiotic that can be safely administered orally and intravenously in large doses. ^{15}N polarizations of up to 34% were obtained for this compound at natural abundance of ^{15}N nuclei using SABRE.[1] Therefore, we developed a synthetic approach for [$^{15}N_3$]metronidazole using $^{15}NH_4Cl$ and $Na^{15}NO_3$ as the ^{15}N source.[2] The overall yield over three steps was around 15%.

Nimorazole is a nitroimidazole-based anti-infective which is also being investigated as a radio-sensitizing agent for the treatment of head and neck cancer. Therefore, we performed the synthesis of isotopically labeled [$^{15}N_3$]nimorazole.[3] In the first step, [$^{15}N_2$]imidazole was prepared with 50–60% yield via condensation of glyoxal, formaldehyde and $^{15}NH_4Cl$ used as a source of ^{15}N isotope enrichment. Subsequent nitration with $H^{15}NO_3/H_2SO_4$ allowed to obtain [$^{15}N_3$]4(5)-nitroimidazole with 30% yield. Next, this compound was alkylated with 4-(2-chloroethyl)morpholine in the presence of K_2CO_3 forming [$^{15}N_3$]nimorazole and its isomer in a 1:3 ratio.

4-Aminopyridine is used as a research tool in characterizing subtypes of the potassium channels. It has also been employed as a drug managing some of the symptoms of multiple sclerosis. 4-Aminopyridine was efficiently hyperpolarized by SABRE with ~8% ^{15}N polarization at natural abundance of ^{15}N nuclei.[4] We synthesized [^{15}N]4-aminopyridine using $^{15}NH_4Cl$ at the first step to obtain [^{15}N]pyridine which was then converted into the product through the three steps.[5]

All of the synthesized compounds showed promising results in the SABRE hyperpolarization experiments at microtesla magnetic fields.

REFERENCES: (1) Kidd, B. E.; et al. *J. Phys. Chem. C*, **2018**, *122*, 16848–16852. (2) Shchepin, R. V.; et al. *Chem. Eur. J.* **2019**, *25*, 8829–8836. (3) Salnikov O. G.; et al. *Angew. Chem. Int. Ed.*, **2020**, *under review*. (4) Skovpin, I. V.; et al. *Chem. Eur. J.* **2019**, *25*, 12694–12697. (5) Salnikov O. G.; et al. *manuscript in preparation*.

ACKNOWLEDGMENTS: This work was supported by the Russian Science Foundation (grant #17-73-20030), NSF CHE-1904780 and NIH 1R21CA220137.

In-situ characterisation of SABRE catalyst activation via T_1 measurements in the Earth's Magnetic field

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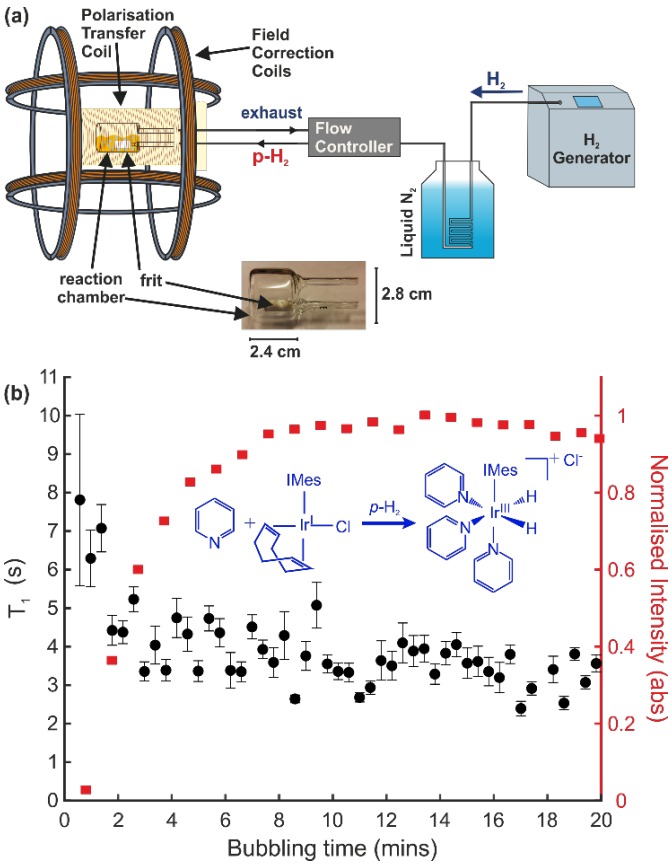

Figure 1. (a) Schematic of the *in situ* SABRE system with Earth's field (EF) detection and a liquid nitrogen-based parahydrogen generator system. (b) SABRE-enhanced ^{1}H NMR signal (red squares) and single shot T_1 values (black circles) for a 4 mL sample of 50 mM pyridine and 5 mM SABRE pre-catalyst in methanol as a function of *p*-H_2 bubbling time during SABRE catalyst activation.

