

Probing the Cybotactic Region in Gas-Expanded Liquids (GXLs)

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ABSTRACT

Gas-expanded liquids (GXLs) are a new and benign class of liquid solvents, which 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. Other advantages include benign nature, low operating pressures, and highly tunable properties by simple pressure variations. The chemical community has only just begun to exploit the advantages of these GXLs for industrial applications. This Account focuses on the synergism of experimental techniques with theoretical modeling resulting in a powerful combination for exploring chemical structure and transport in the cybotactic region of GXLs (at the nanometer lengthscale).

Introduction

Gas-expanded liquids (GXLs) are a versatile and benign class of liquid solvents, which 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 trans-

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Charles L. Liotta and Charles A. Eckert have been research partners for 17 years; they occupy a common laboratory space and co-direct students in both Chemistry and Chemical Engineering. Their research focus is on the use of novel solution chemistry for sustainable technology, and for the implementation in industry of their findings, they received jointly for the 2004 Presidential Green Chemistry Challenge Award. Dr. Liotta is a Regent's Professor and the Vice-Provost for Research and Dean of Graduate Studies. Dr. Eckert is the J. Erskine Love, Jr., Institute Professor and Director of the Specialty Separations Center.

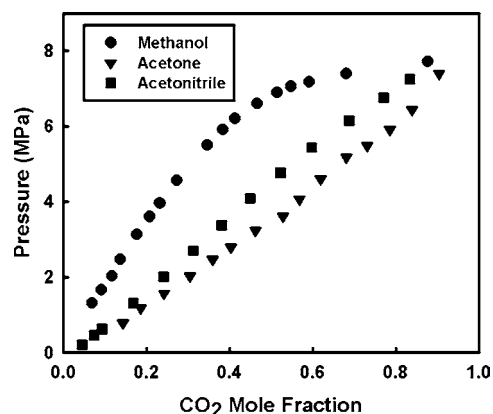


FIGURE 1. Bubble point curves for CO₂ with methanol, acetone, and acetonitrile at 40 °C. Data from Chang et al.²

port properties, which are highly tunable by simple pressure variations. GXLs are formed by the dissolution of a gas, usually CO₂, into organic liquids. In general, liquid CO₂ is a poor solvent, whereas typical organics such as acetone and methanol are good solvents; thus a wide range of solvent properties are easily accessible through solvent expansion.¹ At moderate pressures (less than 8 MPa), gaseous CO₂ has a considerable solubility in many organic solvents, including alcohols, ketones, ethers, and esters (Figure 1).² This provides the opportunity to alter the physicochemical properties of the liquid solvent—most notably the polarity, dielectric constant, and solubility—at much lower pressures than those required for supercritical fluid processing. Moreover, CO₂ is an ideal antisolvent, because it is environmentally benign, easily removed, and recyclable.

Recently, exciting developments in the use of GXLs have resulted in a vast expansion of opportunities to use these solvents for chemical reaction processing. This field has grown from the roots of GXLs as an antisolvent-type media for materials preparation, an application that dominated GXL use until the last five years. Because of this recent growth in GXL applications and the exciting work left to be done, a review of GXLs and new applications is appropriate. This Account will (1) summarize the experimental and computational advances relevant to the use of GXLs as reaction media and (2) provide our vision of the future direction of research in this field and the opportunities that various experimental and computational tools provide for this direction.

Interest in the use of GXLs as processing media arose from developments with supercritical fluids (SCFs). SCFs and GXLs have been used as solvent media for four main reasons: (i) high diffusivities and low viscosities reduce mass transfer limitations, (ii) solvent properties are easily tuned by pressure, (iii) downstream processing and solvent removal are straightforward, and (iv) they provide environmentally benign alternatives to traditional liquid solvents.

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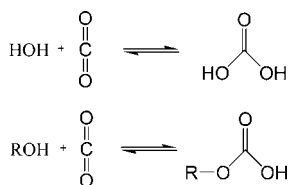


FIGURE 2. Structures and formation of (a) carbonic acid from water and CO₂ and (b) methylcarbonic acid from methanol and CO₂.

Tunability is a powerful tool for facile separation of solvent from solute, as well as products from reactants. Any chemical process inevitably involves a reaction followed by a separation or purification of the product. Separations typically represent 60–80% of the total cost of a chemical process. The ability to reduce separations costs represents one of the most significant processing advantages inherent to GXLS.

The chief disadvantage of scCO₂ is the inability to dissolve most polar or charged species. Traditionally, this limitation has been ameliorated through the addition of cosolvents. Different cosolvents and cosolvent concentrations can affect the affinity of the medium for different species and even increase the solvent tunability. Usually, cosolvents enhance the SCF's solvation power by increasing the polarity of the fluid.³

Although the addition of cosolvents increases the solubility of polar compounds in SCFs, the addition of 1–5% organic modifier increases the mixture's critical pressure significantly. This has detrimental effects on both economic and processing variables. The use of GXLS avoids this by utilizing lower pressure mixtures of CO₂ and organic solvents. It enables the use of a significantly higher organic loading (10–50%), providing vastly superior solvating power with only a moderate sacrifice in solute transport. The use of GXLS for chemical synthesis thus represents a sensible step toward more environmentally benign chemical processing, because up to 90% of volatile organic compound (VOC) emissions can be eliminated.

Gas-Expanded Liquids

A. Definition of a GXL. The boundary that separates a “gas-expanded liquid” from a “cosolvent-modified supercritical fluid” is vague at best. In general, we consider a GXL to be any mixture of a neat gas (usually CO₂) and an organic solvent at conditions *below* the mixture's critical point. While some of the more interesting properties of GXLS occur only at high CO₂ concentrations, such as improved gas solubility, other properties, notably diffusivity, do change at low expansions (<50% volume expansion). As another example, the interaction between CO₂ and alcohols (most notably methanol) to form alkylcarbonic acids⁴ can occur at very low CO₂ pressures (Figure 2). In fact, the use of methylcarbonic acid as an acid catalyst has been demonstrated by us at pressures as low as 15 bar,⁵ corresponding to volume expansions of only 10–15%. While these are technically GXLS, they display few of the changes in solubility present at higher CO₂ loadings.

