IONIC LIQUIDS USED AS REACTION MEDIA FOR THE SYNTHESIS OF ORGANIC COMPOUNDS: CHARACTERIZATION AND PURIFICATION

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Ionic Liquids are low melting salts (up to 100° C) and represent a new class of solvents with unusual physico-chemical properties. In the present work ionic liquids have been used as reaction media for the synthesis of phenylacetylphenylglycine and of phenylacetylphenylalanine.
3 ionic liquids: 1-Octyl-3-methylimidazolium tetrafluoroborate, 1-Butyl-3-methylimidazolium hexa fluorophosphate and 1-Octyl-3-methylimidazolium hexafluorophosphate are synthesized. Solubilty data in supercritical carbon dioxide of phenylacetylphenylglycine and of phenylacetyl phenylalanine are determined for the evaluation of the supercritical fluid extraction conditions of such products from the reaction media in order to design a continuous process

INTRODUCTION

A major concern in the chemical processing industry is the use of large amount of organic solvent as liquid media for chemical reaction, extraction and purification. Due to the volatility and flammability of the solvents and to the necessity of reducing the volume of industrial pollutants connected also with the treatment of spent solvent wastes, there is an emphasis on the search for less toxic and harmful alternatives. The development of new technologies for pollution prevention can help to reduce VOC usage and the most damaging solvents. One of the promising technology is the application of neoteric solvents [1] such as supercritical carbon dioxide (CO_2), aqueous biphasic systems [2] and ionic liquids (ILS). In particular ionic liquids are known for many years (the first description goes back to 1914) but only in the past few years there is an interest on them as solvents for synthesis and catalysis [3,4]. They are good solvents for a wide range of both inorganic and organic materials; they are often composed of poorly coordination ions, so they have the potential to be highly polar yet non coordinating solvents. Moreover they are immiscible with various organic solvents, non volatile, thermally stable so they can be also used in high vacuum systems since they do not evaporate. Due to the many advantages offered, ionic liquids seem to be suitable for many industrial application so that chemical and physical properties [5] of these compounds (polarity, hydrogen bonding ability, density, viscosity, melting point, …...) merit their investigation for a proper selection in a practical application such as in dissolution or reaction media for some given solutes since these properties are related to determining solubility, partition constants , reaction rates and to evaluate the performance of a process. Aim of the investigation will be the characterization of some ionic liquids on the basis of their chemical properties for evaluating the possibility to use them as reaction media and to apply the supercritical fluid extraction for the recovery of the products of the reaction in order to design a continuous process with the recycle of the solvents to the reaction. The catalytic reaction

investigated is a standard reaction of protection of amino acids, the synthesis of an amide starting from methyl phenyl acetate and a methyl ester of L phenylglycine or methyl ester of L-phenil alanine [6]. The catalyst used for the reaction, PGA-450, has been obtained from Roche: it consists in an enzymatic preparation of penicillin G acylase from Escherichia coli covalently immobilized on a polymer (enzymatic activity 401 U/g). The activity of PGA-450 is determined evaluating the hydrolysis of a chromogenic substrate, 2-nitro-5-phenylacetylaminobenzoic acid (NIPAB) by measuring the content of 6-nitro-3-aminobenzoic acid (NABA) producted. In the case of the synthesis of the amide PhAc-PhGlyOMe the use of [BMIM][PF6] as a solvent gives a conversion after 120 minutes in the order of 80%, the use [BMIM][BF4] shows a 50% of conversion, while the use of toluene as a solvent gives a conversion in the order of less than 5%.

The process can be improved if it will be possible to extract the amide produced and to recycle the ionic liquid; the ionic liquids show a very low solubility in supercritical carbon dioxide while the amides show a good solubility in carbon dioxide in supercritical conditions and so they can be extracted.

