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Chapter 8

Catalysis Using Supercritical or Subcritical Inert Gases under Split-Phase Conditions

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Compressed CO_2 and other gases can serve as media for catalysis in a number of different ways. While use of such gases as supercritical fluids (SCFs) under single-phase conditions has been studied intensively over the past decade, the use of inert gases under split phase conditions has received less attention. Having a condensed phase such as water, an ionic liquid, or even a solid below a SCF allows one to perform reactions combined with simultaneous or subsequent separation of product from catalyst or excess reagent. Performing a reaction in a condensed phase below a subcritical gas allows one to modify the reaction behaviour by adjusting the choice of inert gas or pressure of the gas. Examples of these possibilities are described, with an emphasis on applications to homogeneous hydrogenation and phase-transfer catalysis.

There has been a great deal of attention paid recently to the use of supercritical fluids as substitute media for chemical reactions (*1*), including catalytic reactions (*2,3*). Much of this research has focused on the use of single-phase conditions (particularly for homogeneous catalysis), because it is thereby easier to establish that the reaction is taking place in the supercritical phase. However, for practical purposes it may be preferable to perform the reaction under split-phase (i.e. biphasic) conditions. This paper summarizes several studies of reactions performed in this manner.

Liquid/SCF biphasic systems, where the liquid is essentially insoluble in the SCF, have many advantages over single-phase SCF media, including the ability to separate the catalyst from the product and the ability to use catalysts which have poor solubility in common SCFs. In liquid/SCF biphasic systems, the SCF can be used to deliver the starting material to and/or extract the product from the lower phase. The reaction can be performed while the SCF is present, or if the substrate is soluble in the lower phase then the SCF need not be introduced until the reaction is complete. In either case, it is preferable that the catalyst be soluble only in the lower phase and that the lower phase solvent be insoluble or nearly insoluble in the SCF.

Solid/SCF biphasic systems, which often require a phase-transfer catalyst, allow reactions between a SCF-insoluble reagent and a SCF-soluble reagent. The product can then be isolated, uncontaminated by the SCF-insoluble reagent. In some cases, tuning of the SCF can lead to the extraction of kinetic products, which prevents further conversion to the undesired thermodynamic product.

In solid/gas or liquid/gas biphasic systems, the upper phase is a subcritical inert gas which has insufficient density to dissolve any of the reagents (other than reagent gases). The inert gas is used to modify the properties of the condensed phase in some manner which accelerates the reaction or improves the selectivity. The possibility that subcritical gases can affect reactions in this manner has only recently been discovered.

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Liquid/SCF Biphasic Systems

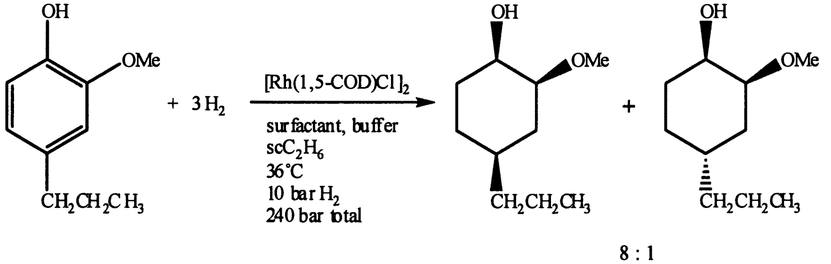
Aqueous/SCF biphasic medium. There are several types of biphasic catalysis currently being used or investigated (Table 1). Each of these systems has inherent advantages and disadvantages. The aqueous and fluorous systems have the disadvantage that the catalyst must be modified to make it hydrophilic or fluorophilic. The fluorous/organic and organic/organic systems have partitioning problems, meaning that the catalyst can have substantial solubility in the upper phase. This leads to significant activity loss after the upper product-containing phase is removed. The organic-containing systems have environmental problems, including the cost of the disposal of the organic solvent, and the cost of separating the organic solvent from the product. Many

Table 1. Biphasic solvent systems being used for catalytic transformations.