Perhaps the most important physical changes that occur in the gas-expanded regime involve simple accelerations in volume expansion with changes in pressure. As a GXL moves toward a SCF, the rate of volume expansion with increased pressure rises dramatically. Research into gas-expanded liquids has generally focused on the saturated liquid phase at VLE conditions, following the bubble point curve of the mixture. However, as the critical point of the mixture is reached (generally around 90% CO₂), the vapor and liquid phases coalesce and the solution becomes a cosolvent-modified SCF instead of a GXL.

Mixtures of CO₂ and organic solvents have sometimes also been called “enhanced fluidity liquids”, which are typically used as HPLC mobile phases for chromatographic separations.⁶ As such, the mixtures are often pressurized far above the bubble point. In this region, the fluid resembles a highly compressed SCF more than a GXL, and the pressures are more typical of SCF processing.

B. Applications of GXLS. Diffusion coefficients of organic solutes in GXLS⁷ indicate that addition of 50–80% CO₂ to methanol can increase solute transport by 1–3 orders of magnitude. Thus, GXLS provide opportunities to enhance multiphase chemical reactions by improving gas solubility and diffusivity. Gas/liquid reactions are an important area of catalysis, most notably for oxidations, hydrogenations, and hydroformylations, and are often limited by transport of the gaseous reactants to the liquid or solid substrates and catalysts. Further gas solubility significantly increases in GXLS.^{8–10} The H₂ mole fraction in CO₂ expanded methanol was demonstrated to increase by as much as 100%. For oxygen, CO₂ has an inerting effect, raising the upper explosion limit of the mixture and enabling much higher concentrations of O₂. Subramaniam¹¹ took advantage of the increased oxygen solubility, performing oxidation reactions in CO₂-expanded solvents, and observed significantly higher conversions than in either neat organic solvent or scCO₂. In addition, the catalyst was precipitated postreaction by simply increasing the CO₂ pressure of the system.

Transport across liquid/liquid interfaces is another common feature in multiphase catalysis. The problem of interacting species in separate phases is often overcome by using a highly polar organic solvent, such as DMSO, which often leads to contamination and product isolation difficulties. Another option, phase-transfer catalysis (PTC), employs an amphiphilic molecule, for example, quaternary ammonium salts, to “shuttle” polar species from an aqueous phase into an organic phase for reaction.¹² Our group first reported the use of SCFs to overcome mass transfer limitations in solid/liquid PTC systems¹³ offering benign alternatives to greatly improve transport, product separation, catalyst recycle, and facile solvent removal. We are currently investigating the benefits of GXL transport properties combined with increased solvent power as applied to liquid–liquid PTC reactions.

We have also investigated GXLS for the recovery of PTCs using aqueous extraction.¹⁴ In current practice, PTC recovery is achieved by repeated washings of the organic

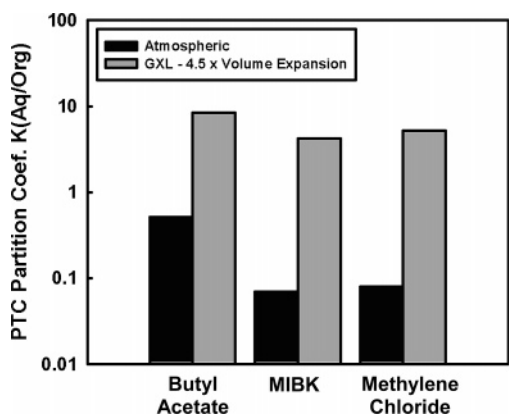


FIGURE 3. TBAP distribution coefficient as a function of CO₂ expansion at room temperature.¹⁴

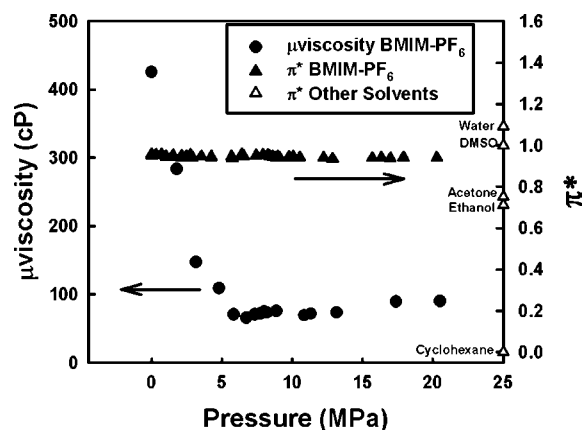


FIGURE 4. Estimated microviscosity (left axis for [bmim][PF₆]/CO₂ as a function of CO₂ pressure at 35 °C and Kamlet–Taft π^* parameter (right axis), which is constant for the [bmim][PF₆]/CO₂ system (pure liquid solvent π^* values are shown for comparison). Data from Lu et al.¹⁸

phase, followed by an expensive reconcentration process. CO₂ expansion of the organic phase can dramatically alter the distribution of PTC into the aqueous phase, reducing the amount of wash water by 95% as compared to current industrial processes. An example of the shift in distribution coefficients, often in excess of an order of magnitude, is presented in Figure 3.