A wide range of hyperpolarisation techniques exist to overcome the well-known sensitivity limitations of NMR spectroscopy. One such technique is the *para*-hydrogen (*p*-H_2) based Signal Amplification By Reversible Exchange (SABRE) method, which catalytically transfers nuclear singlet order from *p*-H_2 to a target analyte via a reversible exchange reaction mediated by a transition metal catalyst. Polarisation transfer is achieved in the low to ultra-low field regime. [1]

Efficient SABRE hyperpolarisation for a given analyte requires the optimisation of a wide range of experimental conditions. In the standard approach, experiments are achieved using a two-stage method, where hyperpolarisation and detection are separated in time and space. Integration of a liquid nitrogen-based *para*-hydrogen generator with Earth's Field NMR (EFNMR) detection enables SABRE experiments to be performed *in situ* (Figure 1(a)). As a result, time-resolved, multi-step experiments, such as the monitoring the formation of the SABRE-active catalyst, can be performed in a simple and reproducible manner.[2]

In this work, we demonstrate the implementation of a single-shot, variable flip angle T_1 lifetime measurement[3] on an Earth's field NMR spectrometer. This method is applied to monitoring the activation of the SABRE catalyst by detecting changes in both the amplitude and lifetime of the SABRE-enhanced ^{1}H EFNMR response (Figure 1(b)).

References: [1] Adams R.W. et al., Science, 323, 1708-11 (2009). [2] Hill-Casey, F. et al,, *Molecules*, *24*(22), 4126 (2019). [3] Semenova, O. et al., Anal. Chem. *91*(10), 6695–6701 2019.

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SQUID-based ultralow field MRI of hyperpolarized material by using SABRE

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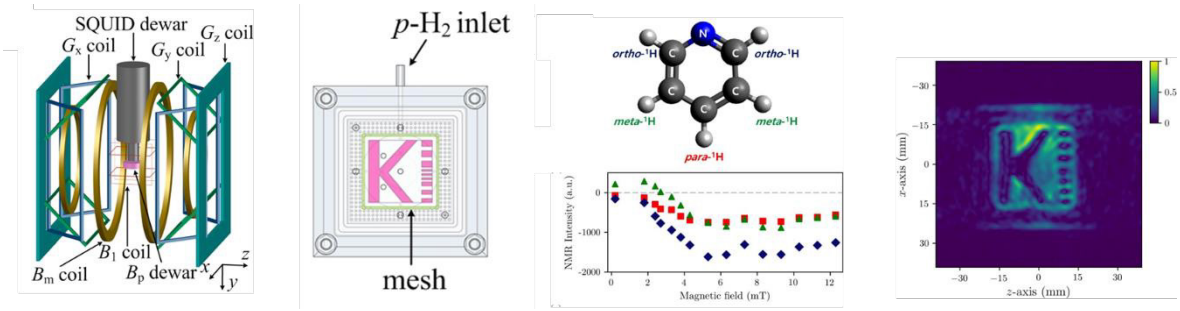
Low-field (earth field) and ultra-low-field magnetic resonance imaging (MRI) is the promising tool in several fields that can surpass the merits of high field MRI. It holds larger relaxation contrast in low field MRI and simultaneous detection of various MRI active nuclei is powerful tool to obtain much important information in short time. However, magnetic signal stemmed from Zeeman effect in low magnetic field is extremely low, therefore, we built the superconducting interference device (SQUID) combined with hyperpolarization technique, which can polarize materials in extremely high order of magnitude. Signal Amplification by Reversible Exchange (SABRE) technique, which is utilizing para-state of hydrogen, is actively harnessed to overcome the low sensitivity of the SQUID-based MRI. Based on these concepts, the first-ever SABRE-based hyperpolarized MRI image was obtained, which will open the new range of low-field and ultra-low-field MRI applications.



Practical Aspects of RASER with the Parahydrogen-Induced Polarization Technique

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Experimental evidences of the occurrence of radio amplification by stimulated emission radiation (RASER) with the parahydrogen-induced polarization (PHIP) technique will be discussed. Under both ALTADENA and PASADENA conditions, i.e., when the pairwise addition of *p*-H_2 is performed respectively at low and high field, PHIP experiments with substrate concentrations >100 mM show strong RASER activity of the parahydrogen-derived protons observed without any radiofrequency excitation. The RASER relaxation dynamics passes through several non-linear regimes with distinctive spectroscopic features that are often measured at higher resolution than the nominal spectrometer resolution. These PHIP-RASER experiments are carried out with a commercial 62 MHz benchtop NMR spectrometer and proton polarization levels down to "only" a few percent; their simplicity give further evidence of the significance and large scope of PHIP.

