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Articles

Selective Catalytic Hydrogenation of Organic Compounds in Supercritical Fluids as a Continuous Process

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Abstract:
We report a new method for continuous hydrogenation in supercritical fluids (CO_2 or propane) using heterogeneous noble metal catalysts on Deloxan aminopolysiloxane supports. The method has considerable promise both for laboratory-scale hydrogenation and for the industrial production of fine chemicals. It can be applied to a wide range of organic compounds including alkenes, alkynes, aliphatic and aromatic ketones and aldehydes, epoxides, phenols, oximes, nitrobenzenes, Schiff bases, and nitriles. Conversion of starting materials, product selectivity, and space−time yields of the catalyst are all high, and the reactors themselves are very small (5- and 10-mL volume). Supercritical hydrogenation enables the reaction parameters to be controlled very precisely. Results are presented for a series of different reactions showing product distributions, which are dependent on temperature, pressure, H_2 concentration, and the loading and nature of the catalyst. The hydrogenation of cyclohexene has been studied in some detail, and our results are related to the phase diagrams of the ternary system cyclohexane + CO_2 + H_2, which we present in a novel way, more suited to continuous reactors. Finally, we report that the supercritical hydrogenation of isophorone has advantages over conventional methods.

Introduction

Supercritical fluids are becoming increasingly attractive as solvents for environmentally more acceptable chemical processes. Applications range from extraction and chromatography in analytical chemistry to reaction chemistry and preparation of new materials.[1−9] These fluids are gases heated above their critical temperatures (T_c) and pressurized above their critical pressures (P_c).[10,11] Their densities are comparable to those of organic liquids, and the gaslike nature of the fluids renders them completely miscible with permanent gases[12] such as H_2. By contrast, the solubility of gaseous H_2 in conventional organic solvents is relatively low. Thus, supercritical fluids are potentially attractive solvents for hydrogenation reactions with significant advantages over conventional methods, particularly because gas-phase reactions often generate significant amounts of by-products and conversion can be poor in liquid-phase reactions.

The properties of supercritical fluids make them highly suitable as solvents for continuous flow reactors. Compared to liquid-phase reactions, reactions in supercritical fluids are characterized by reduced viscosity and enhanced mass transfer. In addition, the good thermal transport properties

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of supercritical fluids are an advantage because hydrogenation is usually a highly exothermic reaction. However, relatively few articles have been published on hydrogenation in supercritical fluids,[13−23] and most of those have involved hydrogenation as a batch process, carried out in sealed autoclaves. Reports on supercritical hydrogenation as a continuous process are even rarer.

Industry, in particular, favours continuous processes because they are more cost efficient and the reactors can be kept smaller in size.[23,24] This reduction in size reduces both costs and safety problems of the high-pressure equipment needed for supercritical reactions. There have been two investigations into the hydrogenation of fats and oils in continuous flow reactors using near-critical or supercritical CO_2 ($scCO_2$, $T_c = 31.1$ °C, $P_c = 73.8$ bar) and propane (scPropane, $T_c = 96.8$ °C, $P_c = 42.6$ bar).[21,22] In a very recent communication,[25] we described a much more general method for the selective hydrogenation of organic substrates in supercritical fluids using a laboratory-scale continuous flow reactor.

In this paper, we describe our approach to supercritical hydrogenation in greater detail. We begin by summarizing the essential features of our reactor. Then, we describe a series of reactions which illustrate the breadth of chemistry accessible via the reactor. Next, we report a more detailed study on the hydrogenation of alkenes, aimed at investigating the effects of carrying out such reactions on a larger scale, and in the final section, we describe the supercritical hydrogenation of isophorone, a reaction with significant industrial and environmental benefits.

Experimental Section

Safety Hazard. *CAUTION! The experiments described in this paper involve the use of relatively high pressures and require equipment with the appropriate pressure rating. It is the responsibility of individual researchers to verify that their particular apparatus meets the necessary safety requirements. The individual components, which we describe below, work well, but they are not necessarily the only equipment of this type available nor the most suitable for the purpose.*

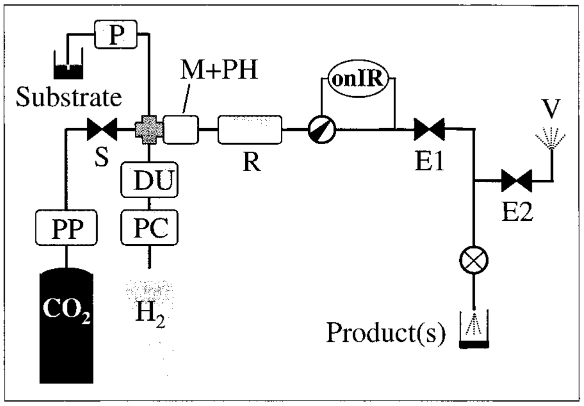

Figure 1. **Flow apparatus for catalytic hydrogenation in supercritical fluids, based on high-pressure modules (NWA GmbH, Lörrach, Germany); see text for details of operation. The components are labeled as follows: DU, pneumatically operated dosage unit for adding H_2; E1 and E2, expansion valves to control the flow rate and to separate the product(s) from the fluid and excess H_2; M, mixer; onIR, on-line FTIR monitoring (Nicolet Impact 410); P, pump for the organic substrate (Gilson 305); PH, preheater; PP, pneumatic pump for CO_2 or propane (module PM 101); PU, pneumatic compressor for H_2 (module CU 105); R, reactor (plus heater block not shown) which is fitted with three thermocouples as illustrated in Figure 8; S, pressure regulator for controlling the system pressure; V, vent with flow meter (not shown).**

Figure 1 shows a schematic view of the apparatus. The pump, PP (PM 101, NWA GmbH), compresses the supercritical fluid to maintain a system pressure of 40−200 bar, which is controlled by the regulator, S. The organic substrate is pumped with a standard HPLC pump, *P* (0.3−20.0 mL/min, Gilson 305). H_2 is compressed to 200−280 bar, PC (CU 105, NWA GmbH), and is added pulsewise via a dosage unit, DU (based on pneumatic Rheodyne 6-port injection valve) at a pulse rate chosen to give the desired H_2:substrate ratio. The fluid, substrate, and H_2 mixture is stirred mechanically and preheated, M+PH. The reaction mixture then enters the reactor, R, which can be heated independently by an aluminium block. We found that alkynes, alkenes, and Schiff bases reacted readily at an initial reactor temperature of 40 °C but, in most cases, additional heating of the reactor was necessary.

