LA-UR-97- 1476

Title: **Chemistry and Catalysis in Supercritical Media**

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Submitted to: **DOE Office of Scientific and Technical Information (OSTI)**

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ST 2629 10/91

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Chemistry and Catalysis in Supercritical Media

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Abstract

This is the final report of a three-year, Laboratory-Directed Research and Development (LDRD) project at the Los Alamos National Laboratory (LANL). The aim of this research is to explore the potential of supercritical fluids as reaction media for stoichiometric and catalytic chemical transformations in an effort to develop new, environmentally-friendly methods for chemical synthesis or processing. This approach offers the possibility of opening up substantially different chemical pathways, increasing selectivity while enhancing reaction rates, facilitating downstream separations and mitigating the need for hazardous solvents. We describe investigations into a number of catalytic processes for which carbon dioxide represents a viable solvent replacement. In several cases we have observed significant enhancements in selectivity and/or reactivity relative to conventional organic solvents. We have investigated the following catalytic processes: a) selective oxidation including dihydroxylation and epoxidation, b) asymmetric hydrogenation and hydrogen transfer reduction, c) Lewis acid catalyzed acylation and alkylation, and d) coupling of amines with carbon dioxide to make isocyanates.

1. Background and Research Objectives

The aim of this research was to explore the potential of supercritical fluids (SCFs) as reaction media for stoichiometric and catalytic chemical transformations in an effort to develop new, environmentally-friendly methods for chemical synthesis or processing. This approach offers the possibility of opening up substantially different chemical pathways, increasing selectivity while enhancing reaction rates, facilitating downstream separations and mitigating the need for hazardous

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solvents. A more detailed description of the motivation for this research, experimental considerations as well as a summary of many of the results from this work can be found in two chapters we have recently written.^{1,2} The attraction of supercritical fluids for chemical synthesis lies both in their unique solvating capabilities and in their relatively benign nature. There are a number of inherent properties of supercritical fluids that distinguish them as superior reaction media including:

- High diffusivity
- High compressibility
- Continually adjustable "solvent strength"
- Miscibility
- Thermochemical (kinetics/thermodynamics) effects
- Ion-Product (equilibria)
- Solvent participation.

The promise of controlling reaction pathways and even opening up new reactivity patterns by controlling reaction conditions in supercritical media has been laid out in several recent reviews,^{3,4} and several studies have demonstrated that controlling properties such as solvent strength and solvent participation can impact the selectivity of reactions. Despite a clear understanding of the potential advantages of supercritical reaction media and their industrial significance, this extremely promising technology area is in its infancy -- a wide range of organic reactions and catalytic processes has remained largely unexplored. We have chosen to explore several catalytic processes in supercritical fluids, particularly CO₂. Initial work focused on selective catalytic oxidations⁵ of olefins, aromatics and alkanes due to their rich chemistry and industrial importance. In addition, we have expanded the scope of this project to include studies on catalytic hydrogenation reactions, particularly asymmetric hydrogenation and transfer hydrogenation, as well as the development of photochemical and spectroscopic probes of solvation effects and the use of CO₂ as a solvent and a reagent for isocyanate synthesis.

2. Importance to LANL's Science and Technology Base and National R&D Needs

U.S. industries must accelerate development of new methods for chemical processing and synthesis to maintain global competitiveness. Our research has provided much valuable information on what types of catalytic processes can proceed in supercritical fluids, and also has begun to delineate the potential advantages of this reaction medium. This research could lead to conceptually new methods for direct oxidative functionalization, the introduction of asymmetric centers into molecules and new methods for forming carbon-carbon bonds, which could have

considerable industrial impact. Selective oxidation is the most widely applied technology for conversion of base chemicals such as olefins and aromatics to commercially important products and stands to benefit considerably from supercritical reaction media. Our work in asymmetric catalysis, which takes advantage of the unique properties of SCFs could have a significant impact in the pharmaceutical and agrochemical industries where there is an increasingly large interest in new technologies for generating a wide variety of enantiomerically-enriched compounds as well as a greater sensitivity to environmental and competitiveness issues. Our research should also have important ramifications for waste minimization. Increasingly stringent environmental regulations require processes that minimize waste, energy and hazardous emissions. The ability to carry out currently practiced chemical processes in supercritical media would facilitate separation and recovery of products and catalysts as well as eliminate the need for hazardous reaction media. A large part of the investment and cost of chemical production entails product isolation/purification, catalyst recovery/recycle and waste disposal. On a higher plane, the ability to control reaction pathways through changes in process conditions would yield enhanced reactivity (i.e. smaller reactors) and selectivity (i.e. reduced waste) thereby providing the ultimate in waste minimization.

