

## PHASE EQUILIBRIUM AND REACTION IN BIPHASIC SOLVENTS IONIC LIQUID + SUPERCRITICAL CO<sub>2</sub>

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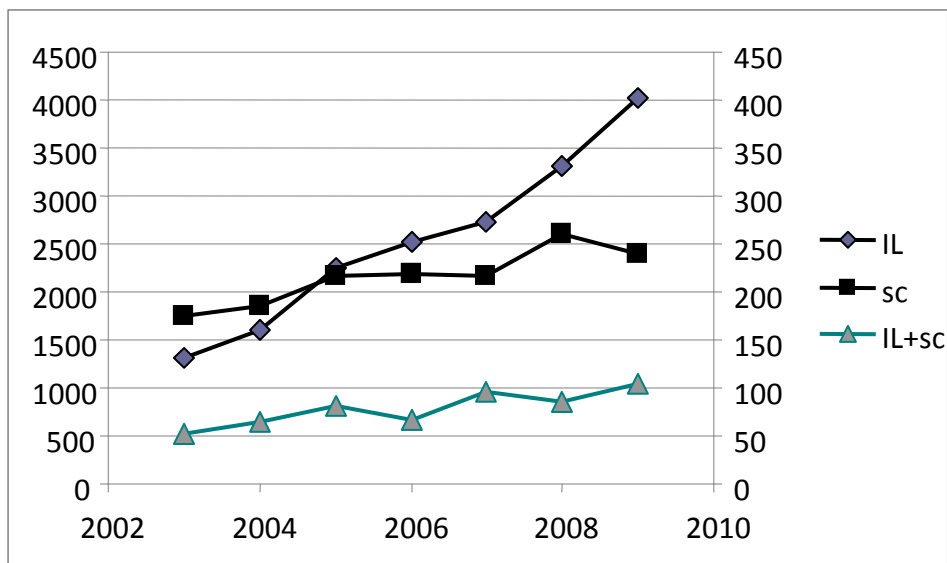
Biphasic mixtures of ionic liquids with supercritical CO<sub>2</sub> can be an ideal combination to carry out integrated reaction + separation processes. Phase equilibrium, and in particular partition of reagents, products and catalysts between the two phases, plays a crucial role in these processes. The possibility of tuning the solvent properties to the problem to be addressed, which is typical of supercritical solvents, can be enhanced in those mixtures by the multiple available choices of cations and anions that may form the ionic liquid. Examples of the importance of phase equilibrium are given:

- (1) The formation of new ionic liquid + CO<sub>2</sub> mixtures by gas-induced melting point lowering of ionic solids.
- (2) Reaction-separation in biocatalytic resolution of enantiomers.

### Introduction

Ionic liquids are salts with low melting points, close to room temperature. They are formed solely of ions. The cation is organic, and usually contains groups that provide delocalization of the positive charge. Anions are either organic or inorganic, and in some cases they may be as simple as chloride. Although the existence of this type of liquids was known for a long time, interest on studying them started only when chemically resistant ones, especially to air and water, were discovered in 1992 [1]. The last ten years witnessed a very substantial and sustained focus of attention on ionic liquids, which translated into an enormous increase of scientific papers published on the subject. A simple search on ISI web of Science with the words (ionic liquid OR ionic liquids) yielded three times more papers in 2009 than in 2003, as shown in Figure 1 (the numbers are slightly inflated, due to a few papers where ionic and liquid appear as separate key words). During the same period, the number of papers published annually corresponding to the search word “supercritical” increased by one third. Figure 1 plots the results of these searches, where the total numbers of papers are represented on the left side axis. It can be seen that in 2003 the “supercritical” papers clearly exceeded the number of “ionic liquid” ones, in 2005 numbers were on a par, and in 2009 papers on ionic liquids were almost double those on supercritical.

This extraordinary increase is, at least in part, due to the perception that ionic liquids are “green” solvents due to their very low volatility. In fact, although Rebelo and colleagues [2] have recently shown that ionic liquids are sufficiently volatile to be distilled, their vapour pressures are indeed negligible for practical purposes in most applications. The almost endless possibilities of combining different cations and anions to tailor the properties of ionic liquids has also contributed to multiply new studies, and to diversify the fields of potential new applications.



