

Mobile Para-Hydrogen Enhanced Magnetic Resonance

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Para-hydrogen induced polarization is a fast technique of hyperpolarization that allows to signal enhance metabolites within seconds. Such metabolites are of particular interest to investigate the real-time metabolism of cells and of more complex organisms *in vivo*. Since the spin order of para-hydrogen can be harvested at mild conditions to produce highly polarized molecules it offers opportunities to be performed in portable devices. Additionally, generated large enhancements also allow for detection possibilities in mobile magnetic resonance devices. I will be presenting the progress that my group has made in the past years with respect to the aim of observing real-time metabolism at low magnetic fields. On one side we have shown that highly hyperpolarized metabolites can be generated in portable magnet systems of 1 Tesla. On the other side we have constructed a low-field magnetic resonance system based on electromagnets that operates at 20 millitesla. Within this system it is possible to monitor the conversion of hyperpolarized 2-¹³C pyruvate enhanced to 10% ¹³C polarization into lactate in real-time. Despite the low magnetic field, all of the chemical shift and *J*-coupling information is retained that can also be observed at standard high magnetic field systems. Lastly, I will be presenting our efforts to design new molecules that exhibit very long longitudinal relaxation times that allow for storing hyperpolarization for more than 10 minutes. Such long times open the stage to design new functional contrast agents and to be traced for longer periods of time compared to the standard ¹³C enriched metabolites.

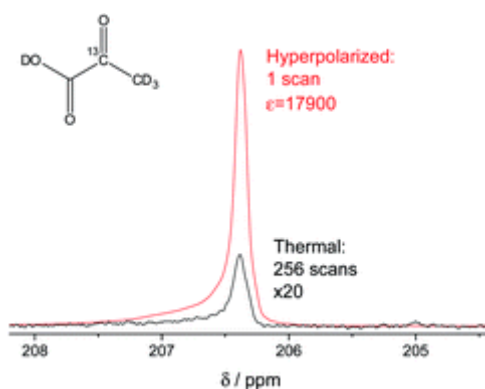


Figure 1. Para-hydrogen enhanced 2-¹³C pyruvate displaying >10% ¹³C polarization. The signal enhancement is 17 900-fold compared to the thermal signal detected at $B_0 = 7$ Tesla

PHIP guided studies of unusual [Cp*Ru]-catalyzed *trans*- and *gem*-hydrogenation reactions

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The detection of intermediates is essential to support mechanistic details of catalytic reactions, but is complicated by their typically low concentration and short lifetimes. In 2013 Fürstner and coworkers reported the unusual *trans*-selective hydrogenation of alkynes catalyzed by [Cp*Ru] complexes.^[1] Inspired by previous parahydrogen induced polarization (PHIP) studies of a similar reaction by Bargon and coworkers^[4], we used the same approach to detect key intermediates in the novel catalytic system. During the investigations, we were able to observe previously undescribed hyperpolarized NMR signals. Further NMR examination revealed the structure of these compounds to be carbene intermediates, which was later confirmed by X-ray diffraction. Most interestingly, the PHIP experiments demonstrate that the hydrogen molecule in these intermediates is transferred to a single carbon atom. The mechanism of this “*gem*-hydrogenation” and the role of the yet unprecedented carbene intermediate in the catalytic cycle was further investigated by PHIP-EXSY-NMR experiments and DFT calculations.^[3] The reaction pathways of the hydrogenation reactions can be tuned by the steric and/or electronic properties of the substrate and the catalyst as revealed by OPSY-NMR studies.^[4,5] Carbenes formed via *gem*-hydrogenation are valuable reaction intermediates for a variety of transformations, e.g. [3+2]-cycloadditions,^[4] hydrogenative cyclopropanations or hydrogenative metathesis.^[6]

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Rethinking SABRE Dynamics and Pulse Sequences to Improve Performance