With respect to the Los Alamos National Laboratory (LANL), we have enhanced the Laboratory's capabilities in supercritical fluids by adding a strong synthetic and catalysis component. This supercritical fluid program was also one of the drivers for initiating a catalysis initiative at the Laboratory and developing a strategy for industrial partnering with the chemical industry. We have initiated a number of specific collaborations with the chemical industry including: Hoechst (polyester synthesis), Dow (selective oxidation), Monsanto (inorganic oxidations). We have also interacted with a number of other companies, which may lead to further collaborations. In addition, we have gained an external reputation in chemical synthesis in supercritical fluids and have presented a number of invited talks at international conferences:

Industrial Seminars

Hoechst Celanese, February 1994

DuPont, December 1994

Monsanto, February 1995

Dow Chemical, November 1995

Monsanto, December 1995

Course on SCF for Fiber and Textile Industry at LANL 7/11-7/12/94, joint
with American Fiber Manufacturer's Association

Invited Presentations

ACS Symposium: Benign by Design, Washington, 8/94.
North American Catalysis Society Meeting, Snowbird UT, 6/95
1995 Organometallic Gordon Conference, Newport RI, 7/95
Joint Assoc. for Advancement of Supercritical Fluid Technology Symposium, 7/95
ACS Symposium: Green Chemistry, Chicago 8/95
ACS SE/SW Regional Meeting, Memphis, 11/95
ACS Symposium: New Perspectives in Environmental Chemistry, New Orleans, 3/96
Florida Catalysis Conference, 4/96
Benign Synthesis Gordon Conference, 7/96
ACS National Meeting, San Francisco, to be presented 4/97
4th Internat. Symposium on Supercritical Fluids, Sendai, Japan, to be presented 5/97
Inorganic Gordon Conference, to be presented 7/97

Other Presentations

1994 AIChE National Meeting, San Francisco, 2 talks
1995 Organometallic Gordon conference, poster
1995 ACS Spring meeting, Anaheim, 3 talks, 2 posters
1995 AIChE National Meeting, Miami, 2 talks
1996 ACS Spring meeting, New Orleans, 3 talks, 4 posters
1996 ACS Fall meeting, Orlando, 2 talks, 2 posters

3. Scientific Approach and Accomplishments

Our main scientific approach has been to explore several fundamentally and industrially important catalytic processes in supercritical fluids in order to define the potential and scope as well as the inherent advantages of supercritical fluids as reaction media. We started with several known catalytic processes and investigated rates and selectivities in comparison to conventional organic solvents. Specifically we have investigated the following catalytic processes:

1. Dihydroxylation of olefins using Ru and Os phase transfer catalysts
2. Vanadium catalyzed epoxidation of allylic and homoallylic alcohols
3. Iron-porphyrin catalyzed oxidation of cyclohexene
4. Ruthenium and rhodium catalyzed asymmetric hydrogenation and reduction of olefins
5. Lewis-acid catalyzed Friedel-Crafts acylations and alkylations
6. Use of CO₂ as a solvent and reagent for isocyanate synthesis
7. Development of photochemical probes of solvation

Some of the key results are summarized below. Detailed results as well as descriptions of the research approach and experimental aspects from this research can be found in our publications which are listed with the references below.