**Figure 1:** Annual number of scientific publications listed by the ISI web of Science, corresponding to searches using the words (ionic liquid OR ionic liquids)  $\diamond$  – IL, (supercritical)  $\blacksquare$ – sc, both to be read in the scale on the left side axis, and [(ionic liquid OR ionic liquids) AND supercritical]  $\blacktriangle$ – IL+sc, to be read on the right side scale.

Brennecke and collaborators [3] were the first to propose, in 1999, high-pressure carbon dioxide + ionic liquids as an interesting combination of solvents to carry out chemical processes. They used the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate,  $[\text{C}_4\text{mim}][\text{PF}_6]$ , and they reported that mixtures of supercritical  $\text{CO}_2$  with  $[\text{bmim}][\text{PF}_6]$  remained biphasic up to high pressures, and also that, while carbon dioxide dissolved significantly into the liquid phase, no ionic liquid dissolved in the gas phase.

The potentially enormous variety of ionic liquids, due to the vast number of cations and anions that may be combined, makes it likely that different kinds of phase equilibrium with carbon dioxide be possible. For instance, high solubility in  $\text{CO}_2$  of some phosphonium-based ionic liquids has been reported [4]. On the other hand, in multi-component mixtures, Buxing Han and collaborators [5] have called attention to the increase in solubility that results from the presence in the ionic liquid of polar molecular substances, like alcohols, that may act as cosolvents. However, in the vast majority of cases studied so far, the main features discovered by Brennecke et al. are maintained, even if the solubilities of carbon dioxide in the liquids differ markedly.

Solubility of gases, carbon dioxide in particular, in ionic liquids is a matter that has deserved much attention. Weingärtner has addressed this subject in his review of the properties of ionic liquids from a molecular perspective [6]. The solubility curves of carbon dioxide measured by Peters, Kikic et al. [7] resemble an adsorption isotherm, as if carbon dioxide molecules were stuck at “some kind of inner surface of the ionic liquid”, as stated by Weingärtner. This means the amount of carbon dioxide in the liquid phase increases very rapidly with pressure, until it attains a “saturation” limit, at high mole fraction of  $\text{CO}_2$ . These high amounts may lead, as suggested by Blanchard *et al.* [3, 8], to use supercritical  $\text{CO}_2$  to extract dissolved compounds from the liquid. For the majority of ionic liquids that remain insoluble in carbon dioxide, like the imidazolium-based ones initially studied, this process can be carried out with no contamination of the extract by the ionic liquid solvent. This is an interesting application, coupling benign solvents for sustainable technology, one of the main focus of attention in Green Chemistry.

This type of application has been extended to the design of continuous reaction-separation processes, where carbon dioxide carries the reactants into an ionic liquid containing an ionic catalyst, and takes the products out of the reaction medium. The work of Cole-Hamilton and collaborators [9] is a good example.

Supercritical carbon dioxide can additionally be thought of as a property-modifier. For instance, ionic liquids are highly viscous - the lowest viscosity observed to date is more than twenty times the viscosity of water [10]. The large amounts of carbon dioxide that accumulate in the liquid phase lower the viscosity in much the same way as for polymers. This may extend the applicability of ionic liquids or facilitate existing applications. Another important property that may be improved is the melting point itself, which in some cases may be dramatically lowered, as explained below.

Francis [11] discovered long ago that CO<sub>2</sub> can induce liquid-liquid phase separation in mixtures of otherwise miscible liquids. When contacted with dense carbon dioxide, multicomponent liquid mixtures containing ionic liquids may show that sort of phase behaviour. Scurto et al. [12,13], Najdanovic-Visak et al. [14] and Zhang et al. [15] reported on the formation of three phase liquid-liquid-vapour equilibrium when carbon dioxide pressure was increased over homogeneous mixtures of ionic and molecular liquids. The separation of liquid phases can lead to the extraction of target substances from the ionic liquid into the liquid CO<sub>2</sub>-rich phase.

Phase equilibrium measurement and correlation are critical to design processes based on ionic liquid + carbon dioxide. A recent review by Roth [16] lists the main achievements obtained. In all cases studied until recently, when an ionic liquid and dense carbon dioxide meet, there is the formation of at least two phases. However, Kroon et al. [17] have recently discovered that one single liquid phase can be obtained in the system 1-hexyl-3-methylimidazolium tetrafluoroborate – carbon dioxide – propanol, in some conditions of pressure, temperature and composition. This discovery further extends the possibilities of utilization of ionic liquids + carbon dioxide solvents.