I - EXPERIMENTAL MATERIALS AND METHODS

The ionic liquids were synthesized with standard procedures at the Department of Pharmaceutical Sciences. 1-Octyl-3-Methil-ImidazoliumTetrafluoroborate [OMIM][BF4], has been dehydrated in a rotavapor for 2 days at 70°C e 250 mm Hg until the water content was lower than 0.2 %.

1-Buthyl-3-Methyl-Imidazolium Hesafluorophosphate, [BMIM][PF6] has been also dehydrated in a rotavapor for 17 hours until water content lower than 0.2 % is reached.

1-Omim-3-Methyl-Imidazoiumo Hesafluorophosphate, [OMIM][PF6], has been dehydrated in a rotavapor for 2 days until a water content lower than 0.2 %.

All the compounds for the synthesis of ILS liquids, methyl phenyl acetate methyl ester of L phenylglycine, methyl ester of L-phenil alanine and all the other reactants have been obtained from Aldrich-Fluka_Lancaster.

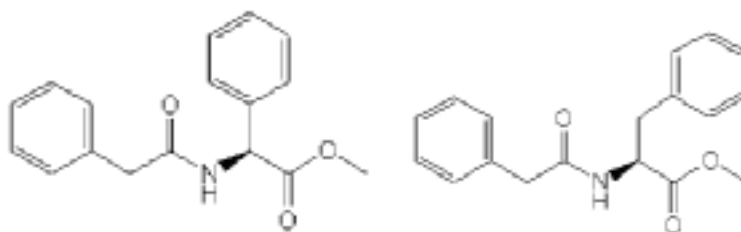CO_2 was obtained from SIAD with a purity of 99.98%.

Figure 1: Molecular structure of Phenylacetyl-L-phenylglicylmethylestere (left) and Phenylacetyl-L-phenylalaninmethylester (right)

The purity and characterization of the various compounds have been made with a Varian-Gemini-200 spectrometer NMR while the determination of the conversion of NIPAB to NABA in the study of the residual specific activity of the catalyst has been made with a UV Perkin Elmer Lamdba 20 spectrophotometer.

A dynamic method has been used for the determination of the solubility in supercritical carbon dioxide; the apparatus and the procedure is described in [7, 8].

For the determination of the melting points in presence of supercritical CO_2 an apparatus described in [9] has been used.

II - EXPERIMENTAL RESULTS

The characterization of ionic liquids was performed starting from the gas chromatographic experimental determination of retention volumes at infinite dilution V_g^0 calculated from the retention times of different solutes injected in the ionic liquids used as stationary phase (Details are available in DECHEMA Chemistry Data Series [10]). The natural logarithm of the specific retention volumes are then correlated by means of the solvation equation proposed by Abraham et al. [11]

$$\ln V_g^0 = c + rR_2 + s\pi_2^H + a\alpha_2^H + b\beta_2^H + l\log L^{16}$$

Abrahm Parameters for

[OMIM][PF6]

Temperature	c	r	s	a	b	l	n	R
313.15 K	-0,3670	0,1299	1,8046	1,6991	0,5369	0,6138	32	0,9614
323.15 K	-0,3857	0,1604	1,7399	1,5840	0,5093	0,5683	32	0,9603
333.15 K	-0,4251	0,1752	1,6983	1,5266	0,4680	0,5305	32	0,9595
343.15 K	-0,4575	0,2017	1,6455	1,4160	0,4469	0,4939	32	0,9596

[BMIM][PF6

Temperature	c	r	s	a	b	l	n	R
313.15 K	-0,4942	0,5141	2,1918	1,5902	0,7477	0,4487	32	0,9770
323.15 K	-0,5386	0,5188	2,1300	1,4924	0,7097	0,4158	32	0,9764
333.15 K	-0,5626	0,5155	2,0682	1,4223	0,6562	0,3819	32	0,9760
343.15 K	-0,5922	0,5109	2,0093	1,3637	0,6169	0,3524	32	0,9760

[OMIM][BF4]

Temperature	c	r	s	a	b	l	n	R
313.15 K	-0,1560	0,1229	1,6322	2,7654	0,2107	0,5677	32	0,9350
323.15 K	-0,1855	0,1671	1,5292	2,7324	0,2645	0,5244	32	0,9368
333.15 K	-0,2105	0,2036	1,4351	2,7000	0,3012	0,4846	32	0,9392
343.15 K	-0,2300	0,2326	1,3439	2,6446	0,3447	0,4465	32	0,9398

Table 1: Values of Abraham parameters for the ionic liquis investigated.

