Homogeneous Catalysis in Supercritical Fluids

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Supercritical fluids (SCFs), compounds heated and pressurized beyond the critical point, have many unusual properties. Homogeneous molecular catalysts, which have far greater control over selectivity than heterogeneous solid catalysts, are now being tested in SCFs, and early results show that high rates, improved selectivity, and elimination of mass-transfer problems can be achieved. As industry moves away from toxic or environmentally damaging solvents, supercritical carbon dioxide may be an ideal replacement medium for nonpolar or weakly polar chemical processes. More than simply substitutes for nonpolar solvents, SCFs can radically change the observed chemistry. Supercritical carbon dioxide is also an excellent medium for its own fixation, as demonstrated by studies of its hydrogenation.

Molecular catalysts are homogeneous catalysts of adjustable molecular structure that have high selectivity for the production of a range of small to large molecules and are even capable of being made chiral to effect asymmetric catalysis (*1, 2*). In particular, organometallic molecular catalysts offer high selectivity and tunability (Fig. 1). On the other hand, heterogeneous solid catalysts are widely used in industry because they normally allow high rates of reaction and are easily separated from the product, although they are not selective, tunable, or chiral. The ideal catalyst would have the best of both worlds: high reactivity, high selectivity, and operational simplicity. To create an ideal homogeneous molecular catalysis system, the reactivity must be increased, slow mass transfer or diffusion must be eliminated, reactants must be in high concentrations, and the catalyst must have a weak solvation sphere. For nonpolar or weakly polar reactions, especially those involving a gaseous reagent, adopting SCFs as unorthodox reaction media may allow molecular catalysts to meet these goals (Fig. 2).

Supercritical fluids have been used as media in research and industry for extraction and chromatography. They also offer many advantages as reaction media. Improved performance or novel behavior of stoichiometric reactions, particularly in supercritical carbon dioxide ($scCO_2$) and water (scH_2O), has been reported recently (*3–5*). Attention is turning to organometallic chemistry and particularly homogeneous catalysis in SCFs. Replacement of conventional liquid solvents by SCFs can increase the rate and change the selectivity of homogeneously catalyzed reactions.

For researchers of catalysis, the principal benefits of interest are increased reaction rates and selectivities resulting from (i) the high solubility of reactant gases in SCF (*6–8*), (ii) rapid diffusion of solutes into, out of, and within the supercritical phase, (iii) weakening of the solvation around reacting species, (iv) local clustering of reactants or solvent and very large negative activation volumes near the critical point (*9, 10*), and (v) reduction of the cage effect in radical reactions. For chemical technology, SCFs eliminate solvent residues and wastes, can be nontoxic and nonflammable (for example, $scCO_2$ and scH_2O), and allow facile separation of reactants, catalyst, and products after reaction by selective precipitation. Examples of homogeneous catalysis in SCFs are still rare. This review concentrates on coordination chemistry and homogeneous catalysis through complexes based on transition metals, after an introduction to the properties of SCFs.

Properties of SCFs

The critical point of a pure compound is the end point of the liquid-gas line in the phase diagram (Fig. 3) and the point at which the liquid and gas phases become indistinguishable. The supercritical region of the diagram is the region at temperatures higher than the critical temperature (T_c). Properties such as density (Fig. 4) are continuous above T_c and discontinuous below it. Thus, intermediate densities, which are impossible below T_c, can be obtained in the supercritical region. The properties of any compound above its critical point can differ greatly from those below that point. For example, compared with liquid water, scH_2O is much less polar, can dissolve organics (*11*), and has a low dielectric constant ϵ [$\epsilon = 6$ at the critical point versus 90 at the freezing point (*11*)] and a large dissociation constant [pK as low as 8 versus 15 at the freezing point (*12*)]. Near the critical point itself, many properties such as density (Fig. 4), heat capacity, and viscosity vary greatly with only minor increases in temperature or pressure. This region offers both intriguing phenomena and practical difficulties for experiments and industrial applications.

