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Palladium on Carbon Encapsulated in POEPOP$_{1500}$: A Resin-Supported Catalyst for Hydrogenation Reactions

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ABSTRACT

$$\begin{array}{l} R\text{-}CH_2\text{-}CH{=}CH_2 \\ R'\text{-}CH_2\text{-}C{\equiv}CH \\ R''\text{-}OBzl \end{array} \xrightarrow[H_2]{POEPOP_{1500}\text{-}Pd/C} \begin{array}{l} R\text{-}CH_2\text{-}CH_2\text{-}CH_3 \\ R'\text{-}CH_2\text{-}CH_2\text{-}CH_3 \\ R''\text{-}OH \end{array}$$

A new a versatile catalyst for hydrogenation reactions wherein palladium on carbon is encapsulated in POEPOP$_{1500}$-resin is described. This polymer-supported catalyst has been successfully used in solution phase hydrogenation of a double and a triple bond as well as hydrogenolysis of a benzyl-protecting group. While the activity of the new catalyst is marginally lower than standard 10% Pd/C, it has the advantage of being reused several times without significant loss of reactivity.

The use of polymer-supported catalysts in organic chemistry has continued to be an area of rapid development.[1] The intrinsic advantage of these catalysts in synthetic chemistry is that they can be removed by filtration upon completion of the reaction. Furthermore, the polymer-supported catalysts are easily recycled, thereby reducing the costs. Using a polymer-supported catalyst also makes monitoring of a reaction by simple analytical techniques more straightforward.

Solution-phase hydrogenation using palladium as catalyst is widely used, and there are only a few examples reported in the literature where the catalyst is polymer-supported. Jo et al. have reported gel-like and macroporous polymer supports for palladium(II) complexes,[2a] and the use of ion-exchange resins as support for a palladium catalyst was published by Zecca et al.[2b] However, broad usage of these polymer-supported catalysts was limited as a result of their poor solvent compatibility. Recently, Niu et al. reported size-selective hydrogenation of olefins by dendrimer-encapsulated palladium nanoparticles.[2c]

We report herein a new and versatile catalyst for hydrogenation reactions, where the palladium on carbon is encapsulated in POEPOP$_{1500}$ resin, a polyoxyethylene−polypropoxylene polymer containing only ether bonds.[3] The POEPOP resin was chosen as solid support because of its excellent swelling properties in solvents ranging from water to dichloromethane. The POEPOP$_{1500}$−Pd/C resin was synthesized by introduction of 10% Pd/C directly in the mixture of reactants used for anionic suspension polymerization.[4] A mixture of the monomer, Pd/C, *t*BuOK (acting as base) and surfactant was added to silicon oil at 120 °C with stirring. The resulting beads were fractionated according to

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particle sizes by sieving. To investigate whether the presence of palladium particles had any influence on the polymerization process, the swelling of the $POEPOP_{1500}$–Pd/C resin was measured[5] in tetrahydrofuran (THF), MeCN, dimethylformamide (DMF), water, and dichloromethane (DCM) and compared to conventional $POEPOP_{1500}$ resin[3b] (Figure 1).

