

Tetraalkylammonium Ionic Liquids as Dual Solvents–Catalysts for Direct Synthesis of Sugar Fatty Acid Esters

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Received: 9 September 2015 / Accepted: 26 January 2016
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Abstract As nonionic surfactants derived from naturally renewable resources such as sugars and fatty acids, sugar fatty acid esters have been widely utilized in food, cosmetic and pharmaceutical industries. Our present study has demonstrated that the inexpensive and halogen-free tetraalkylammonium salts (e.g., [Bu₄N][Ac], [Et₄N][Ac] and [Me₄N][Ac]) can act as dual solvents–catalysts for regioselective acylation to produce glucose laurate. This non-enzymatic synthesis can proceed under mild conditions with high specificity, and the conversions obtained were superior to that when an enzyme catalyst (lipase, EC 3.1.1.3) was added. A higher yield was obtained in the ammonium salt with a longer alkyl chain on the cation, while no product was obtained in [Bu₄N][HSO₄] and [Bu₄P][Ac]. A reaction mechanism has been proposed, which is supported by phase-transfer catalysis and law of matching water affinity.

Keywords Ionic liquid (IL) · Sugar fatty acid ester (SFAE) · Glucose laurate · Tetraalkylammonium salts · Dual solvent–catalyst · Phase-transfer catalysis

Electronic supplementary material The online version of this article (doi:10.1007/s11743-016-1798-7) contains supplementary material, which is available to authorized users.

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Introduction

Sugar fatty acid esters (SFAE) are nonionic surfactants produced from naturally renewable resources such as carbohydrates and fatty acids through O-acylation. They are biodegradable, biocompatible and nontoxic with broad applications in food, cosmetic and pharmaceutical industries [1, 2]. Hydroxy group O-acylation is also extensively employed in carbohydrate chemistry as a protection strategy and for isolation and identification of sugars. However, the synthetic processes require the use of organic solvents and catalysts that usually cause concerns regarding their environmental health risks and have to proceed under harsh conditions [3]. In particular, it is hard to find an appropriate solvent that can solubilize the two substrates of opposite polarity. Therefore, a search for greener solvents and catalysts for this application has always been an ongoing issue.

Ionic liquids (IL) have gained intense attraction as a promising new reaction medium for a variety of synthetic processes due to their low volatility, high chemical and thermal stability, superior solubilizing power, and tunable solvent properties [4, 5]. Some IL have also been shown to act as catalysts further augmenting their already widespread applications [6]. For instance, O-acylation of alcohols and carbohydrates can proceed rapidly in high yield under mild conditions in a dicyanamide-based imidazolium IL, which is both a solvent and a base catalyst [6], and a few Lewis/Brønsted acidic IL have shown the ability of working as dual solvents–catalysts for esterification/trans-esterification reactions [7–17].

In this work, we report for the first time the use of tetraalkylammonium IL as dual solvents–catalysts for the synthesis of SFAE, and the synthesis of glucose laurate in this unique solvent system with and without addition of an

enzyme catalyst has been compared and discussed. Our recent study in enzymatic synthesis of glucose laurate has revealed that when lipase (EC 3.1.1.3) was added as the catalyst, among the 16 IL screened tetrabutylammonium acetate ($[\text{Bu}_4\text{N}][\text{Ac}]$) was the one in which the highest conversion was obtained [18]. A serendipitous experiment later has revealed that glucose laurate could also be produced in this particular IL in the absence of the enzyme.

Experimental

Materials

Ionic liquids (99 %) were obtained from Shanghai Cheng Jie Chemical Co., Ltd. Vinyl laurate (VL) and the Reichardt's dye (2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate) were from Sigma-Aldrich China Inc. α -D-Glucose (Glc), lauric acid (LA), 2-methyl-2-butanol (2M2B) and all other reagents used were of analytical grade from local manufacturers in China. Novozym 435 (*Candida antarctica* lipase B immobilized on acrylic resins) was purchased from Novozymes (China) Investment Co., Ltd.