In the experiments described here, we used two interchangeable reactors made of 316 stainless steel tubing (9-mm i.d.): length 78 mm (5-mL volume) and length 152 mm (10-mL volume). A frit at the bottom of the reactor keeps the catalyst in place. The system has three thermocouples situated (i) inside the catalyst bed (T_{cat}), (ii) against the reactor wall (T_{wall}), and (iii) in the product stream leaving the reactor (T_{out}). All three are used for monitoring the reaction, but in practice, we have found that T_{wall} gives the most reproducible control of the heater.

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After passing through the reactor, the product stream can be optionally flowed through a high-pressure IR cell[26] for on-line monitoring (Nicolet Impact 410 FTIR interferometer) before the pressure is dropped stepwise to separate the product(s) from the fluid and excess H_2 using an expansion module (PE 103, NWA GmbH). In this module, both of the expansion valves E1 and E2 control the flow rate of the exhaust gases. Additionally, a flow meter (not illustrated) is connected to the vent (V) to measure the flow rate of the fluid, which is typically set to 0.5−1.5 L of gas at 1 atm and 20 °C. This flow rate corresponds to 0.9−1.8 g of CO_2/min. Thus, in summary, the fluid *pressure* is controlled at the start of the system, together with the flow rates of the *substrate* and/or *H_2*. The *total flow* of the reaction mixture is controlled at the end of the system. This arrangement means that *increasing* the flow rate of reactants will automatically *reduce* the flow of fluid unless the total flow is also increased. Thus, the faster the reactor runs, the less fluid is used. This has important and beneficial consequences for the operation of the reactor, as discussed in the last sections of this paper.

A number of catalysts were tried, including Pt/C and Ni metal. Several were effective, apart from Pt/C, which tended to block the system, but we found Deloxan precious metal catalysts (Degussa AG, Frankfurt, Germany) to be the most reliable and convenient catalysts for use in our continuous flow reactor. Therefore, these catalysts, which are based on aminopolysiloxane supports, have been used in all the experiments described here.

The organic products are recovered free of any solvent. Thus, they can immediately be analyzed by NMR (Bruker DPX 300), GC (Philips PU 4500), or GC−MS (Shimadzu QP-5000) without further work-up. All reactions were run using commercially available substrates (Aldrich). The reactor described in this paper gives a good degree of reproducibility between runs.

Results and Discussion

Table 1 summarizes some of the reactions which we have investigated. These reactions have been chosen to test different features of the reactor. The hydrogenations have involved a wide range of organic functional groups including alkenes, alkynes, aliphatic and aromatic ketones and aldehydes, epoxides, phenols, oximes, nitrobenzenes, Schiff bases and nitriles. The hydrogenolysis of aliphatic alcohols and ethers has also been studied. For those hydrogenations where several products were possible, we have investigated the effect of the reactor conditions on the selectivity of the reaction. We have found that the most important reaction parameters are the temperature of the reactor and the concentration of H_2. Surprisingly, changes in the absolute pressure—typically values of 40−200 bar—only became important when the pressure was close to or below the critical pressure of the fluid.

Compared to conventional methods of hydrogenation, the particular advantage of using supercritical fluids is that the various parameters in a supercritical flow reactor can be controlled more or less independently. For example, in a flow reactor, unlike a batch system, the temperature can be altered without causing any change in the pressure inside the reactor. Thus, reaction conditions can be controlled with considerable precision and with high reproducibility of the results.

(a) Hydrogenation of *m*-Cresol, 1: Effects of Temperature and of H_2 concentration. Our 5-mL reactor is a relatively short tube so that residence times are <5 min with the CO_2 flow rates typically used in our experiments. This means that high reaction temperatures are needed to achieve full conversion of substrates which have high activation energies for hydrogenation. The disadvantage, however, is that product selectivity decreases rapidly with increasing temperature. This problem can be overcome, when necessary, by using a longer reactor; the 10-mL reactor doubles the residence time of a substrate, and a lower temperature can be used with a correspondingly improved selectivity. Thus, we have investigated the hydrogenation of *m*-cresol, **1**, in $scCO_2$ in a 10-mL reactor containing 9 mL of the 5% Pd APII Deloxan catalyst (particle size: 0.3−0.8 mm) (Scheme 1). Both the total pressure (120 bar) and the flow rate of **1** (0.5 mL/min) were kept constant throughout the investigation. Even with this 10-mL reactor, temperatures of at least 250 °C and a H_2:**1** ratio of 3.5:1 were needed to obtain 100% reaction of **1**, see Figure 2. Under these conditions, 3-methylcyclohexanone, **2**, and 3-methylcyclohexanol, **3**, were formed in yields of 42% and 55%, respectively. Increasing the temperature favoured hydrogenolysis to methylcyclohexane, **4**, and small amounts of toluene, **5**. Figure 3 shows how the yield of **3** can be raised at the expense of **2** when the ratio of H_2:**1** is increased from 3.5:1 to 5:1 at a constant temperature of 250 °C. On the other hand, lowering the H_2:**1** ratio to 2.5:1 increases the yield of **2** to 61.5%. It should be noted that the 5% Pd Deloxan catalyst survived for at least 16 h with no signs of coking or degradation even at reactor temperatures of up to 400 °C.

(b) Hydrogenation of Aldehydes and Ketones: Comparison of Aromatic and Aliphatic Compounds. The hydrogenation of the CO group of aromatic ketones or aldehydes required temperatures lower than those used for the hydrogenation of *m*-cresol. Thus, benzaldehyde, **6**, could be hydrogenated quantitatively at only 95 °C (Scheme 2). Using the 5-mL reactor filled with 4 mL of the 5% Pd APII Deloxan catalyst, benzyl alcohol, **7**, was isolated in 92% yield as the major product, see Figure 4. The yield of **7** decreased rapidly as the temperature of the reactor was increased; at 140 °C, toluene, **5**, was formed in 77% yield. Significant hydrogenation of the aromatic ring was observed only above 200 °C, and a sample collected at 270 °C contained 49% methylcyclohexane, **4**, and equal proportions of toluene, **5**, and cyclohexane, **9** (22−25%).

