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Catalytic hydrogenation of trivinyl orthoacetate: mechanisms elucidated by parahydrogen induced polarization

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Abstract: Parahydrogen (pH_2) induced polarization (PHIP) is a unique method that is used in analytical chemistry to elucidate catalytic hydrogenation pathways and to increase the signal of small metabolites in MRI. PHIP is based on adding or exchanging at least one pH_2 molecule with a target molecule. And thus, the spin order available for hyperpolarization is often limited to that of one pH_2 molecule. To break this limit, we investigated the addition of multiple pH_2 molecules to one precursor. We studied the feasibility of the simultaneous hydrogenation of three arms of trivinyl orthoacetate (TVOA) intending to obtain hyperpolarized acetate. It was found that semihydrogenated TVOA underwent a fast decomposition accompanied by several minor reactions including an exchange of geminal methylene protons of a vinyl ester with pH_2 . The study shows that multiple vinyl ester groups are not suitable for a fast and clean (without any side products) hydrogenation and hyperpolarization that is desired in biochemical applications.

Introduction

Magnetic resonance (MR) is a versatile physical effect that is widely used in science and clinical medicine. Its applications span from analysis of protein structure with a sub-angstrom precision and microseconds times scale^[1,2] to anatomical and physiological imaging.^[3–6] Some applications, like measuring metabolites,^[7] are severely hampered by the low sensitivity of the technique or a low signal-to-noise ratio (SNR). To address these shortcomings, the sensitivity of MR was increased steadily by hardware developments. About one order of magnitude of the signal gain can be reached using cryoprobes^[8,9] or cryomagnets with higher magnetic fields.^[10,11]

Nuclear spin hyperpolarization is a family of methods that brings a 10 to 10⁵ fold signal gain using physical or chemical effects.^[12–15] Instead of improving the detection electronics^[16,17] or increasing the magnetic field, these methods use special techniques to increase the polarization of the spins directly.^[18–20]

Parahydrogen based methods employ the highly ordered spin state of parahydrogen (pH_2) to achieve net polarization of a target molecule. To do so, a pH_2 molecule is either added to a target

molecules by a catalytic hydrogenation reaction (**Figure 1**),^[20] or exchanged.

Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment (PASADENA) is an experiment that exploits pH_2 hydrogenation at high magnetic fields.^[21] The unique property of PASADENA is its *anti-phase* shape of spectral lines in the basic excitation and acquisition NMR experiment, while *normal* or *thermal* MR resonances are always *in-phase*. This feature is used to study hydrogenation routes and also reveals a fraction of pairwise hydrogenation.^[22] The advantage of PHIP as a hyperpolarization method is its cost-efficiency: with only little investment^[23–25] highly polarized samples can be produced in a batch process^[26,27] or continuously^[28].

Although PHIP has many powerful features, its scope was restricted until recently to a few organic molecules with few biochemical applications.^[29] The utilization of functionalized vinyl or propargyl groups, so-called PHIP side arm hydrogenation (PHIP-SAH) opened new applications. Here a side arm is hydrogenated and then polarization is transferred to the target site of the polarized molecule, which often is the ¹³C nucleus of a carboxyl group. PHIP-SAH enabled hyperpolarization of a larger number of endogenous molecules including acetate (**Figure 1a**), pyruvate,^[30] amino acids^[31] and peptides.^[32]

Recently, metabolites hyperpolarized with PHIP-SAH were tested in cell-cultures^[33] and in vivo.^[34] PHIP-SAH at high magnetic fields demonstrated more than 50% ¹³C polarization of ethyl acetate- d_6 and 19% of acetate- d_3 within seconds.^[35]

Still, there is much room to improve the polarization level of PHIP. While exchange based methods^[36,37] allow continuous re-hyperpolarization of the target molecule,^[38] the spin order available to hydrogenation-based methods to polarize the target is limited to that of a single pH_2 molecule.

Thus, we investigated the question, if multiple pH_2 molecules can be added to a target molecule and used for hyperpolarization of the target site of the molecule. We pursued the hypothesis that multiple hydrogenations of the same molecule with pH_2 will lead to a higher level of polarization of the target fragment.

Towards this goal, we introduce a new experiment: PHIP by hydrogenation of three sidearms (PHIP-HOT, **Figure 1b**). Here,

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the target fragment (acetate) is functionalized with three equivalent vinyl groups, resulting in trivinyl orthoacetate (TVOA). Employing a reaction similar to PHIP-SAH, we aimed at hyperpolarizing the same molecule, acetate. Contrary to our

expectations, however, an entirely different reaction took place. These findings are reported in this paper.

