

## FEATURE ARTICLE

## Sustainable Reactions in Tunable Solvents

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There are now available a variety of tunable solvents; these have been used extensively for extractions and in a variety of materials applications. Our focus has been to apply these techniques to chemical reactions to take advantage of the special properties available, primarily for sustainable technology, to create processes that are potentially more benign and more advantageous. We report here our work in using supercritical fluids, near-critical fluids, and gas-expanded liquids to couple organic reactions with separations. In this paper, we review applications involving improved transport, catalyst recycling, and product separation as well as the in situ generation of catalysts. Although such tunable solvents are in no way a panacea, they do offer the chemical community alternatives that can often be applied creatively to many reaction opportunities.

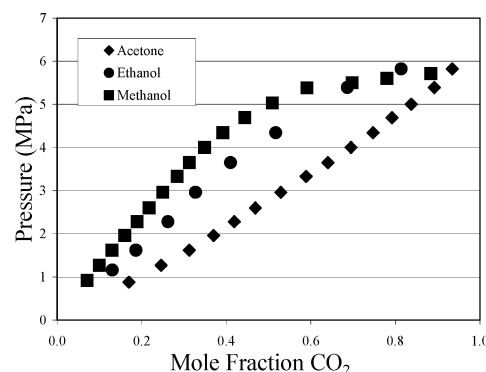
## Background

Green chemistry is good, but it is not enough. For industry to use green chemistry, there must be additional advantages—the need to comply with new government (or industry) mandates, the desire for improved public perception, or the amelioration of regulatory requirements. Most often, however, the overriding issue is process economics. We work for sustainable technology, often described as leaving the planet in better shape for our children and grandchildren, but we define it as a combination of greener chemistry and improved economics.

Any chemical process inevitably involves a reaction followed by a separation or purification of the product. Usually from an economic point of view most of the capital and operating costs are in the separation, typically about 60–80%. Thus, improvements in the reaction alone have limited economic benefit. What we describe here is the use of nontraditional, greener tunable solvents to couple the separation with the reaction and maximize the process benefits. The examples we shall discuss are supercritical fluids (SCF), especially CO<sub>2</sub> (scCO<sub>2</sub>), near-critical water (NCW), and CO<sub>2</sub> in gas-expanded liquids (GXLs).

Many reviews have been written on the advantages of scCO<sub>2</sub> for both extractions and reactions.<sup>2</sup> In general, the advantages of such processes include vastly improved mass transfer and simplicity of solvent removal. Generally, somewhat volatile substrates and products are soluble in scCO<sub>2</sub> at 10 to 30 MPa pressure but, especially if water is present, may require capital-intensive stainless steel pressure vessels. Solubilities are often less than in liquids, and completely involatile compounds and catalysts are rarely soluble.

The use of hot water (NCW) in the range of 200–350 °C was pioneered in the classic work of Siskin and Katrisky<sup>3</sup> and has been continued by many others.<sup>4–6</sup> NCW has a much lower dielectric constant than ambient water and will dissolve both ionic species and slightly polar organics—even benzene and toluene have upper critical solution points around 305 °C.<sup>1</sup>



**Figure 1.** Bubble-point curves for CO<sub>2</sub> with acetone, ethanol, and methanol at 25 °C.<sup>3</sup>

Separations are often as simple as cooling and decanting the organic layer. Moreover, the ion product of water ( $K_w$ ) increases by 3 orders of magnitude around 260 °C,<sup>1</sup> giving increased concentrations of hydronium and hydroxyl ions.

Gas-expanded liquids (GXLs) are a new and benign class of liquid solvents that may offer many advantages for separations, reactions, and advanced materials. GXLs are intermediate in properties between normal liquids and supercritical fluids both in solvating power and in transport properties, and these properties are highly tunable by simple pressure variations. GXLs are formed by the dissolution of a gas, usually CO<sub>2</sub>, in organic liquids. In general, liquid CO<sub>2</sub> is a poor solvent whereas typical organics such as acetone and methanol are good solvents, so a range of solvation properties is easily accessible. Thus, a combination of the low-pressure advantages in liquid CO<sub>2</sub> (vs scCO<sub>2</sub>) and the cosolvent advantages in scCO<sub>2</sub><sup>7,8</sup> exists for GXLs. At moderate pressures (3 to 8 MPa), gaseous CO<sub>2</sub> has considerable solubility in many organic solvents, including alcohols, ketones, ethers, and esters (Figure 1). This provides the opportunity to alter the physicochemical properties of the liquid solvent, most notably the polarity, dielectric constant, and

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gas solubility.<sup>9–11</sup> Moreover, CO<sub>2</sub> is an ideal antisolvent because it is both easy to remove and recycle and environmentally benign.

Gas-antisolvent (GAS) crystallization has been the most common application of GXs to date.<sup>12,13</sup> One of the most attractive features of a GAS system is the potential to nucleate crystals throughout the solution. In a traditional crystallization, cooling is employed to supersaturate the system, inducing nucleation and growth of crystals. The major drawback of cooling is a reliance on heat transfer from a surface, which can lead to nucleation only at the cooler surface. With a GAS system, supersaturation occurs homogeneously throughout the solution, and nucleation may also occur uniformly.

Crystallization using compressed CO<sub>2</sub> has been used to form a variety of particles,<sup>14</sup> for drug delivery,<sup>12,15</sup> the deactivation of explosives,<sup>16</sup> and to produce antibacterial nanoparticles.<sup>17</sup> GAS techniques have also been employed to perform a number of separations. Organic acids<sup>18</sup> and  $\beta$ -carotene<sup>19</sup> have been purified by crystallization from solution. GXs (sometimes called “enhanced fluidity liquids”) have also been used as HPLC mobile phases to perform a number of separations in reversed-phase HPLC,<sup>20</sup> size-exclusion chromatography,<sup>21</sup> and chiral separations utilizing a chiral HPLC column.<sup>22</sup>

There has been recent interest in utilizing GXs as a reaction solvent to take advantage of the increased gas solubility.<sup>23,24</sup> For example, oxidations of substituted phenols have been demonstrated in CO<sub>2</sub>-expanded organic solvents.<sup>24</sup> We have also used GXs in our laboratories, using the tunability to separate and recycle homogeneous catalysts.<sup>25–29</sup>

The separation and recycling of homogeneous catalysts has enormous implications for sustainable technology. Homogeneous catalysts are generally more active and more selective than heterogeneous catalysts; furthermore, they preclude any need for mass transport of reactants and products to and from the site. They are especially useful for chiral syntheses because they almost always result in superior enantiomeric excesses. However, a major barrier to their use is that they are often very expensive and/or toxic—they must be separated from the products.

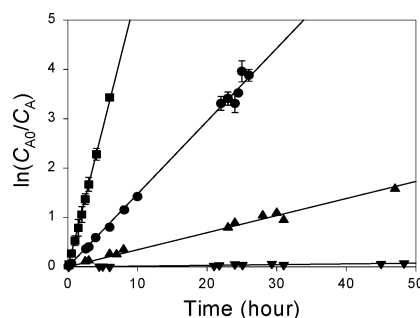
Many researchers have tried various strategies to ameliorate this limitation, for example, tethering the catalyst, and many of these are effective in certain situations. What we relate here is a phase equilibrium approach: run the reaction homogeneously in a single phase and then cause a phase separation to give a heterogeneous system for product recovery and catalyst recycling.