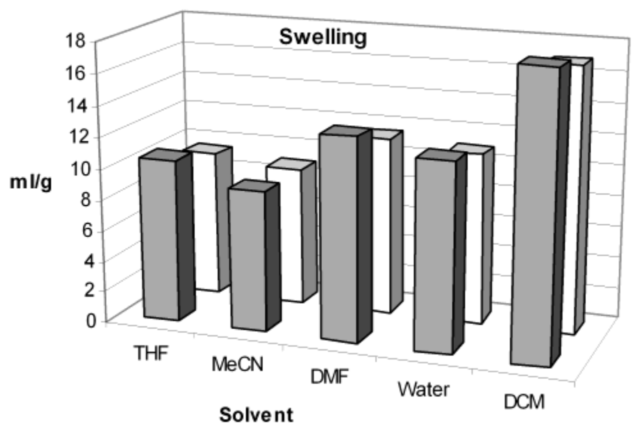
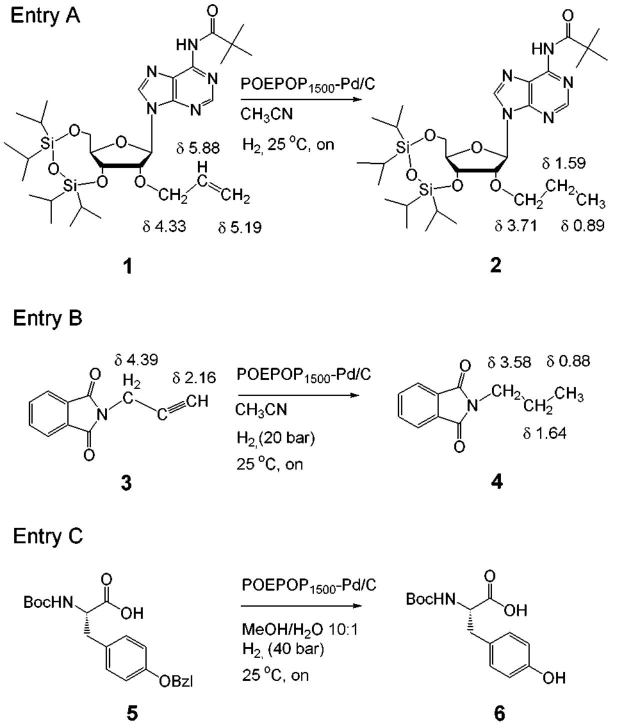


Figure 1. Swelling properties of $POEPOP_{1500}$ resin with encapsulated Pd/C (grey) and conventional $POEPOP_{1500}$ resin (white) in different solvents determined by the syringe technique.[5]

The $POEPOP_{1500}$–Pd/C resin exhibited slightly higher swelling (5–10%) than that of conventional resin, indicating that the palladium particles interfere slightly with the polymerization process, resulting in a lower cross-linking and a marginally higher swelling. The superb swelling of the $POEPOP_{1500}$–Pd/C resin in solvents of ranging polarity is advantageous and broadens the scope of solvents that can be used for hydrogenations.

The loading (quantity of hydroxyl groups available for substrate attachment) for the $POEPOP_{1500}$–Pd/C resin was 0.25 mmol/g,[4] which was significant lower than for conventional $POEPOP_{1500}$ resin (0.4–0.6 mmol/g).[3b] This indicates that the Pd/C particles prevent full access to the functional sites on the resin, probably through coordination of PEG chains to the Pd atoms. However, the amount of functional groups available for attachment was not important for this study since hydrogenation of the substrates takes place on the surface of the palladium.

Scheme 1



With this resin in hand, its usefulness as catalyst in solution-phase hydrogenation was investigated. Three model compounds were chosen (Scheme 1): a double bond (allyl group) of a fully protected adenosyl derivative (entry A), a triple bond of *N*-propyne-substituted phthalimide (entry B), and a benzyl protecting group on the side chain of an N^{α}-Boc-protected tyrosine derivative (entry C).

Hydrogenation was performed in parallel in Teflon tubes in a Parr apparatus at room temperature, under pressure or in atmospheric pressure, overnight (5 μmol substrate, 6 mg $POEPOP_{1500}$–Pd/C resin, 0.4 mL solvent, without stirring).[6] The substrates were dissolved in appropriate solvents (MeCN in entries A and B, and MeOH/water, 10:1 in entry C), the

