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Investigation of ionic liquids as reaction media for enzymatic enantioselective acylation of amines

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Abstract

The use of ionic liquids as reaction media for lipase-catalyzed enantioselective acylation of 1-phenylethylamine (**1**) and 2-phenyl-1-propylamine (**2**) with 4-pentenoic acid was investigated. The best performing ionic liquid for each of these amines as well as its solvent properties were very different. Preparative scale kinetic resolution of **1** was performed efficiently in 1-butyl-2,3-dimethylimidazolium trifluoromethanesulphonate.

Keywords: Enantioselective amine acylation; Ionic liquids; Lipase; 4-Pentenoic acid; Solvent properties

1. Introduction

Enantiomerically pure amines are valuable intermediates in asymmetric synthesis and therefore there is a sustained interest in finding methods for their separation from racemates. Enantiotransformations catalyzed by enzymes such as lipases and amidases have shown a high potential for this purpose [1–3]. Lipase-catalyzed enantioselective acylation of amines has seen relatively limited use due to several limiting factors. Amines react spontaneously with the usual acylating agents and therefore less reactive agents are required. Lipase-catalyzed reactions with simple esters and carbonates are usually slow and more important, the deacylation of the chiral amides obtained is generally difficult to perform either chemically or enzymatically [1]. To overcome the latter problem, Madsen et al. introduced pent-4-enoyl group as an amine protecting group that could be cleaved under mild conditions using iodine and water [4]. Soon, the acylation with 4-pentenoic anhydride became one of the standard methods for chemical derivatization of amines. The same research group introduced afterwards the use of pent-4-enoyl derivatives in the enzymatic enantioselective acylation of amines [5,6]. As the usual irreversible acyl donors such as enol esters are too reactive, new derivatives were investigated. Efficient enzymatic resolution of several amines in organic solvents was achieved by two novel activated esters: cyanomethyl pent-4-enoate [5] and allyl pent-4-enoate [6].

Direct acylation of amines with 4-pentenoic acid circumvents the steps for the preparation of the acylation agent and also ensures that there is no spontaneous background reaction which is sometimes a problem for other derivatives [6]. In a previous work of our group on lipase-catalyzed kinetic resolution of primary alcohols by acylation with carboxylic acids in solvent free-system, it was demonstrated that 4-pentenoic acid was an especially good substrate for the enzyme: *Candida antarctica* lipase B (CALB) [7]. Therefore, in a subsequent study, we investigated its use as acyl donor for acylation of amines under reduced pressure in non-solvent system and in ionic liquids [8]. As expected, the reactions were much slower than for the acylation of alcohols in solvent-free system, but the reaction rates improved considerably when an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), was used as reaction media.

Room temperature ionic liquids are organic salts with the melting point below room temperature. Due to their unique properties, they have emerged recently as a potential replacement for organic solvents in biocatalytic transformations.

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Several excellent reviews on this topic were published recently [9–11]. Unlike organic solvents, ionic liquids have virtually no vapor pressure and therefore vacuum can be used to remove volatile products: methanol in [12], water in our system. Ionic liquids are polar solvents that do not inactivate enzymes like the organic solvents with similar polarities and therefore enzymatic reactions in more polar solvents became possible. The more polar ionic liquids promoted lipase-catalyzed reactions with polar substrates [11].

In the present work, we attempted to improve the efficiency of the amine acylation reactions in ionic liquids taking into consideration the solvent properties of the ionic liquids used as reaction media. The effect of the alteration of the cation and anion correlated with the polarity and nucleophilicity of a range of ionic liquids was investigated.