GXLs have been proposed as a reversible cosolvent/extraction solvent for ionic liquid reactions¹⁵ using methods similar to scCO₂ extraction of volatile organic products synthesized in ionic solvents.¹⁶ Our group has performed catalytic transformations in biphasic scCO₂/ionic liquid media¹⁷ and demonstrated the effect of CO₂ expansion on ionic liquid local polarity and microviscosity¹⁸ (Figure 4). The local viscosity of an ionic liquid can be reduced by 2 orders of magnitude by addition of 200 bar CO₂ pressure, while the local polarity of the gas-expanded ionic liquid is relatively unaffected. Thus, CO₂ expansion can significantly enhance transport within ionic liquid solvents (which is often poor) without detrimental impact on the solvation power.

Gas-antisolvent crystallization has been the most common application of GXLs.¹⁹ One attractive feature of gas-antisolvent systems is the potential to nucleate crystals

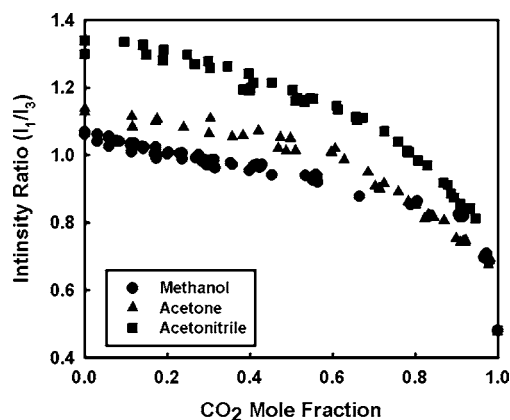


FIGURE 5. Pyrene fluorescence (Py scale) results for GXLS at 40 °C. Data from Lu et al.²⁰

throughout the solution. In a traditional crystallization, cooling is employed to supersaturate the system, inducing nucleation and growth of crystals. One major drawback of cooling is heat transfer from a surface, which can lead to nucleation only at the cooler surface; others are fouling and impurities at the surface. With a gas-antisolvent system, supersaturation occurs homogeneously throughout the solution, yielding highly uniform particles with advanced properties.

Experimental Probes of the Cybotactic Region

The cybotactic region is defined as the region around a solute molecule affected by its presence. The application of GXLs requires characterization of their thermophysical properties and the effect of those properties on the cybotactic region. The most common experimental techniques for accomplishing this use solvatochromic probes.

Solvatochromic effects are a result of probe molecule transitions through structural or electronic rearrangements induced by external moieties. The solvation shell around the probe molecule often influences this transition and can be easily measured by changes in the absorbance or fluorescence emission spectra. Our lab has experimentally investigated the cybotactic region of GXLs using (1) pyrene fluorescence, (2) Kamlet–Taft interaction parameters, and (3) cis–trans isomerizations of substituted azobenzenes.

Pyrene is a widely accepted fluorescence probe for solvent polarity with five characteristic emission bands in its spectrum. The first band is strongly dependent on solvent polarity, while the third band is insensitive to the surroundings. The intensity ratio ($Py = I_1/I_3$) changes with solvent polarity, providing a measure of the local environment around a pyrene molecule. Figure 5 displays the fluorescence intensity ratio as a function of composition for CO₂ expanded methanol, acetone, and acetonitrile.²⁰ The curves indicate a gradual decrease in Py at low CO₂ pressures, followed by an abrupt decrease at higher CO₂ concentration, ~80 mol % for acetonitrile and ~90 mol % for methanol. The nonlinearity of the curves indicates a nonuniform transition of the local environment around the pyrene molecule with increasing CO₂ concentration.

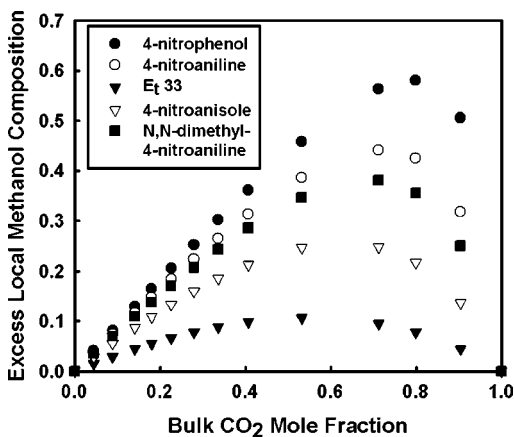


FIGURE 6. Excess compositions calculated from measurement of solvatochromic shifts in GX-methanol at 25 °C. Data from Wyatt et al.²⁵

This suggests an enhanced methanol, acetone, and acetonitrile concentration in the cybotactic region around pyrene, resulting in preferential solvation of the fluorescence probe.

The methods developed by Kamlet and Taft for determining local solvent properties use the solvent parameters dipolarity/polarizability π^* , hydrogen-bond donating (HBD) acidity α , and hydrogen-bond accepting (HBA) basicity β . These parameters have been important indices for providing insight into the solvent strength of both liquids and SCFs.^{21–23} Experimental measurements of π^* , α , and β are based on the solvent-induced spectral shift of certain indicators,²² on a relative scale, and reflect the chromophore's molecular environment. In the presence of the highly nonuniform solvent environment of a GX, one expects that solvatochromic shifts will be nonlinear functions of the relative cosolvent composition. The assumption that spectral shifts are linearly related to local solvent composition has traditionally been used for calculations of local cosolvent compositions in SCFs.²⁴

Results for GX-methanol and GX-acetone suggest a methanol/acetone enhanced local environment,²⁵ similar to that for pyrene. Figure 6 shows an excess local composition function determined with respect to the assumed linear relationship and demonstrates the degree of local composition enhancement for each of the solvatochromic probes investigated. The data illustrate the variation of the local mole fraction of methanol up to 60% over the bulk mole fraction, with the maximum typically occurring at about 75% CO₂ in the mixture. This evidence of local composition enhancement in GXs is similar to that observed in scCO₂–cosolvent systems but reduced in intensity.