Lower phase	Upper phase	Catalyst modification	Leading references
H_2O	Organic	water-soluble	9
H_2O	SCF	water-soluble	4
Fluorous	Organic	fluorous	10,11
Ionic liquid	Organic	none	12-14
Ionic liquid	SCF	none	15
Organic	Organic	none	16

of these problems can be solved or ameliorated by switching to SCFs as the upper phase solvent, usually with water as the lower phase. This approach has now been used for a variety of types of catalysts, including homogeneous (*4,5*), enzymatic (*6,7*), and now colloidal catalysts (*8*).

Rhodium colloids are known to be particularly active catalysts for the hydrogenation of benzene derivatives (*17*). In collaboration with James (at British Columbia), we explored the possibility of using Rh colloids for arene hydrogenation in aqueous/SCF biphasic media (*8*). The test substrate, 2-methoxy-4-propylphenol, was selected because it is a model for some of the phenolic groups in lignin which are notoriously difficult to reduce. The hydrogenation proceeded readily in an aqueous/scC_2H_6 medium (Scheme 1, 88% conversion, substrate:Rh ratio of 50:1, at conditions shown in caption to Figure 1) but did not proceed at all in an aqueous/scCO_2 medium, probably because of the pH-drop in the liquid phase (Figure 2). The hydrogenation of other arenes in aqueous/scC_2H_6 medium was also achieved, even with arenes with negligible solubility in water (conversion shown in Figure 1). The hydrogenation of 2-methoxy-4-propylphenol gave primarily *cis*-2-methoxy-*cis*-4-propylcyclohexanol, with only 10% of the *cis*-2-methoxy-*trans*-4-propylcyclohexanol isomer. The hydrogenation of 4-phenyl-2-butanone had 98% selectivity for hydrogenation at the arene ring only.



Scheme 1. The hydrogenation of an arene in scC_2H_6/H_2O. The products were obtained as racemates

Ionic liquid/SCF biphasic medium. We have seen how the problem of acidity in the aqueous phase of an aqueous/scCO_2 phase can be fatal to a catalyst such as colloidal rhodium. Some other catalysts such as Ru complexes with sulfonated phosphines perform well under such acidic conditions (*4*). However, for those catalysts which are pH sensitive, one would desire an alternative. One possibility is the use of an aqueous/scC_2H_6 medium, which solved the problem for the Rh colloidal catalyst. However, both from an environmental and from a safety standpoint, it would be preferable to use scCO_2 as the upper phase. Therefore a new lower phase is necessary; a lower phase which, like water, is immiscible with scCO_2. Ionic liquids (ILs) such as [bmim]PF_6 (structure **1**) have been found to function in this role.

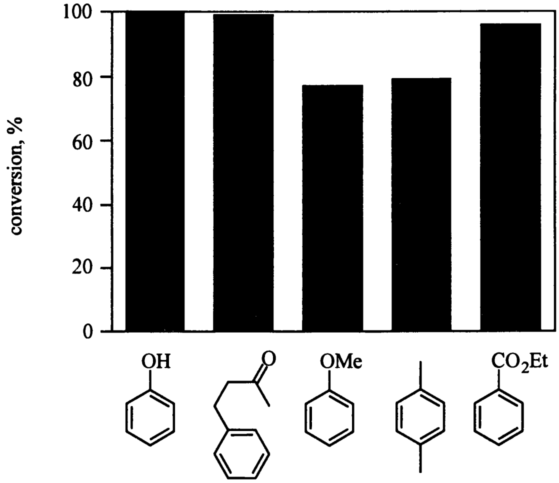


Figure 1. The extent of hydrogenation of arenes in an aqueous/scC$_2$H$_6$ medium. Conditions: 36°C, 62 h, 31 mL vessel, 240 bar (10 bar H$_2$, balance ethane), 9.5 μmol [RhCl(1,5-COD)]$_2$, 76 μmol [NBu$_4$]HSO$_4$], 1.7 mL buffer(0.1 M Na$_3$PO$_4$ buffer) and 1.9 mmol arene. Data from reference 8.