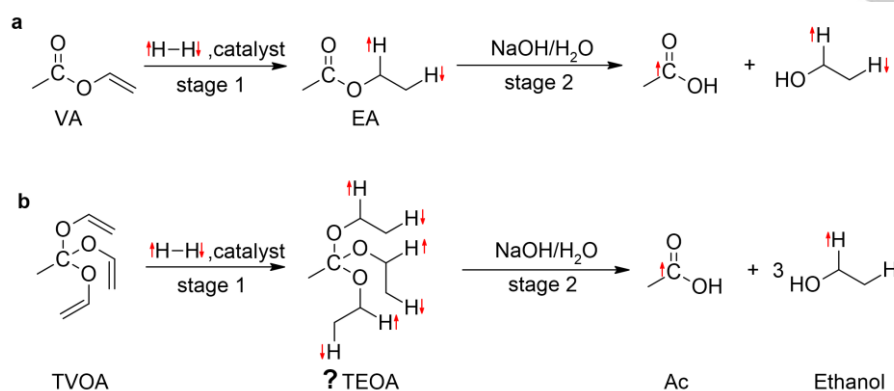


Figure 1. Reaction schemes of hydrogenation and side-arm cleavages confirmed for PHIP-SAH (a) and expected (marked with "?") for PHIP-HOT (b). (a) Hydrogenation of vinyl acetate (VA) results in the production of ethyl acetate (EA). The cleavage of the ester in the presence of a base and water leads to acetate (Ac) and ethanol. (b) Hydrogenation of trivinyl orthoacetate (TVOA) with three $p\text{H}_2$ molecules is expected to lead to triethyl orthoacetate (TEOA). The cleavage of ethyl groups in the presence of NaOH and water was expected to result in acetate (Ac) and three molecules of ethanol. In both cases, only acetate and ethanol would be the products. Note that full hydrogenation of TVOA was assumed. Red arrows indicate expected hyperpolarized spins: ethanol is polarized because of the chemical reaction of the vinyl group with $p\text{H}_2$. Optionally, polarization may be transferred from ethyl to ^{13}C after hydrogenation that is indicated by the arrow next to C of acetate.^[34,35] It has been shown experimentally that rapid TEOA dissociation occurs during stage 1, i.e. without adding NaOH. TVOA hydrogenation with $[\text{Rh}(\text{dppb})(\text{COD})]\text{BF}_4$ catalyst was studied here in details.

Results

PASADENA experiments (Figure 1b, stage 1) were conducted with TVOA and catalyst $[\text{Rh}(\text{dppb})(\text{COD})]\text{BF}_4 = \mathbf{[1]}$ (CAS: 79255-71-3) at 25 °C and ambient pressure with 0.2 bar $p\text{H}_2$ overpressure in acetone- d_6 . Enhanced, PASADENA-type anti-phase signals were observed for the following molecules (Figures 2,3): ethyl acetate (EA), ethanol, acetaldehyde, vinyl acetate, H_2 and other unassigned products. After 5 minutes of constant H_2 bubbling, high-resolution NMR spectra were acquired. A ratio of [ethyl acetate] : [acetaldehyde] : [ethanol] = 1 : 1.95 : 0.2 was found. Also of 2-chloroethanol and cyclooctene were found. 2-Chloroethanol was used in the synthesis of TVOA (see Experimental Section) and traces thereof were found in the pre-hydrogenation sample. Cyclooctene is the side product of the catalyst $\mathbf{[1]}$ activation. It is formed by hydrogenation of the 1,5-cyclooctadiene ligand of the Rh-catalyst. Note that triethyl

orthoacetate or any semihydrogenated TVOA, i.e. divinyl ethyl orthoacetate, were not found.

The experiment was repeated in chloroform- d . EA was found to be polarized to a much higher level, while ethanol was polarized to a lesser extent. The concentration ratio of the products of the TVOA hydrogenation and decomposition was determined by NMR after 20 minutes of H_2 bubbling [ethyl acetate] : [acetaldehyde] : [vinyl acetate] : [ethanol] = 1 : 2.15 : 0.42 : 0.04. Strongly polarized resonances of VA appeared; all these resonances exhibited the PASADENA-type appearance in phase. Rapid decomposition of the substrate after hydrogenation may occur due to residual water and acids; possible decomposition paths are discussed later (Figure 4). To reduce this effect, we additionally purified the solvents by pouring acetone- d_6 through a dry magnesium sulfate powder and chloroform- d through a dry basic aluminium oxide powder column, directly before sample preparation. This filtration did not change our observations.

