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SUPERCRITICAL HYDROGENATIONS — USING A NOVEL, INHERENTLY SAFER APPROACH

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The widespread use of supercritical fluids such as CO_2 for process research is hindered by the lack of a safe and cost-effective method of conducting the work in normal research laboratories. This paper presents a solution to this problem. The system involves a novel concept for generating supercritical fluids (especially H_2/CO_2 mixtures) starting from common hydrocarbon liquids (such as formic acid) thus allowing "gas-less" hydrogenation to be performed. This technology not only eliminates the need for high pressure storage requirements but also simplifies the controlled feeding to the reactor of the supercritical fluids. Application of the technology to optimisation of hydrogenation reactions in particular is presented including a discussion of scale-up to commercial size.

INTRODUCTION

Hydrogenation research in recent years has become increasingly more important in many sectors of the chemical industry, for example, in the pharmaceutical and fine chemicals. These reactions are often very slow and the search for catalysts, especially to perform selective hydrogenations, can be time consuming. An attractive option that is widely recognised as having considerable promise is to perform the reactions under supercritical conditions, using $scCO_2$ as the solvent.[1] Despite the promise, relatively little research under these conditions is being performed in industry due to the experimental complexity and not least the hazards associated with the handling of gases (especially H_2) at pressures in the region of 100 bar or more. This article describes a novel technology that is inherently safer,[2,3] and therefore should open the door for more widespread research into this potentially important area of chemistry.

SUPERCRITICAL HYDROGENATION

Heterogeniously catalysed hydrogenation reactions performed batchwise in organic solvents are notoriously slow due to the poor solubility of molecular hydrogen (H_2) in these common solvents. Producing commercially viable processes can require a lengthy search for a highly active or selective catalyst, leading to the proliferation of tools for high throughput catalyst screening. The final results can still be disappointing in terms of one or more of the key measures – yield, selectivity or reaction time. By replacing the more traditional organic solvent with high pressure CO_2 gas together with H_2 under conditions of pressure and temperature, where the gas or gas mixture is supercritical, the results can be improved substantially.[1,4] At these conditions the CO_2 acts as a solvent in which many reagents are soluble;

equally important, H_2 and CO_2 are totally miscible.[5] The result is that H_2 solubility in the reagent is increased by orders of magnitude with potentially huge improvements to the process economics. It is known that the selectivity of many reactions can be increased compared to the same reaction performed either in the gas or liquid phase. This is mainly attributed to the fact that several key reaction parameters, e.g. temperature, pressure and H_2 concentration, can be independently varied with ease.[6]

Another advantage of using $scCO_2$ as solvent is that recovery of the final product is both easy and clean — as soon as the pressure is released, the gas is flashed off and the liquid or solid product can be collected solvent free.[7] This has lead to interest in this as a "green" technology by eliminating the environmental problems associated with more conventional solvents. Of course in practice, the suitability of CO_2 as a solvent will be limited by the solubility with particular substrates and the ease of product recovery will depend on the form of the product.

Bearing in mind that the critical pressure and temperature of CO_2 are 73.75 bar and $31.1°C$ respectively, supercritical hydrogenation reactions are invariably at high pressure. This is where the problem lies, and why research in this field is stifled. Companies are rightly concerned about the hazards of handling gases at high pressures and in addition, the flammability of H_2. The work has to be performed in restricted areas and many chemists are unfamiliar with the safe use of high pressure equipment.

GAS-LESS TECHNOLOGY: DECOMPOSITION REACTOR

The University of Nottingham has developed the concept of generating high-pressure gases at the inlet of a continuous flow reactor vessel, by using common organic liquids as starting materials.[2] This eliminates the need to store, meter and control any gases used for the reaction process, and substantially reduces the complexity of the apparatus whilst reducing the possibility of H_2 leaks.[3] The technique involves decomposing liquids over fixed bed catalytic reactors.