Another issue for many reactions is to choose a solvent system that permits the dissolution of all reactants as well as catalysts. Often one of these is hydrophobic and one is hydrophilic. We and others have used tunable solvent systems to deal with these issues, such as phase-transfer catalysis and near-critical water. We recently extended this treatment to the use of GXs. Other researchers have explored similar tunable solvent mixtures, such as CO<sub>2</sub> with ionic liquids<sup>30</sup> and CO<sub>2</sub> with water in emulsions<sup>31</sup> and microemulsions.<sup>32</sup>

Finally, we also have used the in situ formation of catalysts in tunable solvents. We have used the increased acidity (and basicity) of NCW for a variety of reactions.<sup>6,33,34</sup> But in addition, we have formed catalysts in GXs where the CO<sub>2</sub> is both solvent and reactant—methylcarbonic acid from methanol/CO<sub>2</sub><sup>25</sup> and peroxycarbonic acid from hydrogen peroxide/CO<sub>2</sub>.<sup>35</sup>

### Phase-Transfer Catalyst Reactions in Supercritical Fluids

Supercritical fluids are usually benign alternatives to conventional organic solvents that may offer improvements in



**Figure 2.** Pseudo-first-order kinetics at 75 °C and 138 bar with 5 mol % acetone: (▼)  $8.8 \times 10^{-6}$  mol catalyst (solubility limit); (▲)  $1.6 \times 10^{-4}$  mol catalyst; (●)  $4.0 \times 10^{-4}$  mol catalyst; (■)  $1.6 \times 10^{-3}$  mol catalyst.

reaction rate, product selectivity, and product separation. Here we review the results of the first use of SCFs for phase-transfer catalysis (PTC), where these benign alternatives also offer greatly improved transport, product separation, catalyst recycling, and facile solvent removal.

PTC is a powerful and widely used technique for conducting heterogeneous reactions between two or more reactants in two or more immiscible phases.<sup>36,37</sup> Traditionally, polar aprotic solvents have been used to dissolve the reactants into a single phase where reactions may be carried out homogeneously. However, these solvents are frequently expensive, environmentally undesirable, and difficult to remove from the reaction products. PTC eliminates the need for these homogeneous solvents by employing a phase-transfer catalyst to transfer one of the reacting species from one phase into a second phase where reaction can occur.

Generally, PTC involves the transfer of an ionic reactant from an aqueous or solid phase into an organic phase across an interfacial area, where it reacts with a nontransferred reactant. Once the reaction is complete, the catalyst must transport the ionic product back to the aqueous or solid phase to start a new catalytic cycle. The most common catalysts in PTC are quaternary ammonium salts,<sup>37</sup> which are inexpensive and separated from the reaction products by water extraction. In both liquid–liquid and solid–liquid PTC, a three-phase PTC system can occur if the phase-transfer catalyst has limited solubility in both phases.

We reported the first examples of PTC reactions in supercritical fluids—the nucleophilic displacement of benzyl chloride with the bromide ion<sup>38</sup> and the cyanide ion.<sup>39</sup> These reactions were chosen as model reversible and irreversible S<sub>N</sub>2 reactions. The next two reactions reported were the alkylation and cycloalkylation of phenylacetonitrile.<sup>40,41</sup>

Catalyst solubility in the SCF was very limited, yet the rate of reaction increased linearly with the amount of catalyst present. Figure 2 shows data for the cyanide displacement of benzyl bromide, and the rate data followed pseudo-first-order kinetics and were not reversible. The catalyst amounts ranged from 0.06 (solubility limit) to 10% of the concentration of the limiting reactant, benzyl chloride.

These results suggested that the reaction mechanism involved the formation of a catalyst-rich third phase in which the reaction actually occurred. The data seem to be consistent with the concept of the reaction occurring in an interfacial phase called an “omega phase,” which has previously been found to be important in other PTC reactions.<sup>42</sup> Figure 3 shows this phase at the interface between the solid PTC and the SCF phase, where the SCF transports substrate in and product out while the reaction occurs in the catalyst-rich omega phase, which is

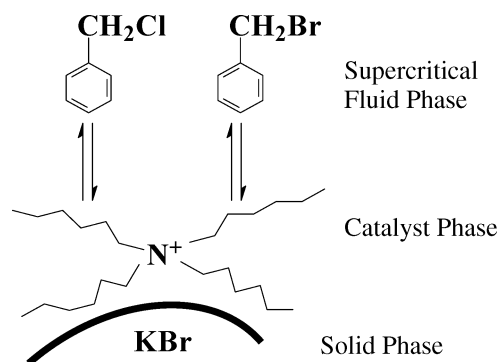
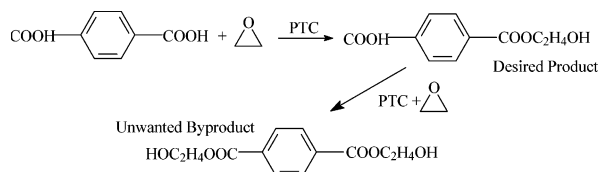


Figure 3. Suggested PTC reaction mechanism in an omega phase.

**SCHEME 1: Interruption of Reaction Sequence by SCF Extraction to Produce Intermediate Product**



sufficiently organic to solubilize the reactant but also sufficiently polar for ions. Because the reaction is generally limited by contact between reactants and catalyst, the SCF offers a diffusivity that is about 2 orders of magnitude better than that of a liquid. Although this reaction could be run homogeneously in a polar organic such as DMSO, solvent removal is a tremendous problem; with CO<sub>2</sub>, this issue is trivial.

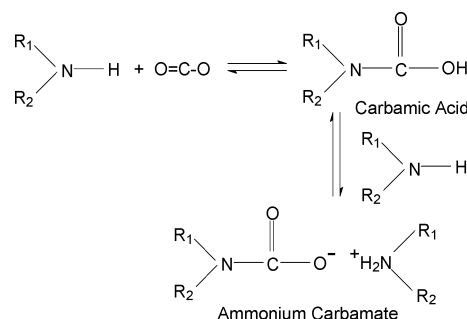
Another manner in which SCFs can be used advantageously for reactions is in the removal of intermediate products or in the protection of products to prevent the formation of undesired byproducts. One example is the use of supercritical dimethyl ether (DME) to stop a series of reactions by removing the product.

Poly(ethylene terephthalate) (PET) can be produced from an atypical monomer, mono(2-hydroxyethyl terephthalate) (MHET). This polymerization is superior to the current process, which uses ethylene glycol and terephthalic acid (TA) because of the lower heat-flux and mass-flux loads in the polymerizer and the removal of only half the water that occurs in the conventional polymerization. In this work, MHET was synthesized from the esterification of TA and ethylene oxide (EO) in the presence of a quaternary ammonium salt catalyst. The catalyst and the diacid are quite involatile, but the desired product ester, MHET, is more volatile and was continuously extracted by supercritical DME before a second esterification could occur (Scheme 1).<sup>43</sup> This is possible because DME has about the same polarity and basicity as acetone and as such is a far superior SCF to other candidates such as CO<sub>2</sub> or propane.