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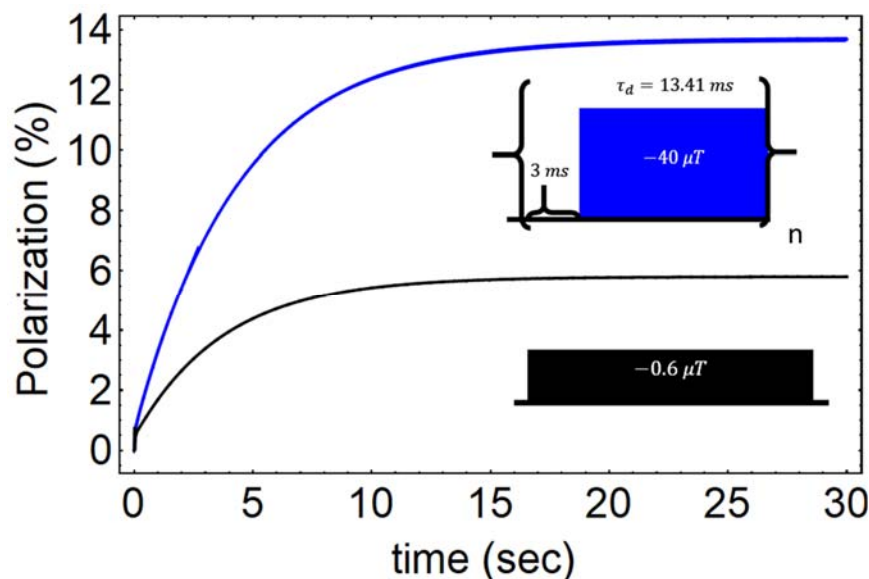


Figure 1. Snapshot of the evolution for an extreme X-SABRE case, oscillating between zero field and $-40 \mu\text{T}$. The average magnetic field is about two orders of magnitude larger than the level anticrossing value, and neither pulse by itself would generate significant polarization, but the combination is very effective in generating polarization. This is one example of two-state SABRE.

polarization-generating and competing pathways. We find that some sequences which deviate greatly from the LAC condition (both in peak and average values) give significantly more signal; one example is shown in Figure 1. Here we will present readily generated field sequences (typically oscillating between two different field values, in what we call two-state SABRE) which show significant polarization enhancements, are robust to experimental imperfections, and are validated by experiment.

SABRE and its heteronuclear variants (which we generically call X-SABRE) have tremendous promise as a low-cost, simple, and general hyperpolarization method which should be scalable to extremely large magnetization in bulk samples. However, total polarization produced to date generally is significantly lower than is produced (for example) as a bolus in dynamic nuclear polarization.

In this presentation, I will show that a significant part of the problem is that the accepted theoretical framework, based on level anti-crossings, often produces highly suboptimal polarization, particularly in the limits of very slow or very fast exchange. This work is enabled by a powerful theoretical framework describing exchanging systems which captures the complex dynamics(1); what really matters is the total polarization accumulated over many seconds, and this requires carefully accounting for both

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Using Hyperpolarization and Parahydrogen in Neutron Science

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While much attention has been directed towards NMR/MRI applications, hyperpolarized nuclei are also key staples of neutron science. Hyperpolarized ^3He is routinely used in "spin-filters" to create spin-polarized neutron beams. Importantly, hyperpolarized nuclei (and parahydrogen (1)) are also used in neutron beam targets where the spin order can be exploited to probe neutron-nucleus interactions. The Neutron Optics Time Reversal Experiment (NOPTREX) collaboration (2) has proposed searches for time-reversal invariance violation (TRIV) in the transmission of spin-polarized neutrons through targets of hyperpolarized nuclei that have low-energy neutron resonances that exhibit large parity (P)-odd asymmetries (3). A discovery of a new TRIVE source would signal physics beyond the Standard Model of particles and interactions and may have important consequences for our understanding of the matter-antimatter asymmetry of the universe. The long-term scientific goal is to search for a P-odd/T-odd term in the forward scattering amplitude proportional to $\vec{s} \cdot [\vec{k} \times \vec{l}]$, where \vec{k} is the neutron momentum, \vec{s} is the neutron spin, and \vec{l} is the nuclear polarization (3)—hence the need for hyperpolarization. Unfortunately, most of the identified nuclides of interest are $I > 1/2$ with large quadrupolar moments (like ^{131}Xe (4)), making them challenging to sustainably hyperpolarize. We also describe the intellectual interest in a TRIV search in polarized neutron transmission through a polarized nuclear target of ^{117}Sn ($I=1/2$), the R&D needed to develop the required hyperpolarized ^{117}Sn target using SABRE, and some of the preliminary NMR (5) and the relevant neutron measurements which have been conducted so far. The enormous parity-odd asymmetry already measured in the L=1 resonance in $n+^{117}\text{Sn}$ at a neutron energy of 1.33 eV implies that the sensitivity to P-odd/T-odd interactions is high for this resonance. We sketch the concept for a hyperpolarized ^{117}Sn nuclear target based on the newly-developed SABRE technique involving spin transfer from parahydrogen.