Selective Oxidation Catalysis in Supercritical CO₂

We have examined a number of oxidation catalysts in supercritical CO₂ that can be divided into three classes of oxidation catalysis: phase-transfer dihydroxylation using RuO₄ or OsO₄ in water/CO₂ mixtures; epoxidation of olefins from oxo transfer from high-valent vanadium complexes using hydroperoxides; and air-oxidation (autooxidation) of cyclohexene using highly fluorinated iron porphyrins. We have translated the two-phase oxidation of alcohols, alkenes, and other substrates mediated by high valent ruthenium oxo complexes from water/halocarbon media to water/supercritical CO₂. We have shown that Ru and Os oxo complexes (e.g. MO₄) can convert cyclohexene to adipic acid and cyclohexanediol, respectively using added oxidants (e.g. NaIO₄) in water/supercritical CO₂ mixtures. This work is summarized in the two chapters we have written for books on environmentally benign synthesis.^{1,2} We have used a number of vanadium catalysts of the general form VO(OR)₃ to mediate the t-butylhydroperoxide epoxidation of allylic and homoallylic alcohols in supercritical and liquid CO₂. A large number of substrates can be selectively epoxidized in this environmentally benign solvent (Figure 1).⁶ In addition, we have shown, for the first time, that high enantioselectivities can be achieved for epoxidations in liquid CO₂ (Figure 2) using chiral auxiliary ligands on vanadium or titanium. This work also revealed that liquid CO₂ could be an effective solvent for a number of catalytic transformations even at relatively low temperatures (e.g. < 0 °C).

We have also demonstrated that highly fluorinated metalloporphyrins are soluble in supercritical CO₂ and can catalyze the oxidation of alkenes with molecular oxygen (Figure 3).⁷ The selectivity of epoxidation over allylic oxidation for cyclohexene was found to be significantly higher in supercritical CO₂ compared to CH₂Cl₂, benzene or CH₃CN as solvents, presumably due to the electrophilicity of CO₂ and its lack of reactivity with chain carrying organic radicals.

Asymmetric Catalytic Hydrogenation

We have developed novel asymmetric catalytic hydrogenation and hydrogen-transfer reduction processes of olefins and ketones in supercritical CO₂. We have found that highly enantioselective reactions may be performed in this environmentally benign solvent. Of particular note, we have shown that higher enantioselectivities can be achieved for certain amino acid precursor substrates in supercritical CO₂ than in conventional organic solvents.⁸ This work focused on rhodium and ruthenium catalysts containing chiral bisphosphine ligands such as DuPhos or BINAP. We also discovered that highly lipophilic counterions such as the tetrakis(3,5-trifluoromethylphenyl)borate, B(Ar^f)₄⁻ anion can solubilize transition metal cationic catalysts or catalyst precursors. The ability to solubilize cationic catalysts could have broad implications for

catalysis in supercritical fluids. As illustrated in Figures 4 and 5, we have examined a number of prochiral substrates, and in all cases find equal or higher enantioselectivities in supercritical CO₂ relative to conventional solvents. A full paper detailing this work should be submitted in early 1997.⁹ In order to probe the origin of the enhanced enantioselectivity in supercritical CO₂, we examined the effects of pressure, temperature, solvent, and hydrogen concentration on enantioselectivity. In short, we have found two mechanistic regimes can be operative for these hydrogenations in supercritical CO₂. The one class of substrates displays concentration and temperature dependences reflective of Halpern's mechanism involving a rate-limiting preequilibrium of diastereotopic intermediates. These substrates show higher enantioselectivities at higher temperature or lower hydrogen concentration. The other class exhibits normal temperature dependence indicative of a fast preequilibrium which is not product determining. Preliminary kinetic studies to explore possible explanations for the selectivity enhancement observed in the hydrogenation of **5**, **7** in supercritical CO₂ have shown that hydrogenation reactions are faster in supercritical CO₂ than in hexane presumably due to the fact that hydrogen gas is miscible in supercritical CO₂.

A diverse range of substrates (β -branched enamide esters, enamides, hydroazones) were found to be reduced with high enantioselectivities, thus offering a practical, environmentally responsible method for the production of many important chiral building blocks of medicinal and agrochemical interest (Figure 5).

