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Surface ligand-directed pair-wise hydrogenation for heterogeneous phase hyperpolarization†

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***para*-Hydrogen induced polarization is a technique of magnetic resonance hyperpolarization utilizing hydrogen's *para*-spin state for generating signal intensities at magnitudes far greater than state-of-the-art magnets. Platinum nanoparticle-catalysts with cysteine-capping are presented. The measured polarization is the highest reported to date in water, paving pathways for generating medical imaging contrast agents.**

Nuclear magnetic resonance (NMR) hyperpolarization aims to overcome the inherently low signal of NMR by increasing spin polarization up to four orders of magnitude compared to thermal polarizations from state-of-the-art superconducting magnets. The most common hyperpolarization techniques include spin exchange optical pumping,[1] the more established technique of dynamic nuclear polarization (DNP),[2] and the use of *para*-hydrogen induced polarization (PHIP) or Signal Amplification by Reversible Exchange (SABRE).[3] Polarization methods are numerous and depend on the context and application.[4] Each technique can potentially lead to the development of promising contrast agents for biomedical imaging,[5] with the most prominent example of dissolution DNP for which *in vivo* human use was recently demonstrated.[6] To generate hyperpolarization using PHIP or SABRE, a *para*-enriched spin state of hydrogen is first created by passing hydrogen over a catalyst at low temperatures, generating close to 100% *para*-state below 25 K.[7] The nearly pure stable singlet spin order of *para*-hydrogen can subsequently be utilized to hyperpolarize a molecule of interest by an addition reaction or by a catalyst-mediated, reversible exchange process.[3] PHIP hyperpolarized substrates have been discussed and investigated in the past as contrast agents for angiography or cancer detection.[5c–f] A major drawback was that the generation of sufficiently high nuclear spin polarization in biocompatible solvents could only be obtained using a homogeneous catalyst. However, homogeneous catalysts raise bio-toxicity concerns. Although a preliminary study has shown that a state-of-the-art homogeneous catalyst produces subclinical hepatic and renal toxicity in rats, further studies are needed to clarify toxicity concerns.[8] To address such concerns, approaches are needed in which the catalyst can be separated from a potential molecular imaging agent. One such approach is a phase separation technique in which the polarization is generated in an organic solvent followed by extraction of the substrate of interest.[9] The extraction process, however, represents a step during which the generated polarization inevitably decays and a loss in polarization results. The use of heterogeneous PHIP or SABRE catalysts is a sensible strategy to generate a pure substrate as the catalyst that may be easily filtered or immobilized to avoid contamination.[10] For *in vivo* applications the use of biocompatible solvents, such as water in combination with a heterogeneous catalyst is desirable. Preliminary evidence of pairwise addition of *para*-hydrogen over a heterogeneous catalyst in water was demonstrated in ref. 11, but no polarization enhancement was reported. In a later publication norbornadiene was hydrogenated in water over a heterogeneous catalyst to generate a hyperpolarized gas that separates from the liquid phase.[12] Recently, glutathione-capped platinum nanoparticles dispersed in water were utilized to generate hyperpolarization.[13] This study (ref. 13) represented the first discovery of a heterogeneous PHIP catalyst in water yielding significant polarization of dissolved molecules that remain in the liquid phase; although the measured levels of proton polarization of hydroxyethyl propionate (HEP) were still relatively low (P = 0.3%) compared to the levels required for *in vivo* studies (P > 1%). High polarization could be achieved by the capped nanoparticles based on the insight that the mobility of

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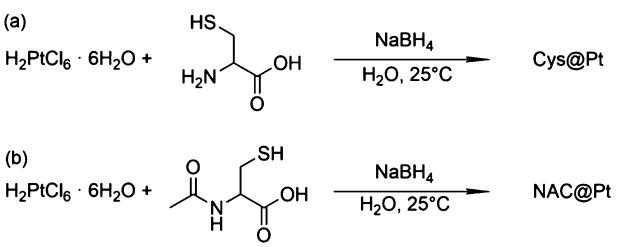
hydrogen atoms is reduced by the ligands, thereby favoring the pair-wise addition mechanism.[14]