2. Materials and methods

2.1. Materials

The immobilized CALB catalyst (Chirazyme L-2, c.-f, C2, Lyo.) (EC 3.1.1.1.) was purchased from Roche Diagnostics (Mannheim, Germany). *R*-, *S*-, and *rac*-1-phenylethylamine (all >98%) (**1**), and 4-pentenoic acid (>98%) were bought from Wako Pure Chemical Industries Ltd. (Osaka, Japan). *Rac*-2-phenyl-1-propylamine (>98%) (**2**) was from Avocado Research Chemicals Ltd. (Heysham, UK). *R*- and *S*-2-phenyl-1-propylamine (both >99%), 1-butyl-4-methylpyridinium tetrafluoroborate ([bmp]BF_4) (>97%), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) (>97%) and 1-octyl-3-methylimidazolium tetrafluoroborate ([omim]BF_4) (>97%) were purchased from Fluka Chemie GmbH (Buchs, Switzerland). 1-Ethyl-3-methylimidazolium tetrafluoroborate ([emim]BF_4) and 1-ethyl-3-methylimidazolium trifluoromethanesulphonate ([emim]-tfms) were bought from Tokyo Kasei Kogyo (Tokyo, Japan). 1-Butyl-2,3-dimethylimidazolium trifluoromethanesulphonate ([bdmim]tfms), 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), 1-hexyl-3-methylimidazolium tetrafluoroborate ([hmim]BF_4), 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim]BF_4), 1-hexyl-2,3-dimethylimidazolium tetrafluoroborate ([hdmim]BF_4), 1-hexyl-3-methylimidazolium hexafluorophosphate ([hmim]-PF_6) and 1-octyl-3-methylimidazolium hexafluorophosphate ([omim]PF_6) were from Acros Organics (New Jersey, USA). 4-Pentenoic anhydride (>99%) was purchased from Aldrich (Milwaukee, USA). Other chemicals used were of analytical grade.

2.2. Lipase-catalyzed acylation of amines in ionic liquids

The reaction was started by adding the biocatalyst (50 mg) to a mixture of amine (1 mmol) and 4-pentenoic acid (0.75 mmol for **1** or 1.5 mmol for **2**) dissolved in an ionic liquid (1.5 mL) under stirring at a specified temperature (40 °C for **1** or 30 °C for **2**) and connecting the system to a vacuum pump through a cooling trap. The pressure was maintained at 5 mmHg.

The preparative scale kinetic resolution of amine **1** was performed by adding 0.200 g CALB catalyst to a mixture **1** (0.484 g, 4 mmol) and 4-pentenoic acid (300 mg, 3 mmol) in [bdmim]tfms ionic liquid (2 mL) and kept under stirring at 40 °C and 5 mmHg for 72 h. The reaction mixture work up was carried out as described below for sample preparation. The enantiomeric excess was determined to be 91% for amine **3** (0.203 g, 84% yield) and >99% for amide **4** (0.328 g, 81% yield) by HPLC analysis.

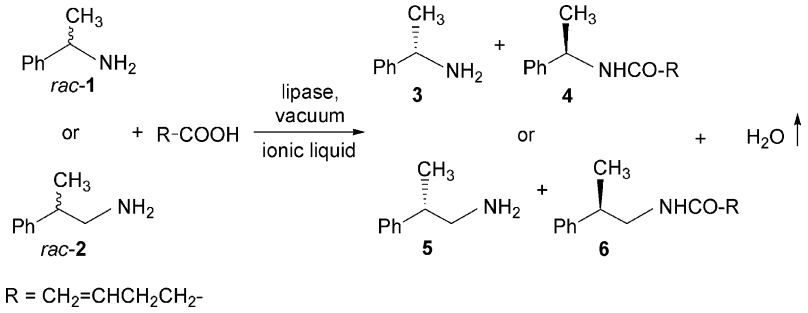
2.3. Analysis

At intervals, samples (0.15 mL) were withdrawn from the reaction mixture and extracted twice with diethyl ether. The combined extract was treated with HCl solution (2 N) that dissolved the amine as a chloride salt. The organic layer containing the amide and unreacted acid was removed and the water layer was washed with diethyl ether. The ether solutions were united and the acid was removed by washing with NaOH solution (2 N). The organic layer containing only the amide was collected, dried over $MgSO_4$ and the solvent evaporated. The water extract with the amine salt was neutralized with NaOH solution (2 N) and extracted twice with diethyl ether. The combined extract containing the free amine was dried over dried over $MgSO_4$ and the solvent evaporated.

The enantiomeric compositions of the residual amine **5** was determined by HPLC on a Chiralpak AD-H (Dicel Chemical Industries, Tokyo, Japan) column eluted with a mixture of hexane/2-propanol/diethylamine (95:5:0.05, v/v/v), at a flow rate of 0.5 mL/min at 20 °C with UV detection at 254 nm. The enantiomeric excess of amine **3** was determined after its transformation into the corresponding acetamide (acetic anhydride, pyridine). The enantiomeric compositions of the amide products **4** and **6** as well as the acetamide derivatives of amine **1** was determined on the above mentioned column eluted with a mixture of hexane/2-propanol (95:5, v/v) under the same conditions.