In contrast to benzaldehyde, propionaldehyde, **10**, could not be hydrogenated in $scCO_2$ over the 5% Pd catalyst even at temperatures as high as 300 °C. Better results were obtained with a different catalyst, 5% Ru APII Deloxan (4

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Table 1. **Summary of the results of supercritical hydrogenation described in this paper**

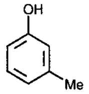
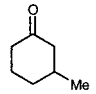
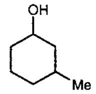
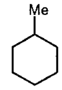
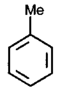
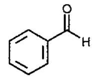
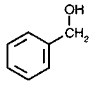
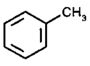
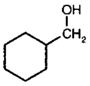
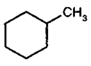
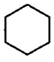
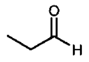
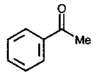
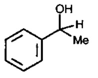
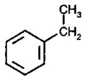
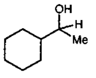
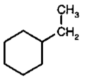
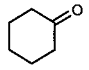
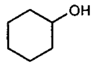
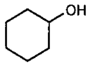
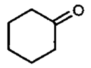
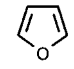
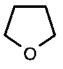
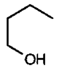
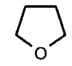
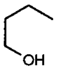
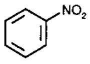
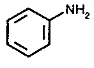
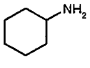
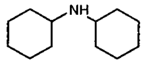
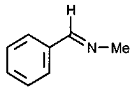
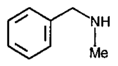
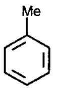
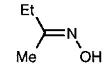
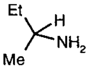
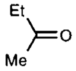
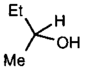
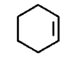
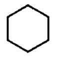
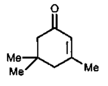
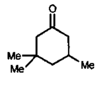
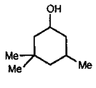
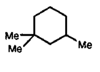
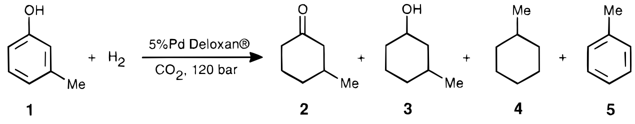
Substrate (% Conv.)	Sub. Flow [mL/min]	Fluid Flow [L/min]$^{a)}$	Deloxan-Catalyst	Substr. : H_2	p (total) / bar	T_{wall} / °C	Products / % (analysis by GC except when marked with $^{\#}$ where analysis is by ^{1}H NMR)				
											
1 (90)	0.5	0.65	5% Pd	1 : 2.5	120	250	**2** (61.5)	**3** (26.0)	**4** (1.5)	**5** (1.0)	
(100)	0.5	0.65	5% Pd	1 : 5.0	120	250	(17.5)	(76.5)	(6.0)	(0)	
(99)	0.5	0.65	5% Pd	1 : 6.0	120	400	(5)	(4)	(73)	(17)	
											
6 (100)$^{\#}$	0.5	1.0	5% Pd	1 : 2.0	120	95	**7** (92)$^{\#}$	**5** (8)$^{\#}$	**8** (0)$^{\#}$	**4** (0)$^{\#}$	**9** (0)$^{\#}$
(100)$^{\#}$	0.5	1.0	5% Pd	1 : 4.0	120	140	(18)$^{\#}$	(77)$^{\#}$	(4)$^{\#}$	(1)$^{\#}$	(0)$^{\#}$
(100)$^{\#}$	0.5	1.0	5% Pd	1 : 6.0	120	180	(22)$^{\#}$	(59)$^{\#}$	(10)$^{\#}$	(7)$^{\#}$	(1)$^{\#}$
(100)$^{\#}$	0.5	1.0	5% Pd	1 : 8.0	120	270	(1)$^{\#}$	(22)$^{\#}$	(3)$^{\#}$	(49)$^{\#}$	(25)$^{\#}$
									unidentified products		
10 (68)	0.5-1.0	1.0	5% Ru	1 : 2.5	120	150	**11** (35)		(33)		
											
12 (97.5)	0.5	1.0	5% Pd	1 : 2.0	120	90	**13** (90.0)	**14** (7.5)	**15** (0)	**16** (0)	
(100)$^{\#}$	0.5	1.0	5% Pd	1 : 5.0	120	180	(14)$^{\#}$	(41)$^{\#}$	(28)$^{\#}$	(17)$^{\#}$	
(91.5)	1.0	1.0	5% Pd	1 : 3.0	120	200	(0)	(73.0)	(0)	(18.5)	
(94)	0.5	1.0	5% Pd	1 : 6.0	120	300	(0)	(4.5)	(0)	(89.5)	
											
17 (17)$^{\#}$	0.5	0.65	3% Ru	1 : 1.5	120	300	**18** (17)$^{\#}$				
											
18 (75)$^{\#}$	0.5	0.65	5% Pd	1 : 3.0	120	400	**17** (12)$^{\#}$	**9** (60)$^{\#}$	**19** (3)$^{\#}$		
											
20 (98)$^{\#}$	0.5	0.75	5% Pd	1 : 3.0	120	300-350	**21** (96)$^{\#}$	**22** (2)$^{\#}$			
											
21 (10)$^{\#}$	0.5	0.2-0.4	5% Pd	1 : 3.0	160	400	**22** (10)$^{\#}$				
											
23 (100)	0.5	0.75 P	1% Pd	1 : 6.0	80	150-200	**24** (100)	**25** (0)	**26** (0)		**9** (0)
(97)	0.3	0.75 P	5% Pd	1 : 9.0	80	200-250	(9)	(29)	(58)		(1)
(91)	0.5	0.75 P	5% Pt	1 : 4.0	80	200	(46)	(13)	(4)		(28)
											
27 (99)	0.3	0.75 P	5% Pd	1 : 2.0	120	40-50	**28** (99.0)	**5** (0)			
(100)$^{\#}$	0.3	0.75 P	5% Pd	1 : 4.0	120	200	(0)$^{\#}$	(100)$^{\#}$			

Table 1 (Continued)

Substrate (% Conv.)	Sub. Flow [mL/min]	Fluid Flow [L/min]$^{a)}$	Deloxan-Catalyst	Substr. : H_2	p (total) / bar	T_{wall} / °C	Products / % (analysis by GC except when marked with $^{\#}$ where analysis is by ^1H NMR)		
									
29 (99)	0.3-1.0	0.75 P	5% Pd	1 : 2.0	80	180-200	**30** (80.0)	**31** (17.5)	**32** (1.5)
(96)	0.5	0.75 P	5% Pt	1 : 2.0	80	150-170	(85.5)	(10.0)	(0.5)
1-Octyne							1-Octene	Octane	
33 (99.6)	0.5-1.0	0.75	5% Pd	1 : 4.0	120	> 40	**34** (0.2)	**35** (99.6)	
1-Octene							Octane		
34 (100)	0.5-10.0	1.0	5% Pd	1 : 2.0	120	> 40	**35** (100)$^{\#}$		
									
36 (99.8)	0.5-20.0	0.75-1.65	5% Pd	1 : 2-4	120-140	> 40	**9** (99.8)		
(99.7)	0.5-2.0	0.75 P	5% Pd, Pt	1 : 2.0	60-80	> 100	(99.7)		
									
37 (100)	0.5-2.0	0.75	5% Pd	1 : 2.0	120	140-200	**38** (100)	**39** (0)	**40** (0)
(100)	1.0	0.75	5% Pd	1 : 3.0	200	350	(51)	(21)	(28)

[a)] P indicates scPropane; all other experiments carried out with $scCO_2$.