Measurement of Electron Pair Acceptor Strength

Electron pair acceptor strength is commonly used as a measure of the polarity of a solvent and is determined spectrophotometrically by means of the Reichardt's dye [19]. The dye was dissolved in an IL at 0.5 mM. After centrifugation, the visible spectrum of the solution was scanned at 25 °C with a PerkinElmer Lambda 25 UV-Vis spectrophotometer. The wavelength of the absorption peak (λ_{max} , in nm) was recorded for determination of the IL's acceptor strength (E_{T}^{N}) following the equation: $E_{\text{T}}^{\text{N}} = [28,591/\lambda_{\text{max}} - 30.7]/32.4$, where E_{T}^{N} is set on a dimensionless normalized scale between 0.0 for tetramethylsilane and 1.0 for H_2O .

Determination of log *P* Values

log *P*, the logarithm of the partition coefficient of a solvent in an octanol/ H_2O biphasic system, is commonly used as a measure of the solvent hydrophobicity [20]. In this study, the KowWin software (<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>) was applied to estimate the log *P* value for each IL. This software has been found to give the best results for log *P* prediction among the four software packages (HyperChem, Pallas, KowWin and TOPKAT) [21].

Synthetic Reaction

A typical reaction was carried out by adding 0.054 g glucose (corresponding to 0.3 mol/l of the reaction system) to a 5-ml capped test tube containing 0.3 M VL in 1 ml solvent (pure IL or IL/2M2B mixture), which was placed in an incubator/shaker with agitation of 300 rpm at 40 °C for the reaction to start. Periodically, a 10- μl sample was taken and four times diluted with dimethyl sulfoxide, from which 10 μl was injected for HPLC analysis, which was performed on a Shimadzu LC-20AT HPLC system equipped with a refractive index detector (Shimadzu RID-10A) and a 150 \times 4.6 mm, 5 μm inertsil ODS-SP column (GL Sciences Inc. Japan). A solvent mixture of methanol/water (85:15 v/v, pH adjusted to 2.3 with acetic acid prior to addition of methanol) was employed as the mobile phase with a flow rate of 1.0 ml/min. The conversion was calculated based on the total amount of glucose added to the reaction system. For reactions to study the effect of water content, water was added to the IL prior to addition of the reactants, and the water content (% w/w) was determined by using a Metrohm 831 KF Coulometer. For reactions to study the impact of enzyme addition, Novozym 435 (100 mg) was added to the reaction mixture to start the reaction. All experiments were repeated at least twice with the results subjected to <10 % error.

Product Characterization

The glucose laurate product was isolated as a white powder and identified as 6-*O*-laurate- α -D-glucopyranose by structural analysis including IR (Nicolet 6700 FT-IR spectrometer, Thermo Scientific), ^{13}C NMR (Avance-400 NMR spectrometer, Bruker), and MS (AB SCIEX TripleTOF[®] 5600 System). IR (KBr) confirms the presence of an ester bond in the product: ν_{max} 1,731 cm^{-1} (C=O ester) (Fig. S1); ^{13}C -NMR (400 MHz, DMSO, TMS) (Fig. S2) suggests that α -anomer predominates with the esterification occurring at the C6 position: δ 13.869 (1C, C-12'); δ 22.012 (1C, C-11'); δ 24.412 (1C, C-10'); δ 28.369, 28.640, 28.823, 28.920 (6C, C-4' ~ 9'); δ 31.219 (1C, C-3'), δ 33.411 (1C, C-2'), δ 63.787 (1C, C-6); δ 69.097 (1C, C-4), δ 70.519 (1C, C-5), δ 72.155 (1C, C-2), 72.833 (1C, C-3); δ 92.234 (1C, C-1 α); δ 172.850 (1C, C-1'). MS (Fig. S3) gave molecular ion peaks at m/z 385 and 363, consistent with the formulations $[\text{NaGL}]^+$ and $[\text{HGL}]^+$ and the monoesterification of glucose.

Results and Discussion

[Bu₄N][Ac] as Dual Solvent–Catalyst for Synthesis of Glucose Laurate

When the two reactants (glucose and VL) were placed in a bisolvent mixture ([Bu₄N][Ac]/2M2B, 0.05/0.95, v/v) for 24 h, the HPLC analysis revealed that the glucose laurate product was produced with a conversion of 11.8 % (Fig. 1). This serendipitous experiment revealed that the transesterification reaction had occurred between the two substrates with no added catalyst. Later, a controlled experiment (Table 1) showed that in pure [Bu₄N][Ac], addition of the two substrates yielded the production of glucose laurate regardless of whether the lipase catalyst was present or not, while in 2M2B no product was detectable in the absence of the enzyme. This suggests that the IL [Bu₄N][Ac] acts as both a solvent and a catalyst for the transesterification reaction. The product obtained in the non-enzymatic reaction possessed the same retention time in HPLC analysis as the one produced from the enzymatic reaction (which has been verified as 6-*O*-lauroyl-D-