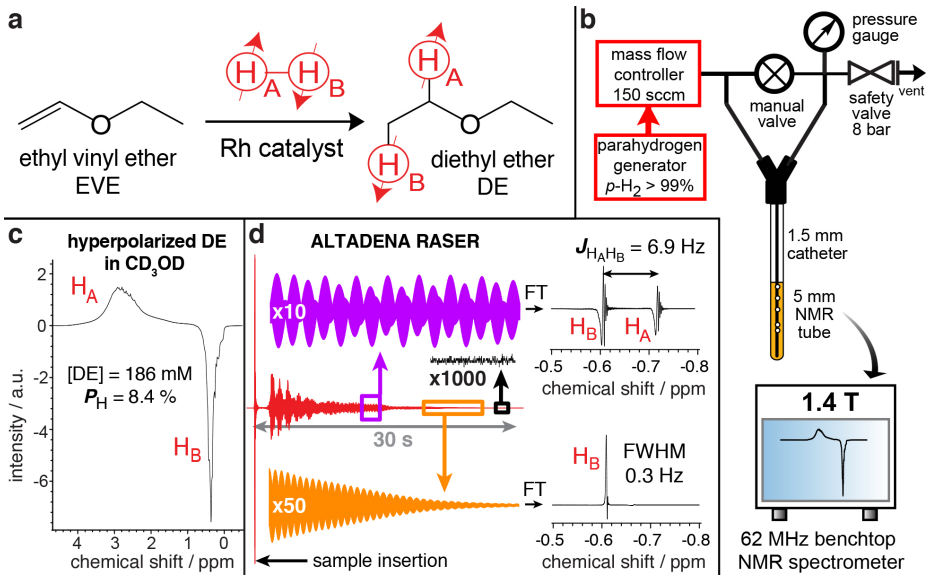

Figure 1. (a) Hydrogenation of ethyl vinyl ether with *p*-H_2 leading to the formation of hyperpolarized diethyl ether (DE). (b) Experimental setup for hydrogenation in an NMR tube. (c) ^{1}H spectrum of hyperpolarized DE (8° pulse angle) after 10 s bubbling at 80 °C and 10 s decay in the Earth's magnetic field (to avoid RASER). ^{1}H polarization of 8.4% is back-calculated. (d) ^{1}H RASER signal of DE (w/o radiofrequency excitation pulse) and Fourier spectra of colored boxes.

Reference

"Parahydrogen-Induced Radio Amplification by Stimulated Emission of Radiation"
B. Joalland, N. M. Ariyasingha, S. Lehmkuhl, T. Theis, S. Appelt, E. Y. Chekmenev
Angewandte Chemie, **2020**, *132(22)*, 8654-8660. doi.org/10.1002/anie.201916597

Acknowledgments

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Quantifying the Effects of Quadrupolar Sink via ^{15}N Relaxation Dynamics in Metronidazoles Hyperpolarized via SABRE-SHEATH

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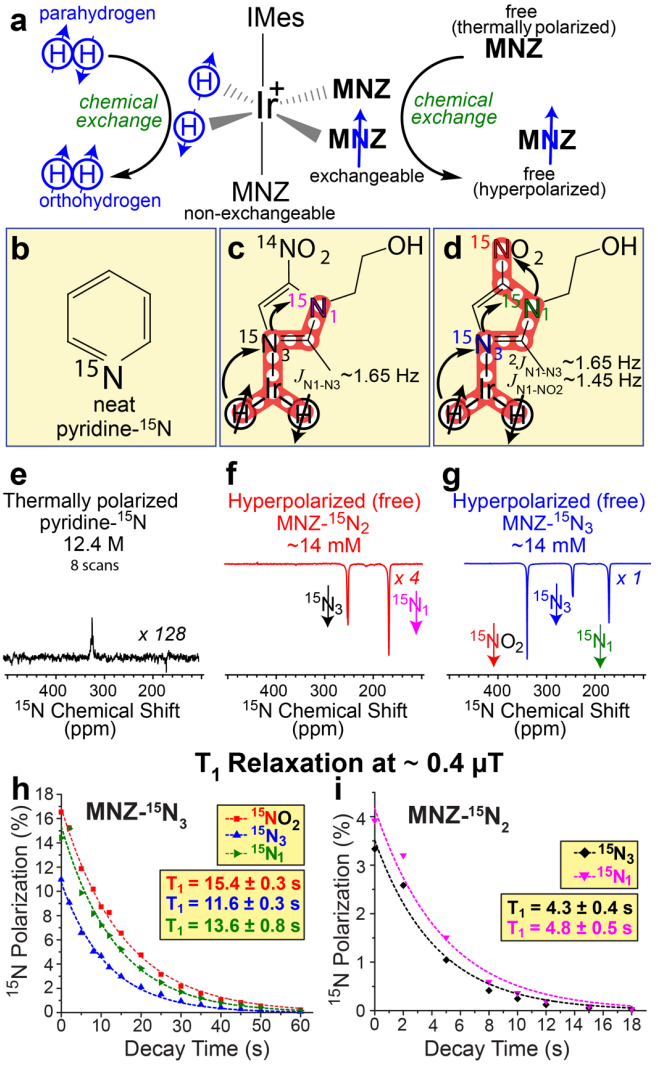

Figure 1. a) Molecular exchange between p-H_2 and substrate, *e.g.*, metronidazole (MNZ) employed here, in SABRE hyperpolarization. b) Structure of pyridine-^{15}N employed as a signal reference. c-d) Corresponding structures and polarization transfer spin-relays (red overlay) between p-H_2 and ^{15}N nuclei in corresponding MNZ ^{15}N-isotopologues. e) Signal reference ^{15}N NMR spectrum of a thermally polarized neat pyridine-^{15}N acquired with 8 scans and 10-minute recovery time. f-g) Corresponding ^{15}N NMR spectra of HP metronidazole-$^{15}N_2$ and metronidazole-$^{15}N_3$. h-i) Corresponding ^{15}N T_1 decay curves at 0.4 μT.