The (*R*)-enantiomer was preferentially acylated for amine **1** while for amine **2**, it was the (*S*)-enantiomer. The absolute configuration of amine **5** was determined by comparison with the retention times of the pure enantiomer standards on chiral HPLC. The (*S*)-configuration of amine **3** isolated from the reaction mixture and transformed in acetamide was determined after comparison of the retention times with the enantiomerically pure (*R*)- and (*S*)-acetamides of **1** prepared chemically from pure enantiomers of **1**. The absolute configuration of the formed amides **4** and **6** was determined similarly using chemically prepared amide enantiomer standards as described below.

The amine acylation was performed by adding 10 μL amine to a mixture of 0.3 mL anhydride (acetic or 4-pentenoic anhydride) and 0.1 mL pyridine in a 15 mL tube with



Scheme 1.

a screw cap. The tube was heated at 80 °C for 30 min. Two milliliters of water was then added and the tube heated at the same temperature for 10 min. The reaction mixture was extracted twice with diethyl ether. The organic extract was washed with NaOH solution (2 N) to remove the acid, then with HCl solution (2 N) to remove the pyridine traces, dried over $MgSO_4$, and finally, the solvent was evaporated. The concentrate was dissolved in the solvent used for HPLC analysis.

The conversion, c, and the enantioselectivity, E, were calculated from the enantiomeric excess of the product, ee_P, and the substrate, ee_S, according to Rackels et al. [13] using the equations below.

$$c = \frac{ee_S}{ee_S + ee_P} \quad (1)$$

$$E = \frac{\ln[(1 - ee_S)/(1 + ee_S/ee_P)]}{\ln[(1 + ee_S)/(1 + ee_S/ee_P)]} \quad (2)$$

3. Results and discussion

It is well known that the role of the solvent can be crucial for heterolytic reactions in organic synthesis and also that it can influence drastically the activity of lipases. Our previous study on enantioselective acylation of 1-phenylethylamine (**1**) and 2-phenyl-1-propylamine (**2**) catalyzed by CALB (Scheme 1) showed that the reaction rates improved dramatically when the reaction was performed in [bmim]PF_6 compared to the solvent-free system [8].

However, the reaction of (**1**) with 4-pentenoic acid remained still sluggish. In this study, we intended to further improve the performance of the ionic liquid system by modifying the properties of the ionic liquids by changes of the anion and cation. Some of the ionic liquids that gave good results for lipase-catalyzed reactions in previous studies were investigated here (Table 1). The reactions were performed at an optimized amine/acid molar ratio for each amine.

The ionic liquids chosen are based on 1-alkyl-3-methylimidazolium and 1-alkyl-2,3-dimethylimidazolium cations combined with the $[BF_4]^-$, $[PF_6]^-$ and $[CF_3SO_3]^-$ = $[tfms]^-$ anions. In addition, 1-butyl-4-methylpyridinium tetrafluoroborate ([bmp]BF_4) was also investigated. The available data describing their solvent properties found in the literature on this topic were summarized in Table 2 [14–16]. Solvatochromic probes were used to measure specific solvent–solute interactions in ionic liquids [14]. The normalized polarity scale, E_T^N,based on solvatochromic interactions of Reichardt's betaine dye (Table 2, column 3) is largely a measure of the hydrogen bond donor strength or hydrogen bond acidity of the system [16], and its values range from 0 for tetramethylsilane to 1.0 for water. The polarity scale, E_{NR},obtained using the solvatochromic dye Nile red [17] measures solvent dipolarity/polarizability (Table 2, column 4). The hydrogen bond acceptor ability, or nucleophilicity of the ionic liquids was correlated with the wave length value, λ_{max}, for the lowest energy d–d absorption band at solvation of acetylacetonatotetramethylethyldiaminecopper(II) tetraphenylborate: [Cu(acac)(tmen)[BPh_4] (Table 2, column 6) [16]. The water miscibility information was obtained from the manufacturer's product description (Table 2, column 6).

The polarity data show that the ionic liquids employed in this study are displaying hydrogen bond acidity and dipolarity/polarizability comparable to lower alcohols (Table 2, entries 16–18), while their nucleophilicity varies in a larger range and seems to be entirely anion dependent (Table 2). The available polarity data are very limited at the present and there were no available data for several ionic liquids employed in this work (Table 2, entries 1, 3, 5). To help with the discussion and data interpretation, the polarity data of two ionic liquids not tried in the experiments here were added to Table 2 (entries 2, 6). The water miscibility of ionic liquids is different from that of lower alcohols and depends on the substituents on the cation.

