SUPERCRITICAL HYDROGENATIONS — USING A NOVEL, INHERENTLY SAFER APPROACH

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The widespread use of supercritical fluids such as CO₂ 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 H₂/CO₂ 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 scCO₂ 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 H₂) 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 (H₂) 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 CO₂ gas together with H₂ 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 CO₂ acts as a solvent in which many reagents are soluble;
equally important, H₂ and CO₂ are totally miscible.⁵ The result is that H₂ 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 H₂ concentration, can be independently varied with ease.⁶

Another advantage of using scCO₂ 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 CO₂ 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 CO₂ 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 H₂. 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 H₂ leaks.³ The technique involves decomposing liquids over fixed bed catalytic reactors.

The first important reaction is the decomposition of formic acid, HCO₂H, over 5% Pt catalyst at high temperature:

\[
\text{HCO}_2\text{H} \rightarrow \text{CO}_2 + \text{H}_2
\]

This produces an equi-molar ratio of the two gases, CO₂ and H₂. It is the control of the H₂: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:

\[
\text{HCO}_2\text{Et} \rightarrow \text{CO}_2 + \text{C}_2\text{H}_6
\]

The two liquids are thermally stable at these elevated temperatures in the absence of the catalyst. The mixture of CO₂ and C₂H₆ can be regarded as pseudo-CO₂ because C₂H₆ has similar critical properties to CO₂ (critical temperature of C₂H₆ = 32.6°C). Hence, by
adjusting the relative flow rates of the two liquids, the molar ratio of “CO₂”:H₂ 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 H₂/CO₂ 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 CO₂ (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 [H₂] 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 [H₂] within the scCO₂ can be achieved by altering the flow

![Figure 1. FTIR spectra at exit of HCO₂H reactor showing conversion to CO₂/H₂](image-url)
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 main-
tained 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 demon-
strated$^8$ that hydrogenation is possible in scC$_2$H$_6$ and, although the solvent properties of
the scCO$_2$ and scC$_2$H$_6$ 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 hydro-
genation 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 hydrogen-
ation 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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Starting material</th>
<th>Product</th>
<th>%Yield</th>
<th>Flow rate of Formic Acid (ml/min)</th>
<th>Flow rate of Ethyl Formate (ml/min)</th>
<th>Temperature of Catalyst 2 (°C)</th>
<th>Pressure of system (Bar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclohexene</td>
<td>cyclohexane</td>
<td>100</td>
<td>0.4</td>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>1-octene</td>
<td>octane</td>
<td>100</td>
<td>0.4</td>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1-octyne</td>
<td>octane</td>
<td>100</td>
<td>0.4</td>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>isophorone</td>
<td>3,3,5 trimethyl cyclohexanone</td>
<td>50</td>
<td>0.4</td>
<td>0</td>
<td>270</td>
<td>120</td>
</tr>
<tr>
<td>5</td>
<td>styrene oxide</td>
<td>1-phenylethanol</td>
<td>35</td>
<td>0.4</td>
<td>0</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>1,4-butanediol</td>
<td>THF</td>
<td>100</td>
<td>0</td>
<td>0.4</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td><em>trans</em>-Cinnamaldehyde</td>
<td>hydrocinamaldehyde</td>
<td>0</td>
<td>0.4</td>
<td>0</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>8</td>
<td><em>trans</em>-Cinnamaldehyde</td>
<td>3-phenyl-1-propenol</td>
<td>90</td>
<td>0.1</td>
<td>0.4</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>9</td>
<td><em>trans</em>-Cinnamaldehyde</td>
<td>3-phenyl-1-propenol</td>
<td>0</td>
<td>0.4</td>
<td>0</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>10</td>
<td>1,3,5-trimethylbenzene</td>
<td>1,3,5-trimethyl-isopropylbenzene</td>
<td>30</td>
<td>0.2</td>
<td>0.2</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>11</td>
<td><em>meta</em>-cresol</td>
<td>3,methyl-4-isopropyl phenol</td>
<td>30</td>
<td>0</td>
<td>0.4</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td><em>meta</em>-cresol</td>
<td>3,methyl-4-isopropyl phenol</td>
<td>25</td>
<td>0</td>
<td>0.4</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>13</td>
<td><em>meta</em>-cresol</td>
<td>3,methyl-4-isopropyl phenol</td>
<td>25</td>
<td>0</td>
<td>0.4</td>
<td>200</td>
<td>300</td>
</tr>
</tbody>
</table>
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: scCO₂ can be generated as needed but the H₂ 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, H₂ is consumed and only CO₂ 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 super-critical 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 CO₂/H₂ 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](image_url). 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, H₂/CO₂ 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
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.

Figure 6. Control software interface for gas-less unit
CONTINUOUS LARGE SCALE HYDROGENATION PROCESS\textsuperscript{10}

The use of a fixed bed reactor for continuous, large-scale hydrogenation has been demonstrated by Thomas Swan,\textsuperscript{10} who recently built a 100 kg/hour (\textasciitilde{}1000 tonne/year) pilot plant.\textsuperscript{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 (\textasciitilde{}7 ml/minute) after suitable selection of conditions, TMCH was produced with 100\% selectivity using supercritical CO\textsubscript{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\textsubscript{2}).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Schematic of Thomas Swan pilot scale fixed bed, continuous flow hydrogenation system}
\end{figure}
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.

**REFERENCES**


**Table 2.** Optimised conditions for hydrogenation of TMCH

<table>
<thead>
<tr>
<th></th>
<th>Laboratory</th>
<th>Plant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor Size</td>
<td>0.85 cm i.d., 25 cm long</td>
<td>Commercially sensitive</td>
</tr>
<tr>
<td>Catalyst</td>
<td>2% Pd</td>
<td>2% Pd</td>
</tr>
<tr>
<td>Temperature</td>
<td>Inlet 56°C outlet 100°C</td>
<td>Isothermal 104–116°C</td>
</tr>
<tr>
<td>H₂/scCO₂ ratio</td>
<td>1.7 to 2.75</td>
<td>1.7</td>
</tr>
<tr>
<td>Substrate feed</td>
<td>2 to 48 wt%</td>
<td>9 to 17 wt%</td>
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</tbody>
</table>