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(4) **Preparation of $POEPOP_{1500}$–Pd/C Resin.** The PEG_{1500} macromonomer (1.5 equiv functionalization) and the polymeric surfactant were synthesized as previously described in ref 3c. A suspension of PEG_{1500} macromonomer (2.0 g, 1.25 mmol) in dichloromethane (4 mL) was mixed with a solution of polymeric surfactant (0.2 g) in dichloromethane (2 mL), and the solvent was evaporated in vacuo. A solution of potassium *tert*-butoxide (0.10 g, 0.89 mmol) in *tert*-butanol (1.0 mL) was mixed with the PEG_{1500},macromonomer at 40 °C, and 10% palladium on carbon (0.4 g) added. After 5 min of rapid stirring the mixture was added to silicon oil (175 mL) at 120 °C, in a 250 mL polymerization flask fitted with an overhead stirrer (300 rpm.). The reaction was stirred at 120 °C for 12 h. The silicon oil was decanted, and the polymer particles were suspended in dichloromethane and placed on a 50 μm filter to remove excess of palladium on carbon and the smallest polymer particles. The beads were washed with dichloromethane, dimethyl formamide, methanol, and water (4 × 5 mL for each solvent); treated with 4 M NaOH (16 mL) for 2 h at 60 °C; washed extensively with water, methanol, dimethyl formamide, and dichloromethane (4 × 5 mL for each solvent); dried under high vacuum for 24 h; and sieved. Yield: 1.69 g (with approximately 20% Pd/C by weight), 77%; $500 < x < 1000$ μm, 0.12 g; $300 < x < 500$ μm, 0.33 g; $212 < x < 300$ μm, 1.09 g; $106 < x < 212$ μm, 0.15 g. The loading of the resins was determined by esterification with Fmoc-Gly activated by MSNT in the presence of *N*-methyl imidazole in CH_2Cl_2 and subsequent measurement of the UV absorbency of the adduct of dibenzofulvene and piperidine formed on treatment of a weighed polymer sample with 20% piperidine in DMF. Loading: 0.25 mmol/g. Swelling was determined by the syringe technique, described in ref 5 (Figure 1).

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(6) **General Procedure for Hydrogenation Reactions.** The substrate (5 μmol) was dissolved in the appropriate solvent (acetonitrile, entry A and B, or methanol/water 10:1, entry C, 0.4 mL), and the solution was added to the resin–Pd/C (6 mg, $500 < x < 1000$ μm) in a Teflon tube. After 30 min of swelling, the Teflon tubes were placed in a Parr apparatus and after flushing with argon and hydrogen, hydrogenation was started under pressure (40 or 20 bar) or under atmospheric pressure in room temperature, overnight, without stirring. The resin was filtered off and washed with acetonitrile (entries A and B) or 50% aqueous methanol (entry C), 2 × 0.2 mL. The combined solutions were analyzed with HPLC and ES-MS (entry A).

POEPOP$_{1500}$–Pd/C resin was added to the solution, and after swelling (30 min) hydrogenation was started.

Solvent was selected on the basis of the solubility of the substrates. The workup involved a simple filtration and washing of the resin, followed by HPLC analysis[7] and ES-MS.[8]

To optimize hydrogenation conditions, the substrates were reduced under three different hydrogen pressures (40 bar, 20 bar, and atmospheric pressure) overnight.[6] Hydrogenation at atmospheric pressure resulted in complete reduction of the double bond of compound **1**. The triple bond of compound **3**, however, needed higher hydrogen pressure (20 bar) for completion (2% unconverted starting material remained when the reaction was performed at atmospheric pressure). Cleavage of the benzyl group of compound **5** was a much slower reaction and required a hydrogen pressure of 40 bar overnight for completion. To investigate if the POEPOP$_{1500}$–Pd/C resin particle size had any influence on the outcome of the hydrogenation, three different particle sizes ($212 < x < 300$ μm, $300 < x < 500$ μm, and $500 < x < 1000$ μm) were used in hydrogenation of compound **5** (40 bar, overnight). Complete cleavage of the benzyl group with all three particle sizes resulted. Since no significant influence of particle size was observed during hydrogenation, the largest particles, $500 < x < 1000$ μm, were used in all following experiments because of ease of handling.

For complete structural determination of the hydrogenation products, the reactions were run on larger scale (0.05 mmol) under pressure (40 bar) following the procedure in ref 6. On the basis of HPLC traces the reactions proceeded cleanly with total conversion of the starting materials,[7] and the crude products were analyzed by ^{1}H NMR.[9] The chemical shifts for the appropriate groups of products **2** and **4** are inserted in Scheme 1. Hydrogenation of compound **1** provided the saturated product **2**. A methyl group at δ 0.89 and a saturated methylene group at δ 1.59 had replaced the allylic signals at δ 5.19 and δ 5.88. Proton NMR also showed that the TIPDS (1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) and the pivaloyl protecting groups were stable under these conditions. The mass of product **2** was confirmed by ES-MS, which showed a peak at m/z 636.3 for $[M + H]^+$ ($M = 635.9$; no peak from the starting material was observed, $M = 633.9$). Proton NMR of the fully saturated triple bond in the substituted phthalimide compound **4** also clearly showed a methyl group at δ 0.88 and a saturated methylene group at δ 1.64. Hydrogenolysis of the benzyl protecting group of compound **5** resulted in compound **6** with no loss of the Boc group. Proton NMR of the product **6** showed no signals for the benzyl aromatic protons (δ 7.28–7.44), nor for the singlet corresponding to the benzylic protons (δ 5.05).