The first important reaction is the decomposition of formic acid, HCO_2H, over 5% Pt catalyst at high temperature:

$$HCO_2H \longrightarrow CO_2 + H_2$$
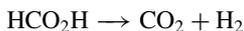
This produces an equi-molar ratio of the two gases, CO_2 and H_2. It is the control of the H_2:substrate ratio that is one of the key variables to successful supercritical hydrogenations.[4] To address this problem, a second liquid, ethyl formate is decomposed over the same catalyst:

$$HCO_2Et \longrightarrow CO_2 + C_2H_6$$

The two liquids are thermally stable at these elevated temperatures in the absence of the catalyst. The mixture of CO_2 and C_2H_6 can be regarded as pseudo-CO_2 because C_2H_6 has similar critical properties to CO_2 (critical temperature of $C_2H_6 = 32.6°C$). Hence, by

adjusting the relative flow rates of the two liquids, the molar ratio of "CO_2":H_2 can be adjusted to any value above 1. Typically, for research scale work, the reactor is a tube of about 5–10 ml in volume loaded with a solid catalyst — this catalyst is adequate for both of the decomposition reactions, which produce the high-pressure gases. Typical liquid flow rates are 1 ml min^{-1} or even less, producing relatively high gas flow rates.

Thus, the creation of a supercritical mixture of H_2/CO_2 is reduced to the pumping of two common liquids into small pieces of heated tubing; the control of flow rate and composition is straightforward and easily adjustable.

Incidentally, if the process requires only supercritical CO_2 (where the reaction is not a hydrogenation) then of course the formic acid feed can be simply omitted.

TYPICAL RESULTS

The first thing to establish is that formic acid does indeed decompose in the manner predicted — because it can act as a hydrogen transfer reagent without its decomposition. This has been confirmed by taking FTIR spectra of formic acid and that of the product gases — see Figure 1. This adequately demonstrates in semi-quantitative terms the fact that the fluid leaving the reactor is the product of decomposition and great accuracy is not implied.

The ease with which the combination of the two fluids can be used to vary the [H_2] to substrate ratio, whilst maintaining a constant fluid flow rate, is illustrated by the hydrogenation of oct-1-yne. The equipment is shown schematically in Figure 2. As it can be seen from Figure 3, the control of [H_2] within the scCO_2 can be achieved by altering the flow
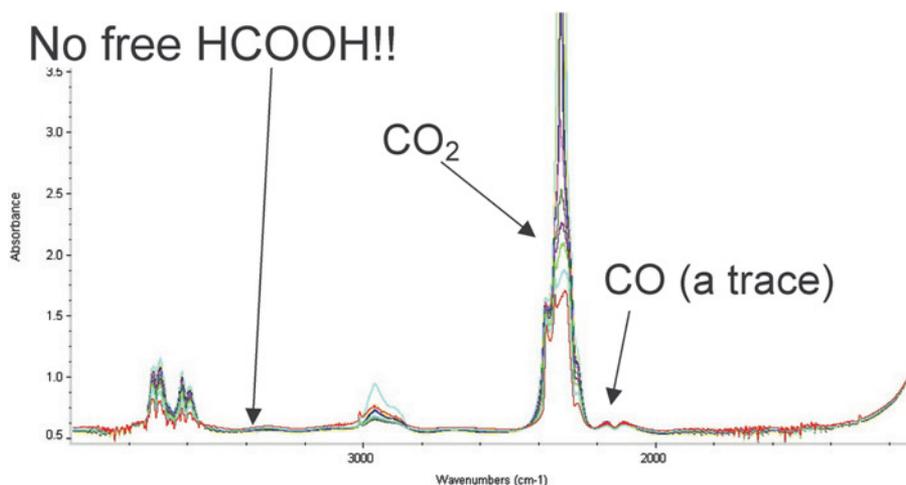
Figure 1. FTIR spectra at exit of HCO_2H reactor showing conversion to CO_2/H_2
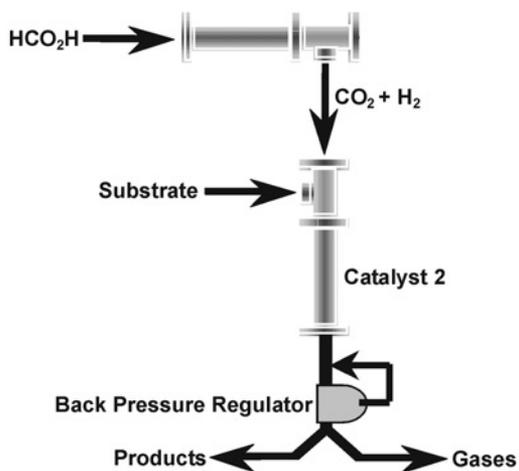
Figure 2. Principle of gas-less hydrogenation system
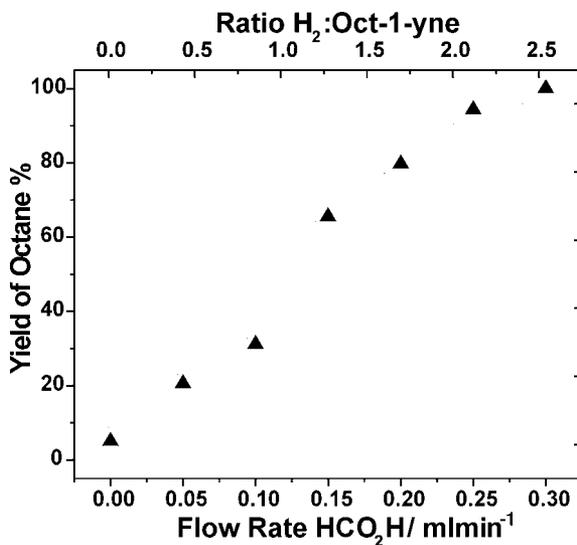
Figure 3. Hydrogenation of oct-1-yne using gas-less method, at constant total flow rate