Chemical reactions provide an outstanding opportunity to probe local inhomogeneities in structure. Therefore, in addition to the equilibrium studies described above, the rate of a sensitive model reaction—the cis–trans isomerization of substituted azobenzenes—has been determined as a measure of both specific and general solute–solvent interactions.²⁶ CO₂ expansion of 1,4-dioxane within a 40 bar pressure range enables reaction rate tunability from

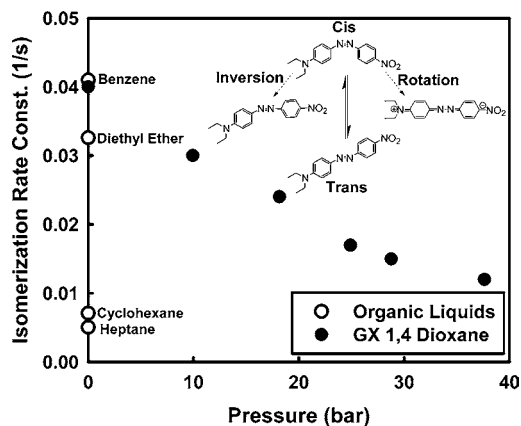


FIGURE 7. DENAB isomerization mechanism and rate in GX-dioxane.

that found in pure dioxane solvent to a nonpolar solvent, such as cyclohexane (Figure 7).

Computational Explorations of the Cybotactic Region

In addition to experimental probes of the cybotactic region, significant theoretical and computational efforts have been dedicated to elucidation of the local structure. While experimental techniques rely on a probe molecule for structural information, computational methods can use tagged solvent molecules to take the place of the solute probe used experimentally. This method eliminates probe-specific effects on the cybotactic region and increases the statistics available for computation. Computational studies are also able to ascertain the local environment around nonpolar solute (or tagged-solvent) molecules, a feat not easily attained through experimental probes alone.

A. The Cybotactic Region in SCFs. Local density enhancements in SCFs have a profound effect on chemical reactions²⁷ and have led to extensive experimental^{28–30} and computational^{31,32} research on the molecular clustering apparent in SCFs near the solvent critical point. The local densities are strongly dependent on pressure and have appeared in some cases to approach twice that of the bulk. These have been measured experimentally using fluorescence spectroscopy,^{27,33} electron paramagnetic resonance spectroscopy,³⁴ FTIR,³⁵ and UV–vis spectroscopy.²⁶ Evidence of significant pressure-dependent local density enhancements was first reported by our laboratory³⁰ and confirmed the existence of large negative partial molar volumes at solute infinite dilution in attractive mixtures near the critical point. These negative partial molar volumes were corroborated by Chialvo and Cummings³⁶ through integral equation theories (correlation function integrals) of dilute pyrene in scCO₂ and dilute neon in supercritical xenon systems. Based on partial molar volume data, excess CO₂ molecules around naphthalene were calculated by Debenedetti using fluctuation theory.²⁷

Early molecular dynamics efforts by Debenedetti examined the effect of solvent–solute interactions on local density enhancements in supercritical Xe, Ne, and CO₂.³¹

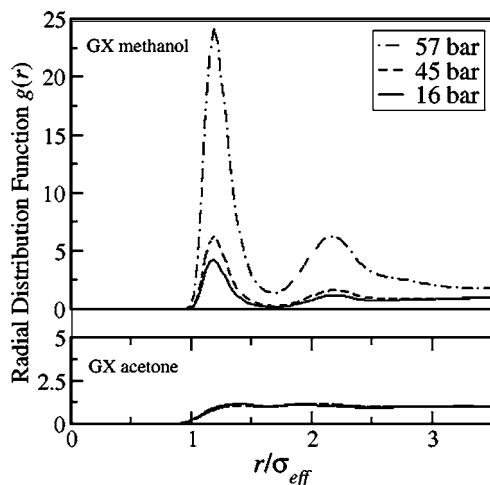


FIGURE 8. Radial distribution function as a function of the reduced correlation length for GX-methanol (intermolecular $g(r)$ between the methanol oxygen and hydroxyl hydrogen, O_m-H_m) and GX-acetone (intermolecular $g(r)$ between the acetone central carbon and oxygen, C_a-O_a).

Maroncelli has developed several simulation techniques for examining various electronic and electrostatic effects on local density augmentation,³⁷ and Egorov studied chemical reactions³⁸ and nanocrystals³⁹ in SCFs. Recent molecular dynamics (MD) simulations by Tucker³² examined local density inhomogeneities of Lennard-Jonesian fluids, mapping out the dynamic behavior of the solvent clusters (solvent relaxation).

B. The Cybotactic Region in GXs. The microscopic structure in GXs is also nonuniform; molecular dynamics simulations on CO_2 -expanded methanol and CO_2 -expanded acetone⁴⁰ yielded nontrivial local structural information (radial distribution functions, Figure 8, and orientational distribution functions), as well as time-dependent properties through local number density autocorrelation functions and diffusion coefficients. In general, as CO_2 expansion of the medium is increased, the properties shift between the limits of a pure liquid (10–35% CO_2) and an expanded liquid in which compressibilities begin to diverge (35–90%).

The clustering of methanol molecules is greatly influenced by the presence of CO_2 , which also increases the lifetimes of the methanol clusters while decreasing the persistence of the CO_2 clustering over a wide range of CO_2 expansion. This result is consistent with the physically intuitive notion that hydrogen bonding within methanol clusters is dominating their structure as shown in Figures 8 and 9. Acetone molecules, on the other hand, are aprotic and the local number densities of acetone molecules about one another decreases concurrently with the bulk number density in the GX. Thus an absence of clustering is observed in GX-acetone (Figure 8).

