TUNABLE FLUIDS FOR SUSTAINABLE RECYCLE OF HOMOGENEOUS CATALYSTS

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As the demand increases for enantiomerically pure compounds the use of homogeneous chiral catalysts becomes ever more desirable. Such catalysts tend to be expensive or toxic, demanding methods for their recovery and recycle. The most common techniques involve tethering catalysts to some physical support, but this can have adverse effects on both activity and enantiomeric excesses. We report alternate techniques for recovering and recycling homogeneous catalysts, using the properties of tunable fluids. These methods constitute more sustainable processes, as they offer both economic and environmental advantages.

While supercritical fluids have enormous processing advantages, they require high pressures, typically hundreds of bars, and often will not dissolve large asymmetric catalysts and substrates. However, gas-expanded liquids, which require only tens of bars, are excellent solvents for such molecules, but still offer substantial advantages over ordinary liquids. They generally have better transport properties than liquids, and often have improved gas solubilities. Most importantly, they are highly tunable with small pressure changes, enabling processes where the reaction is homogeneous, and the separation can be heterogeneous.

Three examples are shown. The first deals with improvements to conventional fluorous biphasic catalysis using CO_2 pressure to homogenize fluorous and organic phases. Further, the same reactions may be carried out using a covalently-coated substrate in place of the fluorous solvent. The second example is the use of miscible organic-aqueous systems for homogeneous enzyme catalysis at ambient pressures, followed by phase-splitting for separation by modest CO_2 pressures. The third involves enhanced recovery of phase transfer catalysts – organic salts that distribute between an organic and an aqueous phase – widely used to facilitate reactions of a nonpolar substrates with ionic species. In this case the CO_2 pressure changes the distribution coefficient of the catalyst by 2-3 orders of magnitude for facile separation.

INTRODUCTION

Homogeneous catalysts possess many advantages over heterogeneous catalysts, such as higher activities and selectivities. However, recovery of homogeneous catalysts is often complicated by difficulties in separating these complexes from the reaction products. The expense of these catalysts makes their recovery imperative. We have developed several techniques using CO_2-expanded liquids 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_2 to fluorous biphasic systems. [1,2] Fluorous biphasic chemistry [3-7] 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 fluorous phase of a biphasic system. The mutual immiscibility of fluorous and organic solvents [8-13] provides an opportunity for facile separations of reaction components and reuse of homogeneous catalysts that must be recycled for reasons of toxicity and/or cost. However, mass transfer limitations in biphasic systems can limit overall reaction rate. In systems containing nonpolar solvents, such as toluene or cyclohexane, it is often possible to increase the temperature to induce miscibility. [3] However for more polar or thermally labile substrates this is not a viable option as the consulate point is much higher than 100 °C. [14,15] Thus, any polar reactants must be diluted into a nonpolar solvent, introducing a volatile organic solvent into the process. Instead of heating, a homogenizing agent such as benzotrifluoride [16] (BTF) can be added to the biphasic mixture to induce miscibility. However, BTF is an expensive agent, and its recovery is not trivial.

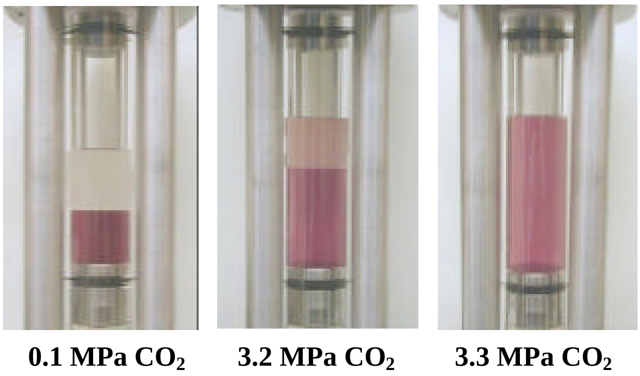


Figure 1. CO_2 used to homogenize an organic (toluene, clear liquid) and a fluorous (FC-75, colored liquid) phase.