Spin-lattice relaxation dynamics of ^{15}N nuclei in metronidazole-$^{15}N_3$ and metronidazole-$^{15}N_2$ isotopologues are studied in the context of developing strategies for rational design of ^{15}N enriched biomolecules for Signal Amplification by Reversible Exchange (SABRE) in microtesla magnetic fields. In this process, parahydrogen and the to be hyperpolarized substrate undergo simultaneous reversible chemical exchange on an iridium complex; nuclear spin polarization from parahydrogen derived hydrides is then spontaneously transferred among ^{15}N nuclei within each metronidazole isotopologue via a network that includes two-bond ^{15}N-^{15}N spin-spin couplings. Quantitative mapping of ^{15}N relaxation dynamics reveals the deleterious effects of interactions with polarization transfer catalyst (containing quadrupolar Ir nucleus) and quadrupolar ^{14}N nucleus within the spin-relayed network. Although the catalyst decreases the ^{15}N spin-relaxation time constant, T_1, of metronidazole isotopologues in the microtesla regime in a concentration-dependent manner, the overall impact on the achievable ^{15}N polarization level is relatively minor. On the other hand, the presence of a ^{14}N nucleus in the scalar coupling network results in an approximately 3-fold decrease of microtesla ^{15}N T_1 values for all ^{15}N sites in the $^{15}N_2$-isotopologue versus the $^{15}N_3$-isotopologue over a wide range of catalyst concentrations. This ^{15}N T_1 reduction results in a corresponding 3-fold decrease of ^{15}N polarization levels. These findings have substantial translational relevance for the rational design of hyperpolarized MRI contrast agents comprising ^{15}N and ^{13}C labeled biomolecules both in general, and in the specific case of SABRE-hyperpolarized metronidazole, an antibiotic that can be potentially employed for non-invasive hypoxia sensing.

ACKNOWLEDGEMENTS: NSF CHE-1904780 and CHE-1905341, NIH R21CA220137, DOD CDMRP W81XWH-12-1-0159/BC112431, W81XWH-15-1-0271 and W81XWH-15-1-0272. O.G.S. thanks the RFBR #19-33-60045 for the support of mechanistic studies with the use of p-H_2. N.V.C. and K.V.K. thank the Russian Science Foundation #17-73-20030 for their support in the synthesis of ^{15}N-labeled compounds. I.V.K. thanks the Russian Ministry of Science and Higher Education (project AAAA-A16-116121510087-5) and the RFBR (grants 19-29-10003, 17-54-33037) for financial support.

Virtual Reality Understanding of Catalytic Mechanisms in SABRE

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Background:

Signal amplification by reversible exchange (SABRE) technique transfers spin polarization from para-H_2 to target substrates, most commonly through an iridium catalyst. Due to its simplicity, cost-efficiency, prolonged spin lifetimes, and improved signal amplification, SABRE has become a very promising hyperpolarization technique.[1] In this study, we present a mechanistic study of the catalytic reaction network of Iridium N-heterocyclic carbene (NHC) complexes through virtual reality. Pyridine was selected as the main substrate in the catalytic species.

Contribution:

The energy landscape of the NHC catalyst reaction network was probed through Ab Initio calculations using density functional theory (DFT). Born-Oppenheimer potential energies of a collection of catalytic species and transition states in the SABRE reaction network were calculated. All calculations were carried out using the FHI-aims all-electron electronic structure code, with the code's preconstructed "tight" numerical settings, at the level of PBE semi local density functional, and corrected with the Tkatchenko-Scheffler term to incorporate van der Waals interactions.[2,3,4] Transition state energies for reaction pathways were calculated using the string method, and further approached with the climbing image technique at the same level of theory.[5]

Virtual Reality rendering was applied through the Blender 3D creation suite to visualize the minimum energy paths and energy diagram of the catalytic reactions. The VR interaction provides direct manipulations of the molecular structures, including the ability to inspect it from different perspectives. It also offers a real-time analysis of changes in molecular structure through animated visualization.

We will present the calculated energy data of the SABRE reaction pathways, as well as the virtual reality visualization of an example minimum energy path.

