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Supporting Information

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A Nanoparticle Catalyst for Heterogeneous Phase Para-Hydrogen-Induced Polarization in Water**

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Supporting Information

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S1 Materials and Methods

Chemicals

Hexachloroplatinic acid, sodium borohydride, absolute ethanol and glutathione were purchased from Sigma-Aldrich. D_2O was purchased from Cambridge isotopes. All chemicals were used without further purification.

Methods for the particle characterization

NMR spectra were recorded on a Bruker AV600 or on a Bruker 9.4 T small animal scanner. All experiments were performed at room temperature and the chemical shift data are reported in ppm for ^1H relative to 4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS). TEM was performed on a FEI Tecnai T12. Thermogravimetric analysis (TGA) was conducted using a Perkin Elmer Pyris Diamond TG/DTA from 25 °C to 720 °C. UV/vis characterization was performed on a Shimadzu UV-3101PC UV-VIS-NIR Spectrophotometer.

S2 Synthetic procedures

Every synthetic step was performed under inert gas atmosphere unless otherwise noted.

Synthesis of glutathione-capped nanoparticles

The nanoparticles were synthesized according to the published procedure under inert gas[S1]:

100 mg of hexachloroplatinic acid hexahydrate and 42 mg of reduced glutathione were dissolved in 25 mL deoxygenated water (ultrapure) under argon atmosphere. 74 mg $NaBH_4$ dissolved in 3 mL water (ultrapure) was added dropwise over 1 minute under argon atmosphere. The brown solution was stirred for an additional hour, concentrated to near dryness (less than 1 mL of water) followed by precipitation of the particles with 30 mL deoxygenated, absolute ethanol. After 30 minutes the ethanol was decanted and the particles dried under vacuum.

S3 Further characterization of the nanoparticles

Particle distribution

In order to determine the particle distribution, 200 nanoparticles were counted and their diameter measured to determine the length. The particle had a mean average diameter of 2.0±0.6 nm, where 0.6 indicates the standard deviation of the diameter. A histogram of the size distribution is shown in figure S1.

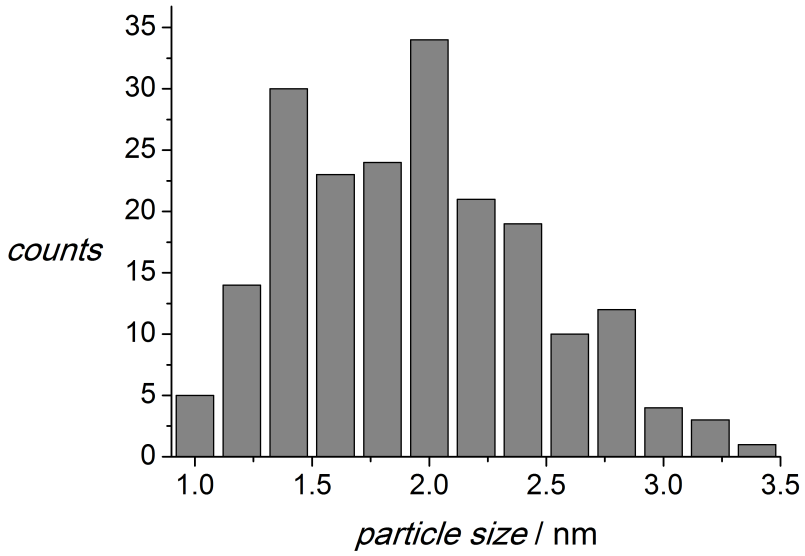

Figure S1. Nanoparticle distribution of the glutathione-capped platinum particles.

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis was performed from 25 °C to 720 °C, at the end the temperature was kept constant for 30 minutes without observing significant loss in mass. The TGA curve is depicted in figure S2 and shows that the surface of the particles are 23% covered, which is in agreement with earlier reported results.[S1]

Mercury Poisoning

In this test, mercury forms amalgams with the nanoparticles, resulting in catalytic deactivation. Platinum ions will not generate such amalgams, and the catalytic activity would be maintained.[S2] For the mercury poisoning test, 1.0 mg of platinum particles were suspended in 2 mL water and 0.2 mL of hydroxyethyl acrylate was added. Hydrogen was bubbled into the solution over 60 minutes with a flow of 100 mL/minute. Two experiments were performed: A control experiment without the addition of mercury and a mercury poisoning experiment in which 20 µL of mercury were added after 15 minutes of the reaction. Aliquots of the reaction mixture were taken every fifteen minutes and the conversion determined with NMR. Figure S3 shows that the reaction stops upon addition of mercury and proceeds if no mercury is present, indicating that the hydrogenation is catalyzed by the platinum particles.