Interaction time constants were also derived from the simulated local number density autocorrelation functions. The increase in time constant upon CO_2 addition to methanol is consistent with the macroscopically observed persistence in hydrogen bonding acidity and basicity of GX-methanol when compared to GX-acetone. Similar

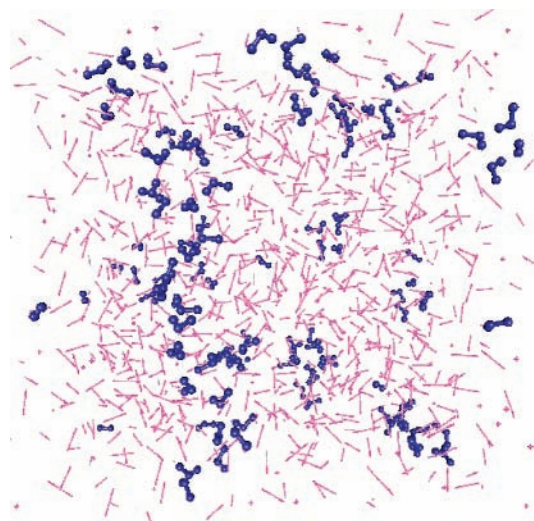


FIGURE 9. MD snapshot of GX-methanol (blue) with 88.4 mol % CO_2 (red).

trends occur for self-diffusion coefficients in GXs, where both self-diffusion coefficients increase with added CO_2 concentration.

C. Synergism between Computation and Experiment.

The challenge to complete understanding of GXs is the fact that interactions and observables at several distinct length scales are important. Solvation and directionality thereof is important to the behavior of solutes (reactants, catalysts, or products) at the angstrom scale, transport is important at the mesoscale, and the thermodynamic behavior (controlling overall morphology, phase behavior, and partitioning) is important at the macroscopic scale. Thus the use of computer simulation and theory synergistically with experiment is paramount to making progress. For example, Siepmann⁴¹ and Gubbins⁴² explored the ternary phase behavior of CO_2 with hydrocarbons and fluorocarbons. These simulations were used to correlate phase data (first reported from our laboratory^{43–45}) regarding the ability of subcritical CO_2 to induce the miscibility of fluorocarbon and hydrocarbon liquids for homogeneous catalyst recycle in fluorous biphasic catalysis. Similar techniques have focused on aqueous biphasic systems.^{46,47}

The SCF community has certainly recognized the value of synergistic approaches, combining computation and experiment to characterize better and design optimal solvent conditions for target processes. For example, Eckert and Debenedetti²⁷ examined the effects of thermodynamic variables on local solvation in $scCO_2$. Randolph⁴⁸ used a Lennard-Jonesian fluid model to describe the local density enhancements observed from EPR measurements. Maroncelli⁴⁹ utilized time-resolved fluorescence techniques to refine theoretical models of rotational lifetimes in SCFs. Johnston and Rossky utilized simulation techniques to reproduce the rates of various chemical reactions in scH_2O .⁵⁰

Theoretical and computational approaches have yielded several nonempirically based successes. Egorov and Skinner⁵¹ used integral equation theory to correlate vibrational

line width broadening in SCFs. More recently, Siepmann has used Monte Carlo techniques to study large negative partial molar volumes of solute molecules in scCO_2 .⁵² Despite these latter successes for 100% theoretical descriptions of SCFs, we believe that the combination of experiment and computation is critical for characterization of GXLs due to increased heterogeneity and large number of important length scales. For example, catalyst simulation in a GXL could yield the optimal conditions (such as CO_2 pressure and temperature) to induce a desired (or preferred) geometry in the solvent structure for maximum yield and selectivity.

One complication that arises for simulation of GXLs is the presence of a coexisting vapor phase, very rich in CO_2 . Siepmann⁵³ constructed the phase diagram for such a system at 60–80 °C and dilute in methanol using configurational-bias Monte Carlo techniques. We instead took advantage of our experimental expertise and used measured phase data to provide the (x, P, T) conditions for a GXL phase operating under VLE conditions. This allowed us to perform MD simulations in a quasi-stable single phase, wherein the interesting chemistry is expected to take place. We validated this approach by testing various macroscopic observables obtained from experimental data, excluding those used as inputs for the phase conditions. Meanwhile the local structure of the GXL, not easily observed experimentally, can be computed readily in the simulations.

Discussion and Vision

The optimal synergism between experimental and computational efforts arises from recognizing the nonoverlapping strengths and weaknesses of each. Experimental probes of solvation phenomena are well developed to yield good numerical answers. However, obtaining structural information from experimental results, such as solvatochromic shifts, requires careful interpretation of the data. Assumptions are made about the effect of mixtures on solvation properties and how the different molecular interactions can be averaged to produce an indirect measure of local structure. In addition, careful consideration of the length scales of the experimental technique is required for proper identification of the particular interactions that are measured. The presence of the probe itself may alter the local structure, yielding a result that is probe-specific and not always generalizable. Finally, while experimental techniques are generally capable of providing structural information that is averaged over a particular region in space; this is generally a nondirectional (surface-averaged) result or a particular number of solvation spheres (volume-averaged) result. These limitations may not be individually restrictive, but it is important to keep a proper perspective on what is being measured, and what is inferred, using a particular experimental technique.

Molecular simulations complement some of the limitations inherent in most experiments dealing with local structure. The local environment is well defined and the

particular orientation of molecules much easier to obtain. The use of probes is unnecessary, eliminating solute-specific effects. The size of the local environment can be defined by the researcher, and specific information about orientation is easily obtained at any length scale, even those too short to produce effects observable by bulk experimentation. Unfortunately, the correlation of microscopically observed phenomena with macroscopic observables is nontrivial and fraught with many of the pitfalls underlying experimental assumptions as well. Finally, force-field generation for highly complex molecules, such as organometallic complexes, is nearly impossible. Nevertheless, such models are being developed and refined as the need arises, and it is only a matter of time before such complex systems can be simulated routinely through molecular dynamics simulations.