These possibilities have been explored by the supercritical fluid community. In Figure 1, the line IL+sc shows the number of papers listed that corresponded simultaneously to the search words ionic liquid and supercritical (the scale to be read is on the right-hand side axis, expanded ten times in relation to the scale of the other two lines). Papers containing both references have increased twofold in the period from 2003 to 2009, evolving from 3 to 4.4 % of the total of “supercritical” papers. Their numbers did not manage, however, to keep up with the fast expansion of “ionic liquid” papers.

Many exciting lines of research remain to be exploited in this field. The majority of the recent papers focus either on phase equilibrium related to reactants and products of reactions in biphasic ionic liquid + carbon dioxide or on the yields of the reactions themselves. This is an area that will certainly continue to expand. However, the role of carbon dioxide as a property modifier will probably get an increased attention. Viscosity and melting point lowering are the most likely candidates.

In this communication, three examples will be presented. The first will deal with carbon dioxide as a melting point depression inducer, allowing the use of ionic liquids at lower temperatures. The other two will address the separation of reaction products from ionic liquid phases by carbon dioxide, using different strategies of phase separation.

### **CO<sub>2</sub> as a property modifier: Melting points of ionic liquid-like salts under carbon dioxide pressure**

High pressure gases are known to lower the melting point of many organic substances, at least up to a certain pressure. In most of the reported cases the effects are relatively low, with melting depressions usually not exceeding 30 K. Even so, these effects are the basis of some interesting processes, like the well-known PGSS (Particles from Gas Saturated Solutions) [18].

In the case of ionic liquid-like salts, the melting point is an essential property, and the ability to make it decrease by applying pressure with carbon dioxide may provide an important tool to broaden the list of substances that may be considered ionic liquids.

Scurto and Leitner [19, 20] reported surprisingly large melting point depressions for a few ionic-liquid like salts, in one case reaching 120 K. Serbanovic et al. [21] have recently extended the available results. Overall, melting point depressions for close to 60 ionic salts have been measured. They were made of a variety of anions and of cations of different families (quaternary ammonium, phosphonium, imidazolium, guanidinium, pyridinium and sulfonium). Most measurements yielded the “normal” 20 to 30 K decreases in freezing temperatures, but the values were higher than 40 K for nine ammonium and two phosphonium salts, with one exceptional value of 120 K, as mentioned above, but also three at around 80 K, two close to 70 K and two about 60 K. Very subtle differences in structure of one of the ions led to remarkable changes in temperatures. This feature made it very hard to interpret the data so far obtained.

Kazarian et al. [22] used in-situ ATR-IR spectroscopy to study of the influence of high pressure carbon dioxide on the melting temperature of  $[C_{16}mim][PF_6]$ , which is reduced by 25 K at 7 MPa. An important conclusion of their work was that carbon dioxide is already present in the crystal lattice when the salt is still in the solid state. This study also provided evidence for a weak Lewis acid-base interaction between  $CO_2$  and the  $[PF_6]$  anion.

Solubility of carbon dioxide in the lattice structure of the solid, inducing disruption of the crystal structure, is therefore the most likely factor determining the size of the melting decrease for each ionic salt. Explanations for the large differences observed for salts composed of very similar ions might be encountered in different packings in the solid phase, which in definite cases may facilitate  $CO_2$ -lattice interactions. However, the currently available database of crystal structures of ionic liquid-like salts is not broad enough to allow a detailed insight on how this mechanism might proceed.

In the case of the solubility of carbon dioxide in ionic liquids, the nature of the anion and its interaction with the carbon dioxide molecule has a predominant influence. However, the results obtained on the melting behaviour determined that abnormally high values were only obtained when the cations were either quaternary ammonium or phosphonium. It might be assumed that in the case of the other families of salts, there is a more efficient cation packing in the solid, which limits  $CO_2$  solubility, and decreases the melting point depression effect.

The largest effects were observed when short alkyl chains quaternary ammonium cations combined with fluorine-containing anions. On the contrary, for non-fluorinated anions, melting point depressions increased with the size of the alkyl chains. It may be speculated that these cations either hinder or allow the anion - carbon dioxide interaction in the solid.

More studies are however needed to allow a better identification of the main parameters that determine this unprecedented effect of high pressure carbon dioxide on melting.