Alternatively, CO_2 can be used to induce miscibility of fluorocarbon-hydrocarbon mixtures (see Figure 1), even those involving polar compounds such as methanol. [2] When this homogeneous reaction is complete, depressurization induces a phase split, with the catalyst available for recycle in the fluorous phase, and the product ready for purification in the organic phase. We have previously shown [2] that a variety of organic solvents are made miscible with fluorocarbon solvents by CO_2. Thus CO_2 acts as a co-solvent used to create a homogeneous, CO_2-rich phase; in which fluorophilic catalysts are readily soluble and active (Figure 1). This CO_2 “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 fluorous-soluble catalyst was dissolved in a fluorous solvent and added to a system containing a neat organic reactant phase. The high solubility of gases in fluorous [7] and CO_2-expanded [17] liquids creates a particular interest in these types of reactions. In both cases, addition of enough CO_2 to merge the phases increased the average turnover frequency (TOF, mole product produced per mole catalyst per time) relative to the biphasic system by 50-70%. [2]

Although these examples illustrate the effectiveness of the CO_2 switch for enhancing the catalytic activity of fluorous biphasic reactions, fluorinated solvents remain both expensive and environmentally undesirable. To remove these limitations, we tried using the CO_2 “miscibility switch” without the fluorinated solvent. We found that expansion of an organic solvent by the application of CO_2 pressure increases the fluorophilicity of the solvent to such an extent that the solvent is able to dissolve highly fluorinated complexes. [18] 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 fluorous biphasic catalysis with no fluorous liquid, analogous to the work of Gladysz [19,20] 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 fluorous silica as a solid supported for “capturing” the fluorinated catalysts. We have covalently bonded fluorous “tails” of about 500 Daltons to the silica surface to create a surface “phase” of highly fluorous character.

The fluorous silica concept involves the selective partitioning of a fluorous-modified catalyst between an organic liquid phase and the fluorinated surface phase. In the absence of

CO_2, the fluorinated catalyst “prefers” the fluorous surface phase and remains partitioned onto the silica. When CO_2 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_2 is removed and the catalyst will partition back onto the fluorous silica surface, which can be easily recovered by filtration.

I - MATERIALS AND METHODS

Fluorous silica distribution coefficients were obtained via UV-vis spectroscopy, as reported in [1]. The UV-active compound was deposited on the surface of the fluorinated silica by de-pressurizing a CO_2-expanded solvent. The coated silica gel was placed in a high-pressure UV cell [21] along with an organic solvent. Spectroscopic measurements determined the original partitioning of the compound between the organic phase and surface phase. Spectra taken in the presence and absence of CO_2 pressure determined the changes in partition coefficient due to CO_2-expansion of the organic liquid. Distribution coefficients and solubilities in the enzyme- and PTC-related systems were also measured using UV-vis spectroscopy [21]. Phase behaviour measurements were made in a high pressure sapphire tube apparatus [22]. Reactions were conducted in a 300 mL stirred Parr autoclave reactor [2,21].

The chemicals used in these investigations were all minimum 99% purity and used without further purification except for carbon dioxide and hydrogen, which went through gas purifiers from the cylinder to other parts of the experimental system. Tetrabutylammonium picrate aqueous solution was made by adding water to the mixture of equimolar tetrabutylammonium hydroxide and picric acid in their aqueous solution form. The fluorinated compounds were synthesized according to literature [1].

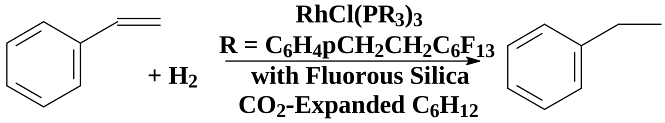
II – RESULTS AND DISCUSSION

In order to demonstrate the feasibility of this concept, we first determined the extent of reversible partitioning of fluorinated compounds or complexes on and off of the fluorous silica support upon the expansion of the solvent with CO_2. [1] For a slightly fluorophilic molecule, bis(perfluorooctyl)benzene, the partitioning in polar solvents, such as acetonitrile, was altered from 8:1 in favor of the silica surface to 45:1 in favor of the bulk fluid phase by adding modest CO_2 pressures (20-50 bar). For a more fluophilic compound, a perfluoropolyether complex, the partitioning can be changed from 100:1 in favor of the silica to 99:1 in favor CO_2-expanded cyclohexane, a change of four orders of magnitude in partitioning (see Table 1).