A more difficult problem arises if we wish to obtain the mechanism and rate of chemical reactions within GXLs that have now been revealed to be heterogeneous in time and space where methods involving analysis of rare events must be extended to allow for such nonequilibrium environments.^{54,55} Recent approaches involving transition path ensembles,⁵⁶ or the non-recrossing geometry of the transition state,⁵⁷ may help overcome such difficulties.

In our work exploring the cybotactic region in GXLs, experimental data describing the macroscopic (thermodynamic) state were used as inputs to the computational models, and in turn, these models reproduced macroscopic experimental data and elucidated elements of the microscopic structure that cannot be observed experimentally. This approach provides both phenomenological and molecular understanding of the cybotactic region, as well as a test for the accuracy of our computational models.

Concluding Remarks

Nonuniformity in the cybotactic region of GXLs will affect the local transport and solvation properties of the fluid, as shown by calculated solvent–solute structures. Such knowledge could be used to design GXLs that would enhance or suppress solubilities. Further, the method could be extended to chemical reactions by looking at transition state and product structures to control rates, equilibria, and selectivity. Therefore, we expect applications of GXLs to appear in increasing quantities soon. The development of models such as ours for understanding local solvation phenomena could provide a means of designing solvents for applications in all fields of chemical research.

Opportunities exist for the use of GXLs in the development of homogeneous and heterogeneous catalysts. With increased emphasis on selectivities for chiral products, such as pharmaceuticals, an understanding of local solvent structure could help, enabling true reaction-specific solvent design. The ability to predict solvent effects on these selectivities would present a huge economic benefit

by greatly reducing process waste and simplifying development efforts.

Further, GXLs have enormous potential for the synthesis and processing of advanced materials, taking advantage of the tunable solvent strength and unique transport properties for nanoscale material synthesis, assembly, and processing.⁵⁸ These examples demonstrate the potential power of local structure within GXLs and how a detailed knowledge can be used to exploit GXLs as advanced solvent media for a wide range of applications.