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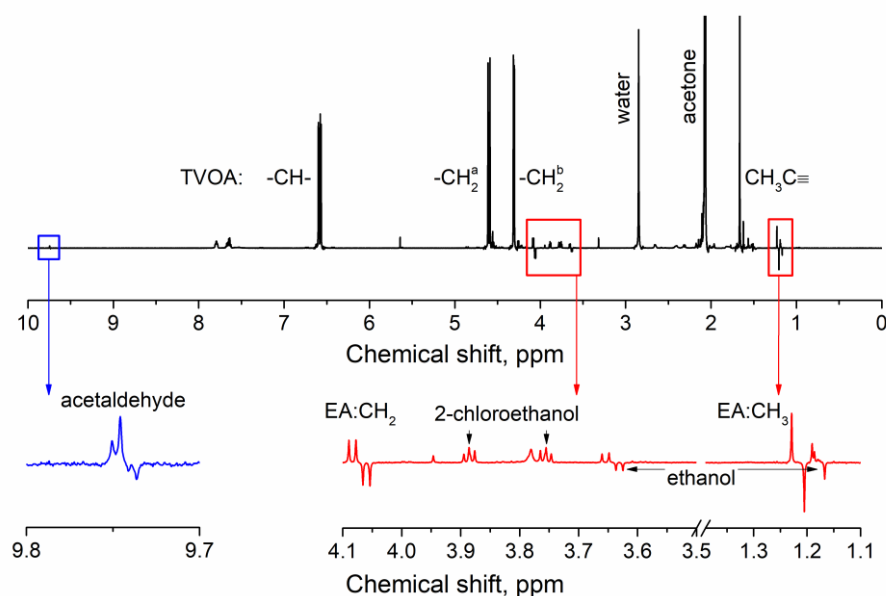


Figure 2. ^1H NMR spectrum of TVOA hydrogenated with pH_2 and [1] in acetone- d_6 at 14.1 T. The main polarized product identified was ethyl acetate (EA). Ethanol and acetaldehyde showed much less polarization. Other side products were 2-chloroethanol, cyclooctene and various unassigned alkanes. Note that cyclooctene is the side product of the catalyst activation and subsequent hydrogenation of 1,5-cyclooctadiene. Relevant sections of the spectrum with hyperpolarized signals are magnified.

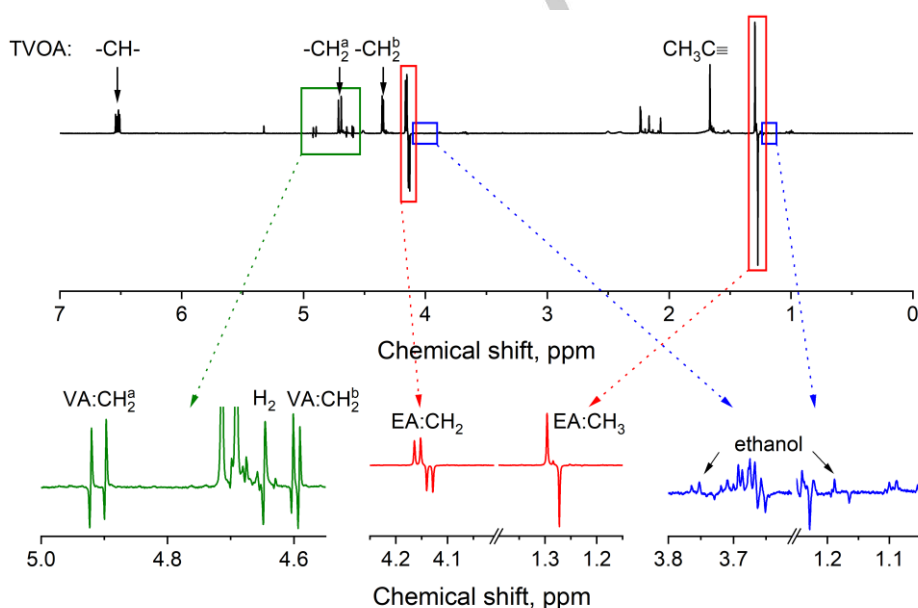


Figure 3. ^1H NMR spectrum of TVOA hydrogenated with pH_2 and [1] in chloroform- d at 14.1 T. Relevant sections of the spectrum with hyperpolarized signals are magnified. The main polarized product identified was ethyl acetate (EA). Ethanol, acetaldehyde, vinyl acetate (VA) and H_2 showed much less polarization than EA. Note the partially negative line of H_2 and polarized antiphase lines of CH_2 protons of VA. Other side products were 2-chloroethanol, cyclooctene and various unassigned alkanes. Note that cyclooctene is the side product of the catalyst activation and subsequent hydrogenation of 1,5-cyclooctadiene.