Asymmetric Hydrogen Transfer Reduction:

We have examined the transfer hydrogenation of prochiral substrates such as α -enamide esters and tiglic acid **7** using a number of known Ru(II) and Rh(I) catalysts containing chiral phosphine ligands in supercritical CO₂ (Figure 6). Our experiments involving the cationic rhodium catalysts of the type, P₂Rh(COD)(BAR')₄ where P₂ = Et-DuPHOS, BINAP, or DIOP, resulted in low conversions and low ee's for the hydrogen transfer reduction of α -enamide esters. Note that the DuPHOS-Rh complexes are excellent catalysts for hydrogenation reactions. We have found, however, that enamide esters may be reduced in high conversion and with high enantioselectivities using the neutral ruthenium complexes (Figure 6). The α -enamides **5** could be reduced cleanly under these conditions to afford the corresponding amino acid derivatives with high enantioselectivities. The reaction was also investigated in hexane and gave comparable ee's for **5a-b**. No reaction was observed for **5c-d** in hexane due probably to the low solubility of the substrates. Reduction of **5a** and **5c** using the analogous [((*R*)-BINAP)Ru(O₂CCF₃)₂] (**1b**) as catalyst also resulted in high conversion and high enantioselectivity in supercritical CO₂. No significant pressure effects were observed for these hydrogen transfer reduction reactions. These

enantioselectivities achieved in supercritical CO₂ are the highest yet reported for hydrogen transfer reduction of α -enamide substrates, particularly esters.

We have also studied reduction of tiglic acid as a model for unsaturated acids in supercritical CO₂. Tiglic acid can be reduced with 93.2 % ee in CO₂ while 84.2% ee in MeOH. Enantioselectivities for hydrogen transfer reduction of tiglic acid achieved here in CO₂ are higher compared with in methanol or with direct hydrogenation in CO₂ or MeOH. These studies demonstrate the feasibility of conducting highly enantioselective hydrogen transfer reductions in supercritical CO₂. We have shown that higher enantioselectivities may be achieved in supercritical CO₂ relative to conventional solvents.

Lewis Acid Catalyzed Friedel-Craft Acylation and Alkylation

The Friedel-Craft acylation and alkylation reactions are two examples of a well studied reaction involving Lewis acids. A great wealth of information has been reported in the literature about the synthetic applications of these Friedel-Craft reactions, however there still lacks the kinetic data necessary for an unambiguous mechanism. The reactivity and selectivity can be affected by the temperature and solvent for a number of Lewis acids and have been well documented in many conventional solvents. We have been able to demonstrate that both acylations and alkylations of aromatics can be effected by aluminum halides and acyl halides and alkyl halides, respectively. For example, naphthalene is acylated with acetyl chloride using AlCl₃ in supercritical CO₂. Alkyl halides give a mixture of alkylbenzenes with benzene and AlBr₃. Further work is needed to delineate whether there are any rate and/or selectivity enhancements in this important class of reactions.

Photochemical Probes of Solvation in Supercritical CO₂

The intriguing variation in selectivity effects of supercritical CO₂ on catalytic systems has prompted us to investigate the effect of solvent pressure and temperature on reactivity at a more fundamental level. Alkylphenone photochemistry proceeds by several pathways to different products in ratios that are strongly solvent-dependent. We have developed experimental procedures and a photochemical reactor which enables us to conduct batch photochemistry in supercritical CO₂ at controlled temperature and pressure followed by quantitative recovery and analysis of the photoproducts. We have found, for butyrophenone photochemistry, that the product distributions are similar to those in benzene, but pressure effects on the product distribution are several times larger than in conventional solvents. In the case of α,α -dimethylbutyrophenone, we have discovered a variable solvent cage effect which allows us limited