Scheme 1. **Hydrogenation of *m*-cresol, 1**



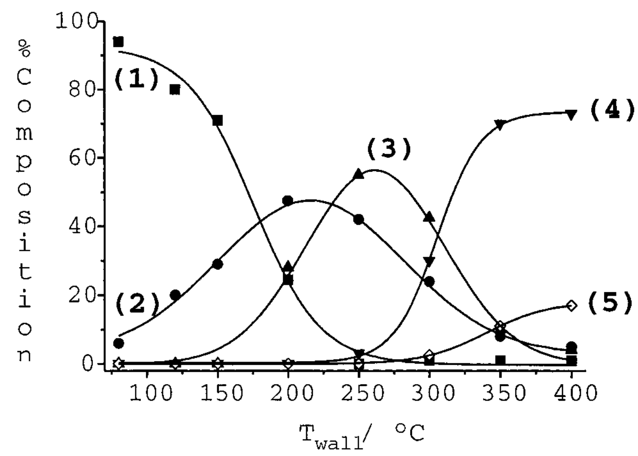


Figure 2. **Plot showing the dependence of the product distribution on the temperature of the reactor wall, T_{wall}, for the hydrogenation of *m*-cresol, 1 (0.5 mL/min), in $scCO_2$ (0.65 L/min) at 120-bar total pressure with 5% Pd APII Deloxan catalyst (9 mL). The compounds are numbered as in Scheme 1. Note that the ratio of H_2:1 was increased from 2:1 to 6:1 at higher temperatures. Product analysis was by GC. In this and subsequent figures, the solid curves are drawn merely to aid visualization of the data.**

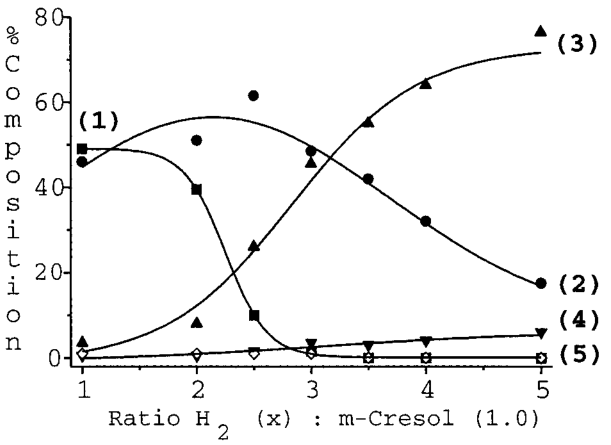
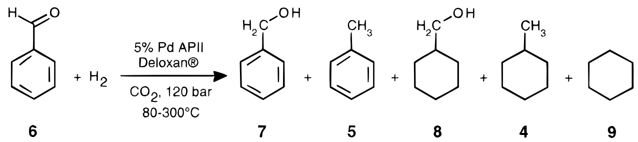


Figure 3. **Plot illustrating the dependence of the product distribution on the ratio of H_2: *m*-cresol, 1 (0.5 mL/min), in $scCO_2$ (0.65 L/min) at constant pressure (120 bar total) and temperature (T_{wall} = 250 °C); catalyst 5% Pd APII Deloxan (9 mL) and product analysis by GC. The compounds are numbered as in Scheme 1.**

Scheme 2. **Hydrogenation of benzaldehyde, 6**



mL, particle size: <0.2 mm). However, even with this catalyst, the overall conversion of **10** was only 68% with a product selectivity to 1-propanol, **11**, of only 35%, see Table 1. It appears that even at relatively modest temperatures (e.g., 150 °C) the Ru catalyst converted a substantial amount of **11** into propene and water.

We found analogous differences in behavior between the hydrogenation of aromatic and aliphatic *ketones*. For example, acetophenone, **12**, could be hydrogenated selectively in $scCO_2$ over the 5% Pd APII Deloxan catalyst to

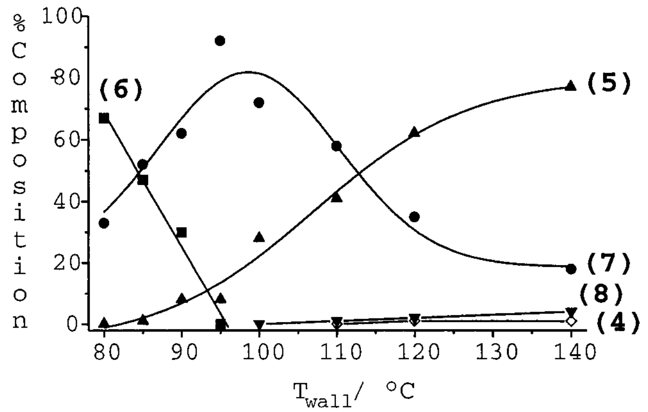
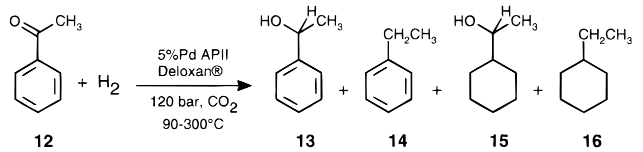


Figure 4. **Plot showing the dependence of the product distribution on T_{wall} (5-mL reactor) for the hydrogenation of benzaldehyde, 6 (0.5 mL/min), in $scCO_2$ (1.0 L/min) at 120-bar total pressure with 5% Pd APII Deloxan catalyst (4 mL). The ratio of H_2:6 was increased from 2:1 to 8:1 at higher temperatures; product analysis by ^1H NMR ($CDCl_3$). The compounds are numbered as in Scheme 2.**

