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Optimization of Enzymatic Synthesis of D-Glucose-Based Surfactants Using Supported *Aspergillus niger* Lipase as Biocatalyst

Alexis Spalletta, Nicolas Joly * and Patrick Martin

Unité Transformations & Agroressources, ULR7519, Université d'Artois-UniLaSalle, F-62408 Bethune, France; alexis.spalletta@univ-artois.fr (A.S.); patrick.martin@univ-artois.fr (P.M.)
* Correspondence: nicolas.joly@univ-artois.fr

Abstract: Surfactants are amphiphilic molecules with the ability to modify the surface tension between two surfaces. They can be obtained by various methods, the main one being synthetic, from petroleum-based substrates. Their universal use in a wide range of fields has created a global market and, consequently, ecological, and economic expectations for their production. Biocatalyzed processes, involving enzymes, can address this objective with processes complying with the principles of green chemistry: energy saving, product selectivity, monodispersity, and reduction in the use of solvents, with energy eco-efficiency. For example, fatty-acid carbohydrate esters are biobased surfactants that can be synthesized by lipases. In this work, we were interested in the synthesis of D-glucose lauric ester, which presents interesting properties described in the literature, with *Aspergillus niger* lipase, rarely described with sugar substrates. We optimized the synthesis for different parameters and reaction media. This lipase appeared to be highly selective for 6-*O*-lauroyl-D-glucopyranose. However, the addition of DMSO (dimethyl sulfoxide) as a co-solvent displays a duality, increasing yields but leading to a loss of selectivity. In addition, DMSO generates more complex and energy-intensive purification and processing steps. Consequently, a bio-sourced alternative as co-solvent with 2MeTHF3one (2-methyltetrahydrofuran-3-one) is proposed to replace DMSO widely described in the literature.

Keywords: biocatalysis; green chemistry; *Aspergillus niger* lipase; D-glucose ester; agro-based

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1. Introduction

Surfactants represent an important part of the chemical industry's production [1,2]. Among them, carbohydrate-based surfactants are particularly interesting surfactants. They are non-toxic, non-irritant, and biodegradable, and some of them also have insecticidal [3] and antimicrobial properties [4]. This ensemble of molecules is principally obtained by chemical or microbial processes, especially for carbohydrate-based surfactants such as rhamnolipids. The use of microorganisms generates a significant cost increase, particularly for purification, and even more, the relatively small quantities produced during biosynthesis are a critical limiting factor [5]. An alternative would be to turn to so-called classical and conventional chemistry syntheses, particularly in terms of synthesis cost, though this chemistry is difficult to implement with carbohydrates [6]. Biocatalysis is an emerging tool to design such biosourced high value-added molecules [7,8]. Over the past two-to-three decades, interest in biocatalytic transformations has increased due to a crucial need for more sustainable industrial processes consistent with green chemistry principles [9,10]. Enzymatic syntheses are supposed to have many advantages compared to chemical syntheses: energy saving, product selectivity, and reduced use of petro-sourced solvents. One of the advantages of enzymes for surfactant synthesis is to minimize the production of undesirable by-products, as well as hydroxyl protection and deprotection steps of carbohydrate molecules platforms [11]. These steps have important costs and

complicate the syntheses. Enzymes have great flexibility and adaptability. Indeed, their active site can interact various substrates, under various temperature conditions and alternative solvents. The main enzymes used are lipases, which catalyze both esterification and hydrolysis reactions. They can be used in several fields [12–14].

The kinetics of ester formation lipase-catalyzed reactions are governed by several factors (temperature, reaction time, stirring, substrates, ratio substrate, reaction medium, etc.) that must be optimized to improve yields [15] or to decrease final product overall carbon footprint. For enzyme selection, it is necessary to look for cheap and catalytically efficient lipases. We chose to work with a commercial, fixed *Aspergillus niger* lipase. *Aspergillus niger* lipases have been reported to catalyze the synthesis of esters from various dicarboxylic acids and diols [16] but also in biodiesel production [17]. However, there are limited data on the use of *Aspergillus niger* for the synthesis of sugar esters despite its good catalytic activity for the synthesis of these molecules [18].