Table 1. Reversible solubility of various fluorinated compounds in CO_2-expanded liquids at 25 °C. PFPE = poly(hexafluoropropyleneoxide); Fl-Wilkinson’s Catalyst = $RhCl(PR_3)$ with R = C_6H_4-*p*-$CH_2CH_2C_6F_{13}$.

Compound	Solvent	Pressure <bar>	Partitioning w/o CO_2	Partitioning with CO_2
$Co(O\text{-}PFPE)_2$	C6H12	68.3	0.010	99.06
Bis(perfluorooctyl)benzene	CH3OH	31.7	0.132	45.97
Bis(perfluorooctyl)benzene	CH3CN	31.1	0.123	45.15
Fl-Wilkinson's Catalyst	C6H12	28.6	0.024	40.84
Fl-Wilkinson's Catalyst	CH3OH	28.6	0.012	68.07

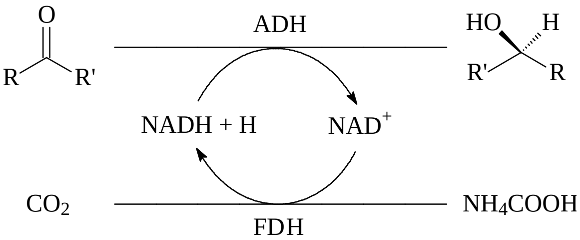
The fluorous silica technology was tested on the catalytic hydrogenation of styrene where the fluorous silica phase consisted of a fluorinated version of Wilkinson’s catalyst deposited onto the surface of the fluorous silica. The organic phase consisted of styrene dissolved in cyclohexane. No fluorous solvent was used. H_2 and then CO_2 pressure were applied, forming a gas-expanded organic phase. The fluorinated catalyst then partitioned off of the fluorinated silica support and into the CO_2-expanded organic phase, where the homogeneous reaction was assumed to occur (Scheme 1). 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 recycle 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.



Scheme 1. Hydrogenation of styrene with modified Wilkinson’s catalyst.

Another way to omit the fluorous solvent would be to utilize a catalyst immobilization solvent that is not fluorinated, such as a liquid polymer [23] or water. One of the most important and active types of homogeneous catalysts is an enzyme, 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 propose the application of a phase change after reaction to permit facile separation and recycle of these enzymes. The method is called OATS (Organic-Aqueous Tunable Solvent).

For proof of principle of the OATS method to enzymes, we chose a dimethyl ether (DME)-water system could be employed for alcohol dehydrogenase (ADH)-catalyzed reduction of hydrophobic ketones coupled with regeneration of the cofactor NADH (Scheme 2). [21] The advantage of this system is that DME is a polar, basic, aprotic solvent which is easy to remove, it can be run at modest pressures (3-4 bars) and liquid additions or depressurization can be used to achieve phase separation.



Scheme 2. ADH-catalyzed reduction of ketones with NADH regeneration.

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 addition of DME stabilized the NADH cofactor, increasing half-life by about a factor of two. There was, however, about a 10-fold reduction in enzyme activity found for the reaction in DME-water mixtures for three substrates (acetone, 2-hexanone, and cyclohexanone).