rates of the two precursor liquids. The total flow rate of SCF liquid precursors was maintained at a constant flow, 0.4 ml min^{-1}, such that the residence time of the substrate was not effected. It is important to stress that the two precursor liquids are decomposed over the *same* catalyst (either Pt or Pd). Therefore tuning the concentration of H_2 does not increase the complexity of the apparatus unduly.[3] We and other authors have previously demonstrated[8] that hydrogenation is possible in scC_2H_6 and, although the solvent properties of the $scCO_2$ and scC_2H_6 mixture will clearly be different from pure $scCO_2$, we believe that these differences are not so large as to mask the overall trends in the reactions. In fact, the hydrogenation of oct-1-yne has been reported previously, and the conditions required to achieve complete conversion to octane, are not dissimilar to those observed in this case.

     Other reactions have been performed to demonstrate the wide variety of hydrogenation reactions that are possible using this methodology. Table 1, includes highlighted/key results. Table 1, also shows results of acid catalysed reactions performed in the fluid produced from the decomposition of ethyl formate alone. It can be seen that simple acid catalysed reactions, such as the cyclisation of 1,4-butandiol, to form the common solvent tetrahydrofuran, perform with identical, if not better yields than the same reactions performed in pure $scCO_2$.[9]

     As stated earlier, the technology is not limited to hydrogenations – any process using $scCO_2$ as a solvent can be investigated. This includes polymerisation, enzymatic reactions and even crystallization.

HYDROGENATION REACTORS

STIRRED REACTORS

Like most of the reactors in the chemical industry, hydrogenation vessels are also CSTR types, in spite of the obvious safety problems associated with large volumes of H_2 at high pressure. In keeping with this tradition, much supercritical fluid work is also performed in stirred reactors. Supercritical hydrogenations involve the pressurisation of the hydrogenation vessel with CO_2 solvent and then addition of hydrogen gas while stirring vigorously. As the hydrogen is consumed, pressure falls and this is restored by the addition of more H_2 gas. In this type of operation, neat H_2 has to be used — if a mixture of CO_2/H_2 were added the inert CO_2 would accumulate.

     This highlights the first limitation of the gas-less technology: the process must be continuous. In the context of a CSTR, there would be continuous purge of gas out of the vessel, as fresh CO_2/H_2 were to be fed, the purge rate would be controlled to hold the pressure constant. In this way the CO_2 can be vented thus making room for fresh H_2 addition to promote reaction. The problem is that there is no way to ensure that the vented gas does not contain H_2 — hence there is no way to be sure of the CO_2/H_2 ratio in the reactor. On the other hand, the addition of CO_2 to the reaction vessel may well increase the overall rate of hydrogenation, as it is known that CO_2 can swell most solvents to form an expanded liquid. This liquid has reduced viscosity, and a will contain a higher volume of H_2 gas dissolved within itself. The reaction may proceed with a higher overall

