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Surfactant-Induced Substrate Selectivity in the Palladium-Nanoparticle-Mediated Chemoselective Hydrogenation of Unsaturated Aldehydes in Water

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A hundred-fold substrate selectivity was observed in the competitive chemoselective hydrogenation of seven α,β -unsaturated aldehydes from C₄ to C₁₀ in water with palladium nanoparticles stabilized by sodium dodecyl sulfonate as the surfactant. The medium makes the longer lipophilic substrates hundreds of times more reactive than the shorter more hydrophilic ones, whereas in an organic medium almost no difference is observed.

The selectivity of a reaction catalyzed by a synthetic catalyst is often referred to as the ability of the given catalyst to produce one product preferentially over several possible chemo-, regio-, and stereoisomers. Natural enzyme catalysts are impressive examples of substrate-selective catalysts^[1–4] thanks to their ability to select the substrate that best fits the geometric and electronic properties of the active site (Figure 1). Substrate se-

lectivity occurs if the recognition event between the catalyst and the substrate takes place before the catalytic event, and a high surface interaction between substrate and catalyst is essential. In this respect, with traditional metal-based catalysts, the interaction with the substrate occurs on reduced surfaces (Figure 1), which leads to very poor substrate selection that indeed remains a challenging task.

Except for the kinetic resolution of racemates,^[5] often substrate-selective homogeneous catalysts are studied by comparing different substrates individually and not in direct competitive experiments. Often such substrates, apart from the common reactive functional group at which the reaction occurs,^[6–8] bear extra functionalities such as hydrogen bonds or ionic moieties^[9–13] that enable secondary interactions with the catalyst to favor their selective recognition. Examples of homologous substrates that differ only in small changes in positions remote from the reactive center and lack extra recognition sites are indeed rare. In such cases the selection of the substrate is usually based on steric interactions^[14–16] because of the complete surrounding of the substrate by the catalyst. To favor the surface interaction between catalyst and substrate, an alternative approach consists of wrapping the two within a solvation sphere with a lifetime long enough to impart steric effects. Impressive examples of this strategy are based on supramolecular water-soluble metal–ligand coordination capsules as catalysts able to select substrates with size and shape that match the dimensions of the cavity.^[17,18] Recently, our group disclosed an example of substrate-selective alkyne hydration driven by the encapsulation of a Au^I catalyst within a hydrogen-bonded, self-assembled capsule in organic media.^[19]

Micelles are supramolecular aggregates that form spontaneously on addition of surfactants in water. They are able to dissolve apolar substrates and catalysts in water and have been demonstrated to enhance product selectivity at all levels.^[20,21] Rare examples of substrate selectivity imparted by micelles are known, specifically the synthesis of esters disclosed by Kobayashi,^[22] the Diels–Alder reaction mediated by Cr(salen)Cl,^[23] and the Heck coupling reaction mediated by Pd precursors from our group.^[24] The hydrophobic effect is the driving force that allows substrate selectivity in water under micellar conditions, and the same effect could also be important in the selection rules observed in enzymes.

Herein we report the hundred-fold substrate selectivity imparted by the use of sodium dodecyl sulfonate in water in the selective hydrogenation of α,β -unsaturated aldehydes mediated by Pd nanoparticles (PdNPs) in water (Scheme 1). Longer