Although water is nontoxic and inexpensive, the high critical point of scH_2O (T_c = 374°C and critical pressure P_c = 218 atm) would thermally decompose most transition metal complexes and the high acidity of scH_2O corrodes reactor walls. The other commonly used SCF, $scCO_2$ (T_c = 31°C

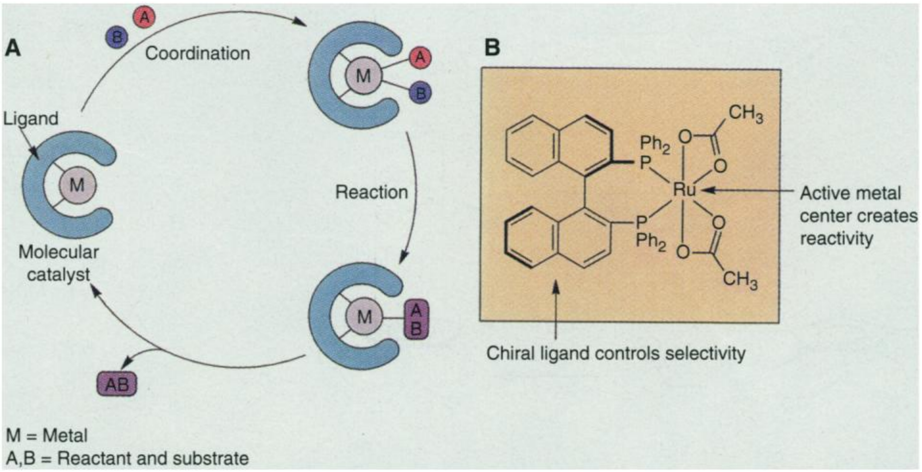

Fig. 1. Organometallic molecular catalysts present a general strategy for selective chemical transformations because of the diverse reactivities of the metallic elements and the unlimited structural permutability of organic ligands. The metallic centers provide reactive sites, the reactivity and selectivity of which are fine-tuned by the surrounding ligands. The advantage of such molecular catalysts is highlighted in asymmetric catalysis by organometallic complexes with well-designed chiral organic ligands (*1, 2*). (**A**) A typical catalytic cycle. (**B**) (*R*)-BINAP–Ru diacetate, an example of a chiral molecular catalyst; Ph = C_6H_5.

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and P_c = 73 atm), avoids these disadvantages and has a large body of published phase and solubility data for binary mixtures with organic solutes (*13*). Solvatochromic studies have found that the dipolarity and polarizability of $scCO_2$, as measured by the Kamlet-Taft π^* parameter, is slightly lower (−0.1 at ~160 atm and 40°C) than that of alkanes (π^* = 0.0) (*14*). Similarly, the polarity, measured on the solvatochromic $E_T(30)$ scale, is 31 to 33, comparable to the value of 31 for alkanes (*15–17*). Supercritical CO_2 can dissolve a wide range of organic compounds. Factors that increase the solubility of organic solutes in $scCO_2$ are volatility, nonpolarity, and the absence of unsaturation or protic functional groups (*13, 18*). However, complete phase diagrams are available for only a few binary mixtures of solutes with $scCO_2$ or scH_2O. Therefore, the phase behavior at operating conditions must be determined for every reaction system.

Although very little quantitative data has been reported on the solubility of transition metal complexes in SCF, neutral complexes with carbonyl (CO), cyclopentadienyl, porphyrin, acetylacetonate, and other chelating ligands have been reported to be soluble to some extent in $scCO_2$. Recently, we established the solubility of a phosphine-containing complex, $RuCl_2[P(CH_3)_3]_4$ (*8, 19*). In that case, trimethylphosphine ligands were used because the triphenylphosphine analog was less soluble in $scCO_2$.

The rates of diffusion of solutes in SCFs are greater than those in liquid solvents. The resulting narrower line widths of quadrupolar nuclear magnetic resonance (NMR) signals allow improved detection of intermediates (*7, 20*). Another result of the high rates of diffusion and low viscosity is a weakened cage effect, which can directly affect rapid reactions.