In this article, we present and describe cysteine-capped platinum nanoparticles as substantially improved catalysts yielding average proton polarizations of $P = 0.7\%$ in water. In comparison, levels of $P = 1.3\%$ were previously achieved with a homogeneous catalyst performing the same experiment using similar conditions and setup.§[13] Thus, our new heterogeneous catalyst is competitive with the best homogeneous catalyst for hyperpolarization in water. In a recycling experiment, we demonstrate that these newly designed particles can be used 5 times without loss of polarization. We further establish that the properties of the ligands for capping the particles and the particles' surface coverage are paramount to achieving high levels of polarization; in fact, these key factors are more important than achieving small particle sizes.

The two new nanoparticles we investigated have been synthesized based on a platinum core capped with L-cysteine (Cys), and *N*-acetyl-L-cysteine (NAC) ligands, respectively. For the synthesis, hexachloroplatinic acid hexahydrate and the desired ligand were suspended in water and reduced with sodium borohydride, yielding ligand-capped nanoparticles (Scheme 1a and b). In order to achieve nanoparticles with narrow size distributions, with *N*-acetyl-L-cysteine, a metal precursor to ligand ratio of 1 : 1.3 was used (NAC@Pt) and for L-cysteine, the ratio was 1 : 1 or 1 : 1.1 (Cys1@Pt and Cys1.1@Pt). Depending on the cysteine concentration, particles with two different average sizes were isolated: 2.4 nm and 1.4 nm. The average size for NAC@Pt was found to be 1.9 nm as confirmed by transmission electron microscopy (a detailed description of the synthesis and characterization of the particles can be found in the ESI†). BET measurements indicate much higher crystallite sizes (6.7 nm for Cys1@Pt and 13.8 nm for NAC@Pt). However, we expect the TEM measurements to better reflect the nanoparticle dispersity for our catalytic system due to the difference in sample preparation (see ESI† for details).

In order to confirm the removal of residual platinum ions originating from the hexachloroplatinic acid, two experiments were conducted with all three nanoparticles: (1) dilute samples with nanoparticles in water were characterized by UV/vis and compared to the signal of hexachloroplatinic acid. For platinum ions, a characteristic absorbance around 260 nm can be observed, which is the case for hexachloroplatinic acid but not for any of the synthesized nanoparticles. (2) A mercury poisoning experiment was performed in which the hydrogenation of hydroxyethyl acrylate (HEA) was initiated in separate experiments with the three different particles.[16] Upon addition of mercury the hydrogenation stopped, proving that the nanoparticles are catalyzing the reaction and not residual platinum ions. The ligand binding on the particles was validated by ^{1}H NMR, resulting in significant dipolar broadening of the ligands' resonances (see ESI†). Furthermore, for all of the particle species, a ligand coverage of 16 wt% was confirmed by thermo gravimetric analysis. Thus, the same amount of platinum catalyzes a reaction if hyperpolarization experiments are performed with identical concentrations. Hyperpolarization experiments were conducted under inert gas with 10 mg mL^{-1} particle concentrations, 2 mg HEA and 5 bar *para*-hydrogen in water at 80 °C. Hyperpolarized HEP shows two characteristic lines in the ^{1}H NMR spectrum around 2.5 ppm and 1.0 ppm (Fig. 1). On average, a polarization of $P = 0.7\%$ was observed for both of the Cys@Pt particles, and a polarization of $P = 0.1\%$ was achieved for NAC@Pt, in contrast to previously investigated GSH@Pt particles reaching $P = 0.3\%$. The deviation (fractional error) of the given values is on the order of 20% of the measured polarization values. We employed a homogeneous catalyst under identical conditions and obtained a proton polarization of 1.3%, merely a factor of two greater than the polarization achieved with the Cys@Pt particles. Typical conversions in the proton experiments were 1% of the starting material. This experiment is, however, not optimized and the use of automatic polarizers should improve the conversion. Proton relaxation studies showed that T_1 of HEP in the presence of Cys@Pt and NAC@Pt correspond to 5.5 s and 7.0 s respectively. This is 1 s longer than previously reported longitudinal relaxation times for HEP in the presence of a homogeneous catalyst.[17] Polarization transfer experiments from ^{1}H to ^{13}C nuclei with a custom built polarizer[18] led to 10-fold ($P = 0.01\%$) signal enhancements and a conversion of 50% in a 3 s experiment. We note that this specific polarizer design was not optimized for heterogeneous experiments (see ESI†).[13,18] Previously, ^{13}C polarizations above 50% of HEP have been achieved with automated polarizers utilizing a homogeneous catalyst.[15a] As the ^{1}H polarization is twice as high as for our new Cys@Pt nanoparticles, we extrapolate that 10–25% polarization should be attainable in an optimized device, as discussed earlier.[13]