Discussion

I. Polarization of ethyl acetate and ethanol

A molecule with three unsaturated side arms TVOA was successfully synthesized and subjected to a PASADENA experiment. Experimentally, TVOA was found to be stable in the presence of [1] and dissociation started only after the addition of H_2 .

NMR showed multiple PASADENA signals but no signals from semi- or fully hydrogenated TVOA (Figure 1-3). Because no hyperpolarized orthoacetate signals were observed, we assume that after the first hydrogenation the product immediately dissociates.

Divinyl ethyl orthoacetate (DVEOA) should be the first product of TVOA hydrogenation and we suggest three main pathways how it can dissociate in the presence of water (Figure 4). First, a

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proton will activate one of the three ether side arms of DVEOA. If the hydrogenated sidearm (ethyl) is activated the dissociation will lead to hyperpolarized ethanol (**Figure 4(1a)**).

The other possibility is that one of the unsaturated sidearms (vinyl) of DVEOA is activated (**Figure 4(1b,1c)**). In this case, the dissociation could lead to hyperpolarized ethanol (**1b**) or hyperpolarized ethyl acetate (EA, **1c**). Note that emerging vinyl acetate (VA) in **1a** and **1b** cases could also be hydrogenated and hence EA will be polarized. All products of TVOA hydrogenation and consequent dissociation pathways are summarized in the table (**Figure 4**).

These possible pathways allow only EA or ethanol to be polarized. Experimentally, fractions of EA and ethanol were changing with the duration of bubbling; therefore, we could not unequivocally determine a major pathway. However, it appears that EA experiences a stronger polarization than ethanol (i) and the obtained concentration ratio [acetaldehyde] : [ethyl acetate] is close to 2 : 1 (ii). Both facts indicate that the reaction path **1c** is preferred (**Figure 2,3**), despite the signal ratios being different in two solvents. The consumption of the H₂O residues is one possible reason for the product distribution varying with time.

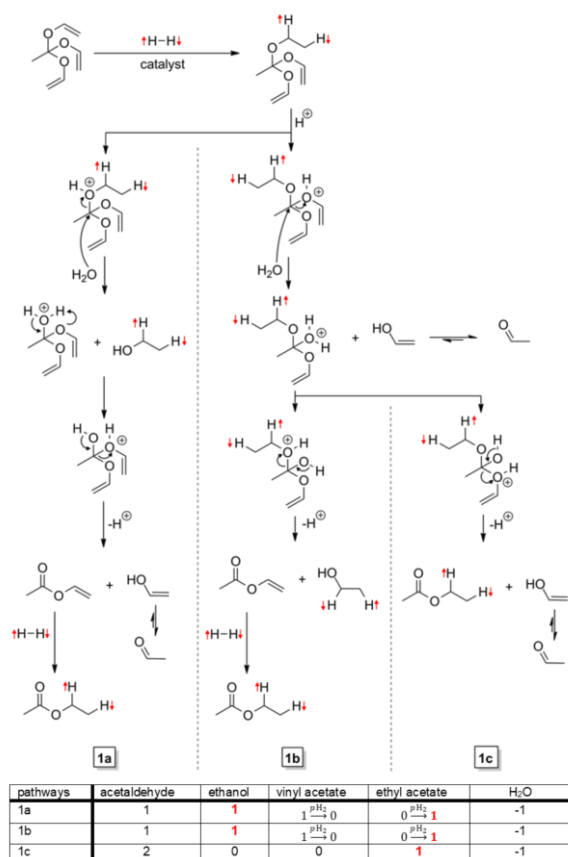


Figure 4. Potential reactions of TVOA disintegration in presence of water after hydrogenation with pH₂ and [1], and corresponding table of products. We assume that hydrogenation of TVOA results in divinyl ether orthoacetate (DVEOA) with a polarized ethyl group. Three cleavage pathways are considered here. If the hyperpolarized ethyl ether sidearm is cleaved first, this will lead to vinyl acetate, acetaldehyde and hyperpolarized ethanol (**1a**). If the vinyl ether is cleaved first, then either the products will be the same (**1b**) or two molecules of acetaldehyde and hyperpolarized ethyl acetate will be produced (**1c**). Red arrows in the scheme and numbers in the table indicate hyperpolarized protons and molecules by hydrogenation with pH₂. This cleavage scheme explains only polarization of ethyl acetate and ethanol.

II. Polarization of vinyl acetate

The PASADENA type polarization of CH₂-protons of vinyl acetate (VA, **Figure 3**) is a rather uncommon effect. It can be explained by the pairwise exchange of CH₂-protons with pH₂ on the transient complex, which consists of [1], TVOA and pH₂ (**Figure 5**). The result of this hydrogen exchange is a TVOA with a terminal hyperpolarized sidearm. If this TVOA undergoes normal hydrogenation and dissociation reaction on the pathways **1a** or **1b** (**Figure 4**), a terminal hyperpolarized VA is obtained. The minor level of polarization (**Figure 3**) indicates that it is not the major polarization mechanism.