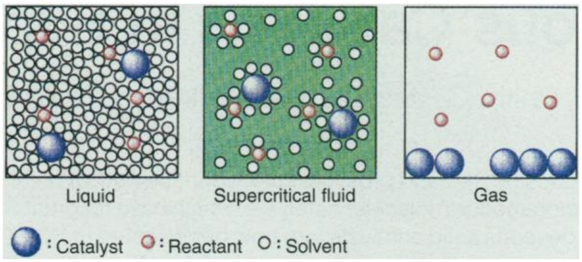
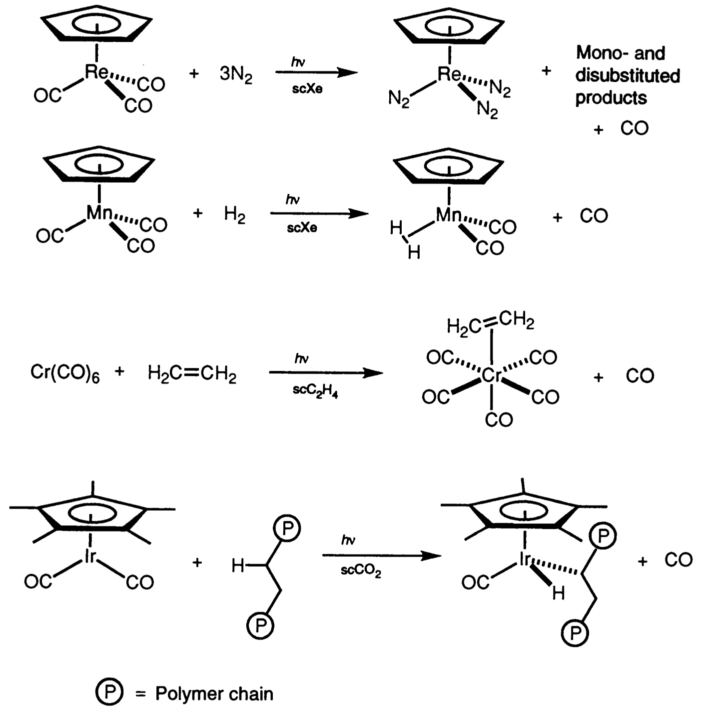


Fig. 2. Illustration of the differences between a homogeneously catalyzed liquid-phase reaction, a homogeneously catalyzed supercritical-phase reaction, and a heterogeneously catalyzed gas-phase reaction.

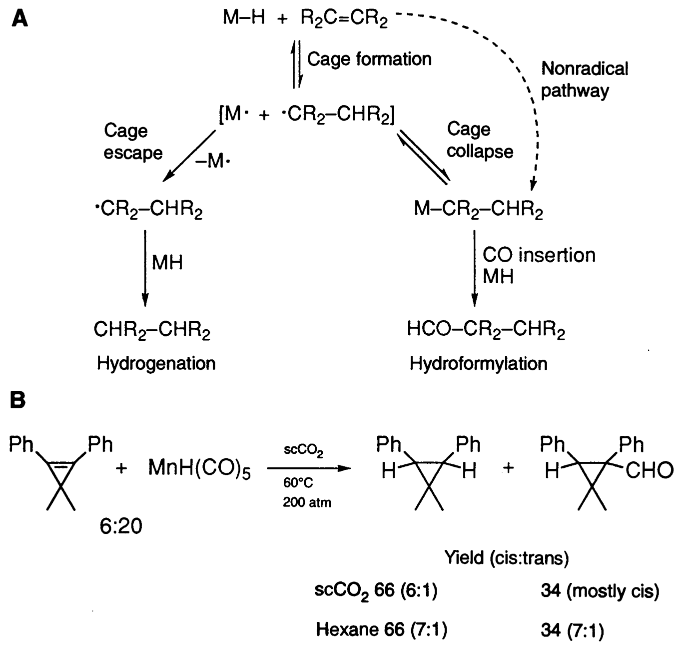
Coordination Chemistry in SCFs

The field of coordination chemistry in SCF has been dominated by Poliakoff and coworkers (*21*), who have exploited the miscibility of gases with SCF (Scheme 1). For example, photolysis of solutions of H_2 or N_2 and carbonyl complexes in scXe or $scCO_2$ generated previously unknown H_2 or N_2 complexes of Mn, Cr, Fe, or Re by substitution of one to three of the CO ligands. These spectroscopically detected products would not have been as stable were it not for the high concentrations of H_2 or N_2 possible in the SCF (*22, 23*). They also isolated a new complex, $Cr(CO)_5(C_2H_4)$, by dissolving $Cr(CO)_6$ in scC_2H_4 in a flow reactor system, passing it through an ultraviolet (UV) photolysis cell, and then venting into a collection vessel (*24*).