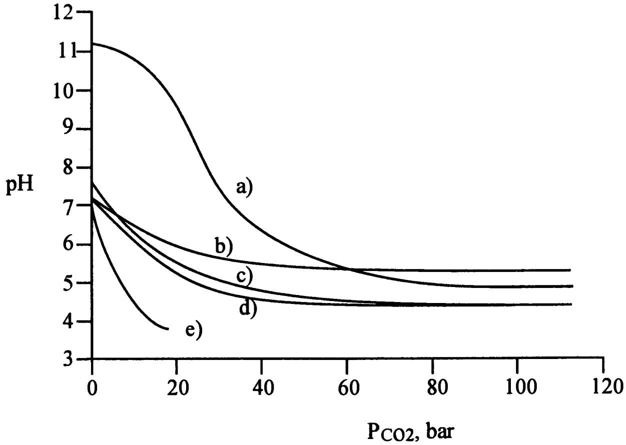
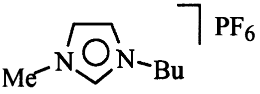


Figure 2. Dependence of the pH of aqueous buffer solutions on the pressure of CO$_2$ at 36°C in the presence of 9 bar H$_2$;(8) a) 0.5 M Na$_3$PO$_4$ buffer (0.05 M citric acid, 0.2 M boric acid), b) 1.0 M MOPS buffer (3-[N-morpholino]propane-sulfonic acid hemisodium salt), c) 0.1 M Na$_3$PO$_4$ buffer (0.05 M citric, 0.2 M boric), d) 0.1 M MOPS, and e) unbuffered water (pH 2.9 at high CO$_2$ pressure (18)). Reproduced by permission of The Royal Society of Chemistry.



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The work of the groups of Brennecke and Beckman (*19*) showed that although CO_2 is soluble in [bmim]PF_6 (0.6 mole fraction CO_2 in the IL phase at 80 bar), the IL is not soluble in the $scCO_2$ (less than 10^{-5} mole fraction IL in the $scCO_2$ phase at 138 bar and 40°C). This observation makes it possible for IL/$scCO_2$ biphasic reactions with extraction of the product by $scCO_2$ and with no contamination of the product by IL.

Several types of catalysts have been used for hydrogenation reactions in IL (in the absence of CO_2), including several molecular catalysts ($RhCl(PPh_3)_3$ (*13*), $RuCl_2(PPh_3)_3$ (*20*), $[bmim]_3[Co(CN)_5]$ (*20*), and $[Rh(nbd)(PPh_3)]PF_6$ (*12*)) for alkene hydrogenation, a cluster catalyst, $[H_4Ru_4(\eta^6\text{-}C_6H_6)_4][BF_4]_2$, for arene hydrogenation (*21*), and a chiral catalyst, $[RuCl_2(BINAP)]_2{\bullet}NEt_3$, for asymmetric hydrogenation (*22*). The last report piqued our interest, especially because the cost of the catalyst makes recycling more appealing, and because the authors reported that the enantioselectivity was pressure independent, a most surprising finding. We chose to test this kind of reaction in combination with $scCO_2$ extraction of the product (*15*)(*45*).

The chiral catalyst $Ru(O_2CMe)_2$((*R*)-tolBINAP) is soluble and active in [bmim]PF_6. While Monteiro et al. (*22*), the authors of the asymmetric hydrogenation study, used atropic acid as their substrate, we chose tiglic acid (Scheme 2), because the enantioselectivity of tiglic acid hydrogenation is usually optimum at low hydrogen concentrations and diffusion rates (atropic acid requires the opposite) (*23*). We anticipated that ILs, which because of their high viscosity should have low diffusion rates, would allow higher enantioselectivity for substrates with those requirements. Indeed, the enantioselectivity of the asymmetric hydrogenation of tiglic acid was higher (*15*) than that found by Monteiro et al. or ourselves for the hydrogenation of atropic acid or its derivatives (Scheme 2, Fig. 3). Also, the enantioselectivity was found to be hydrogen-pressure dependent for tiglic acid. The water content of the ionic liquid was found to have no effect on the enantioselectivity. Extraction of the product, 2-methylbutanoic acid, with $scCO_2$ was efficient (90% recovery), and no IL or catalyst was observed in the extracted product. Recycling of the catalyst/IL solution by addition of fresh tiglic acid and H_2 lead to greater, not lower, enantioselectivity (Figure 3). The manner in which the catalyst solution was recycled is illustrated in Scheme 3. Note that there was no need to modify the catalyst with sulfonated or fluorous groups, as there would have been with aqueous or fluorous biphasic solvent systems.