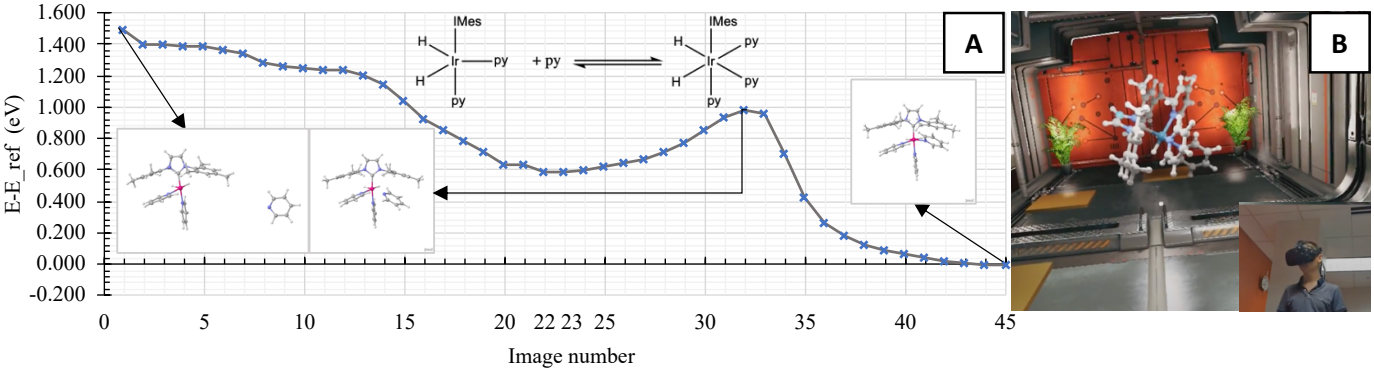

Figure 1. A) The energy diagram of the reaction of $[Ir(H)_2(IMes)(py)_3]^+$, as specified in the equation. The initial state, transition state, and final state geometries were detailed in snapshots. Reference energy was taken as the single point energy of the final state. **B)** The rendering view of virtual reality presentation for $[Ir(H)_2(IMes)(py)_2]^+$, the starting material of the reaction pathway shown in figure A.

References:

[1] Theis, T.; et al. *Science advances* **2016**, 2 (3), e1501438. **[2]** Blum, V.; et al. *Computer Physics Communications* **2009**, 180 (11), 2175-2196. **[3]** Perdew, J. P.; et al. *Physical Review Letters* **1996**, 77 (18), 3865-3868. **[4]** Tkatchenko, A.; et al. *Physical Review Letters* **2009**, 102 (7), 073005. **[5]** E, W.; et al. *The Journal of Chemical Physics* **2007**, 126 (16), 164103.

Cobalt-catalyzed Hyperpolarization of Olefins via SABRE

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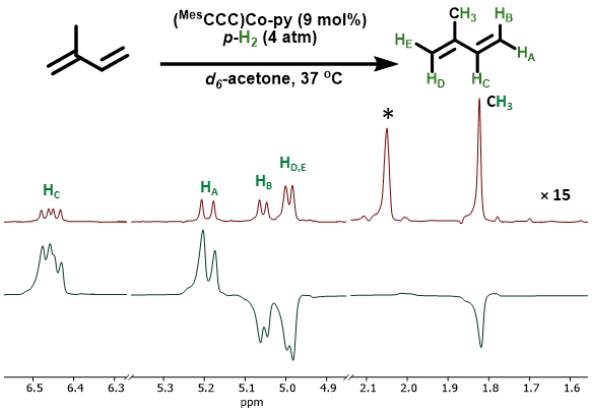

Figure 1. Top: Single scan ^{1}H NMR spectrum of a thermally polarized 65 mM solution of isoprene in d6-acetone (*) with 15-fold vertical expansion relative to the spectrum below it. Bottom: Single scan ^{1}H NMR spectrum taken after hyperpolarization in a 5.0×10^{-3} T field.

The use of the *para*hydrogen as a hyperpolarizing agent to address sensitivity issues in Nuclear Magnetic Resonance (NMR) spectroscopy and, Magnetic Resonance Imaging (MRI) has been well established in literature.[1,2] Rhodium and iridium complexes have widely been used as the homogeneous catalysts of choice to facilitate both hydrogenative and non-hydrogenative transformations.[3–6] However, there are several concerns over the use of second- and third-row transition metals, one being the potential toxicity of such complexes as well as the environmental concerns that accompanies the extraction of these scarcer metals. Thus, our group is interested in developing sustainable first-row transition metal complexes that provide hyperpolarization on par with that afforded by already established *Para*hydrogen Induced Polarization (PHIP) catalysts. We previously reported the use of our hydrogenation catalyst, (^{Mes}CCC)Co-py [^{Mes}CCC = bis(2,4,6-trimethylphenyl-enzimidazol-2-ylidene)phenyl), py = pyridine], in the *para*hydrogenation of ethyl acrylate to produce hyperpolarized ethyl propionate in both ^{1}H and ^{13}C nuclei. Here, we report the first example of a homogeneous non-iridium SABRE catalyst in the application of (^{Mes}CCC)Co-py in the non-hydrogenative hyperpolarization of olefins. The a variety of olefinic substrates is demonstrated and yields signal enhancement values of up to ~150-fold for ^{1}H resonances at 14.1 T. Transfer of polarization to ^{13}C and ^{19}F occurs across 7 bonds and is demonstrated without the use of isotopic labelling or the application of radio-frequency pulse sequences, and both with and without the use of microtesla fields.

REFERENCES: (1) Duckett, S. B.; Mewis, R. E. *Acc. Chem. Res.* **2012**, *45*, 1247–1257. (2) Hovener, J.; et al. *Angew. Chemie Int. Ed.* **2018**, 11140–11162. (3) Kovtunov, K. V.; et al. *Chem. - An Asian J.* **2018**, *13*, 1857–1871. (4) Cowley, M. J.; et al. *J. Am. Chem. Soc.* **2011**, *133*, 6134–6137. (5) Adams, R. W.; et al. *Science* **2009**, *323*, 1708–1711. (6) Bowers, C. R.; Weitekamp, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 5541–5542.