The potential of the POEPOP$_{1500}$–Pd/C resin to be recycled was tested by reusing the resin in hydrogenation reactions of the three substrates (5 μmol substrate, 6 mg resin-Pd/C, 40 bar, overnight).[6] The resin was washed with 50% aqueous methanol (3 × 0.4 mL), water (3 × 0.4 mL), and methanol (3 × 0.4 mL) before it was used in the next cycle. During the whole recycling process analysis of the crude products by HPLC (215 nm) showed complete conversion (>99%) of the starting material to reduced product with all three substrates. The total conversion of compound **5** to product **6** was additionally confirmed by ES-MS (see above) after each cycle (no signal from the starting material was detected). After five cycles the catalyst remained active and gave complete conversion with all the substrates (Figure 2). The loss of palladium from the resin was found to be in average 0.1% per cycle[10] and is in agreement with the retained catalytic activity.

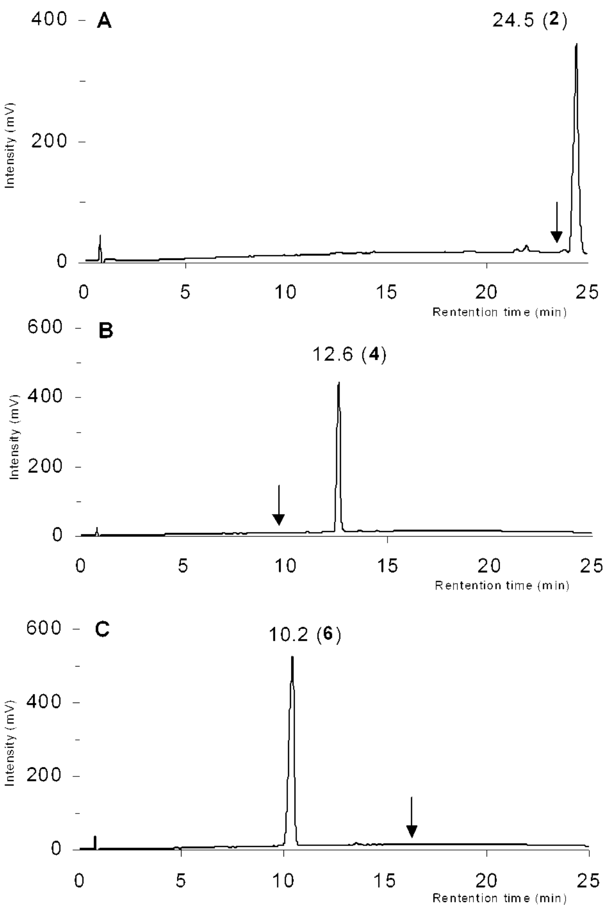

Figure 2. HPLC chromatograms (215 nm) of crude products from entries A, B, and C (Scheme 1) after five cycles of the POEPOP$_{1500}$–Pd/C resin.[7] (Retention times for the starting materials are marked with arrows.)

The efficiency of the POEPOP$_{1500}$–Pd/C resin compared to an equivalent quantity of conventional 10% Pd/C[11] was investigated (3 mg of POEPOP$_{1500}$–Pd/C resin with approximately 20% Pd/C by weight is equivalent to 0.6 mg of

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(7) Analytical HPLC was performed on a Zorbax C$_{18}$ column with buffers A (0.1% TFA in water) and B (0.1% TFA in MeCN/H$_2$O 9:1); linear gradient from 100% A to 100% B in 25 min; flow rate 1 mL/min; wavelength 215 nm. Retention times: entry A, 23.7 min (**1**), 24.5 min (**2**); entry B, 10.5 min (**3**), 12.6 min (**4**); entry C, 16.6 min (**5**), 10, 2 min (**6**).