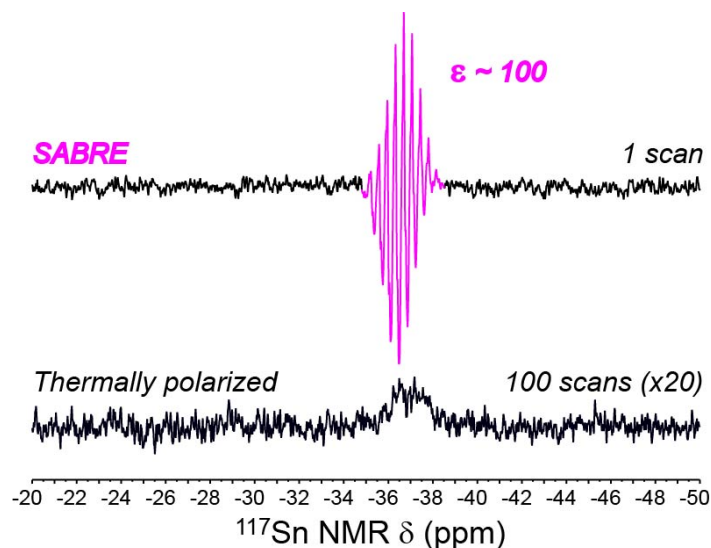


Figure 1: (Top) ^{117}Sn NMR spectrum at 9.4 T of 25 mM 5-tributylstannyl pyrimidine following 30 s p- H_2 bubbling at 0.2 mT, showing the hyperpolarized ^{117}Sn signal obtained with a single scan; catalyst concentration: 5 mM). (Bottom) Corresponding thermally polarized reference, 100 scans.

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Configurations of Long-Lived Order in 2-spin-1/2 systems: a Brief Primer

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Signals from equilibrium magnetization
after 100 minutes of storage!!

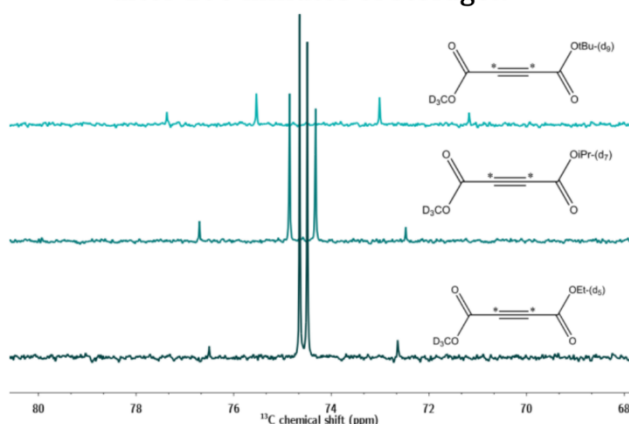


Figure 1: Signals from prototypical systems in a wide range of chemical inequivalence regimes, reconverted from long-lived eigenorder after long storage.

spin dynamics has often been clouded in confusion, which has not uncommonly led to the use of inappropriate rf control methods that may be unsuited to the spin systems under study. Practically, these imperfect methods may manifest as an inefficient, or incomplete retrieval of hyperpolarized magnetization. This is especially true for systems in the so-called *intermediate inequivalence* regime, where neither the J-coupling nor isotropic chemical shift terms dominate.

In this talk, we clearly delineate between the two available modes of long-lived spin order in 2-spin-1/2 systems – *singlet order* and *long-lived eigenorder* – presenting for the first time a complete relaxation theory for the latter. We also present a proof-of-concept for novel pulse sequences efficiently converting these functional spin configurations – in a wide range of inequivalence regimes - to standard observable magnetization.