The present extended study showed that [bmim]PF_6, used in our previous work [8], is not the best reaction media for CALB catalyzed acylation of **1** (Table 1, entry 9). The best reaction rate, more than double of that for [bmim]PF_6, was given by [bdmim]tfms (Table 1, entry 2). Unfortunately, no polarity data for [bdmim]tfms were found and therefore only some considerations based by interpolation are possible. Taking into consideration that the hydrogen bond acidity decreases when the 2-position of the imidazolium cation is replaced by a methyl group (see the values for [bdmim]BF_4 and [bmim]BF_4, entries 4 and 8, respectively, of Table 2)

Table 1
Lipase-catalyzed enantioselective acylation of primary amines with 4-pentenoic acid

Entry	Amine	Ionic solvent	Initial rate (μmol/h mg)[a]	Reaction time (h)	Conversion amine (%)	ee_S[b] (%)	ee_P[c] (%)	*E*
1	**1**	[emim]tfms	0.153	24	18.4	22.6	>99.0	>500
2	**1**	[bdmim]tfms	0.177	24	21.2	27.0	>99.0	>500
3	**1**	[bdmim]BF_4	0.113	24	13.6	15.8	>99.0	>500
4	**1**	[hdmim]BF_4	0.027	24	3.2	3.3	>99.0	>500
5	**1**	[emim]BF_4	0.128	24	15.3	18.0	>99.0	>500
6	**1**	[bmim]BF_4	0.123	24	14.8	17.4	>99.0	>500
7	**1**	[hmim]BF_4	0.058	24	7.0	7.6	>99.0	>500
8	**1**	[omim]BF_4	0.102	24	12.3	14.0	>99.0	>500
9	**1**	[bmim]PF_6	0.077	24	9.2	10.2	>99.0	>500
10	**1**	[hmim]PF_6	0.122	24	14.6	23.2	>99.0	>500
11	**1**	[omim]PF_6	0.050	24	6.0	6.4	>99.0	>500
12	**1**	[bmp]BF_4	0.045	24	5.4	5.7	>99.0	>500
13	**2**	[emim]tfms	0.68	5	16.6	7.5	37.9	2.4
14	**2**	[bdmim]tfms	0.58	10	21.7	7.4	26.7	1.9
15	**2**	[bdmim]BF_4	0.16	24	19.6	8.4	34.4	2.2
16	**2**	[hdmim]BF_4	0.08	24	9.2	3.8	37.3	2.3
17	**2**	[emim]BF_4	0.67	10	18.4	11.8	52.3	3.6
18	**2**	[bmim]BF_4	0.59	5	14.8	8.3	47.9	3.1
19	**2**	[hmim]BF_4	0.16	24	18.9	9.2	39.4	2.5
20	**2**	[omim]BF_4	0.40	24	27.9	12.3	31.7	2.2
21	**2**	[bmim]PF_6	0.76	5	21.6	14.4	52.1	3.6
22	**2**	[hmim]PF_6	0.40	24	25.7	13.1	37.8	2.5
23	**2**	[omim]PF_6	0.08	24	9.5	5.3	50.1	3.2
24	**2**	[bmp]BF_4	0.33	24	23.3	9.2	30.4	2.0

[a] Amount of amine (μmol) esterified per hour and milligram of immobilized enzyme.
[b] Enantiomeric excess of unreacted amine.
[c] Enantiomeric excess of resulting amide.

Table 2
Solvent properties of ionic liquids and some non-ionic solvents determined by solvatochromic compounds and their water solubility

Entry	Solvent	Reichardt's dye E_T^N[a]	Nile red E_{NR}[b] (kcal/mol)	λ_{max}[c] (nm)	Water miscibility[d]	Ref.
1	[emim]tfms				M	
2	[bmim]tfms	0.67		601.5	M	[14]
3	[bdmim]tfms				I	
4	[bdmim]BF_4	0.58			I	[14]
5	[hdmim]BF_4				I	
6	[odmim]BF_4	0.54				[16]
7	[emim]BF_4	0.71			M	[15]
8	[bmim]BF_4	0.67	51.9		M	[14]
9	[hmim]BF_4		51.8		I	[14]
10	[omim]BF_4	0.54	52.0		I	[14]
11	[bmim]PF_6	0.67	52.2	516.5	I	[14]
12	[hmim]PF_6		51.8		I	[14]
13	[omim]PF_6	0.63	52.2	516.5	I	[14]
14	[bmp]BF_4	0.63				[15]
15	Water	1.00	48.2			[14]
16	Methanol	0.77	52.0			[14]
17	Ethanol	0.65	52.2	585		[14,16]
18	2-Propanol	0.55		591		[16]
19	Hexane		59.0			[14]
20	*N*,*N*-Dimethylformamide	0.39		602		[16]
21	1,2-Dichloroethane	0.33		500		[16]
22	Tetramethylsilane	0.00				[15]