**CO<sub>2</sub> as a Protecting Group**

The chemistry of CO<sub>2</sub> can be used to protect an intermediate by preventing further reaction. We have shown that gas-expanded liquids under CO<sub>2</sub> pressure are unique media for amine formation and separation (Scheme 2). In the heterogeneous hydrogenation of benzonitrile and phenylacetone with NiCl<sub>2</sub>/NaBH<sub>4</sub> in CO<sub>2</sub>-expanded ethanol, the primary amines are protected by CO<sub>2</sub> so that the yield of the primary amines is greatly increased and the production of the secondary amines is effectively suppressed. In the homogeneous hydrogenation of benzonitrile and phenylacetone with RhH[P(<sup>*i*</sup>Pr)<sub>3</sub>]<sub>3</sub> and benzophenone imine with Rh(cod){P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>2</sub>PF<sub>6</sub> in CO<sub>2</sub>-

**SCHEME 2: Formation of Carbamic Acid and Ammonium Carbamate between Amines and CO<sub>2</sub>**



**TABLE 1: Primary Amine Yield Improvement by Protecting Agents or CO<sub>2</sub> (30 bar) in the Phenylacetone Hydrogenation Reaction Catalyzed by Sodium Borohydride with Nickel Chloride in Ethanol at 30 °C<sup>a</sup>**

protecting agents	time/h	secondary amine yield (%)	primary amine yield (%)
without protection	1	87 (86)	<0.01
	20	99 (99)	<0.01
acetic anhydride	24	0.91	92 (94)
di- <i>tert</i> -butyl dicarbonate	24	0.12	99 (99)
carbon dioxide (30 bar)	24	0.15	97

<sup>a</sup> Yield data in parentheses were measured by Caddick and coworkers with excess sodium borohydride in methanol at room temperature.<sup>46</sup>

expanded THF, the primary amines are separated in situ in the form of solid carbamic acids and/or ammonium carbamates with increased yield while the catalysts remain in the solution. CO<sub>2</sub> offers the possibility of protecting the primary amine in the form of carbamic acid and/or ammonium carbamate. These carbamate species release CO<sub>2</sub> upon gentle heating,<sup>44,45</sup> which simplifies deprotection and further separation in comparison with protection by acylation.

To demonstrate this, we carried out the hydrogenation reactions of benzonitrile and phenylacetone with NiCl<sub>2</sub>/NaBH<sub>4</sub><sup>46</sup> in ethanol and CO<sub>2</sub>-expanded ethanol (30 bar) at 30 °C. In these nitrile hydrogenation reactions with addition of the protection agents, the yield of the primary amines was greatly increased, and the production of the secondary amines is effectively suppressed, as shown in Table 1. Acetic anhydride and di-*tert*-butyl dicarbonate protect the primary amine from reacting with the intermediate imine species by acylation reactions of the primary amine and CO<sub>2</sub> by formation of carbamic acid and ammonium carbamate with the primary amine. As for increasing the primary amine yield, the effect of CO<sub>2</sub> is comparable to those of acetic anhydride and di-*tert*-butyl dicarbonate but easily reversible. These results demonstrate the potential for using modest pressures of CO<sub>2</sub> to facilitate reactions as well as to separate products.

**Recycling of Homogeneous Catalysts**

Homogeneous catalysts possess many advantages over heterogeneous catalysts, such as higher activities and selectivities. However, the recovery of homogeneous catalysts is often complicated by difficulties in separating these complexes from the reaction products. The expense of these catalysts (particularly asymmetric catalysts) makes their recovery and reuse imperative. This factor has encouraged the use of less active, but easy to separate, heterogeneous catalysts by the chemical processing industry.

We have developed several techniques using CO<sub>2</sub> as a "miscibility switch" to turn homogeneous phase behavior "on"





**0.1 MPa CO<sub>2</sub>      3.2 MPa CO<sub>2</sub>      3.3 MPa CO<sub>2</sub>**

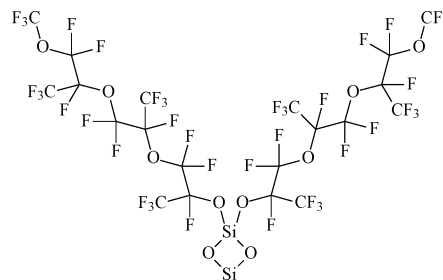
**Figure 4.** CO<sub>2</sub> used to homogenize an organic (toluene, clear liquid) and a fluororous (FC-75, colored liquid) phase. The fluororous phase is colored because of a dissolved cobalt catalyst. Note the slight coloration of the organic phase (middle panel), indicating extensive mutual solubility just prior to miscibility.

and “off”. The goal is to create a medium for performing homogeneous reactions while maintaining the facile separation of a heterogeneous system.

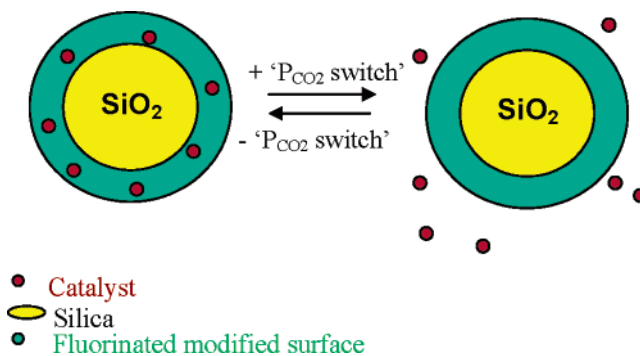
One example of this behavior is the addition of CO<sub>2</sub> to fluororous biphasic systems.<sup>47,48</sup> Fluororous biphasic chemistry<sup>49–53</sup> is an alternative solvent concept for reactions and separations. In this system, a homogeneous catalyst is modified with fluorinated ligands, imparting preferential solubility in the fluororous phase of a biphasic system. The mutual immiscibility of fluororous and organic solvents<sup>54–59</sup> provides an opportunity for facile separations of reaction components and the reuse of homogeneous catalysts that must be recycled for reasons of toxicity and/or cost. However, mass transfer limitations in biphasic systems can limit the overall reaction rate. In systems containing nonpolar solvents such as toluene or cyclohexane, it is often possible to increase the temperature to induce miscibility.<sup>49</sup> However, for more polar or thermally labile substrates this is not a viable option because the consolute point is much higher than 100 °C.<sup>60,61</sup> Thus, any polar reactants must be diluted into a nonpolar solvent, introducing a volatile organic solvent into the process. Further, for nonpolar organics, the solubility of the fluororous compound in the organic at ambient temperature is appreciable and results in expensive and environmentally undesirable losses on separation. All of this precludes industrial application of fluororous biphasic systems.

Instead of heating, a homogenizing agent such as benzotri-fluoride<sup>62</sup> (BTF) can be added to the biphasic mixture to induce miscibility. However, BTF is an expensive agent, and its recovery is not trivial. Alternatively, CO<sub>2</sub> can be used to induce miscibility of fluorocarbon–hydrocarbon mixtures (Figure 4), even those involving polar compounds such as methanol.<sup>48</sup> When this homogeneous reaction is complete, depressurization induces a phase split, with the catalyst available for recycling in the fluororous phase and the product ready for purification in the organic phase.

We have shown<sup>48</sup> that a variety of organic solvents are made miscible with fluorocarbon solvents by CO<sub>2</sub>. Thus, CO<sub>2</sub> acts as a cosolvent used to create a homogeneous, CO<sub>2</sub>-rich phase in which fluorophilic catalysts are readily soluble and active (Figure 4). This CO<sub>2</sub> miscibility switch was demonstrated on two model reactions: the hydrogenation of allyl alcohol to form *n*-propanol and the epoxidation of cyclohexene. In each of these experiments, a fluororous-soluble catalyst was dissolved in a fluororous solvent and added to a system containing a neat organic reactant phase. The high solubility of gases<sup>53</sup> in fluororous liquids (and some CO<sub>2</sub>-expanded liquids) creates particular interest in



**Figure 5.** Schematic of the surface of the silica beads.



**Figure 6.** Schematic representation of the fluororous silica concept. In the absence of CO<sub>2</sub>, the catalyst partitions onto the fluororous silica surface. In the presence of CO<sub>2</sub>, the catalyst partitions into the bulk liquid phase where reaction takes place.