Relaxation is a rapid irreversible process to which all hyperpolarized spin order is subject to. Thus, heated efforts have been devoted to studying *long-lived spin order* as a vessel for hyperpolarization since its discovery by the group in 2004. Nevertheless, robust and generalized methods for generating, preserving, and controlling long-lived spin order remained elusive until recent innovations in coherent control methods, in the form of elegant sequences that may consist of hard pulses, “soft” rf irradiation, and/or field sweeps.

Unfortunately, even in the simplest case of 2-spin-1/2 systems, the underlying

The multimode RASER – High precision or Chaos?

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With the first parahydrogen pumped RASER, molecular couplings could be determined with micro-Hertz precision.¹ Further studies with a RASER at higher detection fields showed that chemical shifts can be probed as well.^{2,3} With a LASER, in contrast to a RASER, such molecular parameters could not be probed due to fundamental differences between a LASER and a RASER: In a LASER, the lifetime of photons in a resonator ($\sim\mu\text{s}$) is relatively long, and the photon dynamics enslave the faster changing atomic degrees of freedom ($\sim 10\text{ ns}$). In other words, the resonator modes enslave the atoms, and therefore, no spectral features of the atoms can be measured⁴. In a NMR RASER, the long lived spin states enslave the electromagnetic modes, and therefore, the NMR transitions of the spins can be probed with high precision.

The crucial point for high precision NMR measurements and other applications of an NMR RASER is multimode operation to measure frequency differences and for internal calibration. For example, multiple RASER modes are crucial for high sensitivity, to compensate for magnetic field fluctuations. Additionally, multiple RASER lines enable extraction of spectroscopic information.

While the difference between two lines can be determined with microHertz precision, the minimum distance between two lines is often higher due to their nonlinear coupling following the RASER equations by Appelt et.al⁴. Depending on their distance, two RASER modes undergo several nonlinear phenomena until ultimately collapsing into a single line, which we describe using nonlinear mathematics, typically encountered in the field of synergetics.

Alternatively, regions of chaotic behavior can be observed depending on the specific sets of parameters (see Fig. 1).⁵ When moving towards a chaotic regime, the modes undergo frequency shifts, frequency combs and multiple period doubling processes until intermittence phenomena and ultimately chaos are observed.

In this talk, I would like to focus on five scenarios depending on mode distance and polarization: The “NMR mode” for precision measurements, line collapse, frequency comb, intermittence and chaos.

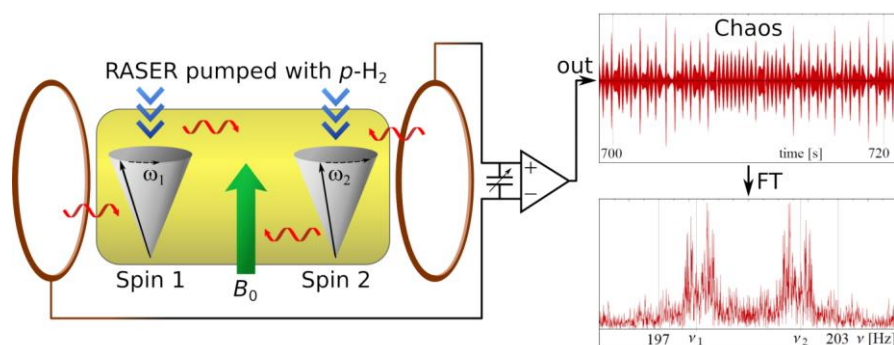


Figure 1. Two nonlinear coupled RASER modes can feature chaos³.