Each term of this equation refers to some particular solute-solvent interaction. In particular there are five parameters which represent solute properties and other six constants (c, r, s, a, b, l), which provide a definite chemical information on the properties of the stationary phase and can

be found by the method of multiple linear regression[6]. c is a constant of the correlation; r measures the tendency of the phase to interact with π- or n-solute electron pairs; s the phase dipolarity; a the phase hydrogen-bond basicity; b the phase hydrogen-bond acidity; l represents a combination of general dispersion interactions and cavity effects. The constants for all the ionic liquids have been reported in the table 1. Examining the constants in the solvation equation it may be noticed that ILS investigated are strong bases and in particular a BF4 > PF6 which means that PF6 is more acid than BF4.

The l-constant is a good measure of the lipophilicity of the solvent phase relative to hexadecane, by definition l = 1 at 25°C. For the ionic liquids investigated the lipophilicity is in the following order BMIM PF6 ‹ OMIM BF4 ‹ OMIMPF6.

The evaluation of the parameters obtained by the model allows the proper choice of the solvent (ionic liquid) for a given reaction: the catalyst to be used should be compatible with it, the reagents and the products should be soluble in the solvent and should not interact with it, moreover the solvent.

These ionic liquids have been used as solvents in the synthesis of the corresponding amide obtained by the reaction of methyl phenyl acetate with methyl ester of L phenylglycine or with methyl ester of L-phenil alanine.

For an evaluation of the influence of the conditions in supercritical regions on the melting point of the amides the melting points were determined in a wide range of temperature and pressure: the results are reported in figure 1
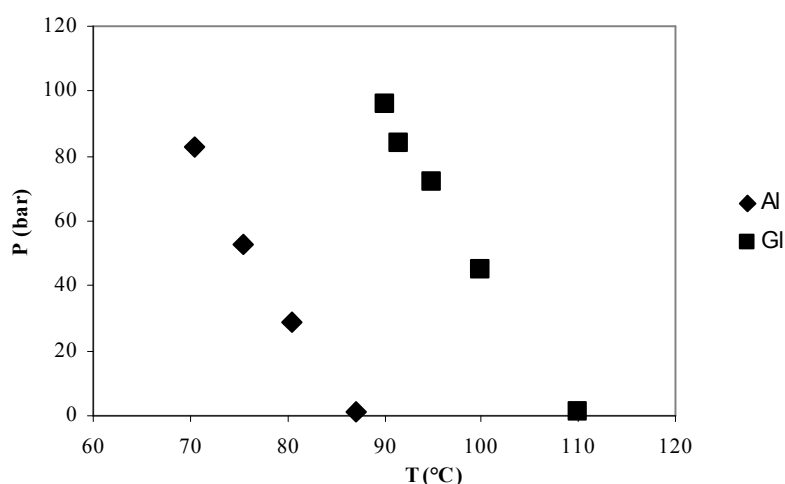

Figure 1: Melting point depression

In figures 2 and 3 the solubility of the two amides are reported.