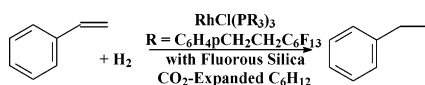
these types of reactions. In both cases, the addition of enough CO<sub>2</sub> to merge the phases markedly increased the average turnover frequency (TOF, mole of product produced per mole of catalyst per time) relative to that of the biphasic system.<sup>48</sup>

Although these examples illustrate the effectiveness of the CO<sub>2</sub> switch for enhancing the catalytic activity of fluororous biphasic reactions, fluorinated solvents remain both expensive and environmentally undesirable. To remove these limitations, we tried using the CO<sub>2</sub> miscibility switch without the fluorinated solvent. We found that the expansion of an organic solvent by the application of CO<sub>2</sub> pressure increases the fluorophilicity of the solvent to such an extent that the solvent is able to dissolve highly fluorinated complexes.<sup>29</sup> This phenomenon made it possible to recrystallize such complexes for the purposes of purification or X-ray crystallography. The phenomenon can also be used as a miscibility trigger in fluororous biphasic catalysis with no fluororous liquid, analogous to the work of Gladysz<sup>63,64</sup> using a temperature switch, but in our efforts the crystallization of a pure catalyst phase from depressurization was unsatisfactory. Therefore, we have explored the use of fluororous silica as a solid support for “capturing” the fluorinated catalysts. We have covalently bonded fluororous “tails” of about 500 daltons to the silica surface (Figure 5) to create a surface “phase” of highly fluororous character.

The fluororous silica concept involves the selective partitioning of a fluororous-modified catalyst between an organic liquid phase and the fluorinated surface phase. In the absence of CO<sub>2</sub>, the fluorinated catalyst “prefers” the fluororous surface phase and remains partitioned onto the silica. When CO<sub>2</sub> pressure is added, the catalyst will partition off of the silica and into the GXL phase (containing reactants), where reaction can take place. After the reaction is completed, the CO<sub>2</sub> is removed, and the catalyst will partition back onto the fluororous silica surface, which can be easily recovered by filtration. A cartoon schematic of this process is shown as Figure 6.

To demonstrate the feasibility of this concept, we first determined the extent of reversible partitioning of fluorinated

### SCHEME 3: Hydrogenation of Styrene with Modified Wilkinson's Catalyst



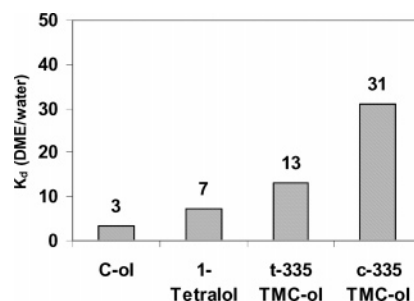
compounds or complexes on and off of the fluorous silica support upon the expansion of the solvent with CO<sub>2</sub>.<sup>47</sup> For a slightly fluorophilic molecule, bis(perfluorooctyl)benzene, the distribution coefficient (ratio of concentration in the bulk fluid phase to concentration on the surface) in polar solvents such as acetonitrile was altered from 0.125:1 to 45:1 by adding modest CO<sub>2</sub> pressures (20–50 bar). For a more fluorophilic compound (a perfluoropolyether complex), the distribution coefficient can be changed from 0.01:1 in pure cyclohexane to 99:1 in CO<sub>2</sub>-expanded cyclohexane, a change of 4 orders of magnitude.

The fluorous silica technology was tested<sup>47</sup> on the catalytic hydrogenation of styrene where the fluorous silica phase consisted of a fluorinated version of Wilkinson's catalyst deposited onto the surface of the fluorous silica. The organic phase consisted of styrene dissolved in cyclohexane. No fluorous solvent was used. H<sub>2</sub> and then CO<sub>2</sub> pressure were applied, forming a gas-expanded organic phase. The fluorinated catalyst then partitioned off of the fluorinated silica support and into the CO<sub>2</sub>-expanded organic phase, where the homogeneous reaction was assumed to occur (Scheme 3). After the reaction was completed, the pressure was released, and the catalyst partitioned back onto the silica surface. The solvent phase was separated and analyzed. No organic compounds other than cyclohexane and ethyl benzene (product) were detected. The organic phase was further tested for Rh content in order to estimate the catalyst contamination of the organic phase (catalyst loss). No rhodium was detected by ICP/AA (i.e., <20 ppm), which confirms the efficiency of the reversible catalyst immobilization. The recycling strategy of the fluorinated catalyst/silica phase was tested via five consecutive runs using the same initial fluorinated catalyst/silica loading, recycled after each run. Quantitative hydrogenation of the substrate was observed for each of the five cycles.<sup>47</sup>

The fluorous biphasic reaction results established the possibility of using a CO<sub>2</sub> miscibility switch to perform homogeneous reactions (at moderate CO<sub>2</sub> partial pressures) using a reversibly immobilized catalyst. The fluorous silica technology takes this process to the next level by omitting the undesirable fluorous solvent. Another way to omit the fluorous solvent would be to use a catalyst immobilization solvent that is not fluorinated, such as a liquid polymer<sup>65</sup> or water.<sup>66,67</sup>

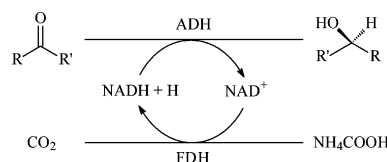
There are many ways to run a reaction homogeneously and then effect a phase change—by variations in temperature, pressure, or composition. One of the most important and active types of homogeneous catalysts is an enzyme, which is generally water soluble and relatively less active in organic solvents. Often, biocatalysis of hydrophobic substrates is carried out in aqueous–organic mixtures to promote substrate solubility. We proposed the application of a phase change after reaction to permit facile separation and recycling of these enzymes. The method is called OATS (organic–aqueous tunable solvent).

For proof of the principle of the OATS method for enzymes, we chose a dimethyl ether (DME)–water system that could be employed for the alcohol dehydrogenase (ADH)-catalyzed reduction of hydrophobic ketones coupled with the regeneration of the cofactor NADH (Scheme 4).<sup>68</sup> The advantage of this system is that DME is a polar, basic, aprotic solvent that is easy to remove, it can be run at modest pressures (3–4 bar), and liquid additions can be used to achieve phase separation.



**Figure 7.** Distribution coefficients  $K_d$  (DME/C<sub>water</sub>) of alcohols in DME–water biphasic solution at  $T = 30\text{ }^{\circ}\text{C}$  (C-ol: cyclohexanol; t,c-335-TMC-ol: *trans,cis*-3,3,5-trimethylcyclohexanol).

