^{1}H and ^{19}F NMR Signal Enhancement Enabled by Spin Polarization-Induced NOE and Parahydrogen-Induced RASER

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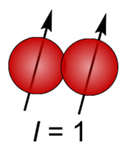
Introduction: Low sensitivity is the main issue of NMR and MRI. One of the ways to improve sensitivity of NMR is to create nuclear spin hyperpolarization, i.e. highly non-equilibrium population of nuclear spin states. Parahydrogen-induced polarization technique (PHIP) allows one to produce hyperpolarized chemicals via pairwise addition of parahydrogen to asymmetric unsaturated precursors in high and low magnetic fields (PASADENA and ALTADENA conditions, respectively). PHIP allows one to obtain more than 50% nuclear spin polarization. However, this technique is substrate-specific since it is only possible to produce hyperpolarized compounds that have corresponding unsaturated precursors. Here we show that using parahydrogen-induced RASER (Radiowave Amplification by Stimulated Emission of Radiation) which may occur during PHIP experiment in ALTADENA conditions it is possible to hyperpolarize broad range of compounds inaccessible via standard PHIP experiment.

Parahydrogen-Induced Polarization (PHIP)

Orthohydrogen — **Parahydrogen**



$T_+ = |\alpha\alpha\rangle$

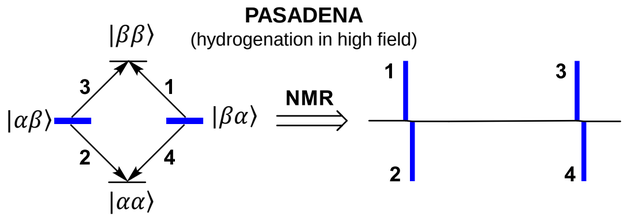
$T_0 = \frac{|\alpha\beta\rangle + |\beta\alpha\rangle}{\sqrt{2}}$ $\quad S = \frac{|\alpha\beta\rangle - |\beta\alpha\rangle}{\sqrt{2}}$

$T_- = |\beta\beta\rangle$

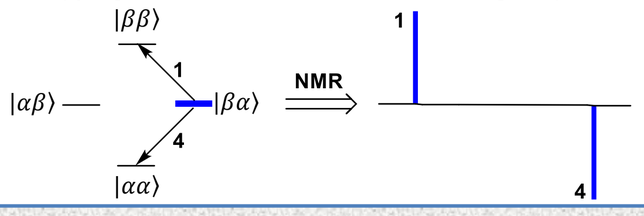
Temperature	*p*-H_2 fraction
298 K (r.t.)	**25 %**
77 K (liquid nitrogen)	**50 %**
24 K (liquid He-based *p*-H_2 generator)	**98 %**

Pairwise addition of parahydrogen (*p*-H_2) to unsaturated precursor molecules leads to hyperpolarized compounds

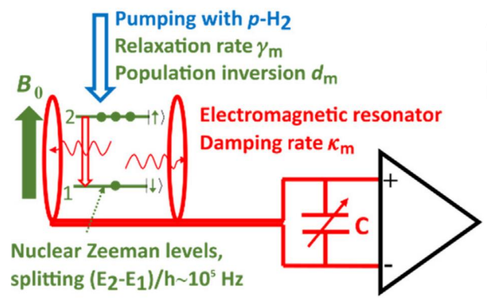
PASADENA
(hydrogenation in high field)



ALTADENA
(hydrogenation in low field and adiabatic transfer to high field)



Radiowave Amplification by Stimulated Emission of Radiation (RASER)



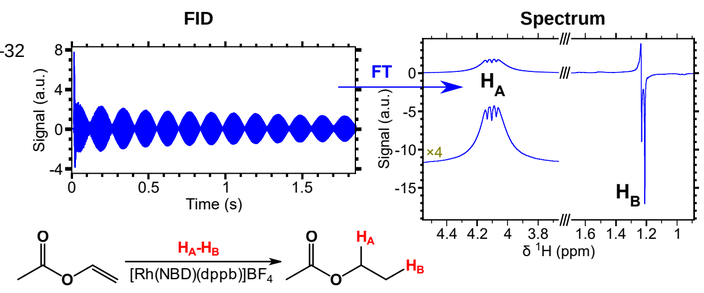
S. Appelt, A. Kentner, S. Lehmkuhl, B. Blümich, *Prog. Nucl. Magn. Reson. Spectrosc.* **2019**, 114, 1–32

PHIP-RASER leads to broadening of absorptive NMR signals and narrowing of emissive NMR signals. Also, the resonances of negatively polarized nuclei quickly deplete due to radiation damping (H_B signal in the figure on the right).