Changes in OATS composition or temperature give relatively incomplete separations – the addition of CO_2 has a far more profound effect. CO_2 is miscible with most organics but virtually immiscible with water. In some systems containing water plus a hydrophilic organic, addition of CO_2 will result in significant absorption of CO_2 into the organic only. This can achieve phase separation of a miscible organic/water mixture, or drastically change distribution coefficients in a two-phase organic/water system. In addition it provides for benign recycle of catalysts which may be expensive and/or toxic. For example, the traditional aqueous biphasic technique, popularized by the Ruhrchemie/Rhône-Poulenc process [24] requires a water-insoluble solvent, which is required to recycle the catalyst but hinders mass transfer. Addition of a polar organic co-solvent, 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 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.

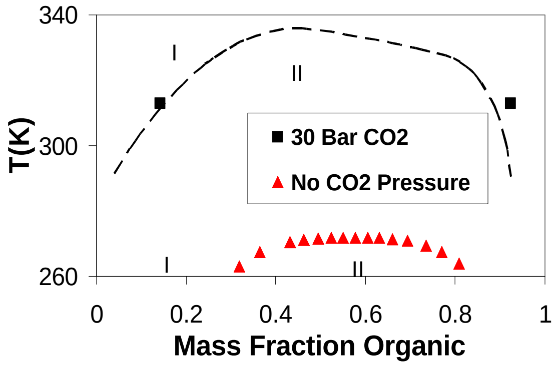


Figure 2. Liquid-liquid phase boundary of acetonitrile/water. I: one liquid phase; II: two partially miscible liquid phases. Dashed line from cubic equation of state.

To investigate the feasibility of these processes, vapor-liquid-liquid phase equilibria in mixtures of water + CO_2 + tetrahydrofuran, 1,4-dioxane, or acetonitrile were studied at 25°, 40°, and 60°C and pressures ranging from 10 to 57 bar. [22] Addition of CO_2 caused a major change in the phase boundary, as shown for the acetonitrile-water system in Figure 2. In this case, 30 bars of CO_2 raised the upper critical solution temperature by 60-70 °C.

The use of CO_2 for enzyme reactions is constrained because even the small amount of CO_2 that does dissolve in water lowers the pH and can cause enzyme denaturation. This can often be overcome by buffering, and currently we are 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.

A final application of CO_2 for 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 a 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 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. Addition of CO_2 can change the distribution coefficient of the PTC by two orders of magnitude. The aqueous phase with the recovered catalyst can then be decanted and the catalyst recycled. Depressurization returns the organic phase with the product free of catalyst. This method is useful for reducing the amount of washwater used in liquid-liquid extraction processes typically used to recover PTC's from industrial processes by 95%. The efficiency of this method toward dilute solutions creates a distinct advantage over the gas anti-solvent (GAS) crystallization method, which requires larger amounts of CO_2 to induce supersaturation of the PTC-containing organic solution.

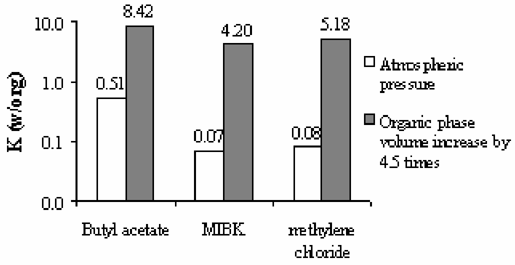


Figure 3. Distribution coefficient of TBAP as a function of CO_2 pressure at 25 °C (20 ml of 87.7 µM aqueous TBAP, 20 ml organic solvent).

An example of CO_2 enhanced aqueous extraction is shown in Figure 3 for a tetrabutylammonium picrate (TBAP), an analog of tetrabutylammonium bromide (a common industrial

PTC). [25] Three common solvents for PTC: butyl acetate, methyl isobutyl ketone (MIBK) and methylene chloride were used as the organic phase.

CONCLUSION

We have developed several techniques using CO_2-expanded liquids to create a medium for performing homogeneous reactions while maintaining the facile separation of a heterogeneous system. Three examples are shown: fluorous silica was used as a reversible catalyst “trap” for fluorinated catalysts; organic/aqueous tunable solvents (OATS) were used for enzyme reactions; and the enhanced recovery of phase transfer catalysts using CO_2 pressure was demonstrated. In each case, the use of CO_2-expanded liquids enabled changes in the distribution coefficient of catalysts by several orders of magnitude.