It should be noted that only the unique signal enhancement caused by pH₂ addition allowed us to find this exchange of H₂ on geminal protons of TVOA. It would have been impossible with normal H₂. A similar effect was observed also by Bargon et al.^[39,40] when using rhodium and palladium catalysts to hydrogenate styrene. In both cases, the structure of the substrate results in the formation of a relatively long-lived intermediate. This is due to the coordination of the benzene ring of styrene^[39,40] or due to the coordination of a second vinyl group of TVOA to the metal ion, which leads to hyperpolarization of geminal protons.

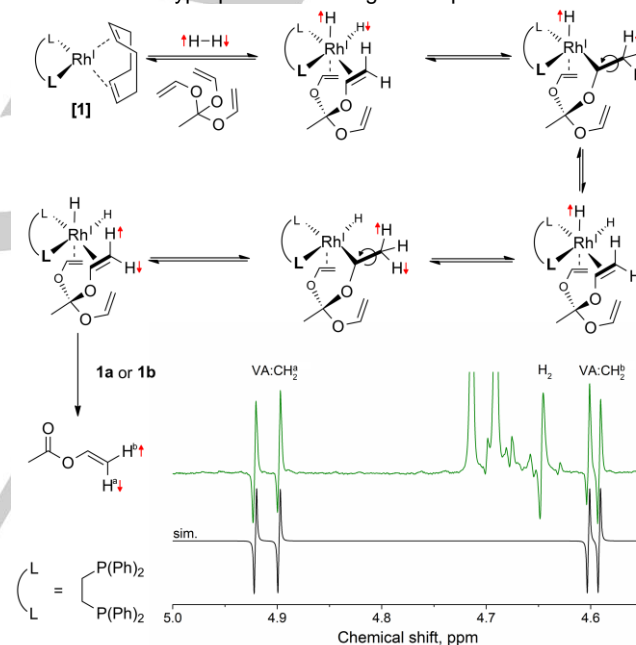


Figure 5. Trivinyl orthoacetate – H₂ exchange with experimental and simulated (sim.) PASADENA spectra. TVOA exchanges its methylene protons with pH₂ when both (hydrogen and TVOA) are coordinating to [1]. After dissociation according to pathway **1a** or **1b**, vinyl acetate (VA) with polarized CH₂-protons is produced. The following NMR parameters were used for simulations of polarized VA (sim.): chemical shifts: $\delta_{CH} = 7.267$ ppm, $\delta_{CH_2^a} = 4.85$ ppm, $\delta_{CH_2^b} = 4.59$ ppm and J-coupling constants: $^3J_{CH-CH_2^a} = 13.9$ Hz, $^3J_{CH-CH_2^b} = 6.34$ Hz, $^2J_{CH_2} = -1.4$ Hz. It was assumed that the CH₂ protons are produced by pH₂ (PASADENA effect, sim.). In the experiment and simulations nonselective 45° excitation RF-pulses were used.

III. Polarization of acetaldehyde

The PASADENA type polarization of the CH-proton of acetaldehyde (AD) is another unexpected hyperpolarized signal (**Figure 2**). Although it is a saturated aldehyde, its origin is unsaturated vinyl alcohol, which was not hydrogenated by pH₂.

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The tentative pathway that leads to the polarization of AD is a pairwise exchange of CH and one CH₂ proton of the vinyl group of TVOA with *p*H₂ on [1] (Figure 6). This unconventionally polarized TVOA would lead to the observed polarized acetaldehyde after the dissociation pathways 1a, 1b or 1c (Figure 4). This vicinal pairwise hydrogen exchange is an H₂ exchange mechanism occurring in addition to the previously discussed exchange of geminal protons with *p*H₂ (Figure 5). Similar vicinal *p*H₂ exchange was observed by Skovpin et al. [41] in the hydrogenation reaction of propylene with a silica-immobilized Rh catalyst.

