Supporting Information

Nanoscale Catalysts for NMR Signal Enhancement by Reversible Exchange

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Experimental Details (Synthesis)

Surface-modified TiO$_2$ nanoparticle core/shell synthesis

The procedure for synthesizing the TiO$_2$ cores was adapted from a related procedure found in Ref. $^51$. 10 mL titanium isopropoxide (Aldrich) was added into a 250 mL flask and 20 µL Milli-Q water were added slowly to the flask. Then 10 mL dried and deoxygenated methacrylic acid (Aldrich) was transferred into the flask with a syringe, followed by 2 mL 75% concentrated nitric acid (Fisher). After 24 h agitation in an incubating shaker at 80 ºC, the raw TiO$_2$/PMAA nanoparticle (NP) core/shell product was produced. Then, the raw NPs were suspended in methanol via the assistance of the sonication, until an evenly distributed, stable (and solution-like/transparent) suspension was formed. The TiO$_2$ NP suspension was centrifuged at 5000 rpm for 10 min. in order to separate the nanoscale particles from larger (microscale) aggregates. The NP/methanol liquid gel was placed on a watch glass and heated in a low-temperature oven (~80 ºC) to remove the solvent overnight. The resulting dried NPs were carefully removed from the wash glass surface and characterized by DLS (see below).

~0.2 g of these NPs was suspended in a vial containing ~10 mL Milli-Q water (with the assistance of bath sonication) also containing ~0.057 g of dissolved 4-aminopyridine. The mixture was stirred for about 1 hour to ensure reaction completion (the reaction should be mostly completed within a few seconds).

Immobilization of SABRE catalyst moieties onto functionalized TiO$_2$ / PMAA core-shell nanoparticles

The standard Ir SABRE catalyst [IrCl(COD)(IMes)], (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; COD = cyclooctadiene; was synthesized as described previously. $^{32,53}$ Briefly, a dimer of 1,5-cyclooctadiene-iridium(I) chloride was reacted with the N-heterocyclic carbene derivative, IMes, 1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene, in benzene and an inert atmosphere; following 24 h vacuum-drying and recrystallization in pentane, the [IrCl(COD)(IMes)] SABRE catalyst was obtained. 0.12 g of the IrCl(COD)(IMes) catalyst and 0.051 g of AgPF$_6$ was mixed in 10 mL of degassed dry ethanol within a glove box / N$_2$ atmosphere. After 2 h of dark-condition reaction, the white AgCl precipitate was filtered via syringe filter to give an orange solution. Next, ~0.056 g of the functionalized NPs was suspended in ~15 mL of degassed dry ethanol and placed in a 20 mL vial. ~5 mL of this NP suspension was then mixed with ~1 mL of the previously prepared orange solution containing the modified (primed, Cl- abstracted) SABRE catalyst. This suspension was stirred in the dark for 12 hours within the glove box (inert N$_2$ atmosphere). The resulting suspension was removed from the glove box and placed in an ultrafilter (Millipore, nominal mol. wt. limit: 5000) and centrifuged at 5000 rpm for 10s of min. The filtrate at the bottom of the tube was removed and tested for the presence of Ir with AAS after the final washing cycle. The NP precipitate and suspension in the top portion of the tube was carefully removed from the filter and transferred to a small round-bottom flask and roto-evaporated; further drying was performed using N$_2$ gas purge. This washing process with dry ethanol was repeated two additional times to provide the final TiO$_2$/PMAA core/shell NP SABRE catalysts.

SABRE catalyst immobilized onto the comb polymer

Within a glove box (N$_2$ atmosphere), 0.0839 g classical SABRE catalyst synthesized previously ([IrCl(COD)(IMes)]) and 0.0635 g of AgPF$_6$ were mixed in 5 mL degassed dry ethanol.
After 2 h of dark-condition reaction, the white AgCl precipitate was filtered via syringe filter to give an orange solution. Next, 0.0695 g poly (4-vinylpyridine) comb polymer (Aldrich, PN# 472344; average mol. wt. ~60,000) was dissolved in the same solution and stirred in the dark for 15 hours. The solution was then filtered by a syringe filter [Millipore, MWCO 5000 Da]. The comb polymer catalyst solution was then dried in the fume hood for 3 d to yield the final product.