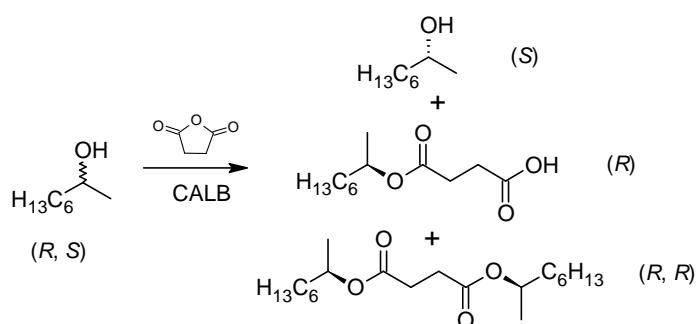
## **CO<sub>2</sub> as a separation agent**

### **1. Enantioselective enzymatic resolution of racemic mixtures in ionic liquids and product separation with supercritical carbon dioxide**

Enzymatic catalysis in non-aqueous solvents has been recently extended to ionic liquid media, as ionic liquids behave similarly to organic solvents in contact with enzymes and may replace them in many enzymatic processes [23].

One of the most interesting enzymatic processes that can be carried out in ionic liquid solvents is the resolution of optically active alcohols through selective acylation of one of the enantiomers. The separation of reaction products from the ionic liquid solvent can, in favourable cases, be achieved by supercritical carbon dioxide. In fact, continuous processes of this type have been proposed by Lozano et al.[24] and by Leitner and collaborators [25].

Bogel-Łukasik et al. [26] studied the resolution of 2-octanol enantiomers via lipase-catalyzed reactions using eleven different ionic liquids as solvents. The resolution was performed via acylation of (*R,S*)-2-octanol with succinic anhydride, catalyzed by immobilized CAL B. The reaction scheme is shown in Figure 2.



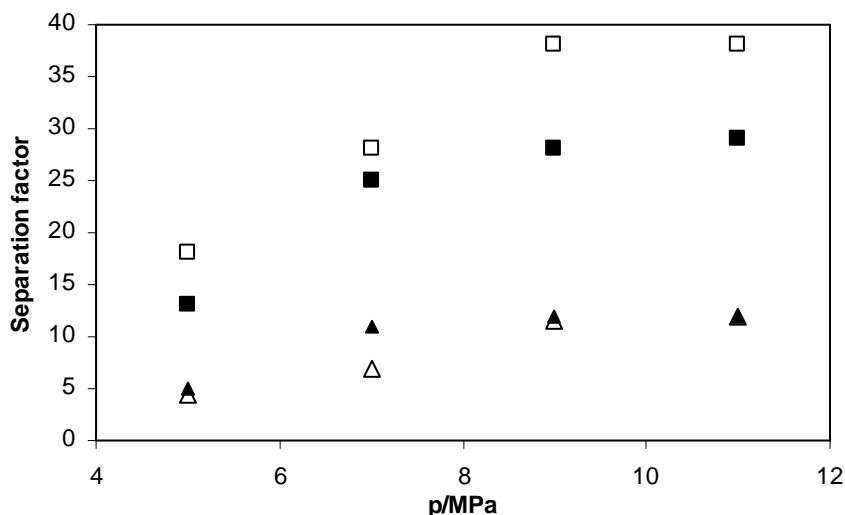
**Figure 2:** Enantioselective acylation of a racemic 2-octanol with succinic anhydride. The major products are an acidic (*R*)-half ester, when only one alcohol molecule reacts, and a (*R,R*) - diester, resulting from the reaction of two alcohol molecules with one anhydride molecule.

Nine 1-alkyl-3-methylimidazolium, and two quaternary ammonium ionic liquids were used. Additionally to the ionic liquid solvents, the reaction was also carried out in four organic solvents with varying polarity. The yields of reaction varied wildly with the nature of the ionic liquids used. The highest yields with high enantiomeric excesses were obtained for reactions performed in 1-methyl-3-octylimidazolium hexafluorophosphate, [omim][PF<sub>6</sub>], and 1-methyl-3-octylimidazolium dicyanamide [omim][N(CN)<sub>2</sub>].

These ionic liquids were chosen by Bogel-Łukasik et al. [27] to measure vapour-liquid equilibrium (VLE) data for systems containing one ionic liquid, carbon dioxide and the main products of the enzymatic reaction, including the unreacted alcohol enantiomer. The data were used to calculate the partition coefficients of reaction products between the ionic liquid-rich phase and CO<sub>2</sub>-rich phase. Separation factors were then obtained as ratios of partition coefficients. The main results are shown in Figure 3.