Scheme 3. **Hydrogenation of acetophenone, 12**



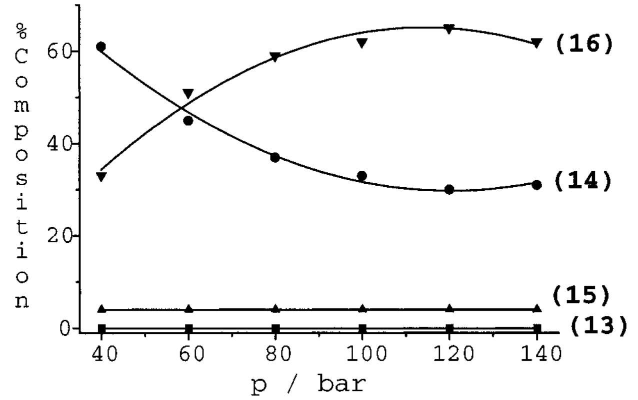
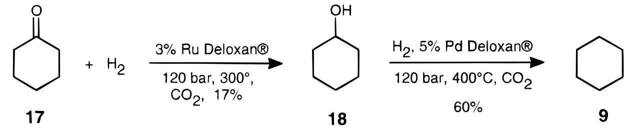


Figure 5. **Plot of the pressure dependence of the product distribution for the hydrogenation of acetophenone, 12 (0.5 mL/min), in $scCO_2$ (1.0 L/min) at T_{wall} = 240 °C with 5% Pd APII Deloxan catalyst (4 mL). The ratio of H_2:12 was constant at 2:1 throughout the experiment while the *total* pressure was varied; product analysis by ^1H NMR ($CDCl_3$). The compounds are numbered as in Scheme 3.**

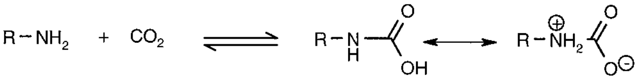
products **13**−**16**, Table 1 (Scheme 3). As we have already reported,[25] it is possible to maximize the yield of any of the hydrogenation products by varying the temperature between 90 and 300 °C, and increasing the H_2:**12** ratio (from 2:1 to 6:1) at a constant pressure of 120 bar, see Table 1.

The total pressure had an interesting effect on the product distribution, see Figure 5. At 240 °C, the yields of ethylbenzene, **14**, and its ring-hydrogenated species **16** were substantially affected by pressure changes while the yields of **13** (0%) and **15** (4%) remained unchanged. The most dramatic changes to **14** and **16** happened near and just below the critical pressure of CO_2 (74 bar). Over the pressure range 40−140 bar, the yield of ethylcyclohexane, **16**, was doubled from approximately 30% to 60%. The most obvious rationalization is that, at constant flow rate, increasing the pressure increases the residence time of the substrate in the reactor and hence the degree of hydrogenation.

Scheme 4. **Hydrogenation of cyclohexanone, 17, and cyclohexanol, 18**



Scheme 5. **Formation of carbamic acids from amines and CO_2**



By contrast, the aliphatic ketone **17** was not hydrogenated over the 5% Pd catalyst. It was hydrogenated selectively, however, to cyclohexanol, **18**, at 300 °C and a pressure of 120 bar by a 3% Ru APII Deloxan catalyst (particle size: 0.8−1.8 mm) (Scheme 4). Even so, the yields of **18** were low (17%), and the reaction generated by-products when run at higher temperatures and pressures.

Interestingly, the hydrogenolysis of cyclohexanol, **18**, itself was best promoted by the 5% Pd catalyst. Even at temperatures as high as 400 °C, the selectivity for cyclohexane, **9**, was 60% compared to the mere 15% which could be achieved with the 5% Ru catalyst.

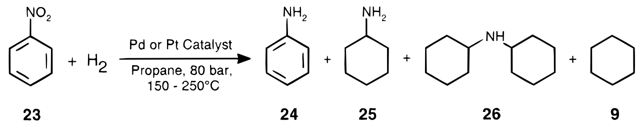
(c) Hydrogenation of Cyclic Ethers. Tetrahydrofuran (THF), **21**, can be obtained in more than 95% selectivity by hydrogenation of furan, **20**, over a 5% Pd catalyst in $scCO_2$ at 120 bar. A very good conversion of 98% was achieved at 300−350 °C with at least a 3-fold excess of H_2, see Table 1. The only side reaction was hydrogenolysis of **21** to 1-butanol, **22** (2%). We were unable to improve the efficiency of the direct transformation of **21** to **22** beyond 10% even under harsher conditions (e.g., 400 °C, 160 bar) or by increasing the residence times with a reduced flow of CO_2 (e.g., from 0.75 to 0.2 L/min).

(d) Hydrogenation of Nitro Compounds: The Use of scPropane. Propane was favoured as the supercritical fluid for the hydrogenation of nitrogen-containing substrates, such as oximes, Schiff bases, nitriles, and nitrobenzenes, to the corresponding amines, to avoid the formation of insoluble carbamic acid salts. Carbamic acids are formed by the reaction of amine groups with CO_2, see Scheme 5. In general we have found that $scCO_2$ can be used for all reactions other than those producing amines. Of course, scPropane has the advantage of a lower critcal pressure than CO_2, but this is offset by its flammability.

Thus, nitrobenzene, **23**, was hydrogenated (0.5 mL/min) with a 2-fold excess of H_2 in scPropane (0.75 L/min) at 80 bar in the 5-mL reactor (150−200 °C) over a 1% Pd APII Deloxan catalyst (particle size: 0.2−0.5 mm) (Scheme 6). Under these conditions, conversion to aniline, **24**, was quantitative with no impurities detectable by either GC or NMR.

The distribution of products, **24**−**26** (and **9**), was strongly dependent on the loading of the catalyst and the choice of

Scheme 6. **Hydrogenation of nitrobenzene, 23**



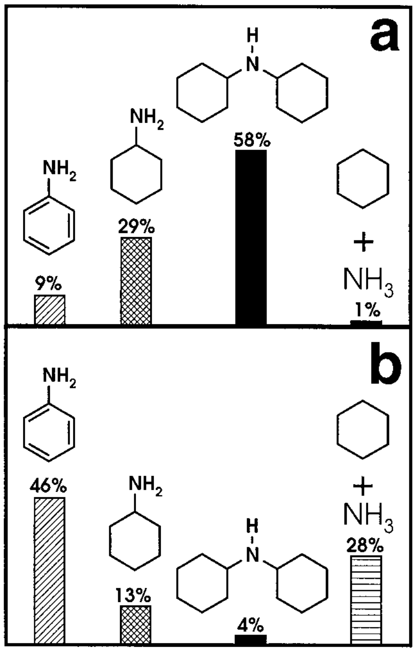


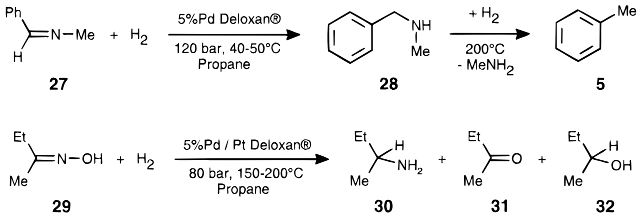
Figure 6. **The effects of catalyst on the product distribution from the hydrogenation of nitrobenzene, 23, in scPropane at 120 bar and at temperatures of 200−250 °C with a 3-fold excess of H_2. Panel a shows how 5% Pd APII Deloxan catalyst transformed 23 into aniline, 24 (9%), cyclohexylamine, 25 (29%), dicyclohexylamine, 26 (58%), and traces of cyclohexane, 9 (1%). Panel b shows that, with a 5% Pt APII Deloxan catalyst, the amount of cyclohexane, 9, increased to 28% at the expense of 25 (13%) and 26 (4%) with aniline, 24, as the major product (46%). By comparison, 1% Pd APII Deloxan catalyst gave quantitative conversion of 23 to aniline, 24, at 200 °C; analysis by GC.**