Scheme 1 (a) Synthesis of cysteine-capped nanoparticles. (b) Synthesis of *N*-acetylcysteine nanoparticles.

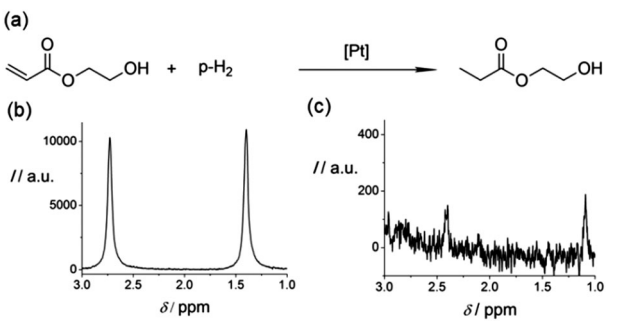


Fig. 1 (a) Reaction of HEA to HEP utilizing *para*-hydrogen. (b) Hyperpolarized ^{1}H NMR spectrum shown in absolute values at $B_0 = 14.1$ T. (c) Thermal polarized ^{1}H NMR spectrum after the polarization at $B_0 = 14.1$ T. The signal enhancement in the shown spectrum accounts to $\varepsilon = 145$, which corresponds to a polarization of $P = 0.7\%$.

Table 1 Summary of particle characteristics

Particle	Ligands/wt%	Ligands/mol g^{-1}	Diameter/nm	P/%	Ligands/nm^2 (sphere)	surface/m^2 mg^{-1}	TOF/h^{-1} (80 °C)
NAC@Pt	16	0.98	1.9 ± 0.4	0.10 ± 0.02	4.8	1.24×10^{-10}	3.0
Cys1@Pt	16	1.32	2.4 ± 0.5	0.7 ± 0.1	8.4	0.94×10^{-10}	31.8
Cys1.1@Pt	16	1.32	1.4 ± 0.3	0.7 ± 0.1	4.7	1.71×10^{-10}	11.0
GSH@Pt[a]	23	0.75	2.0	0.3	4.1	1.09×10^{-10}	87.8

[a] Values from ref. 8.