[a] Normalized polarity values.
[b] Electronic transition energy.
[c] Wave length value for the lowest energy d–d absorption band at solvation of acetylacetonatotetramethylethyldiaminecopper(II) tetraphenylborate: [Cu(acac)(tmen)[BPh_4].
[d] M: miscible, I: immiscible.

and also its value for [bmim]tfms (Table 2, entry 2) which is the same with that for [bmim]BF_4 (Table 2, entry 8), it might be concluded that [bdmim]tfms has probably a hydrogen bond acidity between ethanol and 2-propanol. Regarding its nucleophilicity, [bdmim]tfms is probably very close to *N*,*N*-dimethylformamide (Table 2, entry 20). This estimation was based on the value for [bmim]tfms (Table 2, entry 2) and the fact that, as mentioned above, the nucleophilicity is dependent almost exclusively on the anion and that a methyl group instead of hydrogen on the 2-position of imidazolium [14] produced only a very slight increase of nucleophilicity. [Bdmim]tfms is immiscible with water and therefore, hydrophobic. A quite close value for the reaction rate was obtained in [emim]tfms (Table 1, entry 1). Applying the same rationale at as above, its nucleophilicity is almost the same as for [bmim]tfms and very similar to *N*,*N*-dimethylformamide (Table 2, entry 2). Its hydrogen bond activity places it probably between methanol and ethanol, as its E_T^N value is expected to be lower than for [bmim]tfms. [Emim]tfms is water miscible and therefore hydrophilic (Table 2, entry 1).

The change of the anion countering $[bdmim]^+$ from $[tfms]^-$ to $[BF_4]^-$ produced a decrease in the reaction rate (Table 1, entry 3). The decrease was very sharp when [hdmim]BF_4 was employed.

The ionic liquids based on 1-alkyl-3-methylimidazolium cation combined with $[BF_4]^-$ anion gave better rates (Table 1, entries 5, 6, 8) than those based on the same cation and $[PF_6]^-$ (Table 1, entries 9, 11). The decrease in the reaction rate seemed to be correlated with the increase in the length of the alkyl chain on the 1-position of the cation. The $[hmim]^+$ cation combined with either $[BF_4]^-$ or $[PF_6]^-$ produced strikingly different results than the next higher and lower chain alkyl cation, i.e. $[bmim]^+$ and $[omim]^+$ (Table 1, entries 7, 10). A similar behavior of these two liquids was observed in the polarity studies for the same series using Nile red (Table 2, entries 9, 12). The dipolarity/polarizability of both kinds of ionic liquids rises upon changing from butyl to hexyl and then falls for octyl chain [17]. The same study mentions that the melting point of these two series of ionic liquids (1-alkyl chain varied from ethyl to octadecyl) reaches a minimum for hexyl chain also [17]. The nucleophilicity or donor strength of $[PF_6]^-$ based ionic liquids (Table 2, entries 11, 13) is very low and very close to that of 1,2-dichloroethane (Table 2, entry 21) which is non-polar and has a donor number equal to zero [18]. No nucleophilicity data are available for the $[BF_4]^-$ based ionic liquids, but a study on the donor numbers of anions in 1,2-dichloroethane using $[Cu(acac)(tmen)]^+$ established the donor number 6.03 for $[BF_4]^-$ and 16.9 for $[tfms]^-$ [18]. This indicates that the nucleophilicity order is probably: $[PF_6]^- < [BF_4]^- < [tfms]^-$. The reaction rates for the acylation of amine **1** follow the same order and therefore a correlation with the nucleophilicity of the ionic liquid might be implied.

The enantioselectivity of the lipase in acylation of amine **1** was almost perfect in all ionic liquids investigated with only the (*R*)-enantiomer acylated. The value for enantioselectivity in ionic liquids was actually higher than the previously reported results on CALB catalyzed acylation of **1** with simple esters or carbonates in classical organic solvents [3]. The analytical scale kinetic resolution of amine **1** produced amide **4** (>99% purity) with 81% yield after purification in 72 h.

