Continuous hydrogenation of organic compounds in supercritical fluids

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A small flow reactor (5 ml volume) is used for continuous hydrogenation in supercritical CO_2 or propane with polysiloxane-supported noble metal catalysts; a wide range of organic functionalities can be hydrogenated with good throughput (up to 1200 ml h^{-1} in favourable cases) and the various parameters (temperature, pressure, concentration of H_2, *etc.*) can be controlled *independently* to optimise the selectivity for a particular product.

Hydrogenation of organic compounds is a process of major chemical importance. Gaseous H_2 is an inexpensive and versatile reagent for hydrogenation but it can often be difficult to use in practice. Laboratory-scale hydrogenation is usually slow because H_2 is sparingly soluble in common solvents. By contrast, supercritical fluids are completely miscible[1] with H_2, but it is only recently that this miscibility has been exploited[2–9] for hydrogenation and related reactions, mostly as batch reactions in sealed autoclaves. However, the gas-like nature of supercritical fluids makes them particularly suitable for continuous flow reactors. For any reaction, a flow reactor can be smaller than the corresponding batch reactor needed to generate a comparable amount of product. This reduction in size is particularly attractive for supercritical fluid systems because it reduces both the cost and the safety problems of high pressure equipment. There is a very brief report[10] of an industrial supercritical hydrogenation process with a 250-fold reduction in the volume of the reactor, and more recently small-scale reactors have been used to hydrogenate fats and fatty esters in near-critical or supercritical CO_2 ($scCO_2$) and propane (scPropane).[11,12]

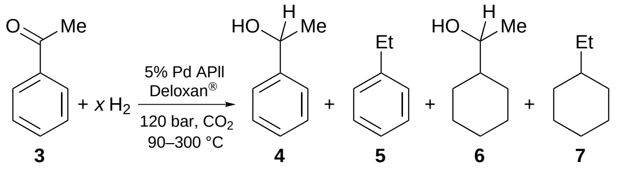
Here, we describe the use of a flow reactor system† for a wide range of continuous hydrogenation reactions. Although the reactor is larger than our previous flow reactors for the photochemical synthesis of organometallic dihydrogen compounds,[13] the entire apparatus can still be accommodated within a standard fume cupboard. The hydrogenation of cyclohexene **1** to cyclohexane **2** was used to establish the performance of the reactor. The reaction was extremely rapid in $scCO_2$ [T_c = 31.1 °C, P_c = 73.8 bar (10 bar = 1 MPa)] or scPropane (T_c = 96.8 °C, P_c = 42.6 bar) and could be initiated without any external heating of the reactor. Table 1 shows that the overall rate of conversion is extremely high, with up to 20 ml (0.2 mol) per minute of **1** hydrogenated in a reactor (5 ml volume) containing only 4 ml of catalyst.

The role of the supercritical fluid is almost certainly more complex than merely enhancing the concentration of H_2. The fluid reduces viscosity and increases diffusion rates compared to the liquid phase, so that transport to and from the catalyst surface is no longer a limiting factor. At flow rates > 1.5 ml min^{-1} of substrate, we have measured temperatures > 300 °C in the catalyst bed, higher even than the critical temperature of cyclohexene itself (T_c = 287.3 °C, P_c = 43.4 bar). Indeed, at high throughput, we have found that once the temperature of the reactor has stabilised, only a very small flow of $scCO_2$ is required to sustain the reaction; the mixture is predominantly cyclohexene and H_2, which measurements in our laboratory have shown to be completely miscible under these conditions.‡ Experiments with a commercially significant derivative of cyclohexene indicate that hydrogenation in $scCO_2$ is more selective than the gas phase reaction and is quicker than the liquid phase, requiring *ca.* 35 times less catalyst.

The particular advantage of supercritical fluids is the ability to control conditions with great precision and, hence, to manipulate the selectivity of reactions. Thus, the hydrogenation of acetophenone **3** can lead to at least four possible products **4–7** (Scheme 1).

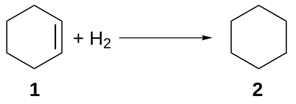
When the reactor is operated with $scCO_2$ at 90 °C, there is almost quantitative conversion of **3** to **4**. As the amount of H_2 and the temperature of the reactor are raised, there is a controllable shift towards the more hydrogenated products so that, by 300 °C, **7** is the major product (see Fig. 1).

However, the presence of a single phase within the reactor means that the various parameters (temperature, pressure, concentration of H_2, *etc.*) can be adjusted *independently*. Thus, reducing the ratio of H_2 : **3** from 4 : 1 to 2 : 1 (at T = 200 °C and



Scheme 1

Table 1 Hydrogenation of cyclohexene **1**



Catalyst	Fluid	Flow rate[a] of fluid/ l min^{-1}	Flow of **1**/ ml min^{-1}	Ratio of **1** : H_2	T_{wall}/°C	Pressure/ bar	Yield of **2** (%)[b]
5% Pd[c]	$scCO_2$	0.75–1.65	0.5–20.0	1 : 2–4	40–320	120	95–98
5% Pd[c]	scPropane	0.75	0.5–2.0	1 : 2	100–170	60	96
5% Pt[d]	scPropane	0.75	0.5–2.0	1 : 2	100–170	80	96

[a] Fluid flow rate measured at 1 atm and 20 °C as determined by bubble flow meter. [b] Analysis by GC using external standards. [c] APII 5% Pd Deloxan®, particle size: 0.3–0.8 mm. [d] APII 5% Pt Deloxan®, particle size: < 0.2 mm.