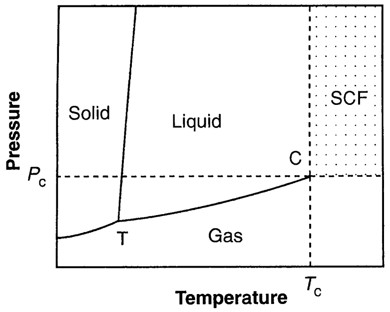
Activation of the C–H bonds of scC_2H_6 is also possible. For example, UV irradiation of $Cp^*Ir(CO)_2$ [$Cp^* = C_5(CH_3)_5$] in H_2-doped scC_2H_6 generated a mixture of $Cp^*Ir(CO)(H)_2$ and $Cp^*Ir(CO)H(C_2H_5)$. The high concentrations of H_2 dissolved in the SCF greatly increased the yield (*25*). The C–H bonds of polyethylene (PE) were activated in a similar study, wherein $scCO_2$ was used to carry $Cp^*Ir(CO)_2$ into PE film and irradiation resulted in C–H bond activation. The unreacted Ir complex was subsequently removed by washing with $scCO_2$ (*26*). This reaction exploits the ability of SCF to rapidly diffuse into and out of polymers. This property also allows $scCO_2$ to carry small complexes into PE, a potentially useful matrix for photochemical studies of coordination complexes. Impregnation of PE



Scheme 1. Stoichiometric reactions of transition metal complexes in supercritical fluids (*21–26*).



Scheme 2. (**A**) The radical pair mechanism for hydrogenation and hydroformylation of olefins by $MnH(CO)_5$ and related complexes. An alternative nonradical route is indicated by the dashed arrow. (**B**) The stoichiometric test reaction of an activated alkene (Ph = C_6H_5 and R is an alkyl group) with $MnH(CO)_5$, which demonstrated equal selectivity for hydrogenation in $scCO_2$ and hexane despite an anticipated weaker cage effect in the former medium (*28*).



Compound	T_c (°C)	P_c (atm)
H_2	−239.9	12.8
C_2H_4	9.9	50.5
Xe	16.6	57.7
CHF_3	25.9	47.8
CO_2	31.0	72.9
C_2H_6	32.3	48.2
CH_3OH	240.0	78.5
H_2O	374.2	218.3

Fig. 3. Generic phase diagram for a compound (T, triple point; C, critical point). In the region above T_c but below P_c, the substance is still supercritical, but it has lower density and is less effective as a solvent. The critical pressures and temperatures of selected compounds are listed in the table on the right (*49*).

with $Mn_2(CO)_{10}$, not normally possible, was achieved by carrying $MnH(CO)_5$ into the PE with $scCO_2$ and then irradiating the complex to convert it into $Mn_2(CO)_{10}$ with loss of H_2 (*27*).

Studies of the stoichiometric reactions of $MnH(CO)_5$ with activated olefins have been performed by Noyori and co-workers (*28*) in order to measure the influence of the solvent cage. No cage effect is expected for reactions that are much slower than the rate of cage escape (*4*); however, for particularly rapid reactions such as those involving radical pairs, the possibility of altered selectivity or rate should be considered. For example, DeSimone and co-workers (*29, 30*) reported that the initiation efficiency of 2,2′-azobis-(isobutyronitrile) for radical polymerization in $scCO_2$ was 1.5 times greater than that in benzene, suggesting a weaker cage effect. Stoichiometric and catalytic hydrogenations and hydroformylations of activated olefins by Mn and Co carbonyls in liquid solvents are generally believed to occur by a radical pair mechanism (Scheme 2A). In this mechanism, hydroformylation requires a solvent cage to trap the alkyl and metal radicals together. A solvent with a weak cage effect should have an increased selectivity for hydrogenation rather than hydroformylation. Surprisingly, a test reaction (Scheme 2B) showed comparable selectivity in hexane and $scCO_2$, indicating that either the cage effects in the two media are comparable or nonradical mechanisms are involved.