pressure control over a fragmentation branch of the photochemical scheme by manipulating the strength of the solvent cage, which induces recombination. The ratio of Norrish Type I to Norrish Type II products for *a,a*-dimethylbutyrophenone photolysis at 60°C varied from 7.3 to 4.7 depending on pressure and wavelength. The data fit well to the diffusional model for solvent cage escape, suggesting that the photogenerated radicals escape the cage by diffusion rather than by cage disintegration. The model could also be fit to data obtained below the critical temperature at 26.9°C, which implies that solute-solvent clustering does not significantly affect the rate of cage escape. Carbon dioxide is a nonpolar, non-hydrogen bonding solvent at all densities. Consequently, the "pressure-tuning" range of carbon dioxide is quite narrow compared to the range of polarities and other solvent properties represented by the usual spectrum of organic solvents. This is reflected in the small magnitude of the variation of the Type II E/C ratio of butyrophenone with pressure. The magnitude of the tuning range for solvent cage effects is somewhat larger. However, the degree to which solvent cage effects can be pressure-tuned depends on the ratio of the geminate recombination rate for the radical fragments to the rate of diffusion. For some photosystems, particularly ones which produce large, slow-diffusing photofragments, the degree of tuning may be larger than that observed here. These results shed light on the problem of developing rational strategies for selectivity enhancement in supercritical CO₂. This work will be submitted for publication in early 1997.¹⁰

CO₂ as a Reagent for Isocyanate Synthesis

The addition of CO₂ to amines to form carbamic acids is a well-known reaction, but works only for aliphatic amines in conventional solvents. We have found that we can shift this equilibrium favorably for aromatic amines by operating in supercritical CO₂. We have found a number of dehydrating agents which then dehydrate the resulting carbamic acids to form isocyanates. Synthesis of diisocyanates by non-phosgene routes is considerably more difficult than that of monoisocyanates, but we have had some success in the presence of alcohols, which trap the diisocyanate as a urethane. By this approach, we avoid the use of the environmentally hazardous reagent phosgene. This reagent is currently used to produce aromatic isocyanates, which are intermediates to polyurethanes.

Publications/References

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R ₁	R ₂	Time	T(°C)	Conversion	Products
CH ₃ -	H-	24h	25°C	>99%	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(85%)</p> </div> <div style="text-align: center;"> <p>(15%)</p> </div> </div>
nCH ₃ CH ₂ CH ₂ -	H-	24h	25°C	96%	<div style="text-align: center;"> <p>(>99%)</p> </div>
CH ₃ -	CH ₃ -	24h	25°C	>96%	<div style="text-align: center;"> <p>(86%)</p> </div>
	CH ₃ -	24h	25°C	>99%	<div style="text-align: center;"> <p>(95%)</p> </div>
CH ₃ -		24h	25°C	>99%	<div style="text-align: center;"> <p>(>99%)</p> </div>

Figure 1. Selected results from the vanadium-catalyzed epoxidation of prochiral allylic and homoallylic alcohols.

L*, R =	Conversion	Selectivity	%ee
(CH ₃) ₂ CH-	>99%	89%	87.4%

Figure 2. Enantioselective epoxidation using chiral titanium catalyst.

Figure 3. Fluorinated Iron Porphyrin Air-Oxidation of Cyclohexene

Substrate	R	Catalyst	% ee ^b		
			MeOH	Hexane	SC CO ₂
3a	H	1a	98.7	96.2	99.5
		1b	99.4	99.1	99.1
3b	Ph	1a	97.5	98.3	99.1
		1b	99.0	98.7	90.9
3c	3,5-(CF ₃)C ₆ H ₃	1a	93.2	96.6	91.9
		1b	99.1	98.6	94.6
3d	Et	1a	98.7	96.8	98.8
		1b	99.7	99.6	98.8

Asymmetric hydrogenation of α -enamides **3** with (R,R)-Et-DuPHOS-Rh catalysts (**1**)^a

Substrate	Catalyst	% ee		
		MeOH	hexane	Supercritical CO ₂
5	1a	62.6	69.5	84.7
5	1b	67.4	70.4	88.4
7	1a	81.1	76.2	96.8
7	1b	95.0	91.2	92.5

Hydrogenation of β,β -disubstituted α -enamides with catalysts **1**^a

Figure 4. Rh-DuPhos enantioselective hydrogenation of enamides.

Figure 5. Enantioselective hydrogenation of enamides.

Figure 6. Asymmetric hydrogen transfer reduction.