As the two ionic liquids share the same cation, the differences in the results must be attributed to the influence of the anions. Separation factors octanol/diester are distinctly larger for the [PF<sub>6</sub>]-based ionic liquid, but virtually indistinguishable for octanol/hemiester. In the first case, separation factors follow the same trend as the solubility of carbon dioxide in the liquid, which is higher for PF<sub>6</sub> than for dicyanamide-based ionic

liquids. In the second case, the acidity of the half-ester molecule presumably increases its interaction with the dicyanamide anion, pushing the separation factors up to the level of those for the other ionic liquid.



**Figure 3:** Separation factors for 2-octanol / diester (squares) and 2-octanol/ hemiester (triangles), between the CO<sub>2</sub> phase and the ionic liquid-rich one: open symbols, [omim][PF<sub>6</sub>]; closed symbols, [omim][N(CN)<sub>2</sub>].

Based on these results, a study of the feasibility to extract unconverted (*S*)-2-octanol from the post-reaction mixture with supercritical carbon dioxide was carried out. At 11 MPa and 35°C, the unreacted enantiomer was recovered with 98.1 % mol purity.

## CO<sub>2</sub> as a separation agent

### 2. CO<sub>2</sub>-induced phase switches for integrated reaction-separation

In 2005, Jessop et al.[29] proposed a switchable solvent, which can become an ionic liquid (an alkylcarbonate) under a low pressure of CO<sub>2</sub> and revert to a mixture of molecular liquids when carbon dioxide is removed by a stream of nitrogen or argon. In this proposal the switch is a reversible reaction that occurs at atmospheric pressure. This represents an extension to chemical reaction of a concept that had often been explored in supercritical carbon dioxide systems, where pressure may induce phase changes that facilitate separations.

A good example involving an ionic liquid is the work of Najdanovic-Visak et al. [14]. It followed in the wake of the discovery that although 1-butyl-3-methylimidazolium hexafluorophosphate is (partially) immiscible with either water or ethanol, the addition of water (or ethanol) to mixtures of [C<sub>4</sub>mim][PF<sub>6</sub>]+ethanol (or water) increased mutual solubility, until a single phase was formed [30-31]. In fact, this is a surprisingly large co-solvent effect, which extends over a wide range of temperatures and compositions.

When this single phase ternary mixture is submitted to pressure of CO<sub>2</sub>, a third phase starts to form between the liquid and gas phases. The value of this pressure is

composition-dependent, and at 40 °C varied between 5.5 MPa and 10 MPa. As pressure continued to increase, this middle phase increased significantly in volume. Finally, the two upper phases merged into a single phase.

In this process, large amounts of water and ethanol are drawn out of the ionic liquid phase by carbon dioxide and into the CO<sub>2</sub>-rich liquid. Indeed, the bottom phase shrinks in volume, and a distinct transformation of the curvature of the meniscus close to the stainless steel walls of the view-cell could be observed, indicating an almost pure ionic liquid.

This succession of phase changes may be used in reaction/separation cycles, producing, as desired, situations of total miscibility, partial miscibility, or almost complete phase separation. Reactions carried out in these media can benefit from monophasic conditions, for increased rates, without losing the advantages of biphasic systems for catalyst recycling and product separation.

As proof of principle of this concept, a case study was performed, based on the work of Bortolini et al.[32], who carried out the epoxidation of several electrophilic alkenes dissolved in [bmim][PF<sub>6</sub>] by aqueous solutions of hydrogen peroxide. These reactions were carried out in biphasic conditions, due to the above-mentioned immiscibility of water and the ionic liquid. Ethyl acetate was used to extract the products from the reaction mixture.

Najdanovic-Visak et al. performed the epoxidation of isophorone (3,3,5-trimethyl-2-cyclohexen-1-one) at 313.1 K, either in the conditions used by Bortolini et al. or by using a solution of hydrogen peroxide in 0.5 ethanol + 0.5 water (mass fraction), which yielded a monophasic reaction mixture. After 3 hours, carbon dioxide at 313.1 K and 10 MPa was passed through the reaction mixture. When the reaction was carried out in biphasic conditions, no products were detectable after 15 min, and the yield was 27 % after 3 hours. In contrast, the reaction in single phase conditions, with the addition of ethanol, produced yields of 38 % after 15 min and 74 % after one hour. The phase separation later induced by carbon dioxide, as described above, allowed complete separation of the reaction products from the ionic liquid.

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