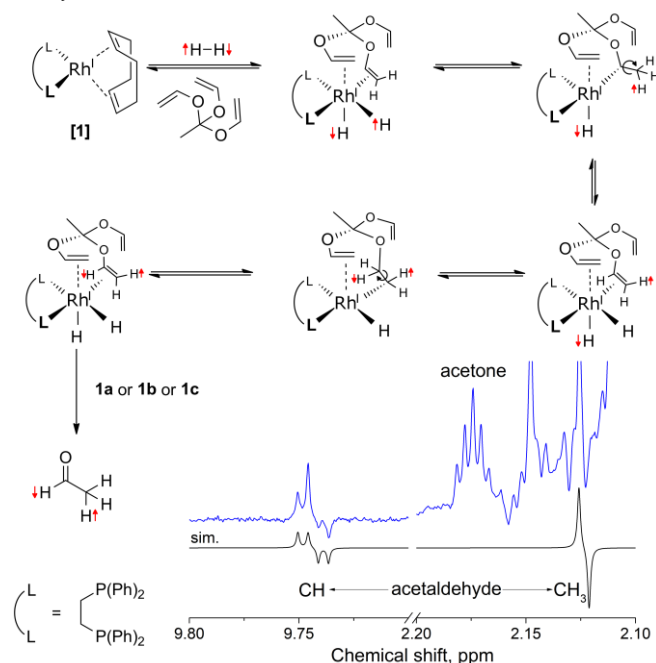


Figure 6. Acetaldehyde exchange reaction pathway with experimental and simulated (sim.) PASADENA spectra. TVOA exchanges one of its CH₂-protons and its CH-proton with *p*H₂ when both (hydrogen and TVOA) are coordinating to [1]. The hydrogenation and dissociation of this hyperpolarized TVOA would lead to the observed polarized acetaldehyde. The following NMR parameters were used for simulations of polarized acetaldehyde: chemical shifts: $\delta_{\text{CH}} = 9.7435$ ppm, $\delta_{\text{CH}_3} = 2.123$ ppm and J-coupling constants: $^3J_{\text{CH}-\text{CH}_3} = 2.85$ Hz. It was assumed that the CH and one of CH₃ protons are resulting from *p*H₂ (PASADENA effect, sim.). In the experiment and simulations nonselective 45° excitation RF-pulses were used.

IV. Polarization of H₂

A partial negative line (PNL)^[42,43] was observed on H₂ in chloroform after hydrogenation of TVOA with [1] (Figure 3). This is a good indicator of a slow catalytic hydrogenation when *p*H₂ is not completely consumed by the catalyst but rather exchanges: $[\text{M}] + \text{H}_2 \leftrightarrow [\text{M}] - \text{H}_2$. Here [M] stands for a metal complex or catalyst. When para-hydrogen associates with [M], its spin order starts evolving in a so-called singlet-triplet conversion. If this hydride dissociates instead of hydrogenating of a substrate, it manifests itself as H₂ with a PNL. One of the possible steps, where this can happen, is the *p*H₂ ↔ H₂ exchange, when vinyl acetate or acetaldehyde are polarized (Figure 5, 6) where [M] stands for [TVOA-[1]] complex.

Conclusion

The attempt to hydrogenate all three double C=C bonds of TVOA was not successful. Ethyl acetate was the main product of hydrogenation and not the expected products divinyl ethyl orthoacetate or other orthoacetate derivatives. TVOA was cleaved immediately in the presence of H₂ and [1]. Even the removal of acid traces in the solvents by filtration over a basic Al₂O₃ column did not stop the instant decomposition of DVEOA. Decomposition of DVEOA leads to the production of polarized ethyl acetate, vinyl acetate, acetaldehyde, ethanol and H₂. Hence, the studies show that TVOA is not well suited for the hydrogenation of "many side-arms". We assume that a similar approach will be also not successful for hyperpolarization of pyruvate e.g. because three (or two) vinyl group will coordinate to the metal complex (catalyst), which will slow down the hydrogenation reaction; possibly side-reactions and products will be observed similar to those that have been identified in this study. PASADENA proved to be key to elucidate the underlying reaction mechanism. Without the unique line shape, the pairwise H₂ exchange of geminal protons of vinyl acetate and vicinal protons of acetaldehyde would have remained unrecognized.

This is yet another proof that labelling with *p*H₂ is a unique tool to distinguish the pathways in hydrogenation reactions; - PHIP provides a sophisticated analytical tool for the elucidation of hydrogenation mechanisms, catalysis and other elementary chemical reactions.

Experimental Section

I. Sample preparation

Samples for PHIP-SAH and -HOT. 10 μL of TVOA (synthesized according to a protocol described below) or vinyl acetate (CAS 108-05-4, Merck) was dissolved in 600 μL of acetone-d₆ or chloroform-d (Deutero GmbH) yielding a 100 mmol/L concentration. For PHIP experiments the catalyst [1,4-Bis(diphenylphosphino)butane(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate] [1] (CAS: 79255-71-3, Strem Chemicals) was added to reach a concentration of 5 mmol/L. Chloroform-d and acetone-d₆ were dried by pouring it through a 3 cm column (ID = 5 mm) of basic aluminium oxide powder and magnesium sulfate respectively directly before preparation of the samples. Both powders were dried overnight at 120°. Note, that even after drying, the residual H₂O concentration was determined to approx. 1 mM. These samples were flushed by *p*H₂ to produce hyperpolarization in the following stage.

