

Biocompatible Ionic Liquids in Liquid – Liquid Extraction of Lactic Acid: A Comparative Study

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Abstract—Ionic liquids consisting of a phosphonium cationic moiety and a saccharinate anion are synthesized and compared with their precursors, phosphonium chlorides, in reference to their extraction efficiency towards L-lactic acid. On the base of measurements of the acid and the water partitioning in the equilibrium biphasic systems, the molar ratios between acid, water and ionic liquid are estimated which allows to deduce the lactic acid extractive pathway. The effect of a salting-out addition that strengthens hydrophobicity in both phases is studied in view to reveal the best biphasic system with respect to IL low toxicity and high extraction efficiency.

Keywords—Biphasic system, Extraction, Ionic liquids, Lactic acid.

I. INTRODUCTION

THE lactic acid (LA) is a simple organic compound that containing both hydroxyl and carboxylic acid groups, which allow it to participate in various valuable chemical reactions. LA represents an inexpensive feedstock for the production of specialty and commodity chemicals such as acrylic, propionic, pyruvic acids, 2,3-pentanedione, and different forms of biodegradable polymer – poly(L-lactic acid). The latter requires high purity of the (L)-LA-stereoisomer and absence of certain impurities.

Whereas *via* chemical synthesis a racemic mixture of LA is produced, the fermentation route is selective to L-stereoisomer and nowadays is preferred for about 90% of worldwide LA production. For the LA downstream processing, conventionally two ways are followed [1]: (i) the clarified fermentation liquor is concentrated to 32% (above the crystallization point) and acidified with H₂SO₄, or (ii) the calcium lactate which precipitates from the concentrated liquor is crystallized, filtered, dissolved and then acidified with H₂SO₄. Following the second procedure, the lactate salt remains to certain extent separated from the dissolved impurities by filtration and washing. The cake, however, still retains some impurities, there is a loss of lactate along with the washes, and finally, large amount of calcium sulfate, difficult to dispose of, is accumulated.

Reactive liquid-liquid extraction has been recognized as

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alternative approach to the LA *in situ* removal which only may prevent the pH-lowering in the culture medium. In the decades of intense research, the extractant/diluent combinations with high distribution coefficients of LA were found [2]–[6]. Some recently designed compounds with multiple nitrogen atoms in the functional group have shown better extracting capacity compared to the referent trioctylamine [7], [8]. All the known organic carriers of LA, however, require medium of organic solvents such as hydrocarbons and water-immiscible alcohols. The high toxicity level of these solvents to the microbial producers actually hinders the coupling between LA fermentation and extraction [9]. Thus, the need for media of emended characteristics from toxicological standpoint can be put forward. Ionic liquids (ILs) are promising candidates that could meet these requirements.

Consisting entirely of ions (usually charge-stabilized asymmetric organic cation and inorganic or organic anion) ILs are liquids at ambient temperature and display a wide range of unique properties, such as negligible vapor pressure (practically non-volatile), low chemical reactivity, finely tunable viscosity, polarity and miscibility with other common solvents [10].

The state of knowledge of LA extraction by ionic liquids shows that few ILs have been investigated. First, the hydrophobic 1-alkyl-3-methylimidazolium hexafluorophosphates were proposed as diluents of reactive organic bases instead of volatile organic solvents [11]. These ILs have proved to be non-toxic towards the bacteria of *Lactobacillus rhamnosus*, but provide low extractant solubility, which results in poor extraction efficiency. Later, phosphinate-based ILs of low toxicity were applied as LA extractants dissolved in organic solvent [12] or pure [12], [13], and systems with Cyphos IL-104 showed, at low LA loading, higher distribution coefficients than some classical reactive extraction systems. Some drawbacks, however, appeared at the higher LA concentrations (those of practical interest), which derived from the particular IL structure – namely, emulsion or a third phase formation between the IL-phase and the aqueous solution.

In our recent study [14], we performed LA-extractions and re-extractions using hydrophobic 3-alkyl-1-methylimidazolium saccharinates ([C_nC₁im][Sac]). The saccharinate anion comprises *N*-acyl-*N*-sulfonylimide group and bears a similarity to some well known anions in IL chemistry [15], [16], but unlike them, the [Sac]-anion is non-fluorous and has well established toxicological profile [17]–[19].