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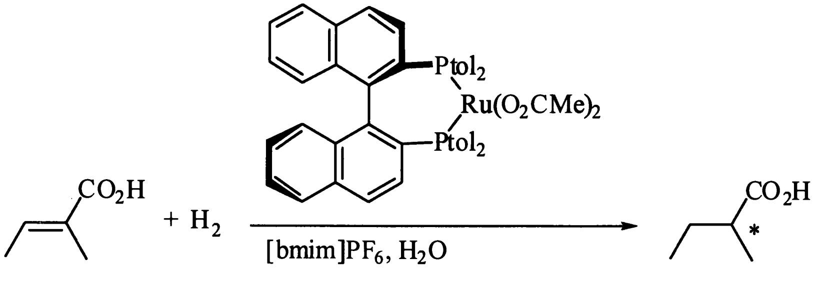

Scheme 2. The hydrogenation of tiglic acid in ionic liquid. The chiral centre in the product is indicated by an asterisk.

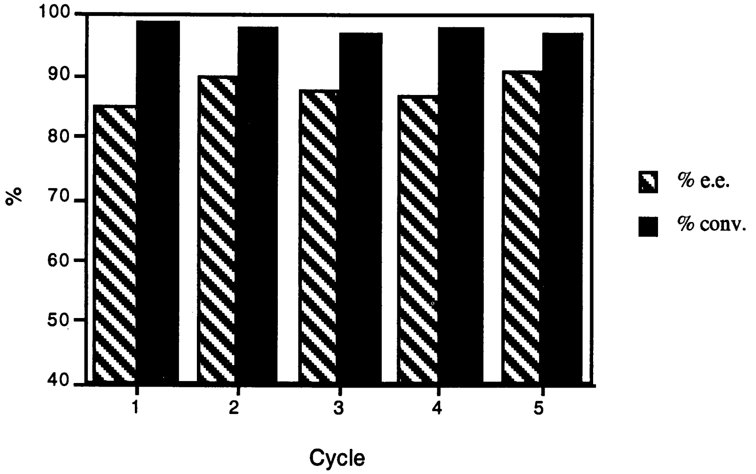

Figure 3. The selectivity and activity for tiglic acid hydrogenation of recycled solutions of Ru(O_2CMe)$_2$(tolBINAP) in [bmim]PF$_6$ (15). During the fifth cycle, the reaction solution was not stirred..

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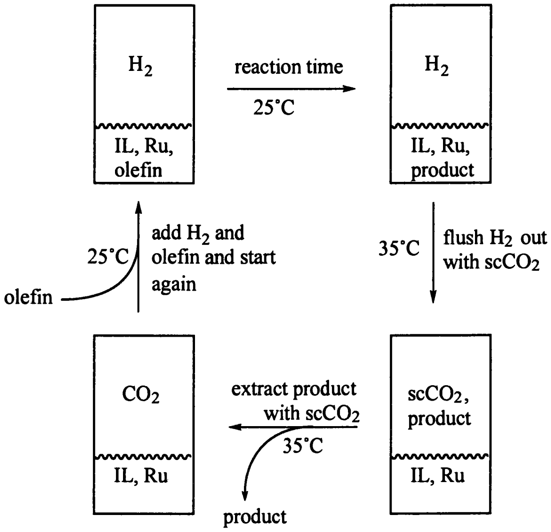

Scheme 3. An illustration of the method for the recycling of ionic liquid/catalyst solutions.