Homogeneous Organometallic Catalysis in SCFs

Simultaneous use of SCFs as both reaction medium and reactant has allowed discoveries of novel or highly selective catalytic chemistry. An early example is a 1966 patent for the polymerization of scC_2H_4 or scC_3H_6 with a dissolved $AlCl(C_2H_5)_2/TiCl_4$ catalyst (Scheme 3). In this case, the advantage of operating under supercritical conditions was the ability to selectively precipitate the product fractions by lowering the pressure (*31*). Industrial production of linear low-density polyethylene by a homogeneous metallocene-catalyzed polymerization of scC_2H_4 has been commercialized (*32*).

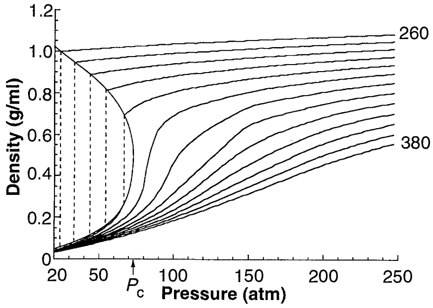


Fig. 4. The density of pure CO_2 as a function of pressure and temperature (*50*).

Two different groups, in Germany and Japan, have independently and simultaneously studied homogeneously catalyzed fixation reactions of CO_2 in the supercritical state. Reetz and co-workers (*33*) reported a coupling reaction between $scCO_2$ and hex-3-yne at 102°C, giving tetraethyl-2-pyrone (Scheme 3) in ~5 TON (turnover number, the moles of product per mole of catalyst). The conversion was lower than in benzene at 120°C (*34*).

The group of Noyori (*8, 35*) discovered efficient homogeneous hydrogenation of $scCO_2$ to formic acid with $RuH_2[P(CH_3)_3]_4$ or $RuCl_2[P(CH_3)_3]_4$ as catalysts and water as a promoter (Fig. 5). The catalytic efficiency of 7200 TON and initial rate or TOF (turnover frequency, TON per hour) of 1400 per hour were greater than any previously reported in subcritical systems. The solubility of $RuCl_2[P(CH_3)_3]_4$ was confirmed by dissolving it in $scCO_2$, passing it through a fine filter, and collecting it at the vent. The conventional triphenylphosphine-based catalyst $RuH_2[P(C_6H_5)_3]_4$ was less active, possibly because it was not as soluble in $scCO_2$. The base, $N(C_2H_5)_3$, was necessary to combat the unfavorable thermodynamics of the reaction. The reaction system was homogeneous at the start of the reaction, but as the reaction proceeded, insoluble $[NH(C_2H_5)_3][HCO_2]$ precipitated. Experiments in which the reaction system had two phases from the start, because of increased amounts of amine or water or because of added tetrahydrofuran or CH_3CN, had much lower rates of reaction that are believed to be a result of dissolution of the catalyst in the liquid phase. The dramatic difference in rate demonstrates the benefits of the homogeneous supercritical phase (Fig. 5).

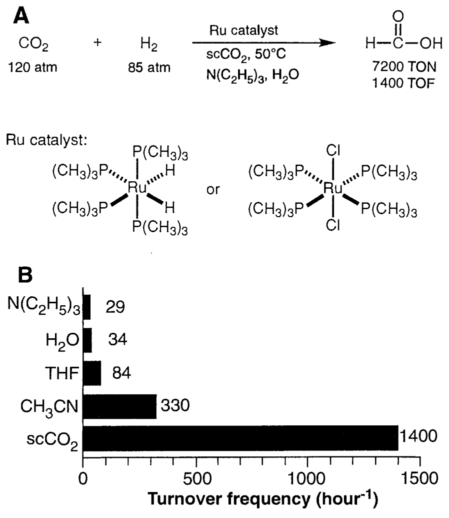
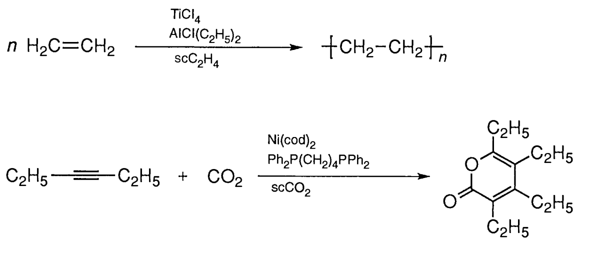