Validating Quantitative Hyperpolarised Reaction Monitoring on a Benchtop NMR Spectrometer

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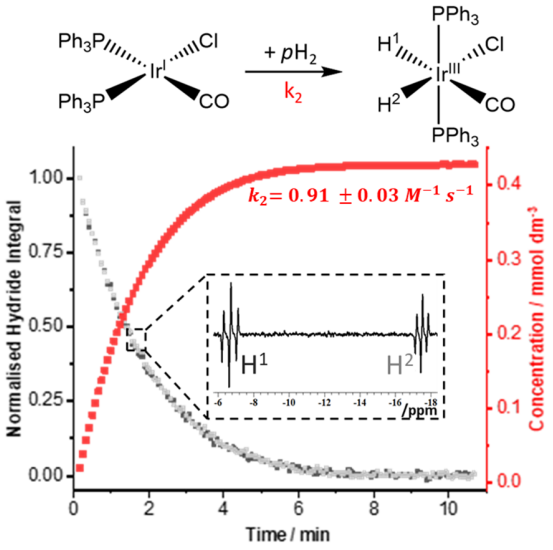

Figure 1. Reaction monitoring for the oxidative addition of pH_2 to $[IrCl(CO)(PPh_3)_2]$ (Vaska's complex), recorded at 28.5 ˚C, highlighting the decay of hyperpolarised hydride signals at 1 T (grey) and growth of the reaction product (red) over time.

Benchtop NMR spectrometers offer unique capabilities for reaction monitoring compared to their high-field alternatives. The increased portability, *protio* solvent tolerance and higher accessibility of these spectrometers (both in terms of the hardware and the level of expertise required by the operator) make them well suited for *in situ* analysis of mixtures and allow for facile incorporation of the spectrometers into flow system setups.[1]

One consequence of moving to a benchtop NMR system is that the lower operational magnetic field strength (1 – 2 T) further reduces the resolution of this inherently insensitive technique. This is especially problematic for reaction monitoring purposes where the detection of low concentration intermediates and transient species is desirable for mechanistic insights. To overcome this limitation, hyperpolarisation techniques which create non-Boltzmann population differences can be employed. One method, known as PHIP (*Para*Hydrogen Induced Polarisation), utilises singlet state, NMR silent *para*hydrogen (pH_2) to chemically modify an analyte. The hydrogenation process breaks the symmetry of pH_2, unlocking its latent polarisation, which enhances the signals observed for the product molecule.[2] This technique has already been effectively incorporated into a range of reaction monitoring experiments that involve hydrogenation steps.[3,4] One potential drawback of this approach is the complicated quantification of the PHIP-derived polarisation, with factors such as polarisation transfer efficiency potentially skewing the observed kinetics.

The work presented focuses on the development of a robust procedure to collect and process reaction monitoring data using the oxidative addition of pH_2 to Vaska's complex as a model system (Figure 1). To validate the resultant kinetic parameters, the impacts of several potential pitfalls, such as relaxation of PHIP-derived signals and the presence of temperature gradients during data acquisition, have been investigated.

REFERENCES:

[1] E. Danieli, J. Perlo, A. L. L. Duchateau, G. K. M. Verzijl, V. M. Litvinov, B. Blümich and F. Casanova, *ChemPhysChem*, 2014, **15**, 3060 – 3066.
[2] S. B. Duckett and R. E. Mewis, *Acc. Chem. Res.*, 2012, **45**, 1247 – 1257.
[3] D. Gołowicz, K. Kazimierczuk, M. Urbańczyk and T. Ratajczyk, *ChemistryOpen*, 2019, **8**, 196 – 200.
[4] K. Jeong, S. Min, H. Chae and S. K. Namgoong, *Magn. Reson. Chem.*, 2019, **57**, 44 – 48.

Exploring SABRE Polarisation Transfer using *in situ* Earth's field NMR

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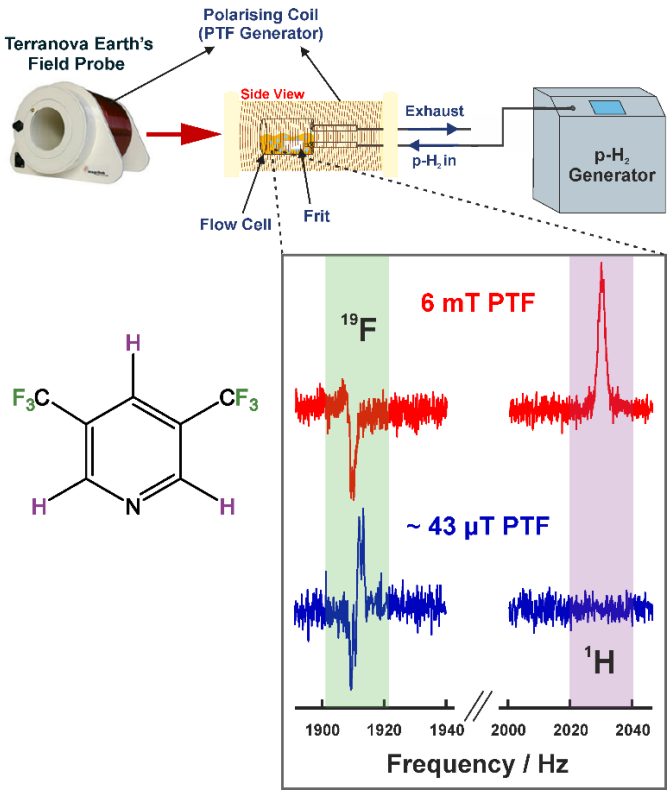

Figure 1. In-situ SABRE hyperpolarised spectra of 3,5-bis(trifluoromethyl)pyridine using a 6 mT (red) and ~ 43 µT (blue) PTF, acquired on an EFNMR setup consisting of a *p*-H_2 generator, glass flow cell, and a Magritek Terranova spectrometer.