Solid/SCF Biphasic Systems

Solid/SCF reactions mediated by phase-transfer catalysts. Phase-transfer catalysts (PTCs) have been employed as a means of facilitating reaction between solid salts and organic reactants that are present in a supercritical fluid phase. We have investigated several types of reactions in these systems, including halogen exchange, cyanide displacement, and base-promoted alkylation.

Phase-transfer catalysts are molecules with characteristics that give rise to an affinity for both ionic and organic environments. The most common are quaternary ammonium salts, which have organic character derived from the alkyl chains attached to the quaternized nitrogen, but also exhibit behavior characteristic of salts, such as ion exchange. This makes possible the phase-transfer-catalytic cycle, depicted in Figure 4. The diagram shows an inorganic salt, M^+Y^-, that is in contact with a SCF phase containing the organic reactant, R-X. The PTC, Q^+X^-, first exchanges anions with the salt, making a complex that is then able to react with the organic reactant to yield the product and regenerate the catalyst (*24*).

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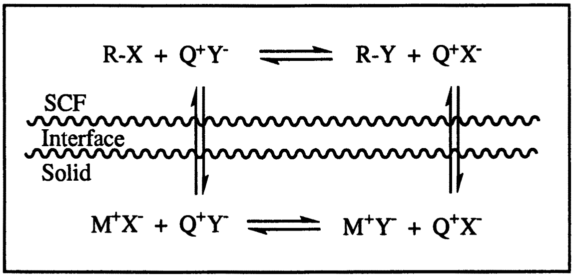
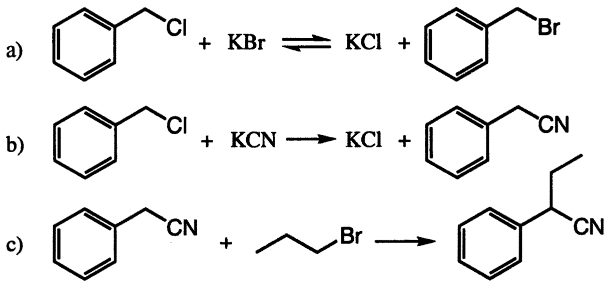


Figure 4. The phase-transfer-catalytic cycle.

The first example of PTC incorporated in a SCF system was the reversible halogen exchange between benzyl chloride and potassium bromide to yield benzyl bromide (*25*) (Scheme 4a). The reaction was performed in $scCO_2$ at 50-75°C and 130-200 bar, with tetrahexylammonium chloride as the catalyst.

Another similar reaction that has been studied is the cyanide displacement on benzyl chloride, producing phenylacetonitrile (*26*) (Scheme 4b). This reaction was also carried out in CO_2 at 138 bar, with temperatures at 60°C and 75°C. Tetraheptylammonium chloride was the catalyst, and acetone was used as a cosolvent.



Scheme 4

A third type of phase-transfer-catalyzed reaction that has been investigated in a SCF system is the base-promoted ethylation of phenylacetonitrile in scC_2H_6 (*27*) (Scheme 4c). This reaction could not be performed in CO_2 due to a complicating side reaction. It was also performed at both 60°C and 75°C and at 138 bar, with potassium carbonate as the base and tetrabutylammonium bromide as the phase-transfer catalyst.

The behavior of these reactive systems indicates that the intrinsic reaction is actually taking place on the surface of the solid salt particles rather than in the continuous fluid phase. This assumption is made based on the behavior observed in the reaction of benzyl chloride to phenylacetonitrile.

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Although the amount of catalyst was well above the measured solubility limit in $scCO_2$, the rate of reaction continued to increase linearly with the amount of catalyst added to the system. It is therefore believed that the reaction is taking place in a catalyst-rich layer on the surface of the salt particles, termed an "omega-phase."