### SCHEME 4: ADH-Catalyzed Reduction of Ketones with NADH Regeneration

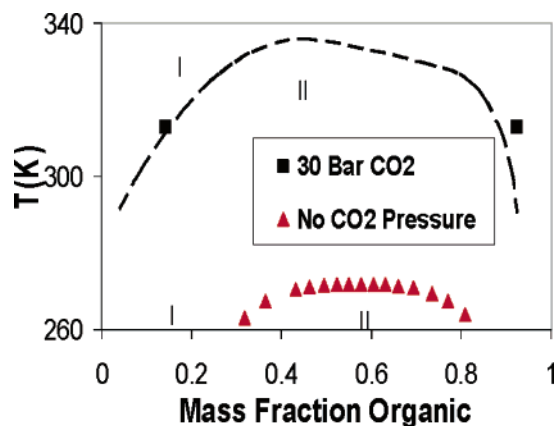


By using OATS, the subsequent downstream processing offers the advantages of easily isolating water-insoluble products from the aqueous phase and recycling the enzyme/cofactor. For enzymatic transformations, enzyme activity is usually increased by increased solvent hydrophilicity, but the overall rate of reaction could be decreased because of the reduced solubility of most hydrophobic substrates. DME–water may be superior to traditional organic solvents such as toluene or alcohols in terms of a compromise of hydrophilicity and hydrophobicity to optimize biocatalytic processes. After reaction, the DME-rich phase, containing the product, is separated from the aqueous phase, retaining the catalyst for reuse. Product recovery is facilitated by simple depressurization and vaporization of the DME, which can be subsequently recondensed for reuse.

Furthermore, the OATS system enhanced the solubility of the hydrophobic substrate 4-*tert*-butylcyclohexanone, with only 10% DME increasing this by about a factor of 5. Also, we were able to see that the addition of DME stabilized the NADH cofactor, increasing the half-life by about a factor of 2. There was, however, about a 10-fold reduction in enzyme activity for the reaction in DME–water mixtures for three substrates (acetone, 2-hexanone, and cyclohexanone).

In addition to a monophasic reaction medium, the DME–water system in its biphasic mode offers a new avenue for advantageous downstream separation. The organic phase can be used to extract organic products from the aqueous phase. Advantages include facile product isolation, elimination of solvent residue, and recycling of biological catalysts. The partitioning behavior of reaction products plays a key role in liquid/liquid extraction. Figure 7 gives the distribution ratio for a number of model products. These results suggest that the less-water-soluble solutes partition rather favorably into the DME phase. Thus, DME has significant potential as an extraction agent for hydrophobic products.

However, changes in OATS composition or temperature give relatively incomplete separations—the addition of CO<sub>2</sub> has a far more profound effect. CO<sub>2</sub> is miscible with most organics but virtually immiscible with water. In some systems containing water plus a hydrophilic organic, the addition of CO<sub>2</sub> will result in significant absorption of CO<sub>2</sub> into the organic only. This can achieve phase separation of a miscible organic–water mixture or drastically change the distribution coefficients in a two-phase



**Figure 8.** Liquid-liquid phase boundary of acetonitrile/water. (I) one liquid phase; (II) two partially miscible liquid phases. The dashed line is from a cubic equation of state.

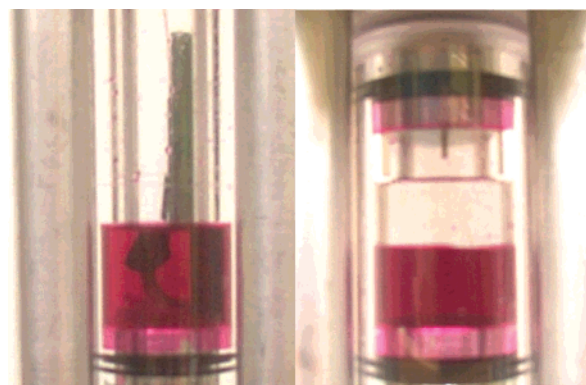
organic-water system. As such, this makes possible homogeneous reactions between hydrophobic and hydrophilic moieties, with facile separation and purification after reaction. In addition, it provides for the benign recycling of catalysts that may be expensive and/or toxic. In OATS reactions between water-soluble catalysts and moderately hydrophobic substrates, reactions can be run homogeneously, with subsequent phase separation for product purification and catalyst reuse.

The potential application of using  $\text{CO}_2$  to alter phase equilibria for better separation of reactants and products and recycling of catalysts is compelling. Not only is  $\text{CO}_2$  inexpensive, nonflammable, nontoxic, and nonreactive, but the pressures anticipated for these separation processes are low, as much as an order of magnitude less than those for supercritical fluid processing. The traditional aqueous biphasic technique popularized by the Ruhrchemie-Rhône-Poulenc process<sup>69</sup> requires a water-insoluble solvent, which is required to recycle the catalyst but hinders mass transfer. In OATS, the addition of a polar organic cosolvent, coupled with subsequent phase splitting induced by the dissolution of gaseous carbon dioxide, creates the opportunity to run homogeneous reactions in an organic-aqueous mixture with a water-soluble catalyst. After  $\text{CO}_2$ -induced phase separation, the catalyst-rich aqueous phase and the product-rich organic phase can be easily decanted and the aqueous catalyst recycled.

To investigate the feasibility of these processes, vapor-liquid-liquid phase equilibria in mixtures of water +  $\text{CO}_2$  + tetrahydrofuran, 1,4-dioxane, or acetonitrile were studied at 25, 40, and 60 °C and pressures ranging from 10 to 57 bar.<sup>70</sup> In each case, the addition of  $\text{CO}_2$  caused a major change in the phase boundary, as shown here for the acetonitrile-water system (Figure 8). In this case, the upper critical solution temperature was raised 60–70 °C by 30 bar of  $\text{CO}_2$ .

Another example that shows the tremendous potential for separations is THF-water, which has a lower critical solution point and is completely miscible below 75 °C. As little as 7 bar of  $\text{CO}_2$  causes phase splitting at ambient temperature. At merely 30 bar of  $\text{CO}_2$ , the partitioning of a colored hydrophilic catalyst surrogate (Figure 9) exceeds a factor of  $10^5$ !

The use of  $\text{CO}_2$  for enzyme reactions is constrained because even the small amount of  $\text{CO}_2$  that does dissolve in the water lowers the pH and can cause enzyme denaturation. Such a limitation can often be overcome by buffering, and we are currently investigating the activity and stability of a variety of enzymes in OATS systems with the goal of running important biosynthesis reactions such as asymmetric ester hydrolyses and enantioselective reductions of ketones.



**Figure 9.** Water/THF mixture with dilute water-soluble dye: ambient pressure (left); 30 bar  $\text{CO}_2$  (right).

The partitioning behavior of reaction products plays a key role in determining the efficiency of the above product purification process. We have measured the distribution coefficient of (*S*)-(-)-*sec*-phenylethyl alcohol, one of our proposed target products, in biphasic acetonitrile-water as a function of  $\text{CO}_2$  pressure at 40 °C. On the basis of the distribution coefficients, the results suggest that as much as 99% of the product can be extracted into the acetonitrile-rich phase with the addition of only 30 bar of  $\text{CO}_2$ .

Yet another application of  $\text{CO}_2$  for the environmentally benign and efficient recovery of homogeneous catalysts is in the recovery of phase-transfer catalysts with aqueous extraction. A PTC is by definition a compound that partitions between an aqueous phase and an organic phase. In current practice, the recovery is achieved by repeated washings of the organic phase, followed by an expensive reconcentration process.