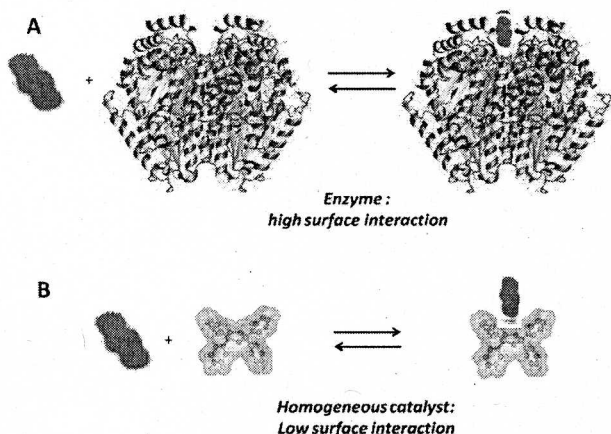
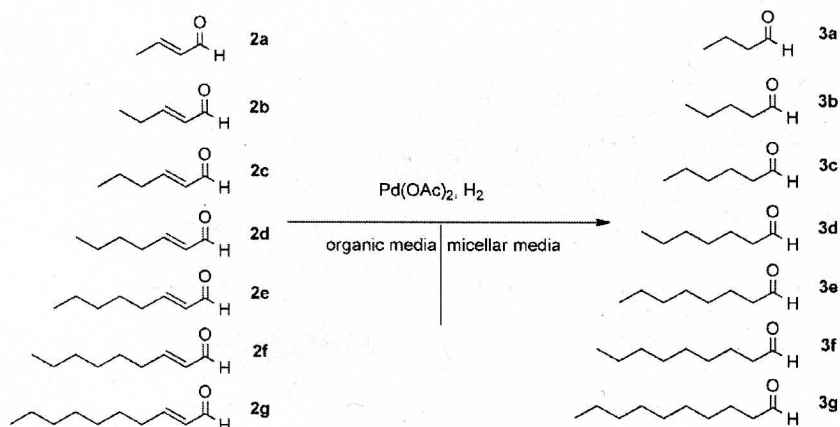


Figure 1. Example of the extended surface interaction between enzyme and substrate in comparison to the same interaction between a homogeneous catalyst and the corresponding substrate.

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Scheme 1. Chemoselective hydrogenation of α,β -unsaturated C_4 – C_{10} aldehydes **2a–2g** to the corresponding saturated aldehydes **3a–3g**. Comparison of the substrate selectivity displayed in organic and aqueous media with surfactant.

and more lipophilic substrates reacted hundreds of times faster than the shorter ones because of their partition between bulk water and surfactant aggregates in which the PdNPs are stabilized.

Initially, the hydrogenation reaction was tested in THF as the organic medium to ascertain the intrinsic relative activity of the series of unsaturated aldehydes. The reaction was performed with 0.6 mol% of $\text{Pd}(\text{OAc})_2$ in the presence of 59.4 mM of each substrate from *trans*-2-butenal (**2a**) to *trans*-2-decenal (**2g**) at room temperature under 1 bar of H_2 . For all substrates, the reaction led to the selective formation of the corresponding saturated aldehyde that was formed quantitatively in approximately 75 min. Following the decrease of the starting reagent over time, it was possible to determine the initial rate of the reaction for each substrate. The experiment was repeated three times, and normalization of the initial reaction rates with respect to the longer substrate **2g** showed a gradual increase of selectivity of the reaction in favor of **2a**, which reacted 3.6 times faster than the longer **2g** (Figure 2).

The slight decrease in activity on increasing the length of the alkyl chain is likely to be imputable to the partial folding of the longer substrates with a consequent small increase in

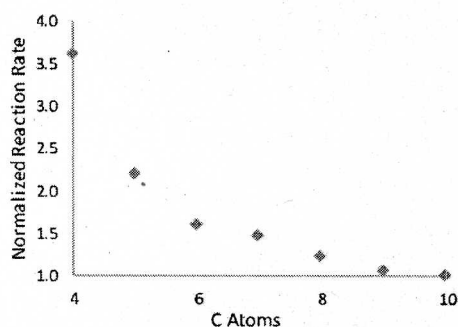


Figure 2. Normalized reaction rates for the hydrogenation of unsaturated aldehydes **2a–2g** with $\text{Pd}(\text{OAc})_2$ in THF at RT.

the steric hindrance of the $\text{C}=\text{C}$ bond. Notably, in the course of these experiments in an organic solvent, the addition of H_2 led to a color change of the solution from pale orange to grey, indicative of Pd metal formation, which did not precipitate as a black element probably thanks to the solubilizing effect imparted by the large excess of substrates present.

Subsequently, we switched to the employment of water as the solvent in the presence of different surfactants characterized by different charge, lipophilicity, and critical micellar concentration (cmc). Examples of the stabilization of PdNPs by micellar

media in aqueous media have been proposed recently for the Matsuda–Heck^[25] and Mizoroki–Heck^[26] coupling reactions in water with the observation of the beneficial effect of the use of cationic surfactants in combination with palladium acetate as the metal precursor. In the present work, in all cases $\text{Pd}(\text{OAc})_2$ (0.6 mol%) was dissolved in water in the presence of a series of surfactants for 1 h followed by activation of the metal under 1 bar of H_2 until the color change, which was indicative of the formation of PdNPs. Initially, we investigated the use of the cationic surfactant cetyl trimethylammonium bromide (CTAB, 80 mM) that required a long activation with H_2 before the color change was observed. Under these experimental conditions, the competitive hydrogenation reaction showed a low activity and only 0.5–9% conversion of the different unsaturated aldehydes **2a–2g** was observed after 1 h.