At critical population inversion level, a non-linear interaction between the magnetization vector and the LC-circuit leads to long-lasting oscillations of NMR signal; this critical population inversion level may be formulated as polarization P_{min}:

$$P_{min} < -\frac{4}{\mu_0 \hbar \eta \gamma^2 T_2^* n_s Q}$$

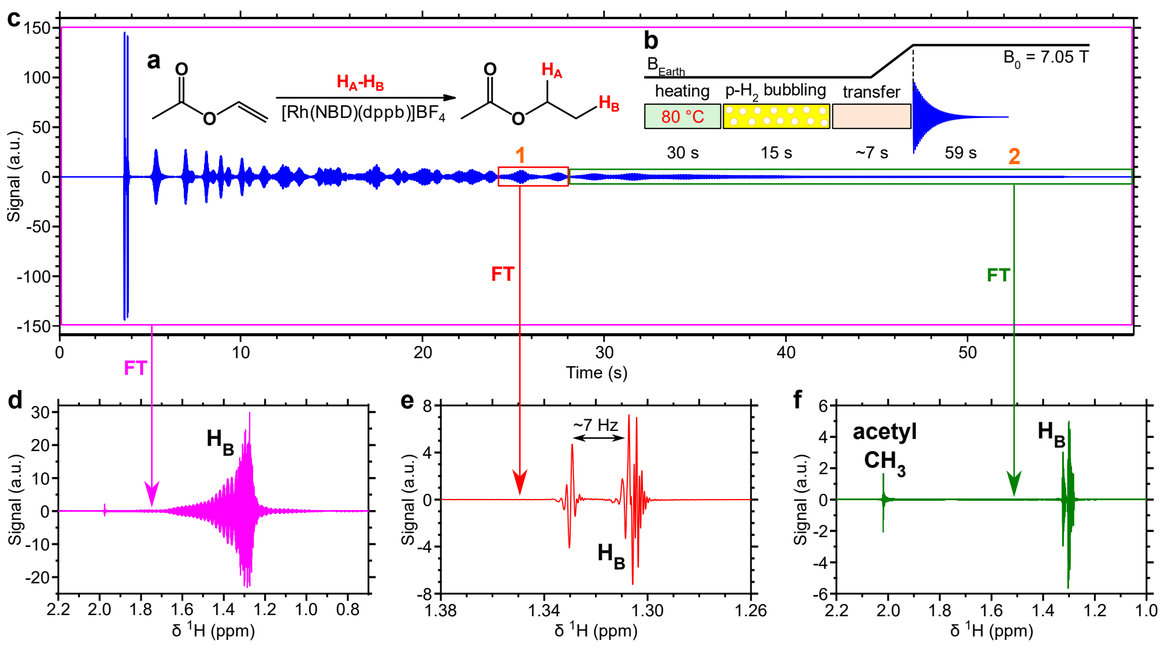
NMR



PHIP-RASER & PRINOE

(**P**arahydrogen & **R**ASER-**I**nduced **N**uclear **O**verhauser **E**ffect)

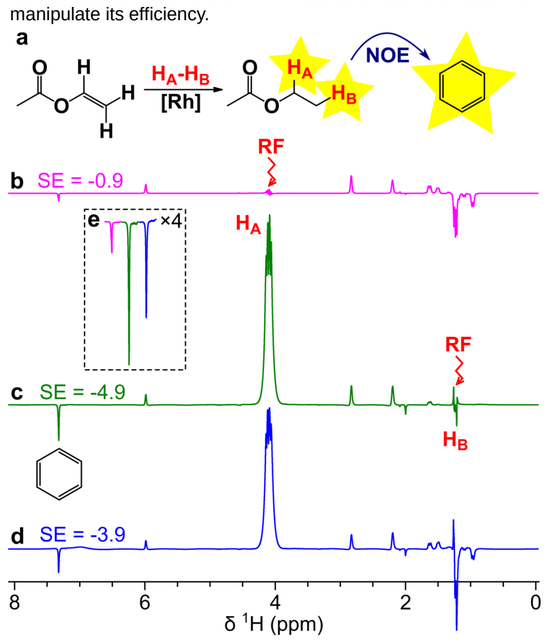
Here we show that RASER effects can be observed using a conventional 7.05 T NMR spectrometer and a standard NMR probe when conducting ALTADENA experiment with vinyl acetate (VA) to yield hyperpolarized (HP) ethyl acetate (EA). Radiation damping leads to depletion of the resonance of negatively polarized H_B proton of EA, resulting in highly non-equilibrium and positive total magnetization of the solution. Next, this magnetization is spontaneously transferred to magnetic nuclei of other compounds present in the solution via NOE. The resultant effect is called PRINOE; positive total polarization of EA (polarization source) is converted to negative polarization of other compounds (target molecules).