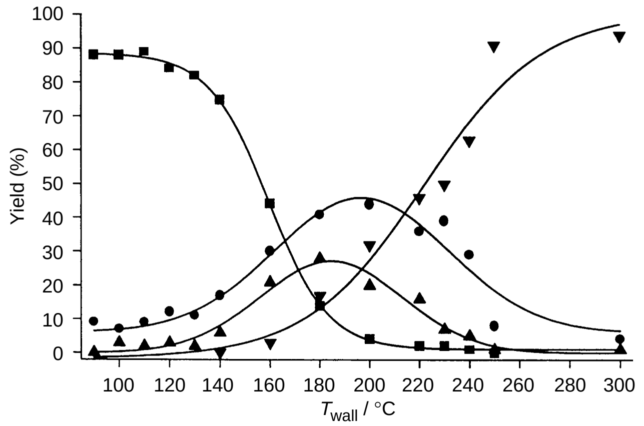
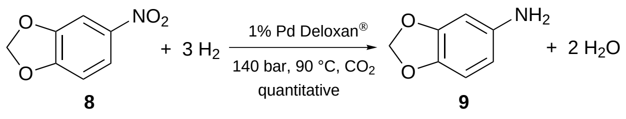


Fig. 1 Dependence of product distribution on reactor wall temperature for the hydrogenation of acetophenone **3** in $scCO_2$ with 5% Pd APII Deloxan® catalyst: (■) **4**, (●) **5**, (▲) **6** and (▼) **7**. Reactions were run with flow rates of 0.5 ml min^{-1} **3**, 1.0 ml min^{-1} gaseous CO_2, and a ratio of H_2 : **3** increasing from 2 : 1 to 6 : 1 at higher temperatures. The total pressure was held at 120 bar throughout. Product analysis by ^1H NMR spectroscopy ($CDCl_3$).

p = 120 bar) increases the yield of **5** from 44 to 69% at the expense of **7**, or reducing the total pressure (at T = 240 °C and with *constant* H_2 : **3** = 4 : 1) from 120 to 40 bar (*i.e.* to the near-critical region) reduces the degree of hydrogenation, changing the ratio of products **5** : **7** from 1 : 2 to 2 : 1, presumably by reducing the residence time. Thus, without changing catalyst, one can tune conditions to maximise the yield of a particular product, and the reactor is then sufficiently stable to maintain those conditions.

The reactor is primarily designed to operate with reactants and products which are liquids at ambient temperature but it can also be used to hydrogenate solids, dissolved in an inert organic solvent. For example, 1,2-(methylenedioxy)-4-nitrobenzene§ **8** (mp 146–148 °C) was hydrogenated quantitatively to **9** in $scCO_2$ by pumping it through the reactor (*ca.* 8 g h^{-1}) in MeOH–THF (2 : 1 v/v) (Scheme 2).



Scheme 2

The flow reactor can be used to hydrogenate a substantial range of other organic functional groups. Epoxides, oximes, nitriles, alcohols and aromatic and aliphatic aldehydes and ketones have been successfully hydrogenated, most with conversions comparable to those described above and several with better selectivity than in non-supercritical hydrogenation. Most significantly, we have shown that compounds can be hydrogenated continuously on a relatively large scale using reactors of very small volume. Thus supercritical fluids can transform hydrogenation with gaseous H_2 into a viable, rapid and highly controllable laboratory technique for organic chemistry on a large preparative scale. At the same time, only modest scale-up will be required to generate compounds in quantities appropriate to the industrial production of some pharmaceuticals and fine chemicals.

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Footnotes and References

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† The substrate, supercritical fluid and H_2 are brought together in a heated mixer, passed through the reactor containing the catalyst, and then expanded to separate the product from the fluid and excess H_2. The reactor is assembled from commercially available units: $scCO_2$ and scPropane pump PM101, H_2 compressor CU105 and Expansion Module PE103 (all from NWA GmbH, Lörrach, Germany), a high pressure mixer (Medimix) and a Gilson 305 pump (for the organic substrate). **Safety note**: Flow reactors have a comparatively small volume under pressure. Nevertheless, equipment with the appropriate pressure and temperature rating should always be used for high pressure experiments.

‡ Although previous reports have shown that hydrogenation catalysts can be rather short-lived under supercritical conditions (ref. 11), we have found that the Deloxan® catalysts (S. Wieland and P. Panster, *Catalysis of Organic Reactions*, Marcel Dekker, New York, 1995, p. 383) have survived several hours under these harsh conditions and can even be used successfully up to 400 °C.

§ The hydrogenation of nitrobenzene itself over a 5% Pt APII Deloxan® catalyst in scPropane is particularly striking, with conversion of *ca.* 25% of the starting material to NH_3 and cyclohexane, a reaction which requires addition of no less than seven H_2 molecules to each molecule of nitrobenzene within a residence time of <5 min in the reactor (200 °C, 80 bar). By contrast, a 1% Pd APII Deloxan® catalyst gives aniline in 100% yield under similar conditions.

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