This amount of polarization has been shown to be sufficient for *in vivo* experiments.[19] Consequently, the investigated particles bear promising potential to serve as a heterogeneous alternative to current standard catalysts. The particle characteristics are summarized in Table 1. Due to the spherical shape of the nanoparticles a cubo-octahedral structure can be assumed for which the amount of surface atoms and thus the surface area can be estimated.[20] The amount of ligands covering the surface was found to be the highest for Cys1@Pt, followed by NAC@Pt, Cys1.1@Pt and GSH@Pt. However, cysteine has two potential coordination sites to the particles' surface: a thiol and an amine moiety. NAC is a derivative of cysteine with the amine group protected; thus the amine moiety does not coordinate to the particles surface and only the thiol group binds to the surface to stabilize the particle (Fig. 2). Recent infrared investigations on GSH- and cysteine-capped platinum nanoparticles of larger size (see reference supplementary information of ref. 21 S5 and S6) revealed that upon the molecules' interaction with the particle surface N–H and S–H vibrations vanish, which can be understood as an indication for binding. Overall, the cysteine ligands with higher coordination restrict the randomization processes of *para*-hydrogen on the particles' surfaces. As a result, the cysteine particles compared to acetylcysteine have a 6.5 fold increase in polarization. Prior results for another dual coordination ligand, glutathione-capped platinum particles (GSH@Pt), support this interpretation. The ligand coverage of GSH@Pt by weight percentage is lower than the NAC@Pt but still yields a higher polarization. With respect to the polarization, an increase can be expected if fewer platinum sites are available on the particles surface. Regarding the turnover frequency (TOF) of HEA and hydrogen at 80 °C and 1 atm hydrogen pressure, it was found that of the newly synthesized particles Cys1@Pt shows the highest reactivity, which is followed by Cys1.1@Pt and NAC@Pt. For the higher amount of ligands, a higher reaction rate is achieved and *para*-hydrogen can react faster with HEA. However, GSH@Pt shows a higher catalytic activity than the new particles, although the achieved polarization is lower. It has been suggested in the literature that GSH on nanoparticle surfaces allows for a better access for reactants to the surface due to their packing properties.[22] A better interaction with the metal surface explains the higher conversion but may indicate that more randomization can occur due to the higher degree of hydrogen diffusion. Thus a loss in polarization can be observed, which makes the Cys@Pt particles superior alternatives to generate polarization.

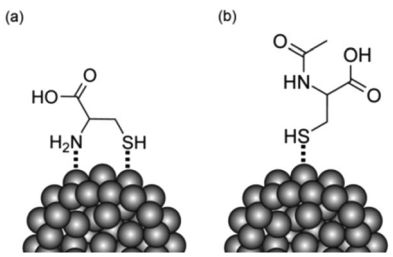


Fig. 2 (a) Schematic of cysteine coordination to a platinum particle. (b) Schematic of acetylcysteine coordination to a platinum particle. Due to a higher amount of coordination in Cys@Pt, less randomization process of the *para*-spin state of hydrogen on the particles surface can occur, leading to higher polarization.

A major advantage of heterogeneous catalysts over homogeneous catalysts is their recyclability.[23] Particles can be filtered and reused if the achieved polarization remains constant following repeated experiments. In order to test for the particles' recyclability, a particle concentration of 15 mg mL^{-1} was used to produce hyperpolarized HEA five times. After each step, the particles were centrifuged, and the supernatant solvent was removed. Subsequently, the particles were re-suspended in water and re-used to generate hyperpolarized HEP. For all three synthesized particles, the polarization measured was reproduced in consecutive experiments (see ESI†).

In conclusion, we have synthesized two new nanoparticles that are dispersible in water and highly effective in inducing hyperpolarization from *para*-hydrogen. Due to the optimization of ligand coverage and ligand-particle interaction, an increase in HEP polarization greater than 2-fold was achieved in water compared to the recently published GSH@Pt particles.[13] Experiments with two different sized nanoparticles indicate that the ligand coordinated to the particles' surface may play a more important role in generating hyperpolarization than the particle size itself. PHIP itself may therefore provide a new method to investigate surface properties of ligand-capped nanoparticles. Additionally, the recyclability of the particles was successfully demonstrated through five consecutive uses without loss in polarization strength. Since the ^1H polarization obtained with the state-of-the-art homogeneous catalyst is only a factor of 2 higher than the polarization achieved in this work, our cysteine-based particles represent heterogeneous alternatives; the crucial ability to mitigate toxicity issues makes them ideal candidates for a variety of clinical molecular imaging applications.

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Notes and references

§ The authors note that in an optimized setup, 20% to more than 50% ^{13}C polarization is achievable in a homogeneous reaction, which is significantly higher than the ^{1}H polarization reported here.[15] However, for such optimized polarizers ^{1}H polarization was not reported likely due to the short relaxation times of protons relative to the long time of the transport process. In order to put the polarization into a context that enables meaningful comparisons with the commonly used homogeneous catalyst, this paper presents ^{1}H experiments with both catalysts in the same manner.

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