Similar experiments were performed with Triton-X100 and Triton-X114 as neutral surfactants (8 mM) but in these cases the activation process with H_2 and the subsequent addition of the substrates caused the precipitation of Pd metal. If the Triton concentration was increased to 80 mM, a stable black suspension was obtained after 20 min activation with H_2 in both cases, but the resulting mixture separated into a lower aqueous and higher surfactant phase if the mixing was stopped. This is indicative of a biphasic system rather than a microemulsion typical of micellar conditions. The reaction led to the selective formation of the corresponding saturated aldehyde with quantitative yield after approximately 40 and 50 min using Triton-X114 and Triton-X100, respectively. The competitive hydrogenation reaction for aldehydes **2a–2g** showed an increase of activity from **2a** to **2d** followed by a small decrease up to **2g** (Supporting Information). The presence of two different phases could explain the activity trend observed with shorter substrates based on their hydrophobicity. In contrast, longer substrates that reside all the time in the organic phase, in which the Pd catalyst is stabilized, react as they do in THF and show a decrease of activity with the increasing length of the aldehyde.

Finally, anionic surfactants were the most suitable to both stabilize the PdNPs and impart substrate selectivity to the catalytic system. If sodium dodecyl sulfate (SDS, 80 mM) was employed as the surfactant, the activation of the metal with H₂ flushing was fast and required only 5 min. The competitive hydrogenation tests with equimolar amounts of unsaturated aldehydes **2a–2g** showed the short **2a** as the less reactive substrate, whereas **2g** was 3.7 times more active. The use of sodium dodecylbenzenesulfonate (SDBS, 80 mM) as an alternative anionic surfactant led to a less efficient catalytic system, which showed only 18–38% conversion of the substrates after 1 h (Supporting Information).

In the case of sodium dodecyl sulfonate (SDSU), we observed interesting results in terms of the catalytic activity and stability of the PdNPs that required a more detailed analysis of the effect of the concentration of the surfactant. Experiments were initially performed at 20, 40, 60, and 80 mM of SDSU in water at room temperature using *trans*-2-hexenal (**2c**) as a model substrate at a ratio of 100:1 with respect to the Pd(OAc)₂ (Table 1). We observed that a higher concentration of

Table 1. Catalytic hydrogenation of **2c** by PdNPs in water with SDSU as the surfactant at different concentrations in water.^[a]

t [min]	Yield [%]			
	20 mM SDSU	40 mM SDSU	60 mM SDSU	80 mM SDSU
10	30	21	35	29
30	70	71	92	>98

[a] Experimental conditions: [**2c**] 120 mM, [Pd(OAc)₂] (2%) 2.4 mM, H₂ 1 atm, water 3 mL, RT.

surfactant caused an increase of the time required for the formation of PdNPs, probably because of a better dispersion of the metal in the medium. Although at lower concentrations of SDSU the PdNPs were not stable and we observed the formation of Pd black after approximately 30 min (20 mM SDSU, 30% yield after 10 min and 70% yield after 30 min), at higher surfactant concentration the PdNPs were more stable. This led to high catalytic activity with well-dispersed NPs and no formation of Pd black at the end of the reaction (80 mM SDSU, 29% yield after 10 min and >98% yield after 30 min).

The latter concentration of surfactant was selected for the following catalytic tests as it was able to ensure the high stability of the PdNPs. Notably, SDSU is characterized by a very low cmc (0.9 mM),^[27] and at 80 mM in water the system is present as a sort of aqueous colloidal system without complete dissolution of the surfactant. It is likely that the catalytic system does not operate under micellar conditions but rather the PdNPs are stabilized by interaction with the organic portion of the medium that stabilizes the NPs and avoids their aggregation to Pd black.