For the acylation of amine **2**, [bmim]PF_6 was the best reaction media (Table 1, entry 21), but [emim]tfms and [bmim]BF_4 afforded comparable reaction rates also (Table 1, entries 13, 17). [bdmim]tfms gave a slightly lower rate than [emim]tfms. The same minimum of the reaction rate for [hmim]BF_4 (Table 1, entry 19) in this series (1-alkyl chain varied from ethyl to octyl) was observed. These results suggest that in the acylation of amine **2**, the difference in nucleophilicity of the ionic liquids affects very little the reaction rates and that the hydrogen bond acidity of the solvent correlates with the reaction rates. The enantioselectivity for acylation of amine **2** was very low and did not vary much with the nature of the ionic liquid employed as reaction media.

The water miscibility of the ionic liquids does not appear to influence the reaction rates for the acylation of both amines.

The two amines used in this study have similar basicity (**1** slightly less polar than **2**), but the amine **1** has the chiral center at the a carbon atom (directly bound to the amine group) while amine **2** was a more remote chiral center at the β carbon atom. This structural difference accounts for the outcome of their enzymatic acylation. Due to the steric hindrance around the amine group of **1** that acts as the nucleophile attacking the acyl enzyme intermediate to form the amide, only the (*R*)-enantiomer can access the active site of the lipase. Moreover, a very strict orientation is necessary by entering the active site of the lipase. This step determines the high enantioselectivity of CALB for **1** and limits the rate of amide formation. The equilibrium of the whole process would be driven towards amide formation by a higher concentration of amine **1** in the unionized form in the reaction system. This rationale was proved in the process of optimizing the molar ratio of the reactants: an excess of amine **1** produced higher reaction rate. The ionic liquid used as reaction medium has a crucial effect on the reaction process. It provides a better solvation of the ionic reactants (when put in contact, the amine and acid spontaneously form a salt that has a low solubility in organic solvents and also is responsible for the very high viscosity of non-solvent system [8]). The best reaction medium for the acylation of **1**, [bdmim]tfms, solves the substrates and does not further ionize the amine as it would be expected in the case of ionic liquids based on 1-alkyl-3-methylimidazolium cation that have a high hydrogen bond donor ability at the 2-position of the imidazolium cation [16,19]. The concentration of the unionized amine in the reaction is therefore higher and consequently, raising the reaction rate. There is no doubt that the ionic liquid properties affect the ionization state of the enzyme too with further effects on the enantioselectivity and reaction rate.

In contrast, amine **2** can access easily the active site of the enzyme due to its more remote stereogenic center and less steric hindrance around the amine group. As a result, the acylation reaction is faster than for amine **1**, but the enantioselectivity of the enzyme is lower. For CALB-catalyzed acylation of amine **2**, the rate-limiting step of the process seems to be the formation of the acyl-enzyme intermediate. A higher concentration of free acid in the reaction media would favor the formation of the acyl-enzyme intermediate and speed up the whole process. To support this assumption, the optimum reactant molar ratio found for acylation of **2** has the acid in excess. An ionic liquid with high hydrogen bond acidity would modify the ionization state of the acid by substituting it in the formation of the salt with the amine, and therefore providing a higher concentration of acyl donor available to lipase in the system and raising the reaction rate as a result.

The results presented in this study demonstrated that finding the best reaction media for a specific enzymatic reaction is quite a tedious task and that it can not be assumed that the most performing reaction media for one substrate would perform the same even for a very similar compound. The interactions involved in ionic liquid systems are very complex and beside the effects on the reaction produced by solvent–solute interactions, the microenvironment of the enzyme is also affected. Although there is a wide range of ionic liquids readily available currently, the data on the solvent properties of the ionic liquids is quite limited and completely insufficient to allow a reliable prediction for selection of the 'best' reaction media. However, ionic liquids have great potential for biotransformations of highly polar substrates such as amines and carboxylic acids in our case. Although they are very polar, the ionic liquids do no inactivate the enzymes as would organic solvents of similar polarity or nucleophilicity (lower alcohols and *N*,*N*-dimethylformamide for our system). Unlike organic solvents specified above, ionic liquids systems can be run under low pressure to remove volatile products such as water here, driving the reaction equilibrium towards product formation.

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