Various techniques have been developed to improve the sensitivity of NMR via hyperpolarisation of the spin system. Of particular interest to this work is the *para*-Hydrogen (*p*-H_2) based technique, Signal Amplification by Reversible Exchange (SABRE) [1] in which a metal catalyst is used to transfer the polarisation from *p*-H_2 to a target substrate that subsequently dissociates allowing free substrate polarisation to build up.[2] Typically, the polarisation transfer and detection stages of SABRE are performed separately in space, time and magnetic field. Integration of SABRE with Earth's Field NMR (EFNMR) provides a route to performing SABRE in-situ of the detection field enabling interrogation of the SABRE Polarisation Transfer Condition (PTC) in order to direct and optimise polarisation transfer to ^{1}H and heteronuclei in the target molecule. ^{19}F is our heteronucleus of choice due to its attractive magnetic properties as well as the very small difference in Larmor frequency between ^{1}H and ^{19}F (~120 Hz) at the Earth's magnetic field, allowing for simultaneous observation of these nuclei in a single spectrum.

SABRE polarisation of ^{19}F in fluorinated N-heterocycles has been demonstrated to achieve high levels of spin polarisation at high-field.[3] The target substrate used here, 3,5-bis(trifluoromethyl)pyridine, exhibits SABRE-enhanced ^{1}H and ^{19}F EFNMR signals under different PTCs, shown in Figure 1. Altering the PTC by varying the Polarisation Transfer Field (PTF) appears to influence which substrate spin-states are hyperpolarised and thus the form of the spectrum. NMR simulations can be implemented to overcome difficulties in interpreting EFNMR spectra and can be utilised to better understand the evolution of the SABRE-hyperpolarisation in the low to ultra-low field regime.

References: [1] R. W. Adams, 2009, **323**, 1708–1711. [2] R. W. Adams, *J. Chem. Phys.*, 2009, **131**, 194505. [3] A. M. Olaru, *ChemistryOpen*, 2018, **7**, 97–105.

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Optimising the SABRE hyperpolarisation of amines using *in-situ* Earth's Field NMR

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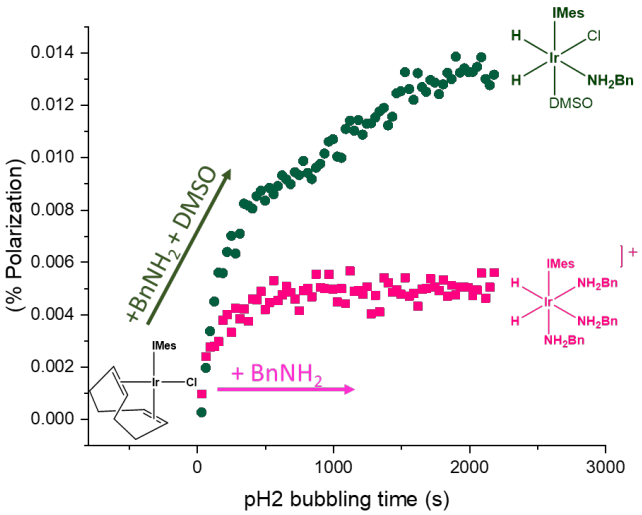

Figure 1: Comparison of the activation curves, detected in the Earth's magnetic field, of two SABRE solutions: 5 mM of SABRE pre-catalyst and 40 equivalents (204 mM) of benzylamine (pink) and 5 mM of the SABRE pre-catalyst, 25 equivalents of benzylamine (127.5 mM) and 25 equivalents of the co-ligand DMSO (51.2 mM).

Traditional NMR is limited by low thermal spin polarization, reducing sensitivity and requiring large superconducting magnets for NMR spectroscopy. Hyperpolarisation methods overcome the sensitivity limitations of NMR, perturbing nuclear spin populations from thermal equilibrium. Among those methods, Signal Amplification by Reversible Exchange (SABRE) catalytically transfers spin order from *p*-H_2, the nuclear singlet isomer of H_2, to the target molecule via a reversible exchange reaction mediated by a transition-metal (Iridium) catalyst in solution. [1]

SABRE hyperpolarisation enables NMR detection in the Earth's magnetic field (~50 μT) for low concentration samples, where *in situ* hyperpolarisation is generated within the detection coil and therefore the activation of the activate SABRE catalyst can be monitored directly (Figure 1).[2]

In this study, *in situ* EFNMR detection is used to explore the SABRE hyperpolarisation of a range of amines. The effect of a sulfoxide type co-ligand on the polarization level, SABRE catalyst activation, and amine hyperpolarisation lifetime is explored. Results are compared for detection in the Earth's magnetic field and in a standard high-field NMR spectrometer. High-field NMR is also used to explore the effect of the dimethyl sulfoxide (DMSO) co-ligand on the chemical exchange rate of both the amine and the hydrides of the active SABRE catalyst. For the classical pyridine case, an optimum substrate exchange rate of ~4.5 s^{-1} has been predicted theoretically and confirmed experimentally.[3] In addition, we find that adding the co-ligand DMSO, brings the exchange rate of the target amines into the desired regime. Analysis of the chemical exchange behaviour of these amine/DMSO systems has provided thermodynamic parameters that we use to compare the activation energy of these complexes.