Fig. 5. (**A**) The homogeneous hydrogenation of $scCO_2$ to formic acid. (**B**) The initial rate of the reaction at 50°C with 82 to 85 atm of H_2, 120 atm of CO_2, 0.1 mmol of water, 5.0 mmol of $N(C_2H_5)_3$, and 2 to 3 μmol of $RuH_2[P(CH_3)_3]_4$ in $scCO_2$ (lowest bar) or in liquid reagents under $scCO_2$ (*8*).

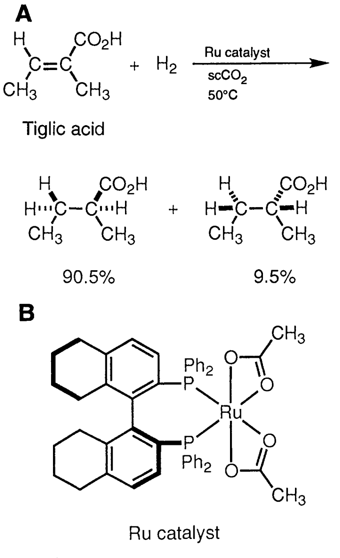
Two related and more industrially significant reactions were also tested. In one, the addition of methanol in amounts below the solubility limit in $scCO_2$ caused the esterification of the formic acid product to methyl formate (*36*). The methanol has two roles, acting as a kinetic promoter of the hydroge-



Scheme 3. Reactions that have been homogeneously catalyzed in SCF include ethylene polymerization in scC_2H_4 (*31*) and the coupling of alkynes with $scCO_2$ (*33*); cod = 1,5-cyclooctadiene, Ph = C_6H_5.

nation of CO_2 and as the esterification agent of the resulting formic acid. In the other related reaction (Fig. 6), use of secondary or primary amines or ammonia resulted in very high yields of formamides: for example, up to 370,000 TON of *N,N*-dimethylformamide (DMF) with up to 99% selectivity (19). The reaction has two steps: hydrogenation to $[NH_2(CH_3)_2][HCO_2]$ is followed by dehydration. The formamide synthesis differs from the formic acid and methyl formate syntheses in that two phases are present from the start. The dialkylamine forms an insoluble liquid carbamate salt with the CO_2. Because the catalyst is insoluble in this liquid salt and probably also in the aqueous product phase that forms later in the reaction (Fig. 6), the hydrogenation is believed to occur in the supercritical phase. The methyl formate and DMF syntheses in $scCO_2$ have far greater TON and, particularly for DMF, greater TOF than have been reported for the same reactions in liquid solvents. There are several possible reasons for the high rates observed, including the high concentration of H_2 possible in $scCO_2$, rapid mass transfer between phases, and perhaps weak solvation of the catalyst. The high TON obtained demonstrate the long catalyst lifetimes possible under these conditions. If hydrogen became readily available by electrolysis that made use of solar or hydroelectric energy, this efficient and nontoxic CO_2 chemistry could replace the current CO-based processes.