Table 1. Examples of systems studied using gas-less technology

Reaction	Starting material	Product	%Yield	Flow rate of Formic Acid (ml/min)	Flow rate of Ethyl Formate (ml/min)	Temperature of Catalyst 2 (°C)	Pressure of system (Bar)
1	cyclohexene	cylohexane	100	0.4	0	80	80
2	1-octene	octane	100	0.4	0	80	80
3	1-octyne	octane	100	0.4	0	80	80
4	isophorone	3,3,5 trimethyl cyclohexanone	50	0.4	0	270	120
5	styrene oxide	1-phenylethanol	35	0.4	0	120	120
6	1,4-butanediol	THF	100	0	0.4	180	200
7	*trans*-Cinnamaldehyde	hydrocinamaldehyde	0	0.4	0	100	120
8			90	0.1	0.4	180	200
9	*trans*-Cinnamaldehyde	3-phenyl-1-propenol	0	0.4	0	180	200
10			30	0.2	0.2	180	200
11	1,3,5-trimethylbenzene	1,3,5-trimethyl-isopropylbenzene	45	0	0.4	200	100
12	*meta*-cresol	3,methyl-4-isopropyl phenol	30	0	0.4	200	100
13			25	0	0.4	200	300

rate compared to a non-expanded solvent, but of course kinetic measurements cannot be made in this manner.

Therefore, in the context of stirred reactors, the gas-less hydrogenation technology is only a partial solution: $scCO_2$ can be generated as needed but the H_2 must be obtained in the conventional way, namely from a gas cylinder.

FIXED BED REACTORS

The ideal combination is the gas-less technology followed by a fixed bed reactor. In this design the gases leaving the decomposition reactor are combined with the liquid substrate to be hydrogenated, which are then fed to the inlet of a tubular fixed bed reactor containing the solid catalyst. As the fluids pass over the length of pipe, H_2 is consumed and only CO_2 and the hydrogenated product (plus any side products) emerge at the outlet. A single control valve at the end of the reactor controls the pressure throughout the decomposition and hydrogenation sections (see Figure 2).

As soon as the gas-liquid mixture is flashed to atmospheric pressure, the gas can be vented and the liquid product directly collected from the outlet of the back pressure regulator.

This constitutes the ideal combination — a continuous flow system with fixed bed reactors. The hold-up of both solvent and reagent gas is minimal, and these are generated *in situ*. The reactors are simple catalyst packed pipes; this offers the possibility of supercritical fluid research, hydrogenation and other types of chemistry, with virtually no safety problems. On this scale, precise packing of the tubes with catalyst is not critical and in any case, pre-packed cartridges are available.

The flow sheet for the commercial form of this research unit is shown in Figure 4. It consists of a compact unit that contains the necessary pumps for the both the CO_2/H_2 liquid source and the reagent source — a minimum of two pumps but possibly up to four — plus:

– a packed bed decomposition reactor, complete with temperature sensors and heaters,
– a similar hydrogenation reactor also complete with heating and temperature sensor,
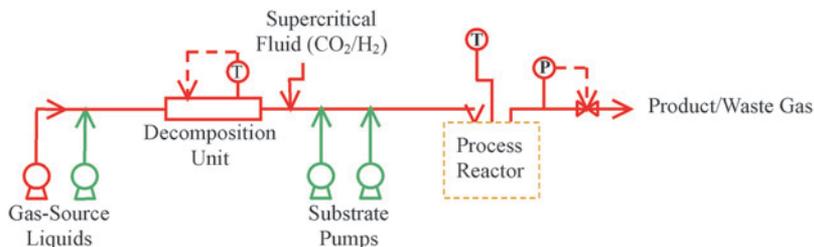
Figure 4. Basic flow sheet for commercial form of "gas-less" technology unit

–   a back-pressure regulator to control the operating pressure
–   a product collection container.

The temperature profile is sufficiently uniform without particular effort to give uniform results, repeatedly.

Also contained in the unit is the set of electronics/software and the computer to control the process (see Figures 5 and 6). Essentially any recipe can be specified and the unit will run for the prescribed amount of time. In fact a series of recipes covering a range of different operating conditions can be entered and the software will run them in sequence. This will permit automatic exploration of a range of parameters — typically, pressure, temperature, H_2/CO_2 ratio — so that optimal conditions can be obtained.