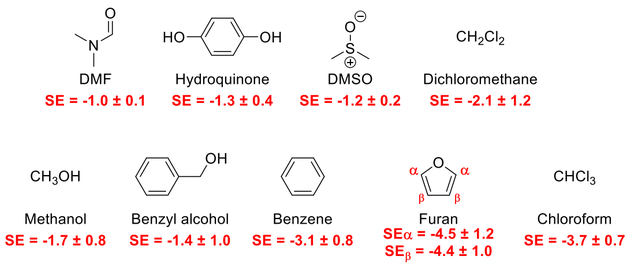
(**a**) Reaction scheme of VA hydrogenation with *p*-H_2 to yield HP EA. (**b**) Event sequence implemented in the experiment (RASER protocol). (**c**) ^{1}H NMR signal acquired in ALTADENA hyperpolarization of EA using the RASER protocol (without an RF excitation pulse). (**d**–**f**) Corresponding ^{1}H NMR spectra obtained after FT of the regions of the time domain signal shown in the panel (c) selected with the boxes of the same color: (d) the full signal, (e) the region 1, and (f) the region 2.

Implementation of ALTADENA PRINOE

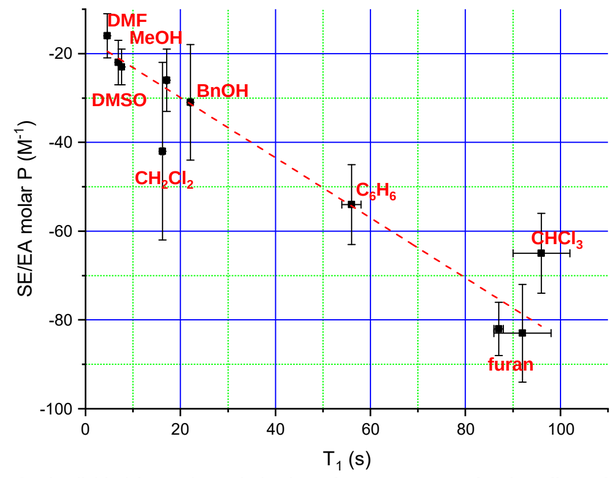
Frequency-selective saturation of EA resonances confirms the mechanism of ALTADENA PRINOE and can be used to manipulate its efficiency.



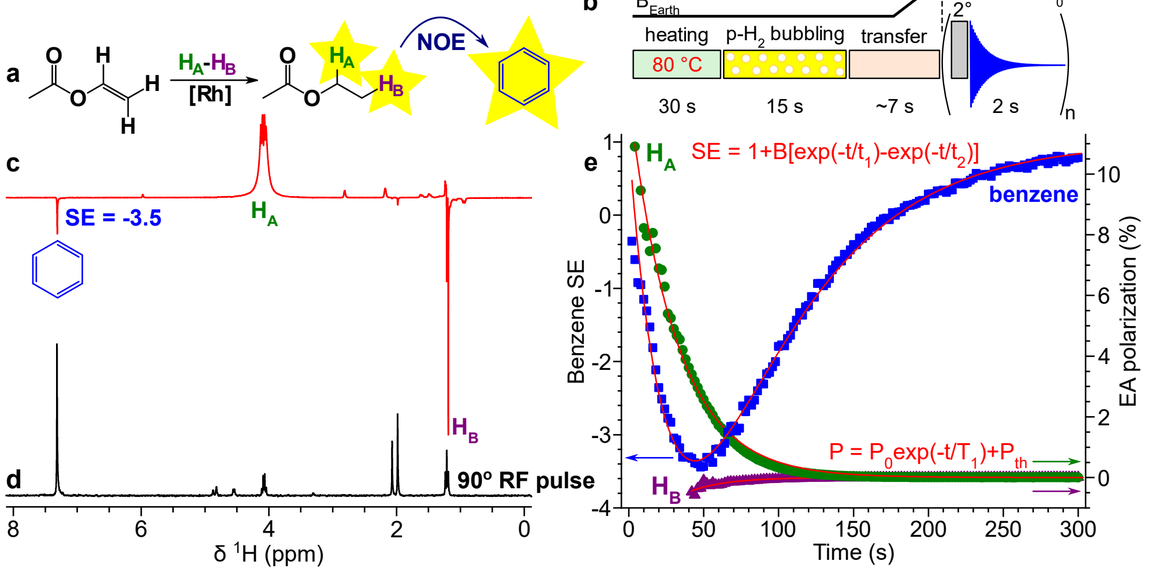
(**a**) Reaction scheme of VA hydrogenation with *p*-H_2 to yield HP EA with a subsequent NOE polarization transfer to benzene. (**b**, **c**) ^{1}H NMR spectra acquired after the saturation of EA H_A (b) or H_B (c) resonance with the 39.9 s-long train of soft RF pulses and the application of a hard 90° RF pulse. (**d**) ^{1}H NMR spectrum acquired after 39.9 s delay and the application of a hard 90° RF pulse (control experiment). (**e**) Signals of the benzene protons in the spectra (b)–(d) multiplied by a factor of 4.