References

- Eckert, C. A.; Liotta, C. L.; Bush, D.; Brown, J. S.; Hallett, J. P. Sustainable Reactions in Tunable Solvents. *J. Phys. Chem. B* **2004**, *108* (47), 18108–18118.
- Chang, C. J. Volume Expansion Coefficients and Activity Coefficients of High-Pressure Carbon Dioxide Dissolution in Organic Liquids at 298 K. *J. Chem. Eng. Jpn.* **1992**, *25* (2), 164–169.
- Dillow, A. K.; Hafner, K. P.; Yun, S. L. J.; Deng, F.; Kazarian, S. G.; Liotta, C. L.; Eckert, C. A. Cosolvent Tuning of Tautomeric Equilibrium in Supercritical Fluids. *AIChE J.* **1997**, *43* (2), 515–524.
- West, K.; Culp, C.; McCarney, J.; Griffith, K.; Bush, D.; Liotta, C.; Eckert, C. In Situ Formation of Alkylcarbonic Acids with CO₂. *J. Phys. Chem. A* **2001**, *105*, 3947–3948.
- Chamblee, T. S.; Weikel, R. R.; Nolen, S. A.; Liotta, C. L.; Eckert, C. A. Reversible in Situ Acid Formation for *b*-Pinene Hydrolysis using CO₂ Expanded Liquid and Hot Water. *Green Chem.* **2004**, *6* (8), 382–386.
- Lee, S. T.; Olesik, S. V.; Fields, S. M. Applications of Reversed-Phase High Performance Liquid Chromatography Using Enhanced Fluidity Liquid Mobile Phases. *J. Microcolumn Sep.* **1995**, *7* (5), 477–483.
- Sassiat, P. R.; Mourier, P.; Caude, M. H.; Rosset, R. H. Measurement of Diffusion Coefficients in Supercritical Carbon Dioxide and Correlation With the Equation of Wilke and Chang. *Anal. Chem.* **1987**, *59*, 1164–1170.
- Bezanehtak, K.; Dehghani, F.; Foster, N. R. Vapor-Liquid Equilibrium for the Carbon Dioxide + Hydrogen + Methanol Ternary System. *J. Chem. Eng. Data* **2004**, *49* (3), 430–434.
- Xie, X.; Brown, J. S.; Bush, D.; Eckert, C. A. Bubble and Dew Point Measurements of the Ternary System Carbon Dioxide + Methanol + Hydrogen at 313.2 K. *J. Chem. Eng. Data* **2005**, *50* (3), 780–783.
- Lazzaroni, M. J.; Bush, D.; Eckert, C. A.; Glaser, R. High-Pressure Vapor-Liquid Equilibria of Argon + Carbon Dioxide + 2-Propanol. *J. Supercrit. Fluids*, in press.
- Musie, G.; Wei, M.; Subramaniam, B.; Busch, D. H. Catalytic Oxidations in Carbon Dioxide-Based Reaction Media, Including Novel CO₂-Expanded Phases. *Coord. Chem. Rev.* **2001**, *219–221*, 789–820.
- Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994.
- Dillow, K.; Yun, S. L. J.; Suleiman, D.; Boatright, D. L.; Liotta, C. L.; Eckert, C. A. Phase-Transfer Catalysis Reaction in Supercritical Fluid Carbon Dioxide. *Ind. Eng. Chem. Res.* **1996**, *35*, 1801–1806.
- Xie, X.; Brown, J. S.; Joseph, P. J.; Liotta, C. L.; Eckert, C. A. Phase-Transfer Catalyst Separation by CO₂ Enhanced Aqueous Extraction. *Chem. Commun.* **2002**, 1156–1157.
- Scurto, A. M.; Aki, S. N. V. K.; Brennecke, J. F. CO₂ as a Separation Switch for Ionic Liquid/Organic Mixtures. *J. Am. Chem. Soc.* **2002**, *124* (35), 10276–10277.
- Blanchard, L. A.; Brennecke, J. F. Recovery of Organic Products from Ionic Liquids Using Supercritical Carbon Dioxide. *Ind. Eng. Chem. Res.* **2001**, *40*, 287.
- Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. Asymmetric Hydrogenation and Catalyst Recycling Using Ionic Liquid and Supercritical Carbon Dioxide. *J. Am. Chem. Soc.* **2001**, *123* (6), 1254–1255.
- Lu, J.; Liotta, C. L.; Eckert, C. A. Spectroscopically Probing Microscopic Solvent Properties of Room-Temperature Ionic Liquids with the Addition of Carbon Dioxide. *J. Phys. Chem. A* **2003**, *107* (19), 3995–4000.
- Bertucco, A.; Lora, M.; Kikic, I. Fractional Crystallization by Gas Antisolvent Technique: Theory and Experiment. *AIChE J.* **1998**, *44* (10), 2149–2158.
- Kitchens, C. K.; Hallett, J. P.; Bush, D.; Lu, J.; Liotta, C. L.; Eckert, C. A. Experimental Determination of Thermodynamic Properties of Gas Expanded Liquids. *Proc. 7th Int. Symp. Supercrit. Fluids* **2005**, 23–24.
- Lu, J.; Brown, J. S.; Boughner, E. C.; Liotta, C. L.; Eckert, C. A. Polarity and Hydrogen-Bonding of Ambient to Nearcritical Water: Kamlet-Taft Solvent Parameters. *Chem. Commun.* **2001**, 665–666.
- Reichardt, C. Solvatochromic Dyes as Solvent Polarity Indicators. *Chem. Rev.* **1994**, *94*, 2319–2358.
- Tomasko, D. L.; Knutson, B. L.; Pouillot, F.; Liotta, C. L.; Eckert, C. A. Spectroscopic Study of Structure and Interactions in Cosolvent-Modified Supercritical Fluids. *J. Phys. Chem.* **1993**, *97*, 11823–11834.
- Kim, S.; Johnston, K. P. Clustering in Supercritical Fluid Mixtures. *AIChE J.* **1987**, *33* (10), 1603–1611.
- Wyatt, V. T.; Bush, D.; Lu, J.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. Determination of Solvatochromic Solvent Parameters for the Characterization of Gas-Expanded Liquids. *J. Supercrit. Fluids* **2005**, *36* (1), 16–22.
- Dillow, A. K.; Brown, J. S.; Liotta, C. L.; Eckert, C. A. Supercritical Fluid Tuning of Reaction Rates: The *cis*–*trans* Isomerization of 4-4'-Disubstituted Azobenzenes. *J. Phys. Chem. A* **1998**, *102*, 7609–7617.
- Knutson, B. L.; Tomasko, D. L.; Eckert, C. A.; Debenedetti, P. G.; Chialvo, A. A. Local Density Augmentation in Supercritical Solutions: A Comparison Between Fluorescence Spectroscopy and Molecular Dynamics Results. In *Supercritical Fluid Technology*; Bright, F. V., McNally, M. E. P., Eds.; American Chemical Society: Washington, DC, 1992; Vol. 488, pp 60–72.
- Brennecke, J. F.; Chateaufneuf, J. E. Homogeneous Organic Reactions as Mechanistic Probes in Supercritical Fluids. *Chem. Rev.* **1999**, *99*, 433–452.
- Eckert, C. A.; Knutson, B. L. Molecular Charisma in Supercritical Fluids. *Fluid Phase Equilib.* **1993**, *83*, 93–100.
- Eckert, C. A.; Ziger, D. H.; Johnston, K. P.; Kim, S. Solute Partial Molal Volumes in Supercritical Fluids. *J. Phys. Chem.* **1986**, *90*, 2738–2746.
- Petsche, I. B.; Debenedetti, P. G. Solute–Solvent Interactions in Infinitely Dilute Supercritical Mixtures: A Molecular Dynamics Investigation. *J. Chem. Phys.* **1989**, *91* (11), 7075–7084.
- Tucker, S. C.; Maddox, M. W. The Effect of Solvent Density Inhomogeneities on Solute Dynamics in Supercritical Fluids: A Theoretical Perspective. *J. Phys. Chem. B* **1998**, *102*, 2437–2453.
- Brennecke, J. F.; Tomasko, D. L.; Eckert, C. A. Naphthalene/triethylamine Exciplex and Pyrene Excimer Formation in Supercritical Fluid Solutions. *J. Phys. Chem.* **1990**, *94*, 7692–7700.
- Carlier, C.; Randolph, T. W. Dense-Gas Solvent–Solute Clusters at Near-Infinite Dilution: EPR Spectroscopic Evidence. *AIChE J.* **1993**, *39* (5), 876–884.
- Meridith, J. C.; Johnston, K. P.; Seminario, J. M.; Kazarian, S. G.; Eckert, C. A. Quantitative Equilibrium Constants Between CO₂ and Lewis Bases from FTIR Spectroscopy. *J. Phys. Chem.* **1996**, *100*, 10837–10848.
- Chialvo, A. A.; Cummings, P. T. Solute-Induced Effects on the Structure and Thermodynamics of Infinitely Dilute Mixtures. *AIChE J.* **1994**, *40* (9), 1558–1573.
- Song, W.; Biswas, R.; Maroncelli, M. Intermolecular Interactions and Local Density Augmentation in Supercritical Solvation: A Survey of Simulation and Experimental Results. *J. Phys. Chem. A* **2000**, *104* (30), 6924–6939.
- Egorov, S. A.; Rabani, E. Chemical Equilibrium in Supercritical Fluids: Solvent Effects on the Dimerization Equilibrium Constant. *J. Chem. Phys.* **2002**, *116* (19), 8447–8454.
- Rabani, E.; Egorov, S. A. Integral Equation Theory for the Interactions between Passivated Nanocrystals in Supercritical Fluids: Solvophobic and Solvophilic Cases. *J. Phys. Chem. B* **2002**, *106* (26), 6771–6778.
- Shukla, C.; Hallett, J. P.; Popov, A. V.; Hernandez, R.; Liotta, C. L.; Eckert, C. A. Molecular Dynamics Simulation of the Cybotactic Region in Gas-Expanded Methanol-Carbon Dioxide and Acetone-Carbon Dioxide Mixtures. *J. Phys. Chem. B*, submitted for publication, 2006.
- Zhang, L.; Siepmann, J. I. Pressure Dependence of the Vapor-Liquid–Liquid-Phase Behavior in Ternary Mixtures Consisting of *n*-Alkanes, *n*-Perfluoroalkanes, and Carbon Dioxide. *J. Phys. Chem. B* **2005**, *109* (7), 2911–2919.
- Colina, C. M.; Galindo, A.; Blas, F. J.; Gubbins, K. E. Phase Behavior of Carbon Dioxide Mixtures with *n*-Alkanes and *n*-Perfluoroalkanes. *Fluid Phase Equilib.* **2004**, *222–223*, 77–85.
- Ablan, C. D.; Hallett, J. P.; West, K. N.; Jones, R. S.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. Use and Recovery of a Homogeneous