Characterization

**Homogeneous SABRE catalyst characterization**

To characterize the homogeneous SABRE catalyst [IrCl(COD)(IMes)], $^1$H experiments were performed. The chemical shifts are: $^1$H NMR (400 MHz, C$_6$D$_6$, 294 K) $\delta$ (ppm) = 6.78 (s, 2H, Mes); 6.81 (s, 2H, Mes); 6.15 (s, 2H, =CHN); 4.70 (m, 2H, cod); 3.19 (m, 2H, cod); 2.59 (s, 6H, CH$_3$); 2.15 (s, 6H, CH$_3$); 2.05 (s, 6H, CH$_3$); 1.80 (m, 4H, cod); 1.35 (m, 4H, cod). Such chemical shifts matched the previous work done by other groups.$^{34,35}$ Thus, it supported that the homogeneous SABRE catalyst has been successfully synthesized (further confirmed by successful demonstration of homogeneous SABRE after catalyst activation in the presence of excess substrate (e.g. pyridine) and pH$_2$ gas).

**Characterization of nanoscale heterogeneous SABRE catalysts**

Successful preparation of the desired nanoscale heterogeneous SABRE catalysts was supported by qualitative observation, NMR, AAS, and dynamic light scattering (DLS) experiments. The first indication of successful immobilization of the catalyst on the nanoparticle supports is the obvious color change (Figure S1(a,b)): Once the pyridine moieties on the terminal groups of the nanoparticle supports become bound to the Ir atoms—thereby tethering the catalyst to the supports—the color of the NP supports turns red. Similarly, the polymer combs change from yellow-brown to bright orange-red (Fig. S1(c,d)).
Figure S1. Minor but evident color change of the nanoparticle supports before (a) and after (b) addition of 4-amino pyridine and homogeneous SABRE catalyst was immobilized. The similar color change also happened with the PVP combs polymers, before (c) and after (d) addition and immobilization of the Ir-based SABRE catalyst moieties.
Additional information is provided by $^1$H NMR spectra (e.g. Figure S2, and Fig. 7 of main document). For example, the spectrum from the functionalized NP core/shell support provides characteristic signals to support the successful creation of the particle supports; resonances between 1 and 2 ppm are in good agreement with expectations for PMAA (see, e.g., Ref. 56).

![Figure S2. $^1$H NMR spectrum for the nanoparticles with PMAA shell (but prior to addition of 4-aminopyridine).](image)

Then, AAS was performed on the completed nanoscale SABRE catalyst (Table S1) and its corresponding filtration liquid before and after the addition of the substrate (pyridine) and pH$_2$ (Table S2). AAS was performed using a Varian instrument with Ir-specific bulb.

| Trial | Ir Concentration (ppm) |
|-------|------------------------|
| 1     | 74.33                  |
| 2     | 81.44                  |
| 3     | 79.35                  |

Table S1. Results of AAS experiment (measuring iridium) to support that the SABRE catalyst is successfully attached onto the surface of the TiO$_2$/PMAA NPs.
A $^1$H NMR spectrum of the filtrate of the NP SABRE catalysts (after catalyst activation and SABRE) is shown in Fig. S3:

![NMR spectrum of filtrate of NP catalysts](image)

Figure S3. NMR spectrum of filtrate of the NP catalysts (after SABRE; average of 8 scans). All peaks can be straightforwardly assigned to residual pyridine substrate free in solution, dissolved H$_2$, and EtOH solvent.

No peaks that could be assigned to the catalyst were observed in the spectrum of the filtrate.

| Trial      | Ir Concentration (ppm) |
|------------|------------------------|
| Before PH2 | 0*                     |
| After PH2  | 0*                     |

Table S2. AAS experiment supporting that there is effectively no SABRE catalyst dissolved in the filtrate solution taken from the NP catalysts before and after SABRE experiments. Asterisk (*) indicates that a small negative value was reported by the instrument, similar to what is reported from testing simple MilliQ water samples (negative control). Thus, no Ir was observed within the detection limits of the AAS instrument.