(8) Electrospray spectra were aquired in positive mode on a VG Quattro triple quadropole mass spectrometer (Micromass, Ldt.).

(9) ^{1}H NMR spectra (250 MHz) were recorded on a Bruker DRX 250 instrument in CDCl$_3$ (compounds **1**–**4**), and in MeOH-d_4 (compounds **5** and **6**). Chemical shifts were calibrated to internal solvent signals (7.19 ppm for CDCl$_3$ and 3.30 ppm for MeOH-d_4)

Table 1. Conversion of Starting Material to Reduced Product in Hydrogenation Reactions[a] Using POEPOP$_{1500}$–Pd/C (resin–Pd/C) and 10% Pd/C[b]

substrate (μmol)	catalyst	**1**[c]	**3**[c]	**5**[d]
2.5	resin-PD/C	t.c.[e]	t.c.	95%
	Pd/C	t.c.	t.c.	t.c.
5	resin-PD/C	t.c.	t.c.	90%
	Pd/C	t.c.	t.c.	t.c.
10	resin-PD/C	t.c.	t.c.	75%
	Pd/C	t.c.	t.c.	91%
20	resin-PD/C	t.c.	t.c.	n.d.[f]
	Pd/C	t.c.	t.c.	n.d.
40	resin-PD/C	t.c.	98%	n.d.
	PD/C	t.c.	t.c.	n.d.

[a] Reactions were carried out at 20 bar, rt, overnight (ref 6). [b] Percentage converted starting material determined by HPLC, 215 nm. [c] In MeCN (0.4 mL). [d] In MeOH/H_2O 10:1 (0.4 mL). [e] t.c. = total conversion (>99%). [f] n.d. = not detected.

10% palladium on carbon; 20 bar, overnight) (Table 1). A series of experiments were performed[6] in which the quantity of substrate was doubled for each experiment (2.5, 5, 10, 20, and 40 μmol), and the crude products were analyzed by HPLC. The double bond of compound **1** was reduced to completion at all concentrations with both catalysts, which also was confirmed by ES-MS. Reduction of the triple bond of compound **3** was slightly slower with POEPOP$_{1500}$–Pd/C resin (2% unconverted starting material) than with conventional 10% Pd/C (complete conversion) at the highest substrate concentration. Cleavage of the benzyl protecting group of compound **5** was much slower under these conditions. The use of polymer-supported catalyst required higher hydrogen pressure or longer reaction time for total conversion of the substrate, even at the lowest concentration. At 10 μmol concentration none of the two catalysts resulted in complete reaction and the polymer-supported catalyst gave approximately 20% lower conversion of this substrate compared to that of conventional catalyst. In summary, in hydrogenation reactions of compounds **1**, **3**, and **5**, the polymer-supported catalyst is efficient but slightly less effective compared to conventional carbon-supported palladium.

In conclusion, we have developed a stable, readily recyclable polymer-supported catalyst for solution-phase hydrogenation. The POEPOP$_{1500}$–Pd/C resin is easily prepared by an encapsulating procedure, is very convenient to handle, and is compatible with a large range of solvents. While the activity of the new polymer-supported resin is marginally lower than standard 10% Pd/C, it has the advantage of being reusable for several times without significant loss of reactivity.

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Supporting Information Available: ^{1}H NMR data for compounds **1**–**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) . Palladium analysis of filtered hydrogenation solutions was performed by FI-ICP-MS (flow-injection inductively coupled plasma-MS, ELAN-5000, PE Sciex) with Rh as internal standard (detection limit 0.05 μg Pd /L). Sample preparation: After each cycle of hydrogenation (with substrate **3**) half of the volume (0.4 mL), after filtration and washing (ref 6), was concentrated, and the residue was dissolved in 1 M HCl (10 mL) for Pd analysis. The Pd content in samples from cycle 1–5 was measured to be 12, 8, 3, 3, and 3 μg Pd /L, respectively. This corresponds to an average loss of 0.1% Pd per hydrogenation cycle. (Pd content of blank solution with no catalyst added was 0.07 μg Pd /L; all samples were analyzed three times, with RSD < 3%.)

(11) Palladium on activated carbon (10% Pd) was purchased from Aldrich.