the noble metal itself, see Figure 6. The formation of **9** is particularly striking because its formation requires the addition of no less than 7 mol of H_2/mole of **23**. This underlines the high efficiency and process intensification which are possible in supercritical flow reactors.

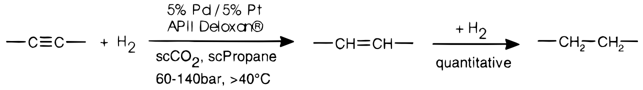
(e) Hydrogenation of Oximes and Schiff Bases. Oximes and Schiff bases were hydrogenated in scPropane to the corresponding amines in high yields and with high selectivity using the 5-mL reactor. For example, benzylmethylamine, **28**, was formed in excellent yield (99%) from *N*-benzylidenemethylamine, **27**, at temperatures of 40−50 °C and a pressure of 120 bar (Scheme 7). Furthermore, toluene, **5**, was obtained in quantitative yield by increasing the temperature to 200 °C and the ratio of H_2 from a 2-fold to a 4-fold excess.

2-Butanone oxime, **29**, reacted with H_2 at 150−200 °C and 80 bar over either the 5% Pd or the 5% Pt APII Deloxan catalyst. In both cases, the conversion of **29** was >95%. The selectivity for 2-butylamine, **30**, was 80.0% with the Pd and 85.5% with the Pt catalyst. A side reaction led to the formation of 2-butanone, **31** (10.0−17.5%), and 2-butanol, **32** (0.5−1.5%).

Scheme 7. **Hydrogenation of Schiff bases, 27, and oximes, 29**



Scheme 8. **Full hydrogenation of acetylenes and olefins**



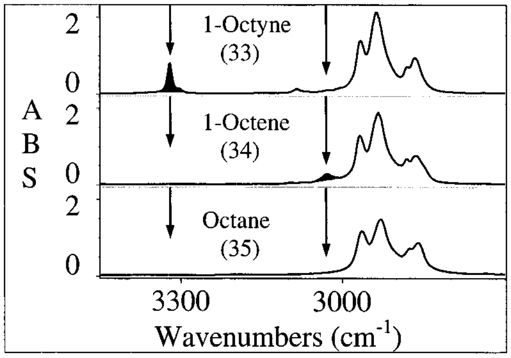


Figure 7. **On-line FTIR spectra showing the differences in the absorptions of of 1-octyne, 33, 1-octene, 34, and octane, 35; spectra were recorded during hydrogenation at 60 °C in CO_2 at 120 bar. The bands are all ν(C−H) vibrations; the left-hand arrow indicates the ν(C−H) band of the acetylenic proton in 33 while the right-hand arrow shows the ν(C−H) band of the olefinic protons in 34.**

(f) Hydrogenation of C−C Multiple Bonds: On-Line Monitoring and Scale-Up. As might be expected, the hydrogenation of C≡C triple bonds or C=C double bonds to single bonds was easily performed in either $scCO_2$ or scPropane (Scheme 8). Both the 5% Pd and 5% Pt APII Deloxan were extremely effective catalysts for this reaction while Ru on Deloxan showed poor conversion. Using CO_2, a reactor temperature of 40 °C and a pressure of 120−140 bar were quite sufficient to start the reaction. With propane, the reactor was preheated to 100 °C to be above the critical temperature of the fluid (T_c = 96.8 °C).

The reactions in $scCO_2$ were monitored in real time by on-line FTIR,[26] which proved to be effective for this purpose because, for example, octane, **35**, showed no absorptions in the region of 3000−3500 cm^{-1} while the starting materials 1-octyne, **33**, and 1-octene, **34**, had characteristic peaks in this region, see Figure 7. The advantage of on-line FTIR over on-line gas chromatography is that FTIR is a much faster method, allowing immediate remedial action to be taken as soon as loss of catalyst activity or product selectivity is observed. Thus, FTIR provides an extremely versatile tool for exploring the performance parameters of laboratory flow reactors (e.g., residence time[27]). Furthermore, FTIR may

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(27) Buback, M.; Hinton, C. Chapter 4 in *High-Pressure Techniques in Chemistry and Physics*; Holzapfel, W. B., Isaacs, N. S., Eds.; OUP: Oxford, UK, 1997; Chapter 4, p 151.

well have considerable potential for process optimization and control of supercritical hydrogenation on an industrial scale.

Most of the reactions described above were carried out with a relatively low flow rate of substrate, 0.3−2.0 mL/min. To explore the limitations of substrate throughput, the hydrogenation of 1-octene, **34**, was tested at a considerably higher flow rate, 10.0 mL/min, using the 5-mL reactor filled with 4 mL of the 5% Pd APII Deloxan catalyst, see Table 1. Even at this rate, octane, **35**, was formed quantitatively over periods of up to 4 h without significant degradation of catalyst performance or leaching of Pd metal. Other catalysts which we tried were less successful; powdered Pd/C (Aldrich) blocked the reactor, and Pd leached from Pd/Al_2O_3 (Degussa AG) at higher temperatures.

Cyclohexene, **36**, was tested at even higher flow rates, 20 mL/min, the limit of our current pump. Again, hydrogenation at the highest flow rate remained quantitative over a period of hours. Hydrogenation at this rate represents a high degree of efficiency. Conventionally, the efficiency of a reactor is judged by its liquid hourly space velocity, LHSV (volume of substrate converted per hour by a unit volume of catalyst) or its space−time yield (kg of product/h per cubic meter of catalyst). With a flow rate of **36** of 20 mL/min and 4 mL of 5% Pd on Deloxan, our reactor achieved a very high LHSV (300 h^{-1}) and space−time yield (2.5×10^5 kg h^{-1} m^{-3}). In general, space−time yields are highest for very small reactors where problems of heat removal are much less serious. Therefore it is gratifying to find that our space−time yield is comparable to that calculated for the hydrogenation of fats[22] in a reactor of much smaller volume (7 μL) than ours (5 mL).