Both AAS and $^1$H NMR show that the concentration of any dissolved freely floating SABRE catalyst molecules in the filtrate solution is below the respective detection limits. Thus, the supported catalyst seems stable and does not appear to significantly leach into the solvent under typical experimental conditions.
Dynamic light scattering (DLS) experiments provided the size distribution (hydrodynamic radii) of the nanoSABRE catalysts (Figs. S4a-c). The NP nanoSABRE catalysts were suspended in Milli-Q water, and then examined with an in-house Wyatt Dynapro Nanostar DLS. Each DLS measurement was averaged from 10 scans.

| Radius (nm) | %Pd | Mw-R (kDa) | %Intensity | %Mass |
|-------------|------|------------|------------|-------|
| Peak 1      | 6.4  | 53.6       | 258        | 18.8  | 99.1 |
| Peak 2      | 62.4 | 55.5       | 53477      | 81.2  | 0.9  |

Figure S4a. Results from DLS measurement of size distribution of TiO$_2$/PMAA core-shell nanoparticles suspended in water, prior to further functionalization.

| Radius (nm) | %Pd | Mw-R (kDa) | %Intensity | %Mass |
|-------------|------|------------|------------|-------|
| Peak 1      | 7.2  | 45.6       | 340        | 89.2  | 99.9 |
| Peak 2      | 343.0| 24.2       | 2879830    | 10.8  | 0.1  |

Figure S4b. Results from DLS measurement of size distribution of TiO$_2$/PMAA core-shell nanoparticles after aminopyridine functionalization.
Results from DLS measurement of size distribution of completed TiO$_2$ / PMAA core-shell nanoparticle SABRE catalysts (after final functionalization with Ir-containing moieties).

The DLS results indicate a slightly bifurcated size distribution (Fig. S4c), with peaks centered at ~8 nm and ~95 nm; however, the scattering intensities indicate that the overwhelming majority of the nanoSABRE NPs (virtually 100% by mass) belong to the ~8 nm (radius) range; the manifestation of the second peak in Fig. S4c simply reflects the much greater scattering intensity produced by much larger particles. The hydrodynamic radius increased by ~0.8 nm during each step.

**PVPC comb SABRE catalyst characterization**

As with the NP core/shell catalyst particles, successful preparation of the desired comb polymer SABRE catalyst is supported by qualitative observation, NMR, AAS, and DLS. The first indication of successful immobilization of the catalyst on the polymer supports is the obvious color change (Figure S1): As mentioned above, once the pyridine moiety on the terminal groups of the polymer support become bound to the Ir atom—tethering the catalyst to the support—the color of the polymer support turns to red.
Figure S5. The top spectrum is the original PVP comb polymer dissolved in ethanol-d6. The bottom spectrum is the completed PVP comb polymer SABRE catalysts dissolved in ethanol-d6.

NMR spectra were taken before and after addition of the IR catalytic moieties (Fig. S5). Due to the large molecular weight (and hence long tumbling time) of the polymer, both of the spectra exhibit broadened peaks; however, broader resonances are observed in the bottom spectrum, consistent with the larger particles indicated by the DLS results (see below). Moreover, we can notice additional peaks between ~7-7.5 ppm and ~1.5-2.5 ppm in the bottom spectrum, which are likely the result of the addition of the immobilized SABRE catalyst.

For the filtrate of PVPC (obtained after performing the SABRE experiment), we have the following $^1$H NMR spectrum (Fig. S6):
Figure S6. $^1$H NMR spectrum of filtrate of the PVP comb polymer catalysts (after SABRE; average of 8 scans). All peaks can be straightforwardly assigned to residual pyridine substrate free in solution, dissolved H$_2$, and EtOH solvent.

Signals that would provide evidence for the presence of free-floating residual SABRE (homogeneous) catalyst are absent; instead, all peaks can be assigned to residual free pyridine substrate, H$_2$, and solvent. AAS was also performed on the samples of the comb polymer SABRE catalyst (Table S3) and its corresponding filtration liquid before and after exposure to the substrate (pyridine) and pH$_2$ gas (Table S2):

| Trial | Ir Concentration (ppm) |
|-------|-------------------------|
| 1     | 98.73                   |
| 2     | 66.04                   |
| 3     | 86.94                   |

Table S3. Results from AAS experiments (measuring iridium) supporting that the SABRE catalyst was successfully attached onto the terminal groups of the comb polymer support.

| Trial | Ir Concentration (ppm) |
|-------|-------------------------|
| Before PH2 | 0*                     |
| After PH2 | 0*                     |

Table S4. AAS experiments supporting that there is effectively no SABRE catalyst dissolved in the filtrate solution taken from the PVP polymer comb SABRE catalysts before or after SABRE experiments. Asterisk (*) indicates that a small negative value was reported by the instrument, similar to what is reported from testing simple MilliQ water samples (negative control). Thus, no Ir was observed within the detection limits of the instrument.
As above, both AAS and $^1$H NMR show that the dissolved SABRE catalyst concentration in the filtrate is below the respective detection limits. Thus, the supported catalyst seems stable and does not appear to significantly leach into the solvent under typical experimental conditions.