Notice that this range of operations can be run without ever shutting down the unit to change the set up or for cleaning. This also adds to the safety of operations as most accidents arise due to setting up errors.

In order that numerous conditions can be investigated without operator attendance, (allowing high capacity or so-called "24/7" operation) it is necessary to sample the product as the process is changed. This can also be automated — either by automatically sampling the liquid product at specified intervals (and saving the samples for later manual analysis) or else by totally automated analysis that includes sample injection into an LC.

LARGE SCALE PROCESSES
SCALE-UP OF GAS-LESS TECHNOLOGY
It would be possible to generate supercritical gases using larger decomposition reactors, exactly as described above. However, on a strictly cost basis, it is cheaper to buy the
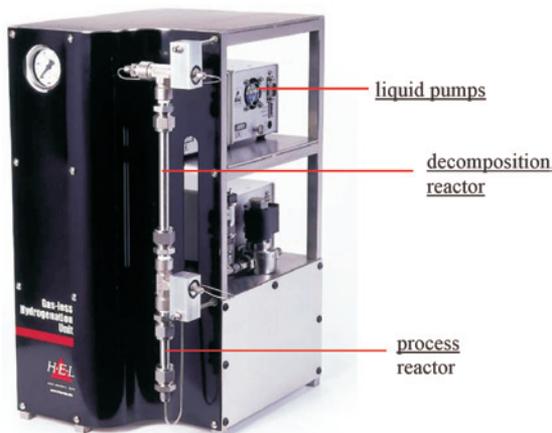
Figure 5. Commercial form of gas-less technology unit (side panel removed)
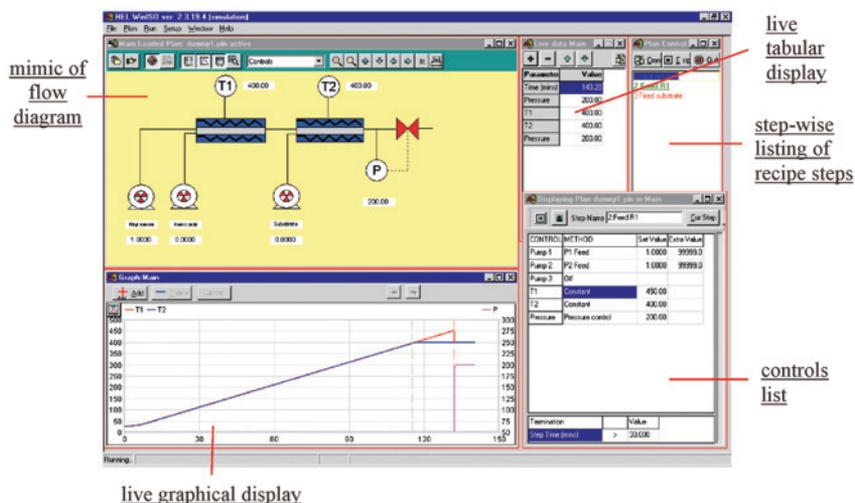
Figure 6. Control software interface for gas-less unit

necessary gases than to decompose formic acid and ethyl formate. It is therefore a matter of economic choice and risk assessment as to when (if at all) the decomposition method becomes inappropriate. However, the initial outlaying cost of a gasless approach is inexpensive compared to the large investment costs of cylinder rental/storage and of course reaction vessel costs.

Regardless of the choice of supercritical fluid source, the process developed — in terms of optimal conditions obtained — will normally be scaleable, based on the key process parameters: selectivity and yield with little modification.

The fact that research was performed on a fixed bed reactor does not limit the design choice for the commercial scale. The choice of reactor type — fixed bed or stirred vessel is still open. If convention dictates that the production be in a stirred vessel, it is relatively simple to translate the research data obtained on a fixed bed reactor. Clearly, in such cases, some confirmation at an intermediate-scale will be useful but this would be fairly routine rather than extensive.

Much more interesting is the fact that the large reactor could also be tubular, similar to the design used in the research, thus allowing almost direct scale-up of the research data and taking full advantage of the safety and flexibility afforded by such a design. The move towards continuous processes from semi-batch has long been recognised as being highly desirable — not least for safety reasons — so this is an opportunity that is difficult to ignore.