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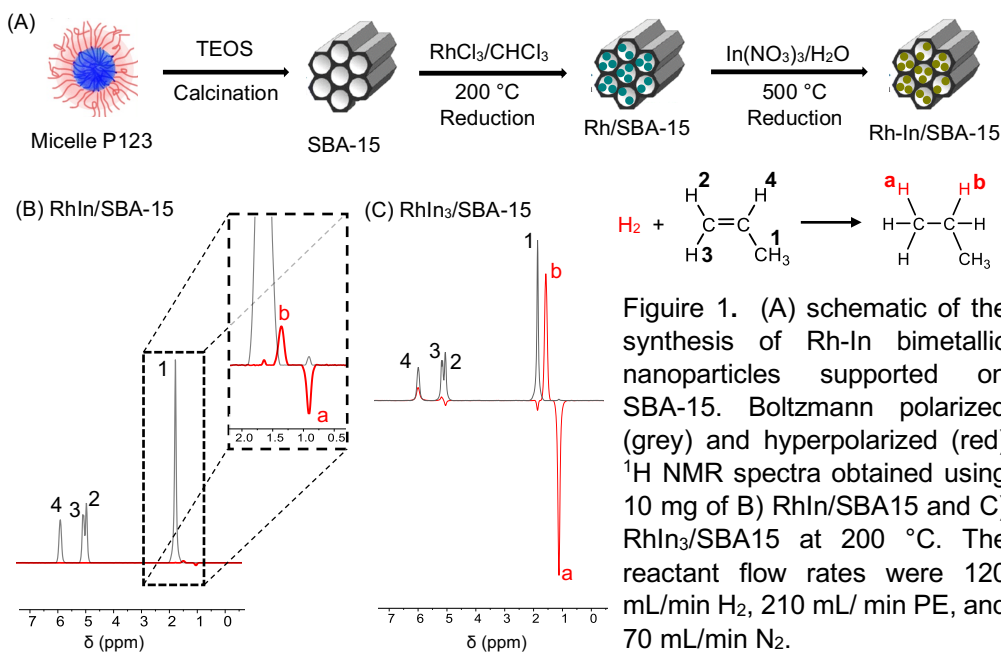
Bimetallic Nanoparticles Tailored for Parahydrogen Enhanced NMR by Heterogeneous Catalysis

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Parahydrogen enhanced NMR can in principle achieve nuclear spin hyperpolarization of order unity, thus boosting the sensitivity of NMR and MRI by several orders of magnitude. Parahydrogen enhanced hyperpolarization by heterogeneous catalysis over supported metals offers facile separation of the solid catalyst, enabling fast, robust, and continuous production of contaminant-free hyperpolarized biomolecules. However, signal enhancements achieved by heterogeneous catalysis over monometallic nanoparticle catalysts have been modest; for example, reaching only a few percent in hydrogenation of propene gas. Recent work in our group has demonstrated the efficacy of certain binary intermetallic phases composed of an active and an inert metal. The inert metal can increase the energy barriers for both H₂ dissociation and H ad-atom diffusion on metal surfaces, thereby prolonging the lifetime of the singlet. For example, PtSn bimetallic catalysts yielded an unprecedented 10.9% pairwise selectivity.¹



In this work, we pursued the tailored design of new bimetallic nanoparticles with higher ratios of inert metal and silica supports with higher surface area and improved transport properties. The novel catalytic nanomaterials afford substantially higher signal enhancement factors compared to conventional monometallic nanoparticle catalysts. As shown in Figure 1, a remarkable 23.6% pairwise

selectivity is achieved using RhIn₃/SBA-15 nanoparticles synthesized by Incipient Wetness Impregnation method, which is a significant enhancement boost comparing to 1.37% using RhIn/SBA-15. We also surveyed a wide range of inert support and bimetallic compositions for both liquid and gaseous substrates. By tailoring the composition and surface structure of bimetallic nanoparticles, parahydrogen enhancement by heterogeneous catalysis can compete with homogeneous catalysis with dissolved transition metal complexes with significant advantages in stability and separability.

Reference

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SLIC Spectroscopy of Common Organic Molecules at 6.5 mT

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One issue limiting the development of inexpensive and portable NMR spectrometers is the loss of spectral information at low magnetic fields. As the field is decreased and the spin system enters the strong-coupling regime ($J \gg \Delta\omega$), its proton NMR spectrum collapses to a single spectral line, which no longer provides structural information. To overcome this challenge, we introduced the SLIC spectroscopy method^{1,2}, which produces unique J-coupling spectra in strongly-coupled spin systems. The technique uses low power spin-lock induced crossing³ (SLIC) pulses to detect the level anti-crossings among dressed spin states, producing dips in the x-axis magnetization at particular spin-lock nutation frequencies.