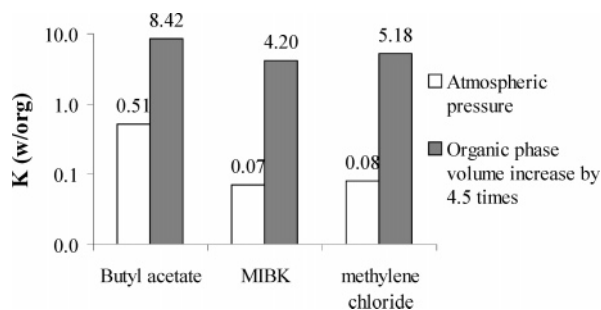
Using  $\text{CO}_2$  can alter the distribution of phase-transfer catalysts so dramatically that even in dilute solutions they can be separated selectively from an organic reaction mixture with only a small fraction of the water required in a traditional aqueous extraction. The addition of  $\text{CO}_2$  can change the distribution coefficient of the PTC by 2 orders of magnitude. The aqueous phase with the recovered catalyst can then be decanted, and the catalyst can be recycled. Subsequent depressurization returns the organic phase with the product free of catalyst. This method is useful for reducing the amount of wash water used in liquid-liquid extraction processes typically used to recover PTCs from industrial processes by 95%. The efficiency of this method toward dilute solutions creates a distinct advantage over the gas antisolvent (GAS) crystallization method, which requires larger amounts of  $\text{CO}_2$  to induce supersaturation of the PTC-containing organic solution.

An example of this principle of  $\text{CO}_2$ -enhanced aqueous extraction is shown in Figure 10 for a tetrabutylammonium picrate (TBAP), an analogue of tetrabutylammonium bromide (a common industrial PTC).<sup>28</sup> Three common solvents for PTC—butyl acetate, methyl isobutyl ketone (MIBK), and methylene chloride—were used as the organic phase in the aqueous biphasic system.

### In Situ, Reversible Formation of Catalyst

**Introduction.** In addition to improving the recycling of homogeneous catalysts, a large portion of our work in recent years has focused on the reversible, in situ formation of acid and base catalysts, which do not require costly recovery or result in salt wastes due to neutralization as do homogeneous catalysts. Each of these catalysts is formed from the benign and inexpensive starting materials of  $\text{CO}_2$  or water and feature





**Figure 10.** TBAP distribution coefficient as a function of  $\text{CO}_2$  pressure at room temperature (23–25 °C). Organic solvents used: butyl acetate, methyl isobutyl ketone, and methylene chloride. 20 mL of  $8.770 \times 10^{-5}$  M TBAP aqueous solution; 20 mL of organic solvent.

simple neutralization by changes in temperature or pressure. Our contributions in this area include

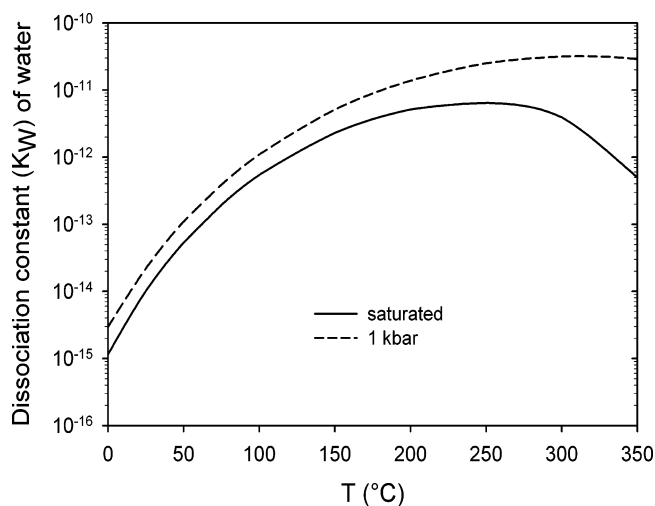
- the use of high-temperature water as a source of hydronium and hydroxide ions for acidic and basic catalysis;<sup>33,34,71–73</sup>
- the addition of carbon dioxide to small alcohols to form alkylcarbonic acid for acid catalysis;<sup>25,74,75</sup> and
- the addition of carbon dioxide to hydrogen peroxide to form peroxycarbonic acid for the oxidation of olefins.<sup>35</sup>

Acids are the most used catalysts in industry, and they produce more than  $1 \times 10^8$  metric tons/year of products.<sup>76</sup> The most commonly used conventional homogeneous acid catalysts include liquid acids ( $\text{HF}$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{HClO}_4$ ,  $\text{H}_3\text{PO}_4$ ) and nonrenewable Lewis acids ( $\text{BF}_3$ ,  $\text{AlCl}_3$ ), which are still used in many well-known industrial processes such as the synthesis of ibuprofen and high-octane fuels.<sup>77</sup> Although high reaction activities and selectivities are commonplace, environmental problems are associated with homogeneous acid catalysts, such as high toxicity, corrosion, catalyst waste, use of large amounts of catalyst, and difficult separation and recovery.

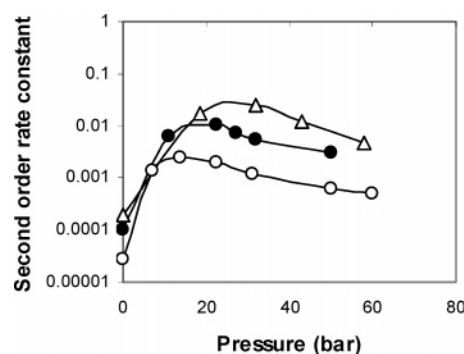
**Near-Critical Water.** Near-critical water (liquid water between 200 and 374 °C) offers an environmentally benign alternative for the replacement of undesirable solvents and catalysts. Siskin and co-workers<sup>78</sup> have suggested that NCW has approximately the properties of ambient-temperature acetone. As the temperature of water increases from 25 to 300 °C, its density decreases from 1 g/cm<sup>3</sup> at ambient conditions to about 0.7 g/cm<sup>3</sup>,<sup>40</sup> and its dielectric constant decreases by a factor of 4.<sup>79</sup> The dielectric constant is still high enough for it to dissolve and even ionize salts but low enough to dissolve organics. Polar organics of any sort are completely miscible, and even hydrocarbons dissolve to a large degree.<sup>80,81</sup> For example, *n*-heptane is 5 orders of magnitude more soluble in water at 350 °C than at 25 °C, and benzene and toluene are both completely miscible above 305 °C. Near-critical water exhibits a wide range of polarity and hydrogen-bond-donor ability for tailoring chemical reactions and separations.

Water also dissociates to a greater extent at higher temperatures:  $K_w$  increases by more than 3 orders of magnitude from 25 to 250 °C (Figure 12),<sup>1</sup> providing hydronium and hydroxide ions that may catalyze chemical reactions.

This increased concentration of hydronium and hydroxide ions eliminates or reduces the need to neutralize conventional acid or base catalysts and dispose of the resulting salts, which can amount to 5–10 kg/kg of product. The ionization constant can be further increased with pressure. If kilobar pressures are applied, then the ionization constant of water can be increased several more orders of magnitude.<sup>1</sup> Near-critical water has been used as a solvent, catalyst, and reactant for a number of hydrolyses that require added mineral acid at ambient



**Figure 11.** Ion product of water at elevated temperature.<sup>1</sup>



**Figure 12.** Rate of cyclohexanone acetal formation in  $\text{CO}_2$ -expanded methanol at various  $\text{CO}_2$  pressures and temperatures. Temperature: 25 °C data (○); 40 °C data (●); 50 °C data (□).