Studying the mechanism of LA extraction in [C_{8/10}C₁im][Sac] aqueous biphasic systems, we assumed a

secondary structure of the water saturated long side chain imidazolium saccharinates [14]. Polar channels separated by non-polar domains were visualized, which channels are composed of polarized water molecules able to entrain (through H-bonding) the undissociated LA. Regarding the potential applications of $[C_{8/10}C_1im][Sac]$ -based aqueous biphasic systems for biomolecules' recovery, the great water uptake into the IL-rich phase might be advantageous (mimic free water microenvironment), but at the same time, some deficiency in the extraction selectivity could be expected. In order to strengthen the hydrophobicity of the IL-rich phase, we previously added a kosmotropic salt ($MgSO_4$) to the $[C_8C_1im][Sac]$ aqueous biphasic system [14].

Here, profiting from the enhanced hydrophobicity of the long side chain phosphonium cationic moiety, we synthesize phosphonium saccharinates and compare them to their precursors, phosphonium chlorides, in reference to the LA extracting capacity.

From another eco- and biotoxicological standpoint, the alkyltributylphosphonium ILs were found less disruptive to the cell plasma membrane than ILs with longer alkyl chain on the imidazolium ring [20] and also, the phosphonium ILs have been proven to possess lower enzyme inhibitory activity [21].

II. MATERIALS AND METHODS

A. Chemicals

The phosphonium chlorides (>95%) were purchased from IoLiTec. Their abbreviations throughout the manuscript mean the following: $[P_{4444}]Cl$ is tetrabutylphosphonium chloride, $[P_{444,14}]Cl$ is tributyltetradecylphosphonium chloride, and $[P_{666,14}]Cl$ is trihexyltetradecylphosphonium chloride. The phosphonium saccharinates were synthesized, purified and characterized by the authors according to recently published protocols for the synthesis of saccharinate-based ILs [22], [23].

L-(+)-Lactic acid, extra pure (90%), was supplied by Merck. A LA stock aqueous solution was refluxed for 12h in order any LA dimers to hydrolyze [12], [13]. The stock solution was further used in preparation of LA aqueous source. The inorganic salt $MgSO_4$ was min. 98% (Sigma-Aldrich). All other chemicals were of analytical grade and were used as received.

B. Equilibrium Experiments

The extractions were performed at 22°C by vigorous shaking of 1 g dried IL and aqueous solution of 0.5 mol dm^{-3} LA, at a certain initial weight ratio of the LA source to the IL. The contact time was set to five minutes since it was found that prolonged shaking (up to 3 h) gave similar equilibrium results. The mixture was allowed to separate overnight at the same temperature, the two phases formed were set aside and their volumes and pH values were measured. Aliquots from both phases were then subjected to analysis as described in the following section.

C. Analysis and Calculations

Acid-base titration was used as an analytical method for the

LA quantification in both phases, as we previously described [14]. The titrimetric determination was performed by means of alcoholic KOH, 0.15 mol dm^{-3} , at phenolphthalein indicator, following the specifications below. In the extractions of native or $MgSO_4$ -containing LA aqueous solutions by $[P_{4444}]Cl$, $[P_{444,14}]Cl$, and $[P_{4444}][Sac]$, the samples taken from both phases were diluted in distilled water and the whole acidity balance was fulfilled within 3% relative error. In the extractions by $[P_{666,14}]Cl$ and $[P_{444,14}][Sac]$ the samples taken from the IL-rich phases were diluted with 50% ethanol aqueous solution and the whole acidity balance was fulfilled within 2% relative error.

Similar to other water-soluble ILs [14], [24], [25], all the ILs used here exhibited acidity in water. The acidity derived from each IL was measured under the titration conditions described above and was evaluated to be, as follows: for $[P_{4444}]Cl$ ca. 11.9% (mol/mol), $[P_{444,14}]Cl$ ca. 8.1% (mol/mol), $[P_{666,14}]Cl$ ca. 6.65% (mol/mol), $[P_{4444}][Sac]$ ca. 11.4% (mol/mol), and for $[P_{444,14}][Sac]$ ca. 8.9% (mol/mol). Since the latter three ILs are hydrophobic and any significant partitioning into the equilibrium aqueous phase was not expected, the acidity of the initial IL was subtracted from the equilibrium acidity of the IL-rich phase, when calculating the LA concentration, the LA extraction yield and the LA partition coefficient. In the case of more hydrophilic $[P_{4444}]Cl$ and $[P_{444,14}]Cl$, for which some partitioning into the equilibrium aqueous phases is expected, the IL's acidity distribution between the two phases was preliminary estimated in blank extractions under the given conditions but without LA.