Samples for reference NMR spectra. NMR spectra of the following compounds dissolved in chloroform-d or acetone-d₆ were measured at concentrations of 10-100 mM: vinyl acetate (CAS: 108-05-4), ethyl-acetate (CAS: 141-78-6), triethyl orthoacetate (CAS: 78-39-7), acetaldehyde (CAS: 75-07-0), 2-chloroethanol (CAS: 107-07-3), ethyl alcohol (CAS: 64-17-5). All compounds were purchased from Merck. These samples and the corresponding spectra were used to assign the products of the TVOA hydrogenation.

II. Synthesis

TVOA was synthesized according to the protocol in ref. [44] with some modifications. The implemented protocol consisted of 2 steps (Figure 7):

Synthesis of tris(chloroethyl)orthoacetate. Trichloroacetic acid (500 mg, 3.06 mmol, CAS: 76-03-9, Merck) was placed in a 2-necked flask with a rubber septum on a short way distillation apparatus. The trichloroacetic acid was dried under reduced pressure (7 mbar) for 3 h. Then the flask was flushed with nitrogen and 10 mL of trimethyl orthoacetate (8.56 g, 71.3 mmol, CAS: 78-39-7, TCI GmbH) was added. The reaction mixture was heated to 90°C and 3 mL of 2-chloroethanol

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(CAS: 107-07-3, Merck) was added to the flask. The pressure was carefully reduced to 500 mbar and further 2-chloroethanol (3 ml) was added every 0.5 h for 2.5 h until a total of 15 ml was reached (17.0 g, 220 mmol). The reaction mixture was heated to 90°C for 3 h. During this time 7.12 g of methanol was distilled from the reaction mixture. The heating bath was then removed and replaced with an ice bath. 400 mg of potassium *tert*-butoxide (CAS: 865-47-4, TCI GmbH) dissolved in 5 ml dry methanol (CAS: 67-56-1, Merck) was added to quench the reaction. The product was obtained by distillation from the reaction mixture as a colourless oil (6.84g, 43.80 mmol, bp. 155°C at 7 mbar). This corresponds to a yield of 62 % relative to the trimethyl orthoacetate deployed.

Synthesis of trivinyl orthoacetate (TVOA). Sodium hydride (60 % suspension in mineral oil) (2.20 g, 54.32 mmol, CAS: 7646-69-7, Acros) was mixed with 5 mL 1,2-dimethoxyethane (CAS: 110-71-4, ABCR) under a nitrogen atmosphere in a 3-neck flask with a rubber septum. Then *tert*-butanol (234 mg, 3.16 mmol, CAS: 75-65-0, Grüssing) was added at room temperature and the suspension was stirred for 5 min. Tris(chloroethyl)orthoacetate (4.41 g, 15.09 mmol) was carefully added to the solution, which was heated under reflux for 5 h. The solvent was removed under reduced pressure (50 mbar, 40°C). The residue was treated with 30 mL of diethyl ether (CAS: 60-29-7, Walter-CMP) and 20 mL of distilled water. The phases were separated and the organic phase was washed three times with 20 ml of water and dried over magnesium sulfate (CAS: 7487-88-9, Grüssing). The solvent was removed under reduced pressure and the remaining liquid was distilled two times at reduced pressure yielding TVOA (358 mg, 2.28 mmol, 80°C at 30 mbar) with a purity of 90 %. This corresponds to a yield of 15 % based on tris(chloroethyl)orthoacetate. Possible impurities and side products are bisvinyl(chloroethyl)orthoacetate, 2-chloroethanol (**Figure 8**).

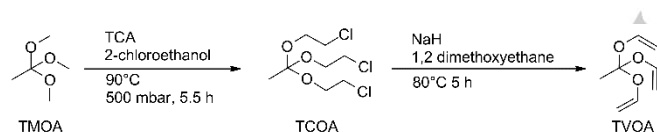


Figure 7. Trivinyl orthoacetate (TVOA) synthesis. Step 1: the methyl ethers of trimethyl orthoacetate (TMOA) are replaced by chloroethyl under acidic conditions to give the tris(chloroethyl)orthoacetate (TCOA). Step 2: sodium hydride is used as a base in an elimination reaction to obtain TVOA.