DLS experiments provided the size distribution of the comb polymer comb SABRE catalysts before and after chemical reactions to add the Ir-catalyst moiety (Figs. S7a,b). The comb polymer catalysts were suspended in ethanol, and then examined with an in-house Wyatt Dynapro Nanostar DLS. Each DLS measurement was averaged from 10 scans. A significant increase in polymer aggregation is observed after the addition of the Ir-based catalytic moiety, as manifested by the much larger average hydrodynamic radius of the completed PVP polymer comb catalysts.

![Graph showing size distribution of PVP comb polymers](image)

| Radius (nm) | %Pd | Mw-R (kDa) | %Intensity | %Mass |
|------------|-----|------------|------------|-------|
| Peak 1     | 2.7 | 11.8       | 35         | 3.9   | 50.6 |
| Peak 2     | 8.2 | 17.4       | 460        | 91.1  | 49.2 |
| Peak 3     | 227.9 | 9.3       | 1105260    | 5.0   | 0.2  |

Figure S7a. Results from DLS measurement of size distribution of PVP comb polymers prior to synthetic addition of Ir-based catalytic moieties.
Figure S7b. Results from DLS measurement of size distribution of completed PVP polymer comb SABRE catalysts (after final functionalization with Ir-containing moieties).

The completed polymer comb SABRE catalysts are generally within the ~30-85 nm range (centered at ~57 nm), which while still nanoscale, is much larger than the original polymer size (shown in Figure S7a).

**Para-hydrogen and pH₂ Decay Calibration**
Para-hydrogen was prepared using ultrapure (>99.9999%) hydrogen gas and a generator located at Vanderbilt. Based on multiple sampling points, the para-hydrogen decay within its storage tank approximately obeys the following equation:

\[ C = 0.75e^{(-0.012t)} + 0.25, \]

where C is the para-hydrogen fraction and \( t \) is the time in days that have passed since the day the para-hydrogen was created and loaded into its cylinder. Correspondingly, the decay time constant in our cylinder is ~83 days. pH₂ was delivered to the sample via 1/16" Teflon tubing of sufficient length to allow the NMR tube to be lowered into the magnet.

**Calculations, Simulations, and SABRE NMR Experiments**
Supplemental molecular dynamics (MD) and quantum chemistry calculations were also performed on the shell moieties of the NP catalysts: methods and software included MD (ChemBio3D 12.0, MM2, minimum RMS Gradient 0.100) and quantum chemistry (Gaussian 09, ground-state DFT B3LYP//6-311G+dp/LanL2DZ).

All NMR experiments were performed with an Agilent DD2 triple-resonance NMR console (400 MHz) with actively-shielded wide-bore AS400 9.4 T magnet. The ~100 G field used for all ex-situ SABRE experiments was located in the fringe field of the NMR magnet, and was measured using a portable Gaussmeter.
References for SI

(S1) Tenaglia, A.; Brun, P.; Waegell, B. J. Organomet. Chem. 1985, 285, 343.
(S2) Barskiy, D. A.; Kovtunov, K. V.; Koptyug, I. V.; He, P.; Groome, K. A.; Best, Q. A.; Shi, F.; Goodson, B. M.; Shchepin, R. V.; Coffey, A. M. J. Am. Chem. Soc. 2014, 136, 3322.
(S3) Shi, F.; Coffey, A. M.; Waddell, K. W.; Chekmenev, E. Y.; Goodson, B. M. Angew. Chem. 2014, 126, 7625.
(S4) Torres, O.; Martin, M.; Sola, E. Organometallics 2009, 28, 863.
(S5) Kownacki, I.; Kubicki, M.; Szubert, K.; Marciniec, B. J. Organomet. Chem. 2008, 693, 321.
(S6) Fyfe, C.; McKinnon, M. Macromolecules 1986, 19, 1909.
(S7) Feng, B.; Coffey, A. M.; Colon, R. D.; Chekmenev, E. Y.; Waddell, K. W. J. Magn. Reson. 2012, 214, 258.