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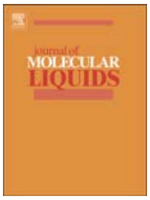

Extraction of organic compounds involved in the kinetic resolution of rac-2-pentanol from *n*-hexane by imidazolium-based ionic liquids: Liquid-liquid equilibrium

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ABSTRACT

This paper focuses on the use of ionic liquids (1-butyl-3-methylimidazolium methylsulphate, [bmim$^+$][MeSO$_4^-$], and 1-ethyl-3-methylimidazolium acetate, [emim$^+$][Ac$^-$]) to extract organic compounds involved in the racemic resolution of *rac*-2-pentanol (*rac*-2-pentanol, vinyl butyrate, *rac*-2-pentyl butyrate or butyric acid) from a mixture of one of these organic compounds with *n*-hexane. Liquid–liquid equilibrium data were experimentally obtained for seven ternary systems comprising an ionic liquid + *rac*-2-pentanol, vinyl butyrate, *rac*-2-pentyl butyrate or butyric acid + *n*-hexane at $T = 303.15$ K and atmospheric pressure. Binodal curves were measured applying the well-known procedure based on the observance of the cloud point while the compositions of the tie lines were calculated from refractive index and density measurements (the phase rich in the ionic liquid) and by gas cromatography (the phase rich in *n*-hexane). Selectivity values and the solute distribution ratio were utilized to test the possibility of the use of these ionic liquids as extractive solvents of the organic compounds implicated in the kinetic separation of the *R*- and *S*-enantiomers of *rac*-2-pentanol. The liquid-liquid equilibrium data of the ternary systems examined here have not previously been described in the literature.

1. Introduction

During the last decades, the interest for enantiopure chemicals has greatly increased in the pharmaceutical industry, largely due to the fact that when chiral mixtures are used as drugs, one of the enantiomers usually presents biological activity, whereas the other may be harmful or toxic or shows antagonism. For this reason, a great variety of enantioseparation techniques exist, although among other types of technique, kinetic resolution using membranes such as supported liquid membranes (SLMs) has attracted great attention [1]. SLMs are porous structures whose cavities contain a liquid. Their main advantages are the small quantity of liquid necessary for the process and the combination in a unique stage of the extraction and stripping processes [2]. However, their industrial development has been scarce, primarily because of the low stability and the problems associated with the long-term usage of the SLMs. Furthermore, SLMs with conventional organic solvents may deteriorate because of liquid evaporation and their dissolution in the surrounding medium and migration from the pores of the support under a low pressure gradient. Moreover, from an environmental point of view, the organic solvents most widely employed for processes involving liquid membranes possess high vapour pressure and high toxicity, meaning that their presence could involve serious hazards [1]. The incorporation of ionic liquids (ILs) [1,3] in SLMs has demonstrated an important increase in their stability enabling long-term experiments for separating the reactants and products of transesterification reactions. Several works in the literature have checked the improvement on the SLM stability when they contain ILs [4,5]. The most noteworthy feature of the ILs is their negligible vapour pressure at room temperature and atmospheric pressure [6] which has led to them being called "green solvents". This property, their high capillary force due to their relatively high viscosity and the possible modulation of their solubility in a specific medium makes the use of ILs a stable and environmentally friendly alternative for the selective transport of organic compounds [3,7].

Furthermore, ILs can be designed for particular applications by the selection of the chemical nature of both the anion and the cation constituents [8]. Accordingly, they have also been called "designer solvents". Solute-solvent interactions in solution are determined by the cation and anion pair that constitutes the ionic liquid. In this context, specific

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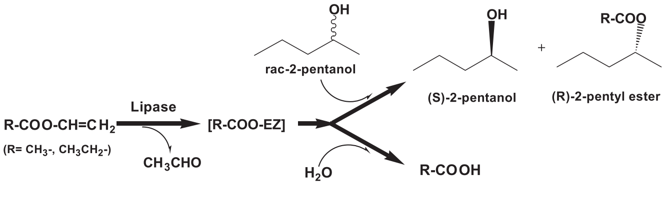
ILs can be used to accomplish the selective extraction of *rac*-2-pentanol by supported ionic liquid membranes. In this case, *S*-2-pentanol has special interest because it is a racemic intermediate involved in obtaining some anti-Alzheimer drugs which restrict the release and the synthesis of β-amyloid peptide [9]. The stoichiometric scheme for the racemic resolution of 2-pentanol by transesterification with a vinyl ester catalysed by a lipase is shown in Scheme 1.

For liquid-liquid extraction processes, the essential equilibrium properties of the solvent phase are important. The measurement of liquid-liquid equilibrium (LLE) data is a widely used method for evaluating the ability of a solvent through the calculation of standard variables such as selectivity (S) or solute distribution coefficient (β). In order to extract *S*-2-pentanol selectively from the reaction medium (i.e. *n*-hexane), knowledge of the LLE data of the ternary systems (ionic liquid + *n*-hexane + an organic compound present in the kinetic resolution of *rac*-2-pentanol) is very convenient. Our research group has already published several studies of this same system using ILs and we have obtained promising results ($[emim^+][EtSO_4^-]$, $[bmim^+][BF_4^-]$ and $[bmim^+][NTf_2^-]$ [10]; $[emim^+][NTf_2^-]$ and $[hmim^+][NTf_2^-]$ [11]). In addition, we have also studied the LLE of other ternary systems (ionic liquid + *n*-hexane + organic compounds implicated in the racemic separation of *rac*-1-phenylethanol) [12]. The selective extraction of *rac*-1-phenylethanol is of special relevance because *R*-1-phenylethanol is broadly employed in pharmaceutical and fine chemical industry [13]. In addition, our previous works [10–12] on the application of ILs in separation processes showed the growing interest of increasing the quantity of available physico-chemical data related to extraction processes.