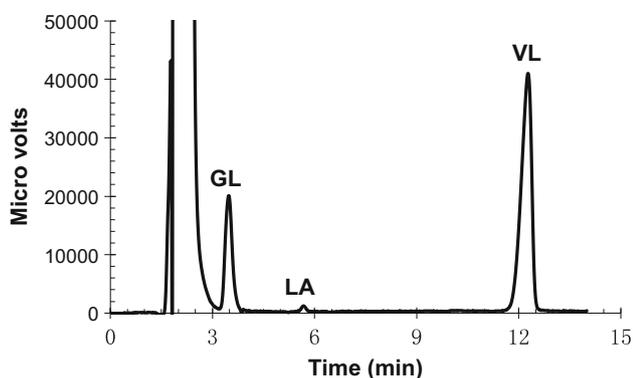


Fig. 1 HPLC chromatogram. 0.054 g glucose was added to 1 ml solvent ([Bu₄N][Ac]/2M2B, 0.05/0.95, v/v) containing 0.3 M vinyl laurate, and the reaction was carried out in an incubator/shaker with agitation of 300 rpm at 40 °C for 24 h. *GL* glucose laurate, *VL* vinyl laurate, *LA* lauric acid

Table 1 A controlled experiment to compare the production of glucose laurate in both solvents ([Bu₄N][Ac] and 2M2B, 1.0 ml each) with and without addition of the enzyme (Novozym 435)

Test no.	1	2	3	4
Solvent	[Bu ₄ N][Ac]	[Bu ₄ N][Ac]	2M2B	2M2B
Substrate 1: Glc (M)	0.3	0.3	0.3	0.3
Substrate 2: VL (M)	0.3	0.3	0.3	0.3
Enzyme: Novozym 435 (mg)	100	0	100	0
[GL] obtained at 24 h (M)	0.10	0.11	0.10	0