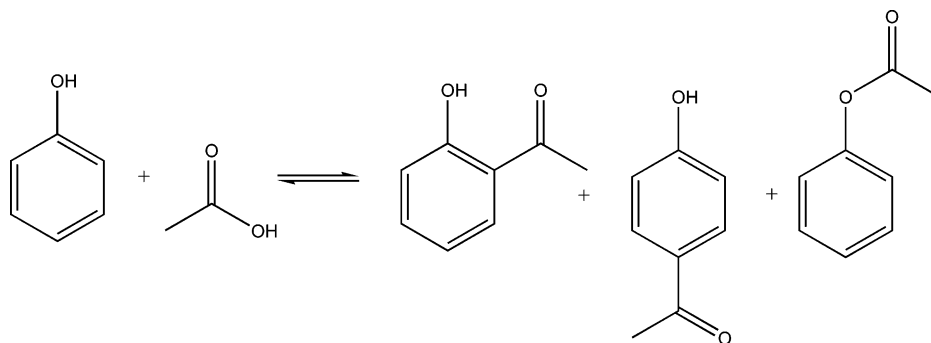
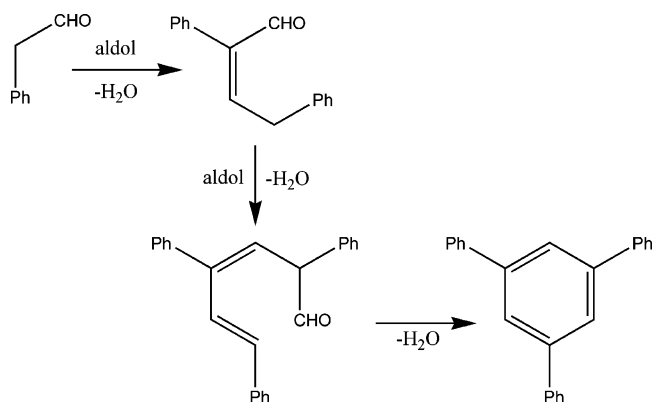
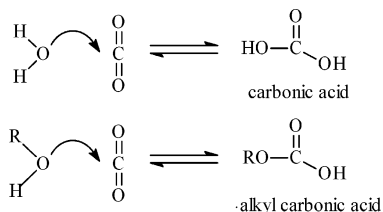
conditions.<sup>33,78,82–84</sup> It has also been successfully used for the Friedel–Crafts alkylation of phenol and *p*-cresol with *tert*-butyl alcohol.<sup>71,72</sup>

In addition to the alkylation of phenol and cresol with alcohols, we have run Friedel–Crafts acylations in near-critical water without added catalyst.<sup>34</sup> In this reaction, acid chlorides, acid anhydrides, or carboxylic acids react with aromatics to form arylalkyl ketones, conventionally in the presence of Lewis acids such as aluminum chloride, ferric chloride, and zinc chloride. Phenol can be converted with acetic acid to produce 2'-hydroxyacetophenone, 4'-hydroxyacetophenone, and phenyl acetate with no added catalyst (Scheme 5).

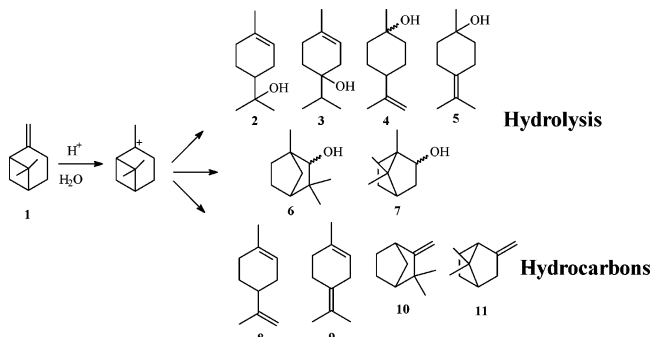
NCW can also serve as a reaction medium for C–C bond formation reactions conventionally catalyzed by added base, such as the aldol condensation of phenylacetaldehyde (PAA; Scheme 6).<sup>85</sup>

Without the addition of any catalyst, high selectivity for the primary condensation product at reasonable conversion can be achieved in appreciable reaction times (less than 1 h).<sup>85</sup> At longer reaction times, subsequent condensation reactions give rise to ring closure and higher-molecular-weight products.

The potential advantages of reactions run in NCW include replacing environmentally undesirable catalysts, eliminating unwanted byproducts, recycling, improving selectivity, and eliminating mass transfer limitations by changing from heterogeneous to homogeneous systems. The tunable solubility of organics in NCW allows for practical and facile combinations of reactions with separations. Often this could be as simple as cooling and decanting.

**SCHEME 5: Acylation of Phenol in NCW without Added Acid****SCHEME 6: Base-Catalyzed Aldol Condensation in NCW****SCHEME 7: Formation of Carbonic Acid and Alkyl Carbonic Acid**

**Methylcarbonic Acid.**  $\text{CO}_2$  may also be used to form acid catalysts reversibly in situ. When  $\text{CO}_2$  and water are combined, carbonic acid is formed (Scheme 7). The acidity of carbonic acid has been investigated in  $\text{CO}_2$ /aqueous systems. Towes et al. measured pH values of 2.8–2.95 in supercritical  $\text{CO}_2$ /water systems.<sup>86</sup> A decrease in pH also occurs in  $\text{CO}_2$  GXLs. Wen and Olesik determined the pH in  $\text{CO}_2$ /water/MeOH gas-expanded liquids.<sup>87</sup> They report pH values of around 4.5 in MeOH/water systems containing from 1 to 20%  $\text{CO}_2$ . The pH actually decreases to 4.22 at 5.6 mol %  $\text{CO}_2$  but increases as more  $\text{CO}_2$  is added. This is a result of a competing effect of the dielectric constant, which decreases with the addition of  $\text{CO}_2$  and thus the dissociation of the weak acid is inhibited as  $\text{CO}_2$  is added above ~6 mol %. We reported that the in situ formation of acid found in water- $\text{CO}_2$  systems (carbonic acid) extends to alcohol- $\text{CO}_2$  systems as well (Scheme 1).<sup>25</sup> We used the reaction with diazodiphenylmethane to monitor alkyl carbonic acid formation, and we found enhanced rates for its disappearance in an acetone- $\text{CO}_2$ -alcohol GXL with methanol and ethanol versus water. The presence of methyl carbonic acid in MeOH/ $\text{CO}_2$  mixtures was further demonstrated by studies of acetal formation with cyclohexanone in  $\text{CO}_2$ -MeOH GXLs (10–40 bar).<sup>74</sup> We demonstrated that the behavior of  $\text{CO}_2$ -

**SCHEME 8:  $\beta$ -Pinene Acid-Catalyzed Hydrolysis**

alcohol systems is comparable to that of  $\text{CO}_2$ -water systems, where carbonic acid is formed.