LLE data of ternary systems involving ILs have been widely studied by a great many authors [10–12,14–46]. The present work is an extension of our investigation into the extraction potential of ILs for the separation of specific compounds involved in the kinetic resolution of racemic alcohols. The principal goal of this paper was to evaluate the LLE of seven ternary systems which contain an ionic liquid, *n*-hexane and an organic compound implicated in the kinetic resolution of *rac*-2-pentanol (*rac*-2-pentanol, vinyl butyrate, *rac*-2-pentyl butyrate or butyric acid) at 303.15 K and $p = 0.1$ MPa. The binodal curves and the tie line data for these ternary systems were also determined in the above mentioned conditions. From the features of the binodal curves and the tie line data, valuable insights can be achieved concerning the potential extractive capability of the ILs.

On the basis of previous results [10,11], it could be inferred that more hydrophilic ILs may be more selective for the extraction of the target compounds. In consequence, (i) 1-butyl-3-methylimidazolium methylsulphate, $[bmim^+][MeSO_4^-]$ and (ii) 1-ethyl-3-methylimidazolium acetate, $[emim^+][Ac^-]$ have been chosen in this paper. LLE data for the system $[emim^+][Ac^-]$ + *n*-hexane + vinyl butyrate have not been included because vinyl acetate was formed as result of the transesterification reaction between $[emim^+][Ac^-]$ and vinyl butyrate and the reactive extraction process is beyond this work. Furthermore, the ILs are regenerated removing the organic compound by vacuum distillation. Figs. S1 and S2 show the ^1H NMR results and GC–MS spectra of the *n*-hexane phase as evidence of the presence of vinyl acetate.



Scheme 1. Stoichiometric scheme of racemic resolution of *rac*-2-pentanol catalysed by a lipase [1].

2. Experimental

2.1. Materials

The ILs 1-butyl-3-methylimidazolium methylsulphate, $[bmim^+][MeSO_4^-]$ (purity > 0.99), and 1-ethyl-3-methylimidazolium acetate, $[emim^+][Ac^-]$ (purity > 0.95) were provided from Iolitec. All other chemicals were supplied by Sigma-Aldrich (purity > 0.98). The ILs and the organic compounds were dried under vacuum in the presence of anhydrous phosphorus pentoxide and kept in a desiccator to avoid any moisture absorption (Table 1). The water contents of the ILs and the organic compounds was determined with a Karl Fischer coulometric titrator (Metrohm, 831 KF). The values of the water content were low in all cases ($w < 0.001$). The standard uncertainty, u, of the water content measurements was $u(w) = 0.1$ μg/mL. The structures and molecular weight are depicted in Table 2 together with the refractive index and density values of the pure ILs measured in this work and those found in the literature. The same samples of butyric acid, vinyl butyrate, *rac*-2-pentyl butyrate, and *rac*-2-pentanol with the same physical properties as in [11] were used.

After use, the ILs have been regenerated following procedures previously published in the literature with other organic solvents [66]. Briefly, organic compound (2-pentanol, vinyl butyrate, 2-pentyl butyrate or butyric acid)/hexane mixtures can be removed from the ILs on a rotary evaporator at 80 °C and 80 mbar. The ILs were kept in a desiccator until reuse.

2.2. Experimental procedure

When possible, the binodal curves of the ternary systems were obtained at 303.15 K and atmospheric pressure through the titration of two-component mixtures of known compositions with the third component. The disappearance of turbidity in the sample was taken as the end point, as in the cloud point method [10–12,16,18,35,46].

Tie line data for the ternary systems studied were obtained from measurements of the compositions of the conjugate phases for several mixtures with a known global composition of the three components within the two-phases region. For this, the ternary mixtures were introduced into a 5 mL glass cell, shaken vigorously for 10 min using a vortex mixer and then for 1 h using a magnetic stirrer before leaving overnight to allow the separation into two phases and to ensure equilibrium between them [10–12,16,18,25]. The tube was tightly closed to prevent vaporization or the absorption of humidity from the ambient. The temperature was regulated using a thermostatic bath with a standard uncertainty value of $u(T) = 0.5$ K.

The index of refraction of the ionic liquid-rich phase and the pure compounds was measured using a RX-5000α refractometer from ATAGO (λ = 589 nm). Earlier, the refractive index of the ternary mixtures was correlated with their respective concentrations by calibration curves in order to obtain the component concentrations in this phase. Standard uncertainties were $u(T^n) = 0.02$ K and $u(n) = 0.00004$ (nD). The density of the ionic liquid-rich phase, which was also correlated

Table 1
Sample table.

Chemical name	Source	Initial mole fraction purity	Purification method
$[bmim^+][MeSO_4^-]$[a]	Iolitec	0.99	Vacuum drying
$[emim^+][Ac^-]$[b]	Iolitec	0.95	Vacuum drying
Butyric acid	Sigma-Aldrich	0.99	Vacuum drying
Vinyl butyrate	Sigma-Aldrich	0.99	Vacuum drying
rac-2-Pentyl butyrate	Sigma-Aldrich	0.99	Vacuum drying
rac-2-Pentanol	Sigma-Aldrich	0.98	Vacuum drying
n-Hexane	Sigma-Aldrich	0.99	Vacuum drying

[a] $[bmim^+][MeSO_4^-]$ = 1-butyl-3-methylimidazolium methylsulphate.
[b] $[emim^+][Ac^-]$ = 1-ethyl-3-methylimidazolium acetate.