The initial impetus for our research, and that of others,[22] was the ability of a supercritical fluid to bring the organic substrate and H_2 into a single homogeneous phase. Supercritical hydrogenation is demonstrably effective, but it is still important to show whether the hydrogenation really does occur in a single phase. We have therefore investigated the hydrogenation of cyclohexene, **36**, to cyclohexane, **9**, in some detail.

The complete reaction involves a quaternary mixture (**36**, **9**, H_2, and CO_2). Fortunately, the critical temperatures of **36** (T_c = 287.3 °C) and **9** (T_c = 280.3 °C) are sufficiently close for the system to be considered as a ternary mixture. Even so, phase investigations of ternary mixtures can be quite involved, but the fact that our reactor runs at constant pressure somewhat restricts the volume of phase space which needs to be investigated. Thus, the temperature (T_{cat}, T_{wall}, T_{out}) was monitored at various points on the reactor, see Figure 8. Figure 9 shows how these temperatures varied as the flow rate of **36** was increased while the total pressure was held constant at 120 bar. At 0.5 mL/min, T_{cat} stabilized at 160 °C while T_{wall} and T_{out} remained at 50 °C. T_{cat} increased rapidly to 340 °C at a flow rate of 2.0 mL/min but then remained constant over a narrow range from 340 to 360 °C as the flow was increased to 10.0 mL/min. At flow rates of 0.5−3.0 mL/min, the highest value of T_{wall} was measured at a point within 0.5 cm from the top of the reactor. As the flow rate increased from 4.0 to 6.0 mL/min, the hottest point moved downwards and then remained at the bottom of the reactor up to the maximum flow rate.

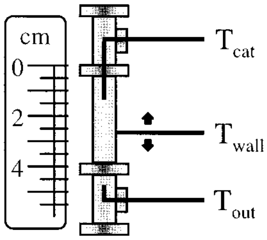

Figure 8. **Schematic view of the 5-mL reactor showing the positions of the three thermocouples, T_{cat}, T_{out}, and T_{wall}. The wall thermocouple could be moved up and down the 5-mL reactor over a distance of 4 cm to locate the position of the hottest zone. When the reactor was used with a heating block, T_{wall} was located in a fixed position in the block itself and its signal was used to maintain the reactor at constant temperature.**

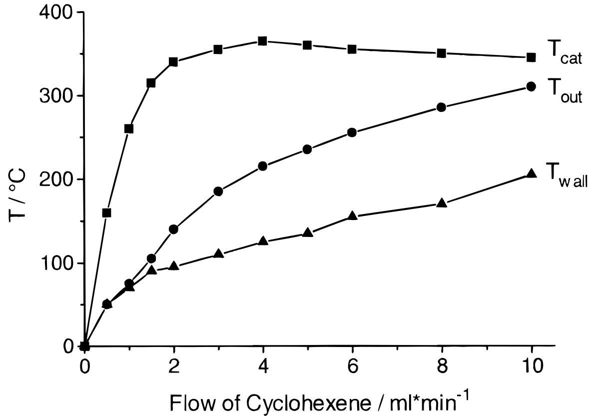

Figure 9. **Plots showing the dependence of temperature as measured by (■) T_{cat}, (●) T_{out}, and (▲) T_{wall} on substrate flow rate. Data were recorded for the hydrogenation of cyclohexene, 36, in $scCO_2$ at 120-bar total pressure with 5% Pd APII Deloxan catalyst (4 mL). The flow rate of 36 was increased from 0.5 to 10.0 mL/min with a 2-fold H_2 excess. The overall gaseous flow rate was held constant at 1.0 L/min (measured at atmospheric pressure). The overall conversion of 36 to 9 remained at 96−98% as analysed by ^{1}H NMR ($CDCl_3$).**

These measurements show that, at the higher flow rates, *the temperature of the catalyst bed is higher than the T_c of **36***. Under these conditions, all of the components are supercritical and therefore the system will be single-phase. However, this will not necessarily be true at lower temperatures, so we have modeled the system to identify the areas of miscibility for the system $CO_2 + H_2$ + cyclohexane and for the system propane + H_2 + cyclohexane at various temperatures and a constant pressure of 120 bar using the Peng−Robinson equation of state.[28,29] The results of such calculations are conventionally represented as a so-called *phase prism*. However, our results are presented in a novel manner, Figure 10. This representation is particularly appropriate for the flow reactor because the regions of miscibility (dark areas) are much easier to visualize than in a phase prism. These calculations show that (a) at any temperature, the miscibility of the system always improves

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(28) Kordikowski, A.; Robertson, D. G.; Poliakoff, M.; DiNoia, T. D.; McHugh, M. A.; Aguiar-Ricardo, A. *J. Phys. Chem. B* **1997**, *101*, 5853.

(29) Peng, D. Y.; Robinson, D. B. *Ind. Eng. Chem. Fundam.* **1976**, *15*, 59.

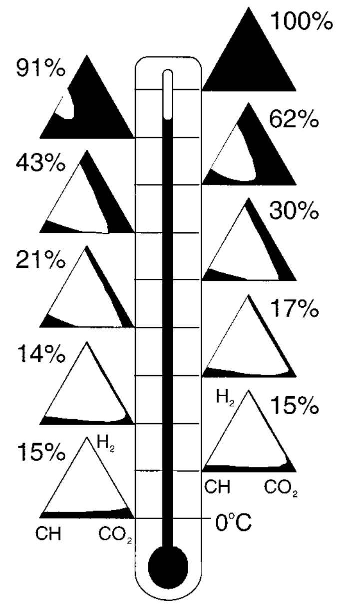
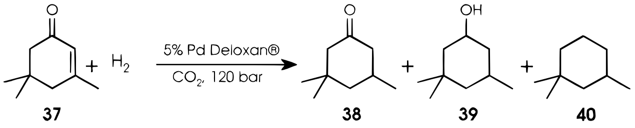


Figure 10. **Pictorial representation of the temperature variation of phase equilibrium for the system cyclohexane + CO_2 + H_2 using so-called "Gibbs triangles" (in steps of 30 °C between 0 and 270 °C). The dark areas represent homogeneous phases (totally miscible) whereas the areas of immiscibility are left white. The figures show the percentage of each triangle occupied by the homogeneous phase. The system was modeled for 120 bar using the Peng–Robinson equation of state. Broadly, similar results were obtained for the system cyclohexane + H_2 + propane.**

Scheme 9. **Hydrogenation of isophorone, 37**



when the concentration of H_2 is reduced; (b) above 60 °C, the regions of miscibility increase as the temperature increases; and (c) at higher temperatures, relatively small amounts of CO_2 are sufficient to ensure miscibility.