We acquired SLIC spectra at $B_0=6.5$ mT for a variety of organic molecules with different proton connectivity, including 2-butanone (A_3B_2), hydrated isopropanol ($(A_3)_2B$), hydrated 1-propanol ($A_3B_2C_2$), N-methyl-2-pyrrolidone ($A_2B_2C_2$), pyridazine ($ABB'A'$), and tetrahydrofuran ($A_2B_2B'_2A'_2$). Molecules with the same connectivity among a group of spins (such as 2-butanone and ethyl acetate) have spectra with the same pattern, but with different shifts and depths depending on differences in J-coupling strength and chemical shifts. Molecules with J-coupling only between identical spins do not produce any dips in their SLIC spectra, for example acetone and water as well as isolated methyl groups.

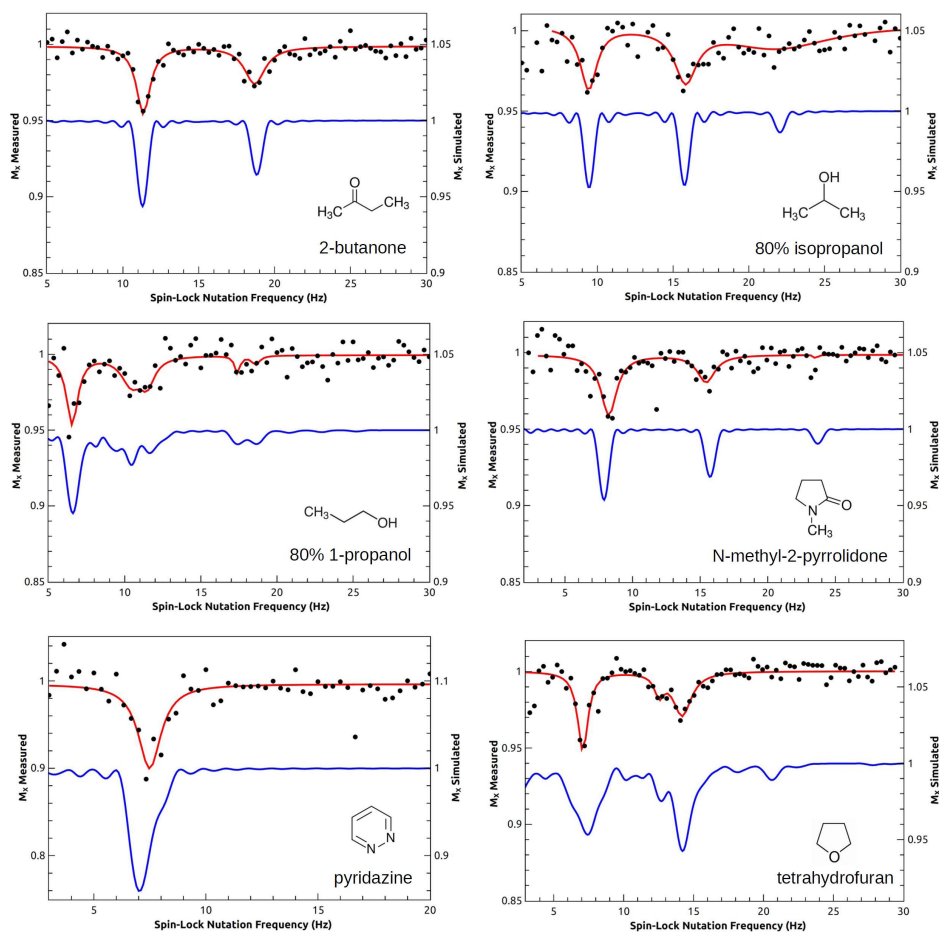


Figure 1: SLIC spectroscopy measurements (red) and simulations (blue) for a variety of organic molecules acquired at 6.5 mT.

We also studied chemical exchange by acquiring SLIC spectra of water-ethanol mixtures between 0 and 25% w/w water. The shape and number of dips in the spectrum are strongly affected by the hydroxyl exchange rate. By matching spectral shapes with simulations, we found that exchange was minimal between 0 and 6% w/w water, but above this concentration the exchange rate was 4.5 s^{-1} (%w/w water)⁻¹.