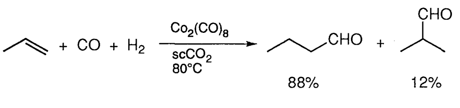
The preceding discussion has described reactions in which the SCF acts as both reactant and reaction medium. Supercritical fluids can also be used profitably as inert media for hydrogenation, hydroformylation, isomerization, and other reactions. An important potential application is the asymmetric hydrogenation of olefinic substrates for the synthesis of chiral pharmaceuticals (1, 2). To investigate the suitability of $scCO_2$ as a medium for such reactions, we tested the hydrogenation of tiglic acid, a model substrate, with Ru complexes of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) derivatives (Scheme 4). For example, with $Ru[(S)\text{-}H_8\text{-}BINAP](O_2CCH_3)_2$, (*S*)-2-methylbutanoic acid was generated in 81% enantiomeric excess at 50°C (37). This selectivity is lower than that in methanol (38, 39) but superior to that in the nonprotic solvent hexane. Importantly, formic acid is not generated as a by-product from the reaction of H_2 and CO_2 because the reaction is performed in the absence of any base.



Scheme 4. (**A**) Homogeneous asymmetric hydrogenation of tiglic acid in $scCO_2$ using (**B**) a Ru catalyst with a partially hydrogenated BINAP ligand (37).

Rathke and co-workers (7, 20, 40) found that the homogeneous hydroformylation of propylene in $scCO_2$ with a Co catalyst (Scheme 5) had a slightly lower rate and higher selectivity for the desired linear aldehyde, butanal, than it did in hydrocarbon solvents. The advantages of using $scCO_2$ were the elimination of gas-to-liquid mass-transfer problems and the narrow line widths of the ^{59}Co NMR spectra, which allowed the species $Co_2(CO)_8$, $HCo(CO)_4$, and even $RCOCo(CO)_4$ to be detected (7, 20). Surprisingly, the rate of hydrogen atom transfer between $CoH(CO)_4$ and $Co_2(CO)_8$ was many orders of magnitude faster than the rate of hydroformylation. This is evidence for the intermediacy of $Co(CO)_4$ radicals in the hydrogen atom transfer reaction and possibly also in the hydroformylation itself.

Many of these studies have cited the beneficial effect of the high solubility of H_2 in $scCO_2$. The first study to report this for a homogeneously catalyzed reaction described the $AlBr_3$-catalyzed isomerization of *n*-hexane (6). This reaction in $scCO_2$ was fivefold more selective for isomerization over cracking than in neat hexane. Further selectivity improvement was obtained if H_2 was dissolved in the SCF.



Scheme 5. Homogeneous hydroformylation of propylene in $scCO_2$ (7).

Despite the high T_c of scH_2O, there has been a report of the oxidation of *p*-chlorophenol with O_2 in scH_2O catalyzed by Cu(II) or Mn(II) salts that were either deliberately added or serendipitously leached from the reactor walls (41). More recently, the cyclotrimerization of alkynes to substituted benzene derivatives has been homogeneously promoted by $CpCo(CO)_2$ in scH_2O (42). Interestingly, thermal decomposition of the complex was not a problem even at the temperature of scH_2O, but the catalytic efficiency was only 1 TON. Selectivity for the 1,2,4-isomer of the product was comparable to that found in organic solvents. In comparison, liquid H_2O at 140°C was an inferior medium because of significant side reactions.

Future Outlook

Possibilities of greater or even outstanding rates and adjustable selectivities is motivating research into homogeneous catalysis in SCF, but the number of reactions tested so far is very small indeed. The field is open for tests of the effect of pressure, temperature, choice of SCF, clustering, solvent cages, cosolvents, and adjustable solubilities on the performance of catalyzed reactions. Because phase behavior and solubility data for multicomponent systems are scarce, experimental studies must include determinations of the phase behavior at reaction conditions. Early successes have established that homogeneous catalysis is possible in SCF and that mass transfer rates, reaction rates, and selectivities have been greatly improved.

The utility of SCF is of course not limited to organometallic catalysis. Many of the potential advantages of SCF as reaction media have been demonstrated in studies of uncatalyzed, heterogeneously catalyzed, or enzyme catalyzed (43, 44) reactions, which have been reviewed (3–5, 11, 45, 46). Observed rate increases and enhancements of catalyst lifetime in heterogeneous catalysis were at least partly the result of higher