CONTINUOUS LARGE SCALE HYDROGENATION PROCESS[10]

The use of a fixed bed reactor for continuous, large-scale hydrogenation has been demonstrated by Thomas Swan,[10] who recently built a 100 kg/hour (~1000 tonne/year) pilot plant.[11] The system (see Figure 7) has been demonstrated to successfully reproduce the laboratory scale data for the hydrogenation of isophorone to trimethyl cyclohexanone (TMCH). This was selected as a demonstration reaction because a conventional process leads to a mixture of TMCH and over-hydrogenated by-products. These by-products not only reduce yield but also introduce separation costs if pure TMCH is needed.

On the laboratory scale (~7 ml/minute) after suitable selection of conditions, TMCH was produced with 100% selectivity using supercritical CO_2 as a solvent. Several catalysts were tested and for one of them the range of operating conditions that gave optimal results is shown in Table 2, as well as a comparison with the plant data. Clearly there is excellent agreement between the two sets of results; note also the degree of flexibility in the process conditions that still gives 100% yield.

The TMCH product from the plant also exceeded the initial specification on all "quality" parameters (such as colour, assay and acid value) without the need for any downstream processing (except degassing of CO_2).
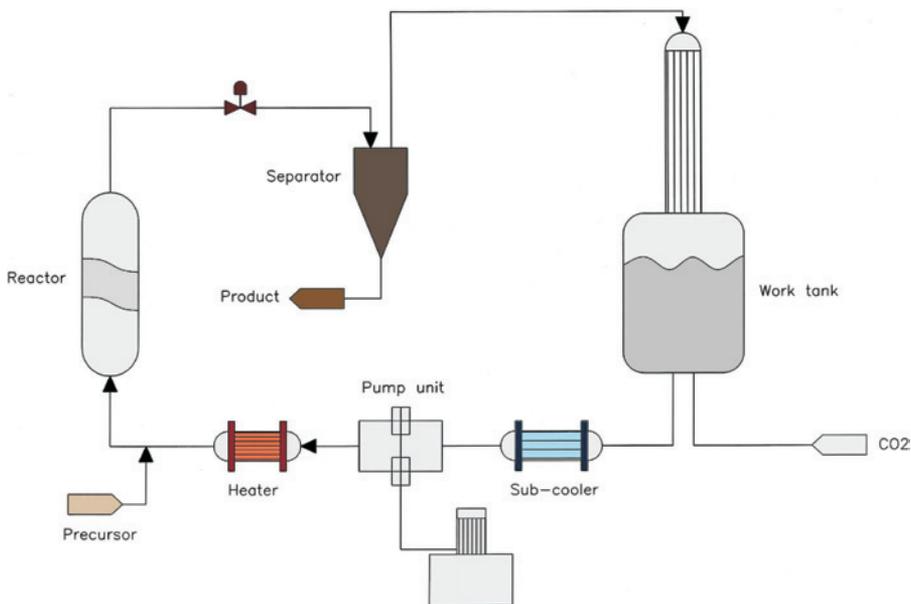
Figure 7. Schematic of Thomas Swan pilot scale fixed bed, continuous flow hydrogenation system

Table 2. Optimised conditions for hydrogenation of TMCH[11]

	Laboratory	Plant
Reactor Size	0.85 cm i.d., 25 cm long	Commercially sensitive
Catalyst	2% Pd	2% Pd
Temperature	Inlet 56°C outlet 100°C	Isothermal 104–116°C
$H_2/scCO_2$ ratio	1.7 to 2.75	1.7
Substrate feed	2 to 48 wt%	9 to 17 wt%

The successful 400-fold scale-up of a difficult reaction shows that the gas-less technology has a huge potential benefit for supercritical research because the results are repeatable on large scale plant.

CONCLUSIONS

The attraction of operating at supercritical conditions for difficult reactions, such as hydrogenations, can now be researched safely in conventional laboratories without the need for special safety features. At the laboratory scale this technology lends itself to fixed bed continuous operation, but the results can then be applied to fixed bed or stirred reactors, operating in batch or continuous mode. The equipment is available as a totally automated compact unit that can run unattended, going through any selected range of process conditions leading to an optimised process.

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