The LA extraction yield (EY%) and partition coefficient (K_{LA}) were calculated exactly as we previously described [14].

The water concentration in the IL-rich phase at equilibrium was determined by Karl Fischer titration on 870 KF Titrino plus (Metrohm, CH).

III. RESULTS AND DISCUSSION

The most thoroughly studied phosphonium IL for the LA extraction is Cyphos IL-104, which is tetradecyltriethylphosphonium bis(2,4,4-trimethylpentyl)-phosphinate [12]. The existence of $(LAH)_p(IL)(H_2O)_2$ complexes was deduced (LAH presents undissociated LA and $p = 1, 2, 3$), and the water molecules involved ranged from ca. 8 (reversed micelles, at low LA loading) to 2 (hydrated complexes, at high LA loading).

Here, we study a series of phosphonium chlorides and saccharinates and the data about the LA extraction is interpreted with a view to visualizing the molecular ratio between LA, IL and water engaged in the process.

The determinations were carried out on aqueous solutions composed of solely LA and others with an addition of $MgSO_4$ in the LA source, which created more hydrophobic LA environment.

A. LA Extraction from Native Aqueous Solutions

The results obtained from the LA extractions deriving from its pure aqueous solutions are shown on Fig. 1. On the

abscissa, the phosphonium ILs are arranged in the order of increasing hydrophobicity considering the water uptake. In the graphical performance, the missing $[P_{4444}]Cl$ was replaced by $[C_8C_1im]Sac$, as the former IL formed a monophasic system. Some $MgSO_4$ was also added in the system of $[P_{444,14}]Cl$ as it was found that min. 0.75 mol dm^{-3} $MgSO_4$ can salt-out 1 mole of this IL and promote phases' separation.

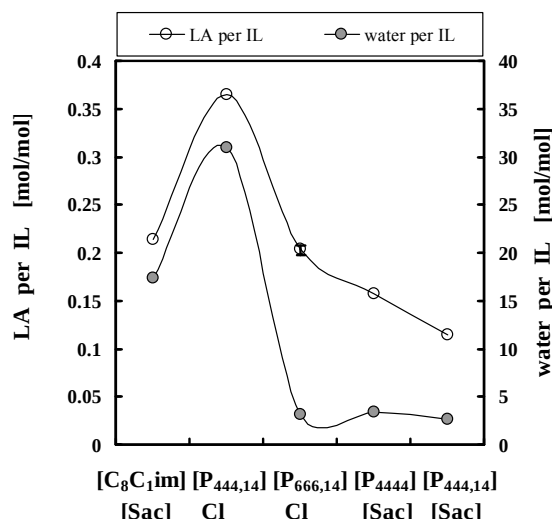


Fig. 1 LA extraction and water solubilization into the ILs from native LA aqueous solutions, initial weight ratio of LA source to IL, 2:1

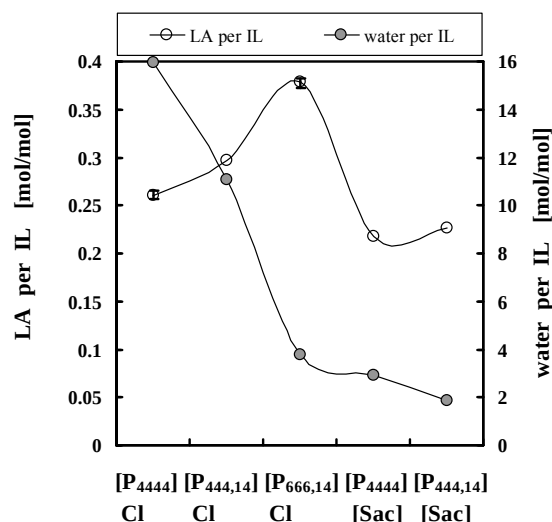


Fig. 2 LA extraction and water solubilization into the ILs from $MgSO_4$ -containing LA aqueous solutions, initial weight ratio of LA source to IL, 2:1

As seen on Fig. 1, the more hydrophilic ILs are the more LA is extracted and its transfer is water-associated. Among the hydrophobic ILs, $[P_{666,14}]Cl$ entrains the largest LA uptake at the smallest water support. It can be calculated that, under the given conditions, 1 in 15 $[P_{666,14}]Cl$ hydrated complexes bears a LA molecule. Further, the phosphonium saccharinates keep a similar level of the water solubilization, but show lower LA

extracting capacity.