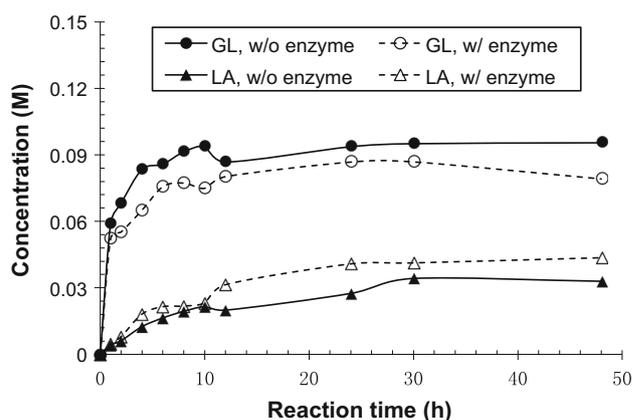


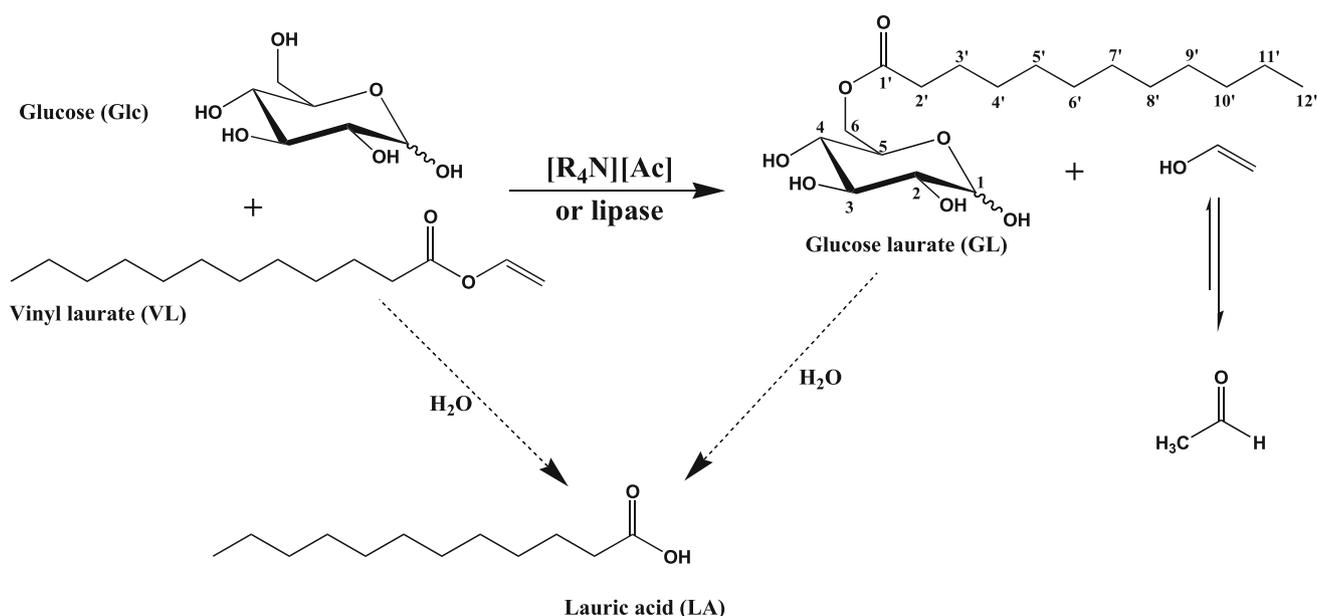
Fig. 2 Production of glucose laurate (GL) and lauric acid (LA) in [Bu₄N][Ac] with and without addition of the enzyme. 0.054 g glucose was added to 1.0 ml [Bu₄N][Ac] (water content 16.0 %) containing 0.3 M vinyl laurate, and the reaction was carried out by agitation of 300 rpm at 40 °C, with and without addition of 100 mg enzyme

glucopyranose by structural analyses with NMR, IR and MS), suggesting that the specificity is retained.

A comparison of the two reactions with and without addition of the enzyme further confirms the above findings (Fig. 2). Both reactions resulted in the production of glucose laurate, but with a slightly higher yield obtained in the absence of the enzyme (a similar phenomenon was also observed in Table 1). Interestingly, during the reaction course a by-product, LA, was also gradually generated, with a slightly lower amount obtained in the enzyme-free reaction. LA is formed mainly because both the co-substrate (VL) and the product (glucose laurate) are easily subjected to hydrolysis, as long as there is a trace amount of water present in the reaction system (see Scheme 1). Therefore, this experiment gives us an indication that the IL [Bu₄N][Ac] was capable of catalyzing the transesterification reaction as well as a side-reaction of hydrolysis, the latter being more favored in the presence of the enzyme. In support of this, Fig. 3 has clearly demonstrated that addition of the enzyme led to a gradual decrease in the production of glucose laurate and a significant increase in the production of LA; in particular when 100 mg of Novozym 435 was added, within 24 h a negligible amount of glucose laurate was produced while almost all VL was converted to LA. The fact that a lower yield of the glucose laurate was obtained in the presence of the enzyme might be related to the preference of Novozym 435 in catalyzing the hydrolysis side-reaction.

Effect of Different Factors on the Non-Enzymatic Synthetic Reactions in [Bu₄N][Ac]

The non-enzymatic reaction can be affected by factors such as water content, IL/2M2B volumetric ratio, and reaction



Scheme 1 Transesterification reaction of vinyl laurate and glucose to produce glucose laurate, accompanied by side reactions of hydrolysis to produce lauric acid

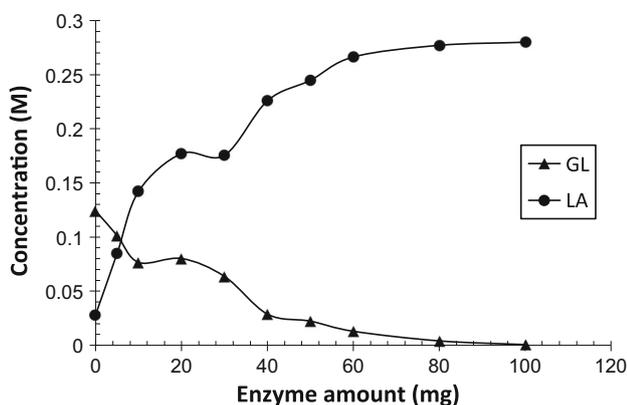


Fig. 3 Effect of enzyme dosage on the production of glucose laurate (GL) and lauric acid (LA) in $[Bu_4N][Ac]/2M2B$ (3:7, v/v) bisolvent system. 0.054 g glucose was added to 1.0 ml $[Bu_4N][Ac]$ (water content 16.0 %) containing 0.3 M vinyl laurate, and different amounts of enzyme (0–100 mg) were added to start the reaction, which was carried out with agitation of 300 rpm at 40 °C