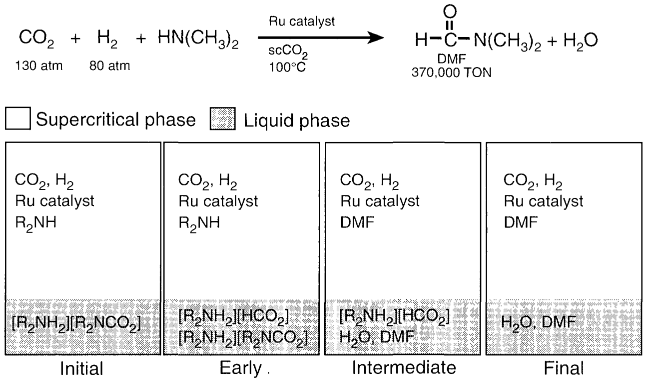


Fig. 6. The composition of the phases during the synthesis of *N,N*-dimethylformamide (DMF) from dimethylamine, H_2, and $scCO_2$ (R = CH_3). The size of the liquid phase is exaggerated.

diffusivities between the SCF and the catalyst surface and of reduced coke deposition, benefits that have no parallel in homogeneous catalysis. The restriction to nonpolar or weakly polar reactants has been overcome through the use of entrainers or surfactants. For example, DeSimone and others have cleverly used soluble fluoropolymers in small amounts as surfactants to achieve greater rates or uniformity of product particle size during polymerization of methylmethacrylate (*47*) or acrylamide (*48*) in scCO$_2$. A similar approach could be used for molecularly catalyzed polar reactions in scCO$_2$.

The industrial outlook for SCFs as reaction media may be favorable because of the beneficial environmental effect of dispensing with organic liquid solvents. High-pressure operations would be facilitated in large-scale production processes and especially continuous-flow systems for which SCFs are well suited. Because of the nontoxicity of scCO$_2$, a future direction for molecular catalysis in that medium could be pharmaceutical synthesis. This is a field in which homogeneous transition metal-based catalysts have had a great impact. It is certain that researchers of homogeneous catalysis will adopt SCF as media for many more reactions and thus broaden the scope of this technique.

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51. We gratefully acknowledge the assistance and advice of Y. Hsiao, J. Xiao, and K. Aoyagi of ERATO.

RESEARCH ARTICLE

Structures of Metal Sites of Oxidized Bovine Heart Cytochrome c Oxidase at 2.8 Å

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The high resolution three-dimensional x-ray structure of the metal sites of bovine heart cytochrome c oxidase is reported. Cytochrome c oxidase is the largest membrane protein yet crystallized and analyzed at atomic resolution. Electron density distribution of the oxidized bovine cytochrome c oxidase at 2.8 Å resolution indicates a dinuclear copper center with an unexpected structure similar to a [2Fe-2S]–type iron-sulfur center. Previously predicted zinc and magnesium sites have been located, the former bound by a nuclear encoded subunit on the matrix side of the membrane, and the latter situated between heme a_3 and $\mathrm{Cu_A}$, at the interface of subunits I and II. The O_2 binding site contains heme a_3 iron and copper atoms ($\mathrm{Cu_B}$) with an interatomic distance of 4.5 Å; there is no detectable bridging ligand between iron and copper atoms in spite of a strong antiferromagnetic coupling between them. A hydrogen bond is present between a hydroxyl group of the hydroxyfarnesylethyl side chain of heme a_3 and an OH of a tyrosine. The tyrosine phenol plane is immediately adjacent and perpendicular to an imidazole group bonded to $\mathrm{Cu_B}$, suggesting a possible role in intramolecular electron transfer or conformational control, the latter of which could induce the redox-coupled proton pumping. A phenyl group located halfway between a pyrrole plane of the heme a_3 and an imidazole plane liganded to the other heme (heme a) could also influence electron transfer or conformational control.

Bovine heart cytochrome c oxidase is a large multicomponent membrane protein complex with molecular size of 200 kilodaltons comprising 13 different polypeptide subunits. Located in the subunits are two heme A moieties, two redox active copper sites, one zinc, one magnesium, and possibly some phospholipids as the intrinsic constituents (*1*, *2*). This enzyme is one of the most intriguing biological macromolecules in the cell. As the terminal enzyme of biological oxidation, it reduces O_2 to H_2O at an active site with the four redox active transition metals coupling to a proton pumping pro-