Based on the above reasoning, the LA extraction in the series could be regarded as supported by two transport processes – the solubilization of bulk liquid-like water inside the IL and the IL's functional capacity to form embedded by H-bonds species, consisting of IL, water and LA. Whereas the former is governed by the hydration and aggregation of both IL's ions, the later is strongly dependent on the anion nature [26].

B. LA Extraction from Kosmotropic Salt-Containing Aqueous Solutions

In order to restrict the water contribution to the LA extraction experiments with the input of a kosmotrope – $MgSO_4$ into the LA aqueous solution (1.8 mol dm^{-3}) were carried out. The initial weight ratio of the LA source to the IL was first kept 2:1 (Fig. 2), and further 1:1 was used (Fig. 3) to diminish the water available for distribution.

Comparing the data for the hydrophobic $[P_{666,14}]Cl$ and $[P_{444,14}][Sac]$ on Figs. 1 and 2, it is noticed that the LA extraction is enhanced twice without any significant change in the water uptake. One in eight $[P_{444,14}][Sac]$ -water complexes is a LA carrier, thus representing the most acid-loaded IL-rich phase in the series. Obviously, the more hydrophobic LA microenvironment in the source, rendered by the water engagement with the kosmotropic salt, facilitates the H-bonding between the acid and the water complexes of the hydrophobic ILs.

In the hydrophilic $[P_{444,14}]Cl$, the water uptake drops about 3-times reaching the value of 11 mol/mol (H_2O to IL), which may imply the existence of aggregates [27], [28], most of them, however, empty of acid.

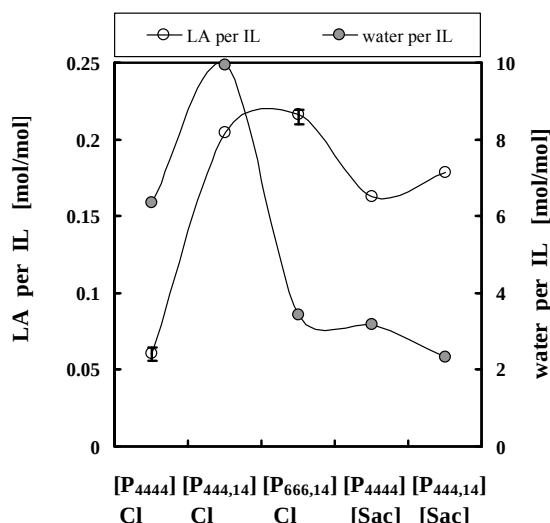


Fig. 3 LA extraction and water solubilization into the ILs from $MgSO_4$ -containing LA aqueous solutions, initial weight ratio of LA source to IL, 1:1

Fig. 3 represents the results obtained under the most hydrophobic conditions (the lowest water uptake) for LA

removal and accommodation in the IL-rich phase. Similar shape of LA extraction efficiency is observed, although, as expected, the LA-loading per IL was lower, due to the reduced initial LA amount with respect to the IL.

It should be also noted that the engagement of the water molecules with the kosmotropic salt favors the undissociated LA state, which is the preferred form for the LA extraction by IL [12]–[14].

C. Comparison of ILs' Extracting Capacity

An attempt to compare the ILs' proper extracting capacity towards the LA is imagined on Fig. 4. On the base of the measurements of the ILs' water content, the LA portion, that might be transferred along with water, was evaluated and subtracted from the total one. This residual LA content was assigned to the IL's "proper" extracting capacity and presented on Fig. 4.