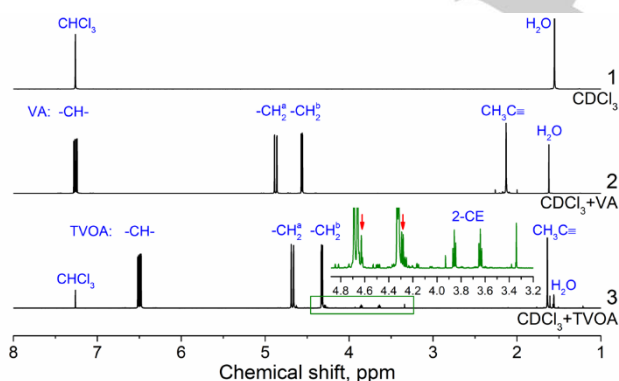


Figure 8. High-resolution ¹H NMR spectra of chloroform-d (1), vinyl acetate (VA, 2) and trivinyl orthoacetate (TVOA, 3) in chloroform-d. Red arrows indicate side products of synthesis (presumably it is bisvinyl(chloroethyl)-orthoacetate). 2-chloroethanol (2-CE) and some other residues from the synthesis are also present. The estimated purity of TVOA is about 90%.

III. Experimental routines

PASADENA experiments. *p*H₂ was prepared using a liquid nitrogen setup that provides *p*H₂ fraction of 50 %.^[45] All experiments were carried out on a 600 MHz NMR spectrometer (Bruker Avance II) with a cryogenically cooled probe (TCI) and 5 mm screw-cap NMR tubes (Wilmad). The gas was delivered into the spectrometer by a 1/16" polytetrafluoroethylene (PTFE) capillary (0.023" internal diameter). A hollow optical fiber (Molex, part. num. 106815-0026, 250

µm internal diameter, 360 µm outer diameter) was glued with instant 2-component adhesive (Loctite 3090, Henkel) to the end of the capillary and inserted into the NMR tube and solution. The used hollow fiber is resistant to aggressive media and does not cause magnetic field distortion: the increase of FWHM after field shimming is below 1 Hz. The pressure was set to about 1.2 bar (0.2 bar overpressure to atmospheric pressure) and adjusted to achieve a steady bubbling. For the experiments, *p*H₂ was supplied (bubbled) to the sample solution for 10-30 s to generate PASADENA. Next, the bubbling was stopped and the system was allowed to settle down for another 2 s. After that, a PASADENA spectrum was recorded after 45° excitation. All NMR experiments were carried out at 25°C and ambient pressure.

Mass spectrometric analysis. Using the same H₂ bubbling setup, the PHIP samples were flushed with *p*H₂ at room temperature for 5-10 minutes in 5 ml amber glass vials. Using a Jeol AccuTOF GCv 4G spectrometer with electron ionisation (EI), mass spectra of the blank samples (before hydrogenation) and corresponding samples after hydrogenation were acquired (cf. SI). No stable products of direct TVOA hydrogenation, namely DVEOA or TEOA were found.

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Keywords: acetate • geminal hydrogenation • homogeneous catalysis • hyperpolarization • parahydrogen • PASADENA • PHIP • sidearm hydrogenation • vinyl

Abbreviations:

- TVOA – trivinyl orthoacetate
- DVEOA – divinyl ethyl orthoacetate
- TEOA – triethyl orthoacetate
- TCA – trichloroacetic acid
- TMOA – trimethyl orthoacetate
- TCOA – tri(chloroethyl) orthoacetate
- VA – vinyl acetate
- EA – ethyl acetate
- AD – acetaldehyde
- CE – chloroethanol
- PHIP – parahydrogen induced polarization
- PHIP-SAH – PHIP-side arm hydrogenation
- PHIP-HOT – PHIP by hydrogenation of three side arms

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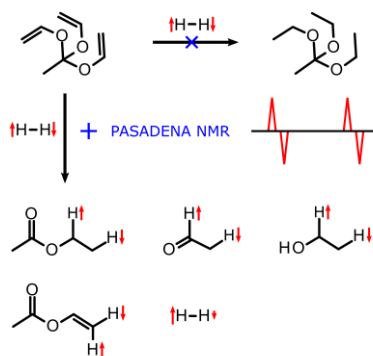
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Supporting material: TOCSY and mass-spectra of the analyzed system (.PDF), the Matlab simulation source code and raw NMR spectra (TopSpin files, .zip) are available as supplementary.

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In an attempt to use multiple parahydrogen molecules to hyperpolarize one molecule, homogeneous catalytic hydrogenation of trivinyl orthoacetate (TVOA) was studied. Hydrogenation of TVOA is accompanied by a fast decomposition of the semihydrogenated reagent. Ethyl acetate, vinyl acetate, acetaldehyde and ethanol are final products. Utilization of parahydrogen and PASADENA NMR spectroscopy together with the expected hydrogenation of vinyl sites revealed also unexpected geminal and vicinal hydrogen exchange.

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