The implications are straightforward. If a mixture is homogeneous before the start of the reaction, it will remain so because hydrogenation is an exothermic reaction which consumes H_2. This conclusion will clearly not be true for all reactions; for example, many of the reactions in Table 1 generate H_2O (T_c = 374 °C) as one of the products.[30] Nevertheless, the main point is almost certainly valid for most systems; one of the principal roles of the fluid is to render the substrate and H_2 homogeneous *as they enter the reactor*, and this homogeneity can often be achieved with relatively low concentrations of fluid.

(g) Advantages of Supercritical Reaction. The Hydrogenation of Isophorone, 37. We now apply these ideas to the hydrogentation of isophorone, **37**, a functionalized cyclohexene derivative of commercial interest in the fine chemicals industry (Scheme 9). An important process is the selective hydrogenation of the ring double bond which yields 3,3,5-trimethylcyclohexanone (dihydroisophorone), **38**, which is used as solvent for vinyl resins, lacquers, varnishes, paints, and other coatings.

Most of the hydrogenation processes described in the patent literature either show low overall conversion but high selectivity for **38** or give high conversion with poor selectivity.[31] A process which combines high conversion *and* high selectivity is very desirable because the boiling points of **37**, **38**, and the by-products **39** and **40** are all very close to each other and so purification of **38** by distillation is difficult and costly.

We have found that our continuous supercritical method combines quantitative conversion with high selectivity for **38**. Furthermore, this is achieved without use of conventional solvents, thereby eliminating the need for any work-up of the product. Thus, we were able to hydrogenate **37** in our 5-mL reactor at flow rates up to 2.0 mL/min at 120 bar in $scCO_2$ (0.75 L/min) over the 5% Pd APII Deloxan catalyst. For reactor temperatures <200 °C, the conversion of **37** to **38** was quantitative with no **39** or **40** detectable by ^1H NMR or GC. At higher reactor temperatures, the selectivity dropped and 3,3,5-trimethylcyclohexanol, **39**, and 1,1,3-trimethylcyclohexane, **40**, were also formed. With the 10-mL reactor, the selectivity of hydrogenation could be maintained at flow rates of **37** of ≤7 mL/min. With this flow rate in the reactor, we were able to hydrogenate 7.5 kg of **37** using only 2 g of 5% Pd on Deloxan, and even at the end of the run the catalyst was giving 89% conversion of **37** to **38**. These are much higher rates and selectivities than are usually obtained in the conventional hydrogenation of **37**. Higher flow rates of **37** cause the temperature of the 10-mL reactor to exceed 200 °C. Using a 100-mL reactor,[32] however, we have already achieved continuous hydrogenation of **37** at 30 mL/min. It is interesting that, following the principles of Figure 10, we have shown that **37** can be hydrogenated successfully in our equipment using a mixture which contained 70 mol % of **37** and only a small excess of H_2. Thus, the process uses a relatively small amount of CO_2, a point of considerable economic benefit for future scale-up.

Conclusion

We have described a new approach to selective hydrogenation. The combination of supercritical fluids and continuous flow reactors permits a step change in the scale and range of hydrogenations which can be carried out in the nonspecialist laboratory. Even with a 5-mL reactor, we have reached a throughput which is larger than that needed by most synthetic organic laboratories. Depending on the conditions, the hydrogenation can be *mild and selective* as in the hydrogenation of the C=C bond in isophorone, **37**, or it can be extreme as in the *full hydrogenation* of

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(30) In reactions where H_2O is generated, the product stream from the apparatus usually consists of a mixture of aqueous and organic phases rather than an emulsion.

(31) See, for example: Cotrupe, D. P.; Wellman, W. E.; Burton, P. E. Patent No. US 3446850, **1969**; Patent No. FR 1549722, **1968**. Bueschken, W.; Hummel, J. Patent No. DE 19524969, **1997**.

(32) The 100-mL reactor was used at Thomas Swan & Co. Ltd. (Consett), with a flow system similar to that described in this paper. Although scaling up from a 5-mL to 10-mL reactor presented no problems, scaling up to a 100-mL reactor necessitated the use of internal baffling to prevent an excessively hot flow through the centre of the catalyst bed.

nitrobenzene, **23**, to cyclohexane, **9**, and ammonia. Both hydrogenations can be carried out on the same piece of equipment, occupying the space of only half a fume hood.

All of the reactions described in this paper have involved substrates and products which are liquids at room temperature. This restriction is not chemical but primarily due to the engineering problems of handling solid materials in a flow system. Nevertheless we have shown[25] that solids can be hydrogenated in our apparatus by dissolving them in an organic solvent (e.g., MeOH/THF). This enables the substrate to be pumped into the system, and the product is recovered as a solution. Although this approach is not as environmenally "green" as using pure CO_2, it works quite satisfactorily at least on the laboratory scale.

One of our most important findings is that high flow rates of substrate do not necessarily require high flow rates of CO_2. In the past, many apparently attractive supercritical processes have proved costly to operate because large quantities of CO_2 are required to obtain even modest amounts of product. The reasons why small amounts of CO_2 are needed for these hydrogenations are clear from our investigation of the phase behavior. An additional attraction of this technique is the possibility of recycling the supercritical fluid. Although recycling has been widely applied to supercritical processes,[10] we have not yet attempted to apply it to our hydrogenation reactor.

We are now actively pursuing scale-up. Already, our maximum substrate flow rate with a 10-mL reactor is close to that needed for the production of fine chemicals, and only minor scale-up would be necessary for certain chemical products of commercial interest. Furthermore, our reactor can be applied to other organic reactions. Thus, we have just shown that, with only minor modification, our flow reactor can be used with a solid acid catalyst for supercritical Friedel−Crafts alkylation of aromatics.[33]

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We thank Dr. A. Kordikowski for his help in modeling the phase behavior of cyclohexane/CO_2/H_2. We thank Thomas Swan & Co. Ltd. for fully funding the work at Nottingham and Mr. D. Campbell and Mr. J. C. Toler for their assistance. We are grateful to Degussa AG for donating the catalysts. We thank Dr. M. W. George, Mr. M. Guyler, Dr. S. M. Howdle, Dr. K.-H. Pickel, Mr. K. Stanley, Dr. T. Tacke, and Dr. S. Wieland for their help. M.P. thanks EPSRC and the Royal Academy of Engineering for fellowship support, and F.R.S. thanks EPSRC for a studentship.

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