REFERENCES:

1. K. D. Atkinson, and al., *Journal of the American Chemical Society*, 2009, **131**, 13362-13368.
2. F. Hill-Casey, and Al., *Molecule*, 2019, **24**, 4126.
3. D. A. Barskiy, and Al., *Progress in Nuclear Magnetic Resonance Spectroscopy*, 2019, **114-115**, 33-70.

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Zero- to ultralow- field NMR spectroscopy of azobenzene hyperpolarized by SABRE

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Azobenzene (AB) molecule exists in two isomeric forms, *cis*-AB and *trans*-AB, switching between the two forms can be performed by using light excitation. Nuclear spins of *cis*-AB can be directly hyperpolarized by "signal amplification by reversible exchange" (SABRE) method [1]. Performing SABRE in zero- to ultralow- fields (ZULF) [2] results in enhancement of NMR signals of *cis*-AB by thousands of times. This hyperpolarization can be stored in ^{15}N magnetization up to several minutes in favorable magnetic field, which is restricted by longitudinal relaxation time of the ^{15}N spins. Recently, it was discovered that nuclear spins in *trans*-AB poses long-lived state, which enables sustaining non-thermal spin orders up to 50 minutes even in high magnetic fields [3]. This paves the way to perform SABRE hyperpolarization of *cis*-AB followed by controllable photo-switching and storage of the nuclear hyperpolarization in the form of the long-lived state of *trans*-AB nuclear spins. We have been developing an experimental protocol for in situ observation of SABRE hyperpolarization of *cis*-AB using ZULF NMR spectroscopy and performing reversible photo-switching between *cis*-AB and *trans*-AB. The possibility to generate hyperpolarized long-lived states is very attractive, notably, for magnetic resonance imaging applications.

References

[1] J.F.P. Colell *et al.*, *J. Phys. Chem. C*, **121**, 6626-6634 (2017)
[2] T. Theis *et. al., Nature Physics, **7**, 571-575* (2013)
[3] K.F. Sheberstov *et al.*, *Sci. Rep.*, **9**, 20161 (2019)

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Chemical Kinetic Aspects of Hyperpolarization Buildup and Decay Revealed via Side-Arm Para-Hydrogenation of Vinylated Fatty Acid Precursors

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Hyperpolarized (HP) fatty acids (FAs) are known to be a convenient target for diagnosing and tracking progression of metabolic syndrome, some forms of cancer, and bowel disorders [1]. We selected vinylated precursors of FAs to assess their ability to undergo side-arm hydrogenation (SAH) [2-3]. We examined the kinetics of hyperpolarization buildup and decay for the products of *para*-hydrogenation of vinylated FA precursors containing aliphatic, unbranching moieties of 2, 4, 5, 10, and 12 carbons in length at various pressures, reagent concentrations, and parahydrogen bubbling times using Nanalysis benchtop NMR spectrometer (60 MHz). To understand the dynamics of polarization buildup and decay, we elaborated a simple analytical model considering dissolution of (para)-hydrogen gas in the solvent and hydrogenation of the reagent (Figure 1A-B). We derive the equation describing the product formation as a function of time and reaction parameters. Modeling of the PHIP kinetics buildup and decay yielded consistent values for rate of hydrogenation of vinyl laurate using 5 mM of [Rh(COD)(dppb]BF_4 catalyst.

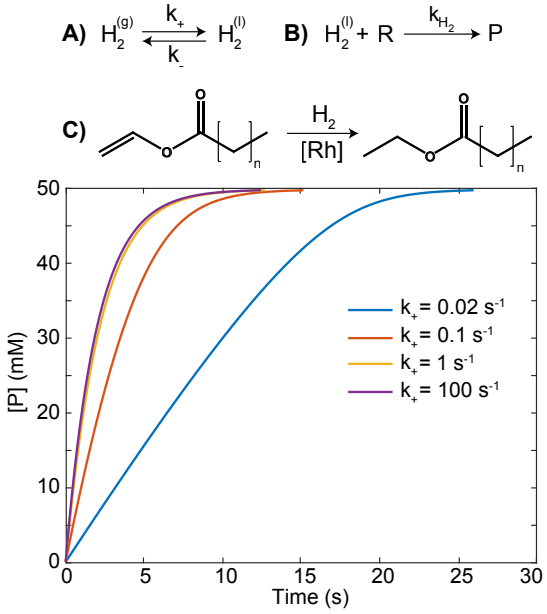

Figure 1: (A-B) Kinetic model of the hydrogen dissolution and side-arm para-hydrogenation of a vinylated fatty acid precursor. C) Calculated product formation using the quasi-steady-state (QSS) assumption for the dissolved hydrogen gas. As k_+ increases, the formation of P follows exponential increase as expected in a first-order kinetic model. For small k_+, hydrogen dissolution if the rate-limiting step and the formation of P follows zero reaction order.

References: [1] G. D. Besten et al., *The Journal of Lipid Research.* **2013**. [2] F. Reineri et al, *Nat. Commun.* **2015**. [3] E. Cavallari et al., *Frontiers in Oncology,* **2020**.

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