temperature (Fig. 4). It appears that the presence of a threshold quantity of water in the IL contributed to higher conversions (Fig. 4a). For a transesterification reaction which is accompanied by hydrolysis as a side reaction, the initial increase in the ester yield along with a gradual decrease in the formation of the hydrolytic by-product (LA) was unexpected. For latter experiments the water content was fixed at 16 % (w/w).

Mixing the IL with 2M2B is advantageous in enhancing the glucose solubility (13 mM in 2M2B vs 173 mM in $[Bu_4N][Ac]$, determined by using the dinitrosalicylic acid

method [22]) and lowering the viscosity of the reaction medium [549.3 cP for $[Bu_4N][Ac]$ vs. 3.5 cP for 2M2B, determined by using an AR1000 rheometer (TA Instruments, USA)]. Adding 2M2B to the IL can also reduce the cost of the synthetic process. As shown in Fig. 4b, the optimal conversion (42 %) was obtained in the 7:3 $[Bu_4N][Ac]/2M2B$ bisolvent system, but for the sake of lowering the formation of the hydrolytic by-product (LA) a volumetric ratio of 3:7 was used for later experiments.

An increase in the reaction temperature seemed to be unfavorable (Fig. 4c), because while the yield of glucose laurate was fairly unchanged, the concentration of LA was dramatically enhanced, indicative of a stronger tendency for hydrolysis.

Use of IL Analogous to $[Bu_4N][Ac]$

The above experiments clearly demonstrated that $[Bu_4N][Ac]$ possesses a catalytic power, thus prompting us to try some other analogous IL such as $[Me_4N][Ac]$, $[Et_4N][Ac]$, $[Bu_4N][HSO_4]$ and $[Bu_4P][Ac]$. A screening test has revealed that the performance of these IL was dependent on both the cation and the anion. The glucose laurate product was produced in all the three tetraalkylammonium acetate salts, whereas neither $[Bu_4P][Ac]$ nor $[Bu_4N][HSO_4]$ yielded any product. For the former three acetate salts, the conversion increased as the length of the alkyl chain on the cation increased ($[Me_4N][Ac] < [Et_4N][Ac] < [Bu_4N][Ac]$) (Fig. 5). This is in contrast to the findings reported by Fang et al. [11] when they evaluated