This technique can also be used with PHIP to convert singlet order to magnetization at low magnetic fields using the same resonance conditions⁴.

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2-State SABRE: Enhanced hyperpolarization from non-intuitive field sequences

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Signal Amplification By Reversible Exchange (SABRE) generates hyperpolarization through transient interactions between parahydrogen and a target molecules, both bound to an iridium catalyst. This effective, low-cost method is a promising alternative for polarizing clinically relevant targets, but translation and optimization will require a more detailed understanding of the underlying spin dynamics. Here we show that highly nonintuitive field conditions significantly increase observed magnetization.

For all SABRE variants to date, the magnetization creation process is understood as a level anticrossing (LAC)¹, either at low field where Zeeman differences are comparable to scalar couplings² or at high field with weak irradiation.

In contrast, in the 2-State SABRE pulse sequence (2S SABRE), a LAC is never established under either the instantaneous or average applied field and polarization transfer is actually improved. For example, using a field sequence with a zero-field condition followed by a far from resonance condition as in Figure 1, the achievable polarization is enhanced by a factor of up to 2.5. These unexpected results can be qualitatively understood using effective Hamiltonian theory, but the complex dynamics is best evaluated using the physically accurate DMExFR2³ simulation framework we recently developed, which finds robust optimal pulse sequences. Experimental application of the 2S SABRE pulse sequence shows rigorous agreement with these theoretical results.

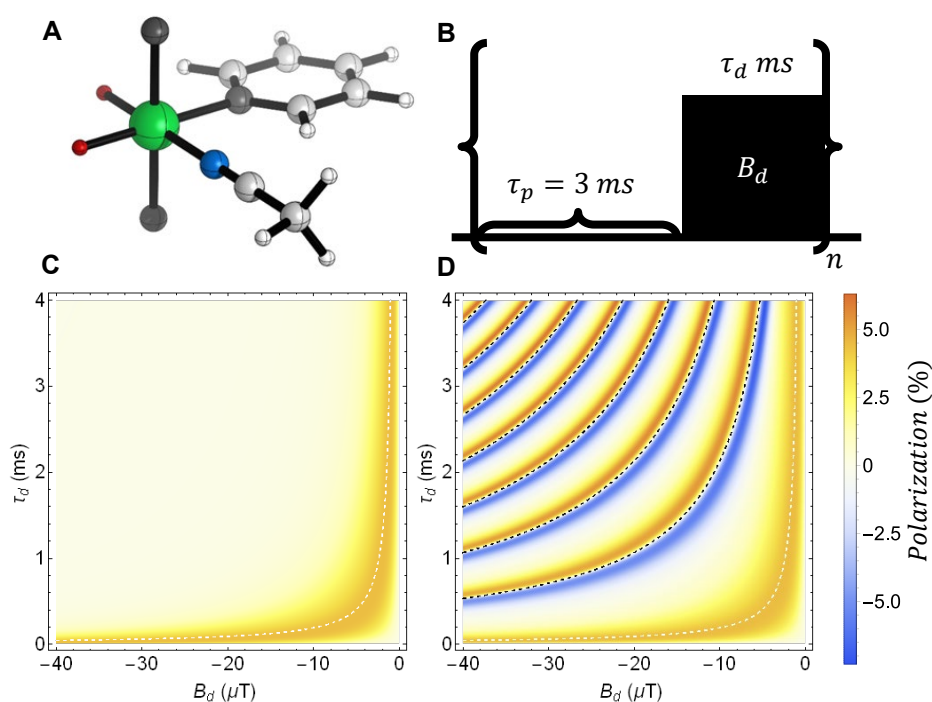


Figure 1. (A) Ir(IMes)(H)₂(pyr)₂(¹⁵N-acetonitrile) complex used in numerical simulations shown in C and D. (B) 2S SABRE pulse sequence used in DMExFR2 simulations with application of a $B_p = 0$ μ T field for duration $\tau_p = 3$ ms followed by a pulse of variable duration τ_d and field magnitude B_d . (C) Expected results from application of the proposed field with observable polarization for field sequences with an average field at the LAC matching condition (D) Results from a physically accurate DMExFR2 numerical simulation of the 2S SABRE sequence in B demonstrating improved polarization without approaching the LAC matching condition.

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