- Catalyst with Carbon Dioxide as a Solubility Switch. *Chem. Commun.* **2003**, (24), 2972–2973.
- (44) Jessop, P. G.; Olmstead, M. M.; Ablan, C.; Grabenauer, M.; Sheppard, D.; Eckert, C. A.; Liotta, C. L. Carbon Dioxide as a Solubility “Switch” for the Reversible Dissolution of Highly Fluorinated Complexes and Reagents in Organic Solvents. *Inorg. Chem.* **2002**, *41* (13), 3463–3468.
- (45) West, K. N.; Hallett, J. P.; Jones, R. S.; Bush, D.; Liotta, C. L.; Eckert, C. A. CO₂-Induced Miscibility of Fluorous and Organic Solvents for Recycling Homogeneous Catalysts. *Ind. Eng. Chem. Res.* **2004**, *43* (16), 4827–4832.
- (46) Lazzaroni, M. J.; Bush, D.; Jones, R.; Hallett, J. P.; Liotta, C. L.; Eckert, C. A. High-Pressure Phase Equilibria of Some Carbon Dioxide–Organic–Water Systems. *Fluid Phase Equilib.* **2004**, *224* (1), 143–154.
- (47) Lu, J.; Lazzaroni, M. J.; Hallett, J. P.; Bommarius, A. S.; Liotta, C. L.; Eckert, C. A. Tunable Solvents for Homogeneous Catalyst Recycle. *Ind. Eng. Chem. Res.* **2004**, *43* (7), 1586–1590.
- (48) Ganapathy, S.; Randolph, T. W.; Carlier, C.; O’Brien, J. A. Molecular Simulation and Electron Paramagnetic Resonance (EPR) Studies of Rapid Bimolecular Reactions in Supercritical Fluids. *Int. J. Thermophys.* **1996**, *17* (2), 471–481.
- (49) Heitz, M. P.; Maroncelli, M. Rotation of Aromatic Solutes in Supercritical CO₂: Are Rotation Times Anomalously Slow in the Near Critical Regime? *J. Phys. Chem. A* **1997**, *101*, 5852–5868.
- (50) Balbuena, P. B.; Johnston, K. P.; Rosky, P. J. Molecular Simulation of a Chemical Reaction in Supercritical Water. *J. Am. Chem. Soc.* **1994**, *116* (6), 2689–2690.
- (51) Egorov, S. A.; Lawrence, C. P.; Skinner, J. L. A Mode-Coupling Theory of Vibrational Line Broadening in Near-Critical Fluids. *J. Phys. Chem. B* **2005**, *109* (14), 6879–6883.
- (52) Stubbs, J. M.; Drake-Wilhelm, D. D.; Siepmann, J. I. Partial Molar Volume and Solvation Structure of Naphthalene in Supercritical Carbon Dioxide: A Monte Carlo Simulation Study. *J. Phys. Chem. B* **2005**, *109* (42), 19885–19892.
- (53) Stubbs, J. M.; Siepmann, J. I. Binary Phase Behavior and Aggregation of Dilute Methanol in Supercritical Carbon Dioxide: A Monte Carlo Simulation Study. *J. Chem. Phys.* **2004**, *121* (3), 1525–1534.
- (54) Hershkovitz, E.; Hernandez, R. Chemical Reaction Dynamics within Anisotropic Solvents in Time-Dependent Fields. *J. Chem. Phys.* **2005**, *122*, 014509/1–12 (doi: 10.1063/1.1829252).
- (55) Popov, A. V.; Melvin, J.; Hernandez, R. The Dynamics of Swelling/Contracting Hard Spheres Can Be Surmised by an Irreversible Langevin Equation. *J. Phys. Chem. A* **2006**, *110*, 1635–1644 (doi: 10.1021/jp054241a).
- (56) Bolhuis, P. G.; Chandler, D.; Dellago, C.; Geissler, P. L. Transition Path Sampling: Throwing Ropes over Rough Mountain Passes, in the Dark. *Annu. Rev. Phys. Chem.* **2002**, *53*, 291–318.
- (57) Bartsch, T.; Hernandez, R.; Uzer, T. Transition State in a Noisy Environment. *Phys. Rev. Lett.* **2005**, *95* (5), 058301/1–058301/4.
- (58) McLeod, M. C.; Kitchens, C. L.; Roberts, C. B. CO₂-Expanded Liquid Deposition of Ligand-Stabilized Nanoparticles as Uniform, Wide-Area Nanoparticle Films. *Langmuir* **2005**, *21* (6), 2414–2418.

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