In order to confirm these results the solutions at the end of the reaction was treated with supercritical CO_2 at 40°C and 130 bar; the extraction can be performed but it will be necessary to use an amount of CO_2 higher than the value corresponding to the solubility of the amides in CO_2 (about 25% more) due to the increase of the presence of water which influences f the viscosity of the ionic liquids at the conditions of the extraction.
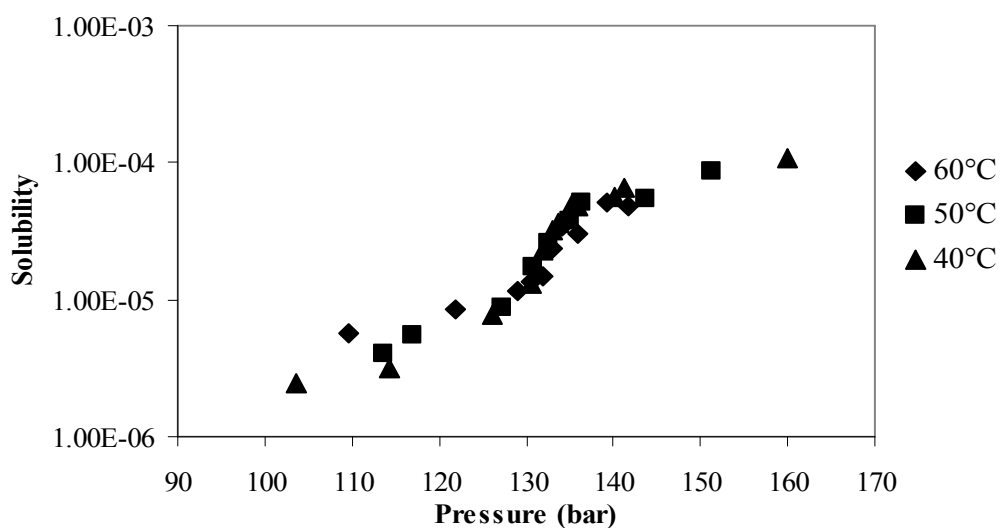
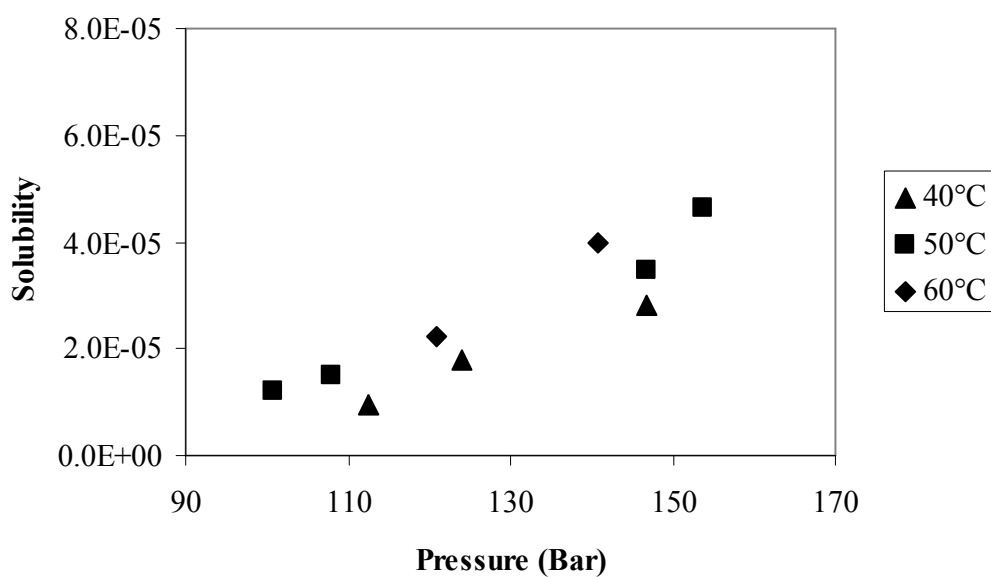**Figure 2:** Solubility of PhAc-L-PhGlyOMe in supercritical carbon dioxide.

Figure 3: Solubility of phenylacetyl-L-phenylalaninmethylester in supercritical carbon dioxide.

Finally the activity of the catalyst has been tested: for the reactions with [BMIM][PF6] or with [BMIM][BF4] as solvents, the residual activity of PGA-450 after extraction of the products is still in the order of 100%.

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