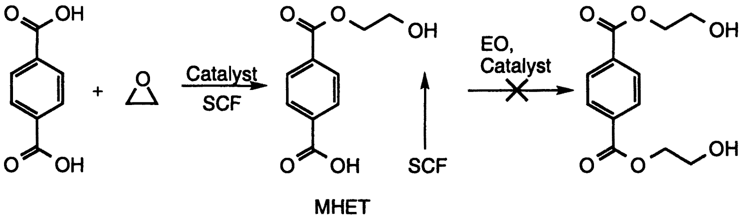
The activity of the catalysts at concentration levels above their solubility limits facilitates separation of the products from the catalyst. Sufficient catalyst may be used to make reaction rates fast, and then the organic product may be removed from the solids with the SCF, leaving behind the PTC, which may then be recycled. The insolubility of traditional PTCs in $scCO_2$ allows the formation of products that are free from catalyst contamination, which is of paramount interest in the pharmaceutical industry.

Biphasic reaction with simultaneous separation. The dissolving power of SCFs can be easily tuned with density (or cosolvents) to selectively solubilize reaction products without dissolving reactants and catalysts. In addition to the easy solvent removal by depressurization, SCFs provide a substantial advantage over traditional liquid solvents that may indiscriminately solubilize the reactant and catalyst along with the product requiring subsequent separations.

This tunable dissolving power of SCFs provides opportunities to couple a biphasic reaction and a separation in a single process unit. For example, SCFs can be used to remove soluble intermediate products as they are formed before subsequent reaction to unwanted byproducts can take place.

This type of reactive separation has been used in a new synthesis of a precursor to poly(ethylene) terephthalate (PET). Using the precursor, mono 2-hydroxyethyl terephthalate (MHET), offers superior chemical processing as compared to conventional PET production from ethylene glycol and terephthalic acid by reducing heat- and mass-flux loads in the polymerizer, increasing the rate of the polymerization reaction, and reducing the required water removal by half.

MHET was synthesized by the esterification of terephthalic acid (TA) and ethylene oxide (EO) in the presence of a quaternary ammonium salt catalyst. The desired MHET was removed from the involatile bed of terephthalic acid by continuous extraction with supercritical fluid before subsequent reaction to the diester could take place (*28*) (Scheme 5). The SCF, dimethyl ether (Tc = 126.9°C, Pc = 52.4 bar), was tuned with temperature and pressure to readily solubilize and remove the MHET from the bed without also solubilizing the quaternary ammonium salt catalyst or terephthalic acid. A solid mixture (0.2 g) of 95 mol % terephthalic acid and 5 mol % catalyst was loaded into a 6 mm diameter reaction thimble for each experiment. The reaction was run at 130 °C and 70 bar with 0.5 mol % ethylene oxide with respect to dimethyl ether. At a sufficient flowrate of dimethyl ether (5 ml/min pumped at 25 °C and 70 bar), 100 % selectivity to MHET was obtained.



Scheme 5. Selective ethoxylation of terephthalic acid

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Solid/Gas or Liquid/Gas Biphasic Systems

Swelling of liquids. In the last two parts of this article, the effect of subcritical inert gases on reactions will be described. When a SCF is used at pressures below its critical pressure, it is no longer technically a SCF but rather a subcritical gas. It has densities too low for it to dissolve any catalysts or reagents other than reagent gases. Organic reagents in the same vessel as a subcritical gas will exist as a condensed phase (liquid or solid) at the bottom of the vessel. If the subcritical gas is chemically inert, then it can only influence the reaction in the condensed phase by dissolving into the condensed phase and modifying the physical properties of the condensed phase.