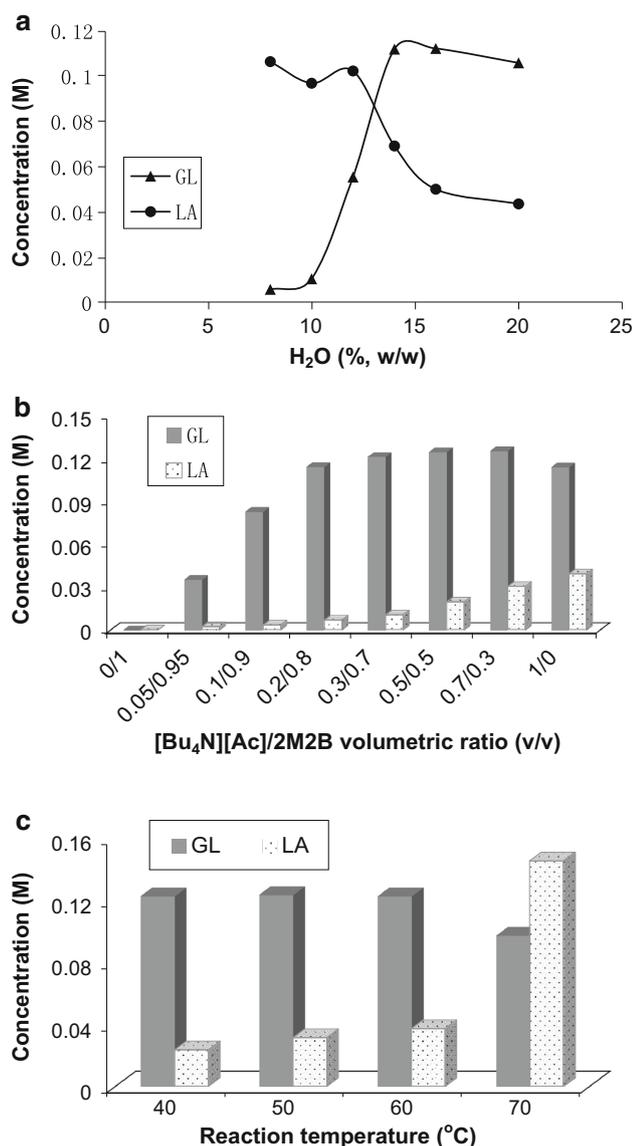


Fig. 4 Study on factors affecting the production of glucose laurate (GL) and lauric acid (LA): **a** effect of water content (% w/w), in pure [Bu₄N][Ac]; **b** effect of [Bu₄N][Ac]/2M2B volumetric ratio (v/v), in the bisolvent system; and **c** effect of temperature (°C), in 3:7 [Bu₄N][Ac]/2M2B bisolvent system. Reaction conditions were the same as in the above figures

the use of some HSO₃-functionalized Brønsted acidic ammonium IL as dual solvents–catalysts for Fischer esterification reactions. Again, the conversions obtained in the three tetraalkylammonium salts became, respectively, slightly lower when the enzyme was added (Fig. 5), in support of our assumption above that Novozym 435 catalyzes the hydrolysis side-reaction preferentially, hence depressing the production of the glucose laurate product.

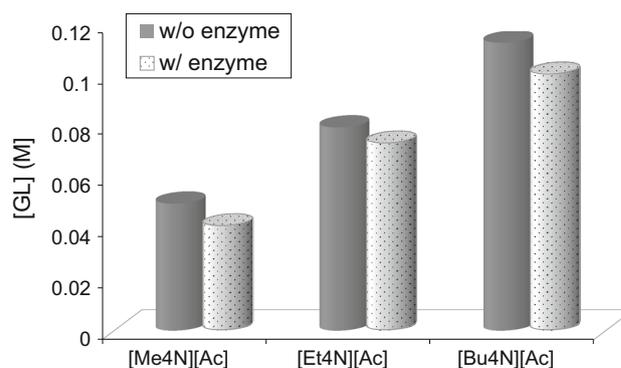


Fig. 5 Production of glucose laurate (GL) in the three tetraalkylammonium IL with and without addition of the enzyme catalyst. Reactions were carried out in the three IL using the conditions the same as those in Fig. 2

A Plausible Mechanism

A plausible mechanism is postulated in Scheme 2 to illustrate the catalytic role of the IL. Dissociated from the salt in the presence of water, the acetate anion would facilitate the nucleophilic attack of the hydroxyl group of glucose to the carbonyl group of the ester. The negatively charged tetrahedral intermediate would be stabilized by the tetraalkylammonium cation, thus leading to the production of glucose laurate and the release of the enolate anion of VL, which subsequently tautomerizes to acetaldehyde.

This mechanism can directly explain why a certain amount of water was required for the non-enzymatic reaction. On the other hand, according to the law of matching water affinities [23], oppositely charged ions in aqueous solution spontaneously form inner sphere ion pairs only when they have equal water affinities. As the acetate anion is highly affinitive to water while the three tetraalkylammonium cations vary in their hydrophobicity in the order of Me₄N⁺ < Et₄N⁺ < Bu₄N⁺ (which can also be judged from their log *P* values listed in Table 2), it is reasonable to assume that the interaction between Bu₄N⁺ and Ac[−] is weaker than the one between Me₄N⁺ and Ac[−]. The enforced large distance between Bu₄N⁺ and Ac[−], due to the larger butyl chains in the cation, is another way of seeing the weaker interaction. Therefore, in the presence of water [Bu₄N][Ac] has a higher propensity of dissociating and ionizing, thus promoting the catalysis by making the glucose hydroxyl group nucleophilic with the aid of the acetate anion and by stabilizing the negatively charged intermediate with the tetraalkylammonium cation. No ester product was produced in the presence of [Bu₄N][HSO₄] presumably because HSO₄[−] is much less basic than acetate. The inability of [PBu₄][Ac] to catalyze the reaction