ALTADENA PRINOE experiments with VA as a polarization source and various target molecules demonstrated that achievable target signal enhancement (SE) correlates with T_1 values of the corresponding protons.

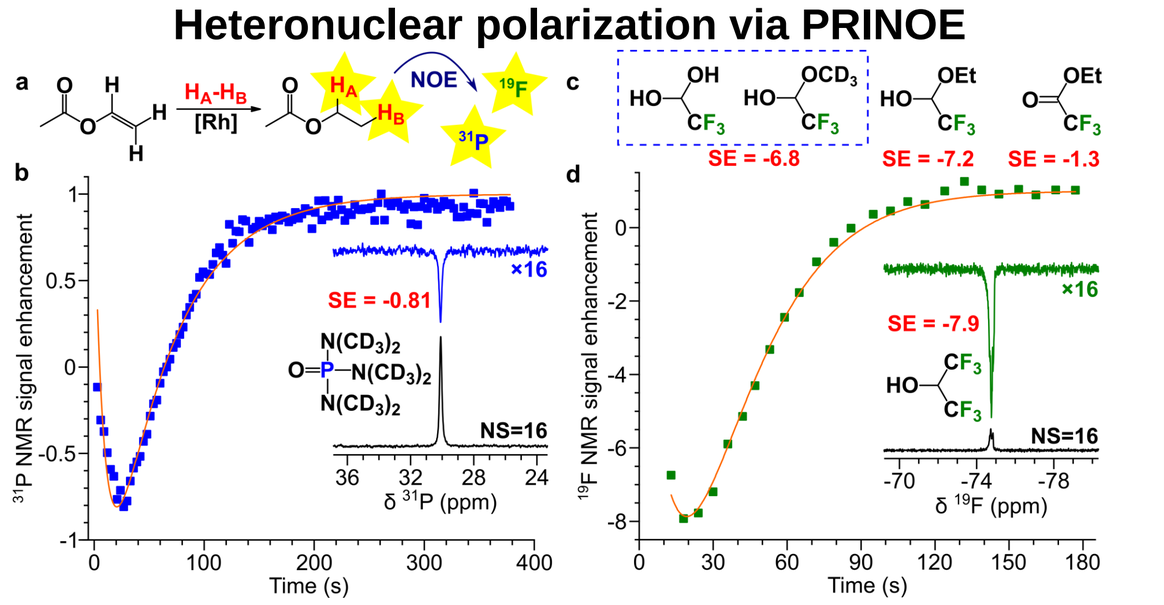


SE is divided by molar polarization of EA to account for the effect of initial magnetization in the solution.



(**a**) Reaction scheme of VA hydrogenation with *p*-H_2 to yield HP EA with a subsequent NOE polarization transfer to benzene as a target molecule. (**b**) Event sequence implemented in the experiment (decay protocol). (**c**) ^{1}H NMR spectrum acquired in ALTADENA hyperpolarization of EA using decay protocol with a 2° RF excitation pulse 48 s after the sample is placed in the NMR probe with benzene added as a target. (**d**) Thermal reference spectrum of the same solution acquired using a 90° RF pulse after relaxation of hyperpolarization. (**e**) Kinetics of SPINOE ^{1}H NMR signal enhancement of benzene (blue squares, left Y-axis) and simultaneous decay of EA ^{1}H hyperpolarization (green circles, H_A proton, and purple triangles, H_B proton, right Y-axis).

Heteronuclear polarization via PRINOE



(**a**) Reaction scheme of VA hydrogenation with p-H_2 to yield HP EA with a subsequent NOE polarization transfer to ^{19}F or ^{31}P nuclei. (**b**) Kinetics of PRINOE ^{31}P NMR signal enhancement of HMPA-d_{18} at 7.05 T. (**c**) List of ^{19}F-containing substrates that were polarized via PRINOE and corresponding ^{19}F NMR signal enhancement values. (**d**) Kinetics of PRINOE ^{19}F NMR signal enhancement of HFIP at 1.4 T.

Acknowledgements: This work was supported by the Grants Council of the President of the Russian Federation (grant # MK-2826.2022.1.3).