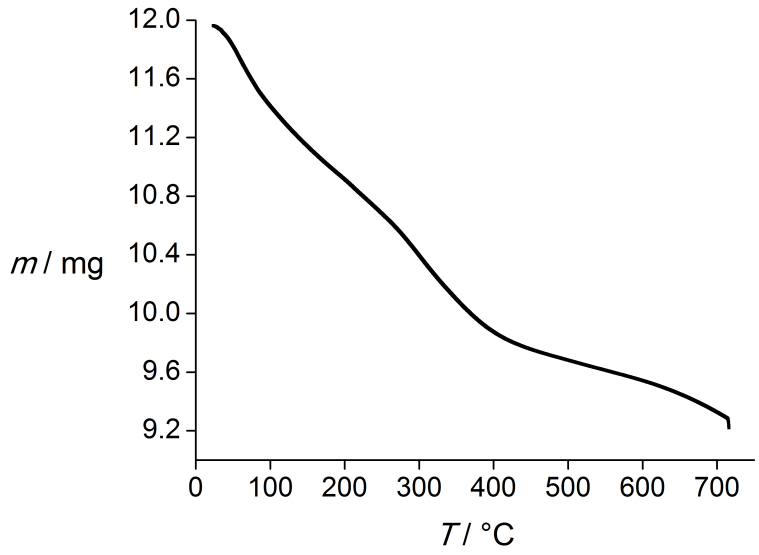

Figure S2. Thermogravimetric analysis of the nanoparticles.

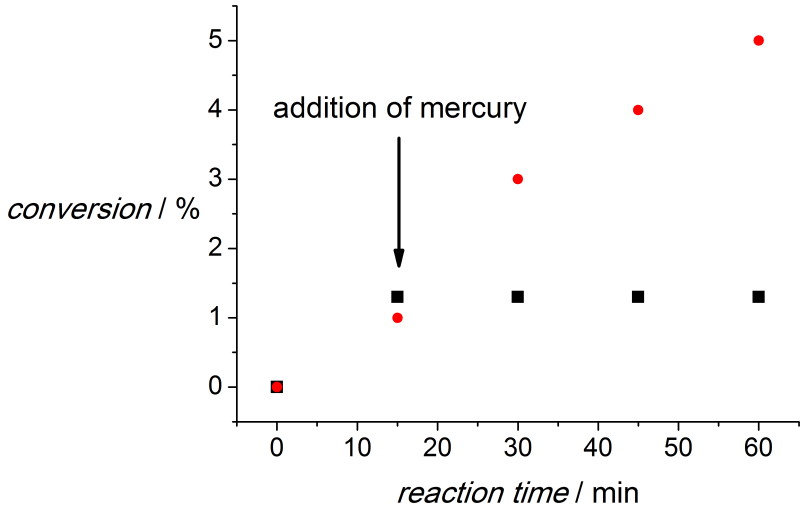

Figure S3. The addition of mercury poisons the catalyst. Without mercury the reaction progresses (red circles) whereas the reaction stops upon addition of mercury (black squares) indicating that the nanoparticles are the catalytic active species

S4 *Para*-hydrogen experiments

Proton NMR experiments with *para*-hydrogen (95% *para*-enriched) were performed on a Bruker AV600 spectrometer (B_0 = 16.1 T). Samples were prepared in 5 mm Young tubes from New Era under inert gas with 2 mg hydroxyethyl acrylate (0.04 mmol) either nanoparticles (5 mg) or 2.5 mM homogeneous catalyst concentration in 0.5 mL D_2O. Each sample was typically heated to 80 °C pressurized with 5 bar of *para*-hydrogen shaken for 10 s in the earth's magnetic field (ALTADENA conditions) and transported into the center of the magnet within 5 s, where the spectrum was recorded in a single scan (45°-

pulse). After the hyperpolarization experiment, a spectrum was recorded with the formed product in thermal equilibrium, the signal enhancement and the corresponding polarization calculated. Figure S4 shows the performed experiment. ^{13}C polarization experiments were performed on a custom-built polarizer at Cedars-Sinai Medical Center according to published procedures. [S3]

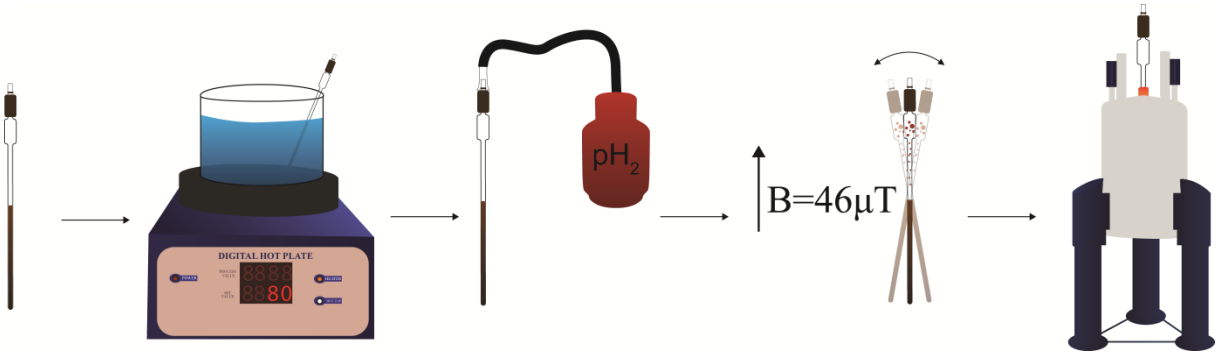

Figure S4. Performing hyperpolarization utilizing nanoparticles and *para*-hydrogen.