Scheme 2 A proposed mechanism to illustrate the catalytic role of tetraalkylammonium salts in the transesterification reaction for sugar ester synthesis (Q = tetraalkylammonium)

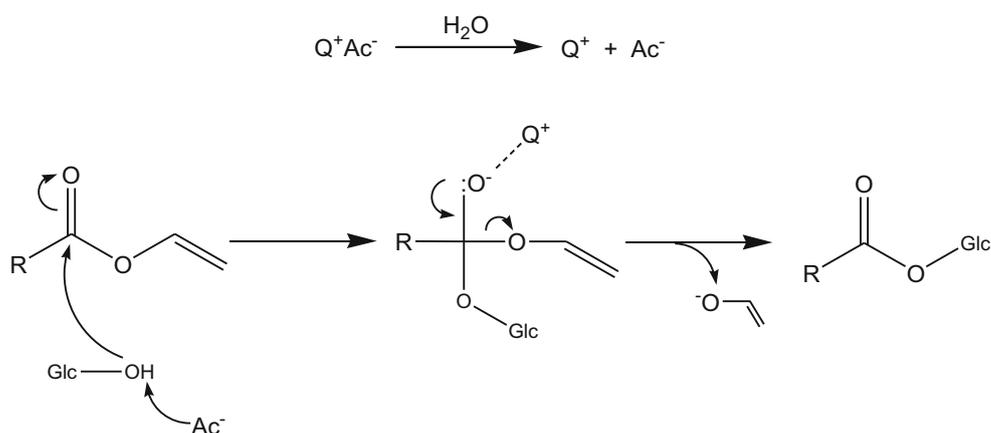


Table 2 Properties of the three tetraalkylammonium IL

	E_N^T	$\log P$	Viscosity (cP)
[Me ₄ N][Ac]	0.69	-2.09	16.49
[Et ₄ N][Ac]	0.51	-0.13	44.03
[Bu ₄ N][Ac]	0.45	3.8	62.69

Both polarity (E_N^T) and viscosity data were obtained in the IL containing 16 % (w/w) H₂O

may be related to the weaker electrophilicity of the cation due to the larger size of *P* versus *N* and hence more dispersed distribution of its electron cloud. Moreover, this mechanism can also provide explanation about the regioselectivity of this chemical synthesis: the preferential acylation of primary over secondary hydroxyl groups in the sugar may be due to the easier deprotonation of the former with the aid of the acetate anion.

In fact, as early as half a century ago quaternary ammonium and phosphonium salts (Q^+X^-) have been discovered to play a catalytic role in reactions between two reactants located in two immiscible phases such as organic solvent and aqueous solution, and Starks [24] had introduced a concept “phase-transfer catalysis” to explain this phenomenon. The accelerating rate of the reaction is believed to be mainly due to the two characteristic features of the pairing cation (Q^+): the high lipophilicity and the large ionic radius [25]. This can be applied to account for our experimental observation: because the glucose molecule tends to be deprotonated with the aid of the acetate anion, the hydrophobic quaternary ammonium cation may have the propensity to associate with the glucose, thus making it more compatible with the hydrophobic VL and in turn facilitating the reaction between them two; this beneficial effect would be stronger when the alkyl chains attached on the cation are longer and hence more hydrophobic. Therefore, it is understandable that as the lipophilicity and the size of the cation varied following the

order of [Bu₄N][Ac] > [Et₄N][Ac] > [Me₄N][Ac], so did the conversions obtained in these IL, regardless of the slightly lower polarity and higher viscosity (Table 2).

Conclusions

This study has demonstrated that tetraalkylammonium IL such as [Bu₄N][Ac], [Et₄N][Ac] and [Me₄N][Ac] possess the potential of acting as both solvents and catalysts for regioselective acylation to synthesize SFAE. This catalytic process offers several advantages: (1) no additional catalyst is required; (2) the IL are inexpensive and halogen-free; (3) the synthetic reaction can proceed directly under mild conditions with high specificity; and (4) water produced does not need to be removed during the reactions. Our experimental results and the proposed mechanism have rationalized the structure–function relationship between the conversions and the choice of the cation and anion of the IL, thus providing useful information regarding the design of these catalytic IL for such applications.

Acknowledgments The authors are grateful to the National Natural Science Foundation of China for its financial support (No. 21276159).

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