We then studied the substrate selectivity of the catalytic system developed in SDSU. The short substrates **2a** and **2b** were characterized by a very low rate of conversion into the corresponding saturated aldehydes (Figure 3), and an increase

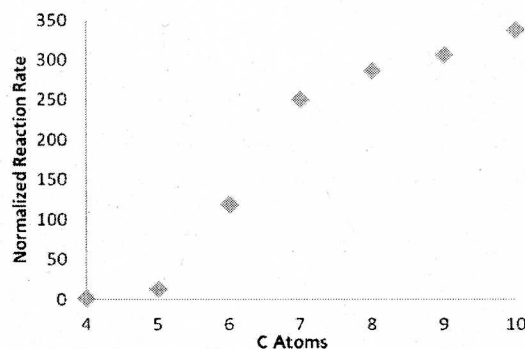


Figure 3. Normalized reaction rates for the hydrogenation of unsaturated aldehydes **2a–2g** with Pd(OAc)₂ in water with SDSU 80 mM as the surfactant at RT.

of the length and hydrophobicity of the substrates caused a linear increase of activity up to **2d** followed by a second linear increasing trend with a lower slope up to **2g**. The latter substrate was completely converted within 40 min, which speaks clearly for the high catalytic activity of the PdNPs obtained under these experimental conditions. Notably, between the most and the least active substrate, a ratio of more than 330 was observed, which is remarkable if we consider that the selection occurs mainly because of the partition properties of the substrates between the bulk water and the apolar support provided by the surfactant in which the NPs are stabilized by the hydrophobic effect.

It has been reported in some cases that surfactants can be used to control the geometry and the stability of PdNPs.^[28,29]

To shed light on the level of aggregation of the Pd, TEM^[30] was used to visualize the presence of PdNPs with an average size of 4.6 nm and a size distribution between 2.0 and 7.5 nm.

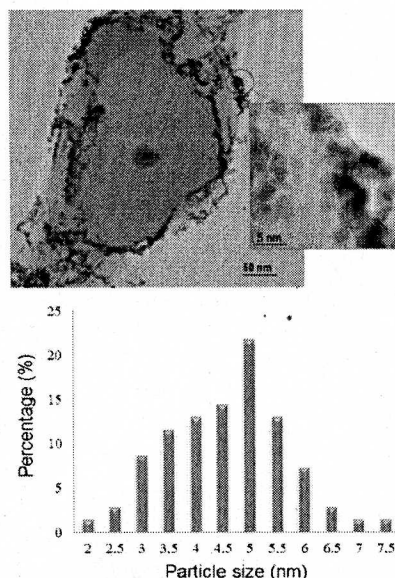


Figure 4. a) TEM image of PdNPs prepared at RT by H₂ flushing of a solution of Pd(OAc)₂ (2.4 mM) in the presence of SDSU (80 mM) as the surfactant in water (3 mL). b) Size distribution determined for the PdNPs.

TEM micrographs of PdNPs obtained at room temperature by H₂ flushing of a solution of Pd(OAc)₂ in water with SDSU are shown in Figure 4. The PdNPs are mainly confined at the edge of the sampled area and appear to decorate the external surface of a much larger organic aggregate formed by the surfactant. The shape of the nanoparticles is rounded and they tend to agglomerate. High-resolution electron microscopy (HREM) evidenced that in most cases the nanoparticles are pure Pd single crystals. Energy-dispersive X-ray analysis (EDX; Supporting Information) of different areas of the specimen evidenced the presence of Na and S in the areas in which the nanoparticles were not present (see the central area marked edx in Figure 4); instead EDX analysis of areas that contained nanoparticles showed the presence of Na, S, and Pd.

In conclusion, we demonstrated that stable PdNPs can be generated in water in the presence of SDSU as a surfactant and that these can catalyze the chemoselective hydrogenation of unsaturated aldehydes efficiently with high substrate selectivity in favor of more lipophilic substrates. The nature of the surfactant employed plays a crucial role in the stability, size, and catalytic activity of the PdNPs. In particular, SDSU was the best surfactant, which provided small nanoparticles with an average diameter of 4.6 nm characterized by a very high catalytic activity. The latter, in combination with the selective binding of longer hydrophobic substrates imparted by the SDSU anionic surfactant provided a very substrate-selective catalytic system with a difference of activity between the shorter **2a** and the longer **2g** substrate of more than 300 times, which reverses completely that observed in an organic solvent in which **2a** was 3.6 times more active than **2g**. The selection rules present in this simple catalytic system are also likely to occur in enzymes in which the hydrophobic effect favors substrate recognition.

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