S5 Particle Recycling

In order to further prove that the hyperpolarized signal is generated due to mediation of the nanoparticles and not dissolved metal clusters, an experiment was performed initially at 60°C with a 20 mg/mL particle concentration followed by recycling of the particles. For the particle recycling the nanoparticles after a successful PHIP were precipitated with an excess of ethanol and centrifuged for 30 minutes at 10 000 rotations per minute (rpm). The supernatant solvent was decanted and centrifuged again for 30 minutes at 10 000 rpm. Afterwards, the particles were resuspended in water, 2 mg (0.04 mmol) HEA was added and the experiment was repeated as described in S4. The supernatant solvent was concentrated to dryness and potential residue was taken up with water, followed by addition of 2 mg (0.04 mmol) HEA and reacted with *para*-hydrogen to test for polarization. Figure S5 shows two example spectra of the experiments. For the first run a signal enhancement of 9 was achieved, whereas for the recycling the signal enhancement yielded 10. The experiment was repeated five times and even in the last run a signal enhancement of 11 was achieved showing that the activity did not decrease. However a few precipitated particles were observable during the last run indicating that the stability of the particles has some limitations upon recycling. No polarization was observed however if the experiment was run with the residue of the supernatant solvent, indicating that the hyperpolarization is generated by the nanoparticles. The recycling experiment was also performed in a way that the particles were concentrated to dryness under vacuum, washed three times with ethanol, dried again, followed by suspension in water. Adding 2 mg HEA and performing the PHIP experiment led to the same polarization as the previously described recycling technique.

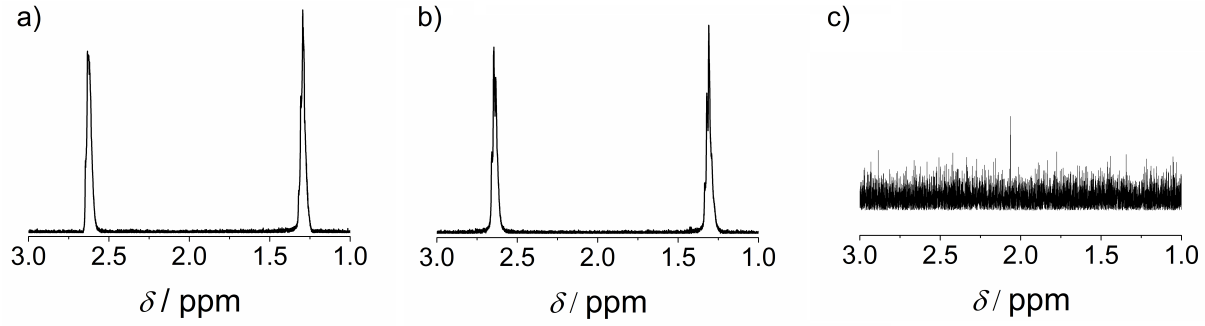

Figure S5. a) Hyperpolarized spectrum of HEP. b) Hyperpolarized spectrum achieved with recycled nanopaprticles. c) No hyperpolarization is observed when the experiment is performed with supernatant solvent during the recycling process. All spectra are shown in absolute values.

S6 Remarks about the Polarizer

Polarization transfer experiments with the nanoparticles lead to a signal enhancement of only 16 compared to a signal in thermal equilibrium at 20°C and 9.4 T. We attribute this to the following reasons:

(1) The transit time to the magnet (20 s) leads to a 33% loss in polarization (T_1 = 50 s). Improvements could be obtained by reducing this transit time. (2) The polarization was executed at a temperature below 60 °C instead of 80 °C which causes a significant loss in polarization, as suggested by the results of Figure 4b, where a factor of 2 was lost when operating at 50 °C. (3) The polarization transfer sequence places the magnetization vector into the xy-plane for 50 ms, during which it decays according to T_2^*.[S4] The nanoparticles however, shorten this decay due to dipolar interactions, accelerating the loss of polarization.

The following improvements can be envisioned: Good temperature control is needed on account of small changes in the reaction temperature leading to substantial losses in the polarization. With regard to the polarization transfer, a field-cycling method might be more beneficial, although it is also subjected to transverse relaxation, albeit in a lower field.[S5] Even more promising would be the utilization of level anti-crossings, as it was recently reported that close to 10% polarization can be achieved in high-magnetic fields without T_2^* relaxation perturbing the polarization transfer.[S6] A physical separation of the particles appears to be necessary before any polarization transfer sequences are applied. Such redesign of the polarizer is expected to procure essential improvements in the polarization transfer.

Work is currently underway in our lab to redesign the polarizer for continued investigations. Future generations of the polarizer should also include an immobilized catalyst or a filtration step prior to injection in vivo to guarantee complete removal of the catalyst. This issue has been addressed by the hyperpolarization community previously. For example, in dissolution DNP experiments, the paramagnetic agent needs to be filtered as well, and this step was recently shown with the aid of a micro porous filtration system rapidly enough to preserve sufficient polarization for in vivo applications.[S7]

S7 References

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