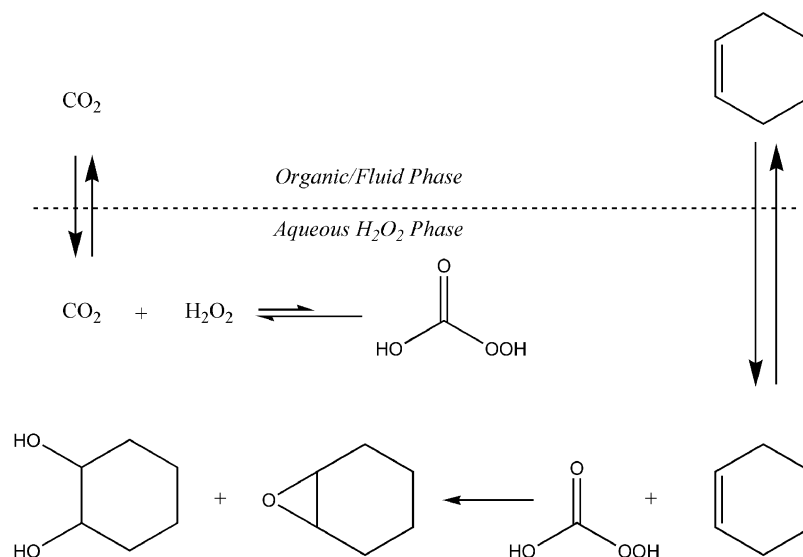
Methylcarbonic acid is a known compound;<sup>88</sup> it was previously shown to exist at low temperatures and to decompose upon melting at  $-36^\circ\text{C}$ . Enhanced acidity and solubilization effects in a  $\text{CO}_2$ -alcohol system may be either beneficial or detrimental to the desired application, which might be reactions, analytical separations, or antisolvent crystallization.

In addition to characterizing the acidity of alcohol- $\text{CO}_2$  systems with probe molecules such as diazodiphenylmethane and Reichardt's dye in  $\text{CO}_2$ -expanded alcohols,<sup>25</sup> we demonstrated the efficacy of these systems for acid catalysis. The kinetics of cyclohexanone acetal formation in  $\text{CO}_2$ -expanded methanol were investigated under various  $\text{CO}_2$  pressures over a temperature range of 25 to  $50^\circ\text{C}$  without the addition of acid.<sup>74</sup> In this work,  $\text{CO}_2$ -expanded alcohols are shown to act as acid catalysts that do not require neutralization, regeneration, or waste disposal. It is known that  $\text{CO}_2$  can react with alcohols to form alkylcarbonic acids<sup>25</sup> and has been used as a reactant in some Ugi reactions.<sup>89,90</sup>

Also, acetal formation reactions of cyclohexanone in methanol and ethylene glycol are shown to be catalyzed under  $\text{CO}_2$  pressure, possibly by the alkylcarbonic acids formed between  $\text{CO}_2$  and alcohols. Acetals are commonly used to protect the carbonyl groups of aldehydes and ketones from basic nucleophilic reagents. They are typically formed by reacting aldehydes and ketones with a large excess of an alcohol in the presence of a trace of strong acid. Because the formation of acetals is reversible, the high yield of acetals is accomplished either by the use of excess alcohol as the solvent, by removal of the water byproduct, or both.

The acetal formation reactions of cyclohexanone in methanol and ethylene glycol are catalyzed under  $\text{CO}_2$  pressure, possibly by the alkylcarbonic acids formed between  $\text{CO}_2$  and alcohols (see example in Figure 12). The pseudo-first- and second-order rate constants were evaluated from the initial rate data and methanol activity in  $\text{CO}_2$ -expanded methanol. For the reactions



SCHEME 9: Cyclohexene Epoxidation in an Aqueous H<sub>2</sub>O<sub>2</sub>/Organic Fluid Phase

in CO<sub>2</sub>-expanded methanol between 25 and 50 °C, the optimal CO<sub>2</sub> pressure is between 10 and 40 bar, where the enhancement factor goes through a maximum and the superficial activation energy goes through a minimum.

For cyclohexanone acetal formation in ethylene glycol, 2 mol % CO<sub>2</sub> has a significant catalytic effect. This work demonstrates the possibility of running homogeneous acid-catalyzed reactions without the addition of mineral acids or nonregenerable Lewis acids, thus precluding both the cost and waste generated by neutralization.

A second example of acid catalysis with in situ formed alkylcarbonic acid is the production of terpineol (Scheme 8).<sup>75</sup> Terpineol was one of the first fragrance chemicals to be commercially produced, and many methods for its production have been reported.<sup>91</sup> Some improvements in the process have occurred, such as the use of emulsifiers<sup>92</sup> and the addition of cosolvents.<sup>93</sup> However, the conventional processes can still involve relatively long reaction times (up to 24 h) and the addition of strong acids (i.e., 0.05 N or greater H<sub>2</sub>SO<sub>4</sub>, HClO<sub>4</sub>, etc.). We were able to achieve a similar and in some cases more favorable product distribution for the hydrolysis reaction of  $\beta$ -pinene in both a CO<sub>2</sub>–MeOH–water GXL and hot water with a cosolvent system compared to that of conventional methods.

**Peroxy-carbonic Acid.** In addition to species for acidic and basic catalysis, we have reversibly formed an epoxidation catalyst.<sup>35</sup> Epoxides and their derivatives are widely used as intermediates in industrial applications, including syntheses of cosmetics, detergents, polymers, and curing agents.<sup>94</sup> The straightforward route to an epoxide is through the epoxidation of the corresponding olefin. Hydrogen peroxide is a cheap and readily available oxidant for this purpose, with innocuous decomposition byproducts of water and oxygen. H<sub>2</sub>O<sub>2</sub> has been used for various applications from bleaching to epoxidations,<sup>95</sup> but it has limited application for oxidative synthesis without activation by the addition of catalysts or conversion to a more reactive peroxy acid.

Peroxy acids are typically formed in situ, because of their unstable nature, through the acid-catalyzed reaction of a carboxylic acid with hydrogen peroxide.<sup>96</sup> Epoxidations using peroxy acids are thought to occur through a bicyclic mechanism resulting in the regeneration of the carboxylic acid starting material.<sup>96</sup> These carboxylic acids must then be recovered for reuse or disposal.

Because of the limitations associated both with the catalyst and with traditional peroxy acid-catalyzed epoxidations, we developed an alternate process using the simplest possible activated hydrogen peroxide species, peroxycarbonic acid,<sup>97</sup> and related studies have recently been performed by other researchers involving epoxidations in CO<sub>2</sub>–H<sub>2</sub>O<sup>98</sup> and CO<sub>2</sub>–acetonitrile<sup>99</sup> systems and systems of sodium bicarbonate and water.<sup>100</sup> Because CO<sub>2</sub> reacts with water to form carbonic acid,<sup>101</sup> the analogous reaction of CO<sub>2</sub> with hydrogen peroxide generates peroxycarbonic acid (Scheme 9).<sup>102</sup> In this system, carbon dioxide acts as both a solvent and reactant in combination with aqueous H<sub>2</sub>O<sub>2</sub>, which is made possible through the in situ formation of peroxycarbonic acid. At 40 °C and 120 bar, cyclohexene was epoxidized to 1,2-cyclohexene oxide and 1,2-cyclohexanediol in this aqueous–organic biphasic system.

### Summary

Tunable fluids offer unique opportunities to enhance the sustainability of reaction processes. They are often more environmentally benign than the fluids they replace; in addition, they may offer enhanced solubility and/or transport properties. Moreover, exploitation of the tunability can result in phase changes or the enhancement of distribution coefficients that can lead to desirable recycling of catalysts and the separation of products. Finally, these solvents can also offer chemical opportunities, such as the in situ generation (and consumption) of acid and base catalysts, precluding the need for neutralization.

**Acknowledgment.** We are grateful for the support of this work from NSF, DOE, and EPA research grants as well as the Georgia Research Alliance and the donors of the J. Erskine Love, Jr. Institute Chair. We also acknowledge the support and collaboration of industrial partners Dow, Degussa, Albermarle, KoSa, and Hercules.

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