There is scattered evidence in the literature that subcritical gases can modify the physical properties of condensed phases. The most obvious change is in the volume of a liquid phase when CO_2 pressure is applied. 1,4-dioxane expands more than 12 fold in volume when 71 bar CO_2 is present (*29*). This swelling or expansion of the liquid phase by a subcritical gas is accompanied by other changes:

- The solubility of hydrogen in liquid pentane (15 bar H_2 partial pressure, 50°C) is only 0.012 mol fraction. However, addition of 55 bar of CO_2 causes the H_2 mole fraction solubility of H_2 in the liquid phase to jump 40% (*30*).
- The dielectric constant of pure methanol is 32.6,(*31*) while that for a liquid phase mixture of methanol and CO_2 (78.6 mol% methanol, 35°C, 41.2 bar pressure) is only 25.6 (*32*).
- The normal melting point of p-dichlorobenzene is 53°C, but under 50 bar of C_2H_4 gas, the melting point of the solid drops to 30°C (*33*).
- For the system CO_2/acetone, mutual diffusion coefficients in the liquid phase are predicted to double as the pressure of CO_2 is raised from 10 bar to 70 bar (*34*).

Whether or not an inert subcritical gas can have an effect on the rate of a reaction in a liquid phase was the subject of a study on homogeneous hydrogenation of CO_2 (*35*). The rate of hydrogenation of CO_2 in a liquid NEt_3/MeOH mixture was studied as a function of gas pressure. While increasing the CO_2 pressure increased the rate, this was likely due to the fact that CO_2 was a reagent and may not have been due to the liquid expansion caused by the CO_2 pressure. In order to test the effect of the liquid expansion, inert gases were added (Table 2). When subcritical ethane was added, the rate dropped dramatically. This is believed to be a result of a drop in the dielectric constant of the liquid phase, because a rate drop was also observed if liquid hexane was added. Adding subcritical fluoroform gas did not cause a rate drop, probably because it has a significantly larger dipole moment. In fact, a small but statistically significant rate increase was observed with fluoroform. These results demonstrate that the presence of an inert gas in the upper phase can have a marked effect on the rate of reactions taking place in the lower, condensed, phase.

$$CO_2 + H_2 + {}^1\!/_2NEt_3 \xrightarrow{RuCl(O_2CMe)(PMe_3)_4} {}^1\!/_2[HCO_2H]_2NEt_3$$

Table 2. Effect of inert gas on the rate of CO_2 hydrogenation in liquid MeOH.[a]

Added gas (bar)	Yield[b]	TON[c]	TOF[c], h^{-1}
none	0.32	390	770
ethane (40)	0.072	79	160
fluoroform (40)	0.40	455	910
fluoroform (50)	0.40	450	900

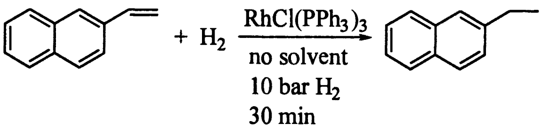
SOURCE: Reproduced with permission from reference 35.

[a] Conditions: 50 °C, 0.5 h reaction time, 31 mL vessel, 40 bar H_2, 10 bar CO_2, 2.5 mmol MeOH, 3.6 mmol NEt_3, 3.0 μmol $RuCl(O_2CMe)(PMe_3)_4$.

[b] Moles of HCO_2H per mole of NEt_3; maximum theoretical yield is 2.0.

[c] TON = turnover number = mol HCO_2H per mol of Ru complex. TOF = turnover frequency = mol HCO_2H per mol of Ru complex per hour.

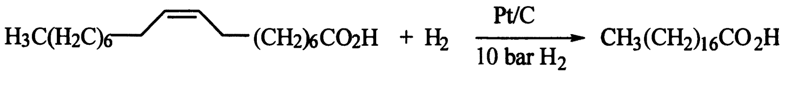
Induced Melting of Solids. Solventless reactions are, environmentally speaking, preferable to reactions with solvents. However, reactions of solids in the absence of a solvent are notoriously slow (there are exceptions (*36*)). We have found that the ability of subcritical gases to lower melting points of organic solids can accelerate some reactions. For example the hydrogenation of solid vinylnaphthalene (mp=62-65°C) (*37*) catalyzed by solid $RhCl(PPh_3)_3$ (Scheme 6) at 33°C is greatly accelerated by the addition of subcritical gaseous CO_2 (*38*).



	% conv.	
T,°C	no CO_2	56 bar CO_2
33	0	52
36	5	73

Scheme 6. The effect of CO_2 pressure on the hydrogenation of 2-vinylnaphthalene (38).