REFERENCES

[1] ABLAN, C. D., HALLETT, J. P., WEST, K. N., JONES, R. S., ECKERT, C. A., LIOTTA, C. L., JESSOP, P. G., Chem. Commun., **2003**, p. 2972
[2] WEST, K. N., HALLETT, J. P., JONES, R. S., BUSH, D., LIOTTA, C. L., ECKERT, C. A., Ind. Eng. Chem. Res., **2004**, in press
[3] HORVATH, I. T., RABAI, J., Science, Vol. 266, **1994**, p. 72
[4] CORNILS, B., Angew. Chem. Int. Ed., Vol. 32, **1997**, p. 2057
[5] HORVÁTH, I. T., Acc. Chem. Res., Vol. 31, **1998**, p. 641
[6] CURRAN, D. P., Angew. Chem. Int. Ed., Vol. 37, **1998**, p. 1174
[7] BARTHEL-ROSA, L. P., GLADYSZ, J., Coord. Chem. Rev., Vol. 190-192, **1999**, p. 587
[8] HASZELDINE, R. N., SMITH, F., Chem. Soc., **1951**, p. 603
[9] REED, T. M., J. Phys. Chem., Vol. 59, **1955**, p. 428
[10] SCOTT, R. L., J. Phys. Chem., Vol. 62, **1958**, p. 136
[11] REED, T. M., J. Phys. Chem., Vol. 63, **1959**, p. 1798
[12] MUNSON, M. S. B., J. Phys. Chem., Vol. 68, **1964**, p. 796
[13] SKRIPOV, V. P., FAIZULLIN, M. Z., J. Chem. Thermodyn., Vol. 21, **1989**, p. 687
[14] HILDEBRAND, J. H., COCHRAN, D. R. F., J. Am. Chem. Soc., Vol. 71, **1949**, p. 22
[15] HILDEBRAND, J. H., J. Am. Chem. Soc., Vol. 72, **1950**, p. 4348
[16] OGAWA, A., CURRAN, D. P., J. Org. Chem., Vol. 62, **1997**, p. 450
[17] BEZANEHTAK, K., DEHGHANI, F., FOSTER, N., J. Chem. Eng. Data, **2004**, in press
[18] JESSOP, P. G., OLMSTEAD, M. M., ABLAN, C., GRABENAUER, M., SHEPPARD, D., ECKERT, C. A., LIOTTA, C. L., Inorganic Chem., Vol. 41, **2002**, p. 3463
[19] WENDE, M., MEIER, R., GLADYSZ, J.A., J. Am. Chem. Soc., Vol. 123, **2001**, p. 11490
[20] WENDE, M., GLADYSZ, J. A., J. Am. Chem. Soc., Vol. 125, **2003**, p. 5861
[21] LU, J., LAZZARONI, M. J., HALLETT, J. P., BOMMARIUS, A. S., LIOTTA, C. L., ECKERT, C. A., Ind. Eng. Chem. Res., Vol. 43, **2004**, p. 1586
[22] LAZZARONI, M. J., BUSH, D., HALLETT, J. P., BROWN, J. S., LIOTTA, C. L., ECKERT, C. A., GLÄSER, R., Proceedings of the 6th International Symposium on Supercritical Fluids, **2003**, Versailles, France, p. 1089
[23] HELDEBRANDT, D. J., JESSOP, P. G., J. Am. Chem. Soc., Vol. 125, **2003**, p. 5600
[24] KOHLPAINTNER, C. W., FISCHER, R. W., CORNILS, B., Appl. Cat. A, Vol. 221, **2001**, p. 219
[25] XIE, X., BROWN, J. S., JOSEPH, P. J., LIOTTA, C. L., ECKERT, C. A., Chem. Commun., **2002**, p. 1156