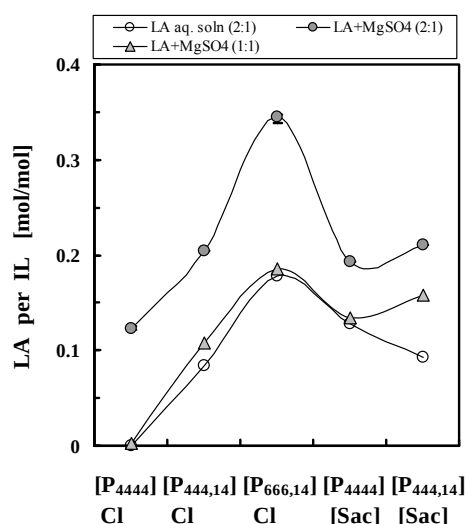


Fig. 4 Comparison between ILs' "proper" extracting capacity towards LA in native or MgSO_4 -containing aqueous solutions

A bell-shaped dependence, with a maximum at $[\text{P}_{666,14}]\text{Cl}$, is observed at any condition. The maximal effect is related to the greater nucleophilicity of Cl^- -anion able to strongly polarize the water molecules and then the acid. The beneficial effect of the increased cation hydrophobicity is pronounced in Cl^- -based ILs, as well as in $[\text{Sac}]$ -ILs under hydrophobic LA medium (with MgSO_4 -addition). In general, the IL's proper extracting capacity follows the order: $[\text{P}_{666,14}]\text{Cl} > [\text{P}_{444,14}][\text{Sac}]/[\text{P}_{4444}][\text{Sac}] > [\text{P}_{444,14}]\text{Cl} > [\text{P}_{4444}]\text{Cl}$.

From a practical viewpoint as extractants, the ILs should also be regarded in reference to the LA extraction yield ($EY\%$) and the LA partition coefficient (K_{LA}). These data are presented in Table I.

It is seen that by applying 1 g of the IL, the $EY\%$ decreases with the increase of the IL hydrophobicity. The major LA yields were achieved by the hydrophilic phosphonium chlorides. These systems, however, could be regarded as

aqueous two-phase systems and due to the large water uptake into the IL-rich phase could miss selectivity. In the biphasic systems of the hydrophobic ILs, apart from $[\text{P}_{666,14}]\text{Cl}$, some valuable partition coefficients ($K_{LA} > 2$) and LA yields ($EY\% > 50\%$) could be gained also by the phosphonium saccharinates if the LA would be extracted from more hydrophobic medium, as the kosmotropic salt-containing ones.

TABLE I
LA EXTRACTION YIELD ($EY\%$) AND LA PARTITION COEFFICIENT (K_{LA})

IL	LA aq. solution		LA solution containing MgSO_4			
	weight ratio LA sn to IL		(2 : 1)		(1 : 1)	
	$EY\%$	K_{LA}	$EY\%$	K_{LA}	$EY\%$	K_{LA}
$[\text{P}_{4444}]\text{Cl}$	-	-	92.7	6.08	40.2	0.91
$[\text{P}_{444,14}]\text{Cl}$	83.1	1.37	74.4	2.71	87.7	3.15
$[\text{P}_{666,14}]\text{Cl}$	40.4	1.34	67.4	3.28	82.9	3.38
$[\text{P}_{4444}][\text{Sac}]$	39.4	1.25	53.4	2.3	74.2	2.33
$[\text{P}_{444,14}][\text{Sac}]$	21.3	0.64	39.6	1.25	63.9	1.59

All data refer to LA extractions by 1 g of the corresponding IL.

IV. CONCLUSIONS

The phosphonium chlorides and saccharinates were compared as LA extractants on the base of a comprehensive study of the lactic acid and the water partitioning in biphasic systems "IL/water".

Among the studied ILs, $[\text{P}_{666,14}]\text{Cl}$, the hydrophobic IL of the strongest anion basicity, was found to exhibit the greatest proper extracting capacity towards the LA.

By the addition of a kosmotropic salt to the LA aqueous source, more hydrophobic LA microenvironment was created, which favored the undissociated acid state. Such condition appeared advantageous to the LA recovery in all studied ILs being pronounced in the saccharinate-based ones.

On the base of the estimation of the molar ratios between IL, water and acid in the IL-rich phases, it was assumed that LA (at the studied concentration of 0.5 mol dm^{-3}) was extracted through hydrated complexes of IL and water molecules.

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