Similarly, reactions that form solid products can be difficult to perform without a solvent because the reaction mixture freezes as the reaction approaches completion. For example, the Pt/C-catalyzed hydrogenation of liquid oleic acid (mp = 13-16°C) (*39*) to form solid stearic acid (mp = 69-70°C) (*40*) at 35°C proceeds readily until 90% conversion is reached. Thereafter no further conversion is obtained, even after 25 h. In the presence of 60 bar CO_2, however, the reaction reaches 97% conversion after only 1 h.



The reason for the rate or yield enhancement is believed to be the melting-point-lowering effect of the subcritical inert gas. This can be explained with reference to the binary phase diagram for a binary mixture of a subcritical gas (component 1) and an organic solid (component 2) having a triple point higher than the critical point of component 1 (Figure 5a). The critical point of the inert gas is shown as C_1 and the solid line extending to the left of that point is the boiling curve for component 1. The phase diagram of the organic solid is shown in solid lines on the right side (notice the triple point Tr_2 and critical point C_2). The lowest temperature at which component 2 could normally melt is its triple point. In the presence of CO_2 or another inert gas, the melting point of the condensed phase (the organic compound with CO_2 dissolved therein) moves along the dotted SLV line towards the UCEP (upper critical end point). Thus the lowest temperature at which the condensed phase could melt is the temperature of the UCEP. Some solid/inert gas binary mixtures such as p-dichlorobenzene/ethylene and menthol/ethylene have no such UCEP (*33*) and thus the melting point lowering can be even greater. The composition of the liquid and vapor phases can be determined from an isothermal slice of the phase diagram, as shown in figure 5b.

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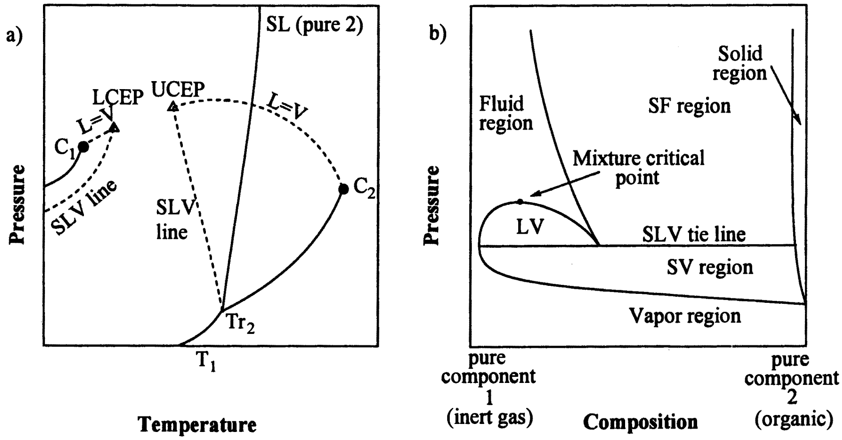

Figure 5. a) The P/T projection of a binary phase diagram (41-44) for a binary mixture of a gas such as CO_2 or C_2H_4 and an organic solid with a triple point higher than the critical point of the gas. b) An isothermal slice of the binary phase diagram at temperature T_1, illustrating the presence of an LV region (a region in which liquid and vapor phases coexist).

Conclusions

Research in the field of reactions in supercritical fluids has been changing from an emphasis on single-phase conditions to a broader approach that includes biphasic conditions. The use of aqueous/SCF or ionic liquid/SCF biphasic catalysis offers an environmentally more benign alternative to the more established methods of aqueous/organic or fluorous/organic biphasic catalysis. Phase-transfer catalysis in solid/SCF biphasic systems allows for clean separation of products from excess reagents and for selective extraction of kinetic products from the solid phase. Finally, we have demonstrated that subcritical pressures of inert gases can alter the rates of reactions taking place in condensed phases. The inert gas affects the rate of the reaction by dissolving in the condensed phase and altering the physical properties of that phase, including its dielectric constant or its melting point.

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