The first parameter to consider when studying an enzymatic synthesis, after selecting the enzyme, is the reaction solvent. The challenge in enzymatic sugar ester synthesis is to find the right solvent to solubilize substrates, with almost opposite polarities, without deactivating the enzyme [19]. It is necessary to compare the logP of solvents to choose the reaction medium. LogP is a measure of differential solubility allowing comparison of solvents according to their hydrophilic or hydrophobic character. The logP of the initial reaction mixture is correlated linearly with the k_{cat} (catalytic constant) of the ester synthesis [20]. This is an important parameter. A strong polarity solvent with a logP > 4 will generate weak enzymatic activity by reducing the water content of the enzyme's microenvironment. The higher the polarity of the solvent is, the lower the enzyme activity is supposed to be. The conversion increases with substrate solubility [21]. Different reaction media have been reported in the literature. *n*-hexane, often described as a very good solvent for enzymatic reactions, combined with THF (tetrahydrofuran), optimal for dissolving D-glucose, or *tert*-butyl alcohol (*tert*-BuOH), seem to be interesting choices [22–25]. Indeed, such mixtures improve water distribution of the system and consequently reduce the effects of water on the enzyme. Nevertheless, THF partially inactivates the enzyme by reducing water enrichment in the protein microenvironment. Other solvents, such as DMSO (dimethyl sulfoxide), pyridine, or DMF (*N*,*N*-dimethylformamide), are considered to be universal solvents able to solubilize almost all organic molecules [26]. Many research works have therefore used tertiary alcohols [27,28], either by saturating the solution in sugar [27], or by adding a solubilizing agent such as DMSO in variable proportion [29]. Tertiary alcohols have the advantage of not being substrates for lipases, and therefore do not interfere with the main reaction. Furthermore, tertiary alcohols do not have an inactivating effect on the enzyme [30]. Tertiary alcohols are reported in co-solvent systems too [31,32]. More recently, agro-based solvents have received attention, such as methylated derivatives of tetrahydrofuran [33], which are biobased and less toxic than THF, but expensive. Mixed organic solvents, so-called co-solvents, are generally preferred to the single solvent because the solvent ratio allows a variation in the solubility at the beginning of the reaction. The solubility of the acyl acceptor, and therefore the enzyme activity, can then be controlled [34].

Another parameter to consider in the enzymatic synthesis of carbohydrate esters is the reagent type, i.e., free carboxylic acid, or corresponding esters to improve the synthesis of carbohydrate esters by enzymatic reaction. This is transesterification, where methyl, ethyl, and vinyl esters are usually employed as acyl reagents instead of carboxylic acids. Transesterification is generally preferred to the esterification reaction, due to the higher reactivity of the ester group compared to the corresponding carboxylic acid. Moreover, the synthesis produces, for example, ethanol when using ethyl ester versus water when using corresponding carboxylic acid [35,36].

The present study focuses on optimizing the parameters for the synthesis of 6-*O*-lauroyl-D-glucopyranose with *Aspergillus niger* lipase (Figure 1), followed by a selectivity study in different reaction media. A sustainable alternative of co-solvent to DMSO is then proposed and discussed.

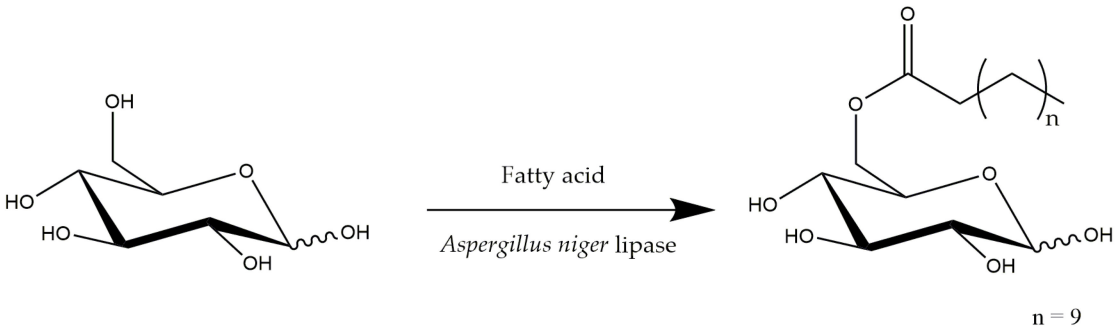

Figure 1. Synthesis of 6-*O*-lauroyl-D-glucopyranose.

2. Materials and Methods

2.1. Materials

All reagents used had a minimum purity of 98% unless otherwise stated.

Tert-BuOH and 2-methyl-2-butanol (2M2B) were from Janssen (Beerse, Belgium). Dichloromethane (CH2Cl2) and 2-methyltetrahydrofuran (2MeTHF) were from Carlo Erba Reagents. Magnesium sulfate (MgSO4) was purchased from Laboratoire Verbiese (Merville, Nord, France). Ethyl Acetate (AcOEt), methanol (MeOH), and petroleum ether were from VWR (Fontenay-sous-Bois, France). DMSO-d6 was purchased from VWR and stored at 4 °C prior to use. A molecular sieve 3 Å (8–12 mesh, preactivated by drying 4 h at 250 °C before use, then dried overtime at 105 °C), DMSO, 2-methyltetrahydrofuran-3-one (2MeTHF3one), D-glucose, lauric acid (C12), ethyl laurate (C12Et), and vinyl laurate (C12V) were purchased from Sigma-Aldrich (USA). TLC were TLC-sheets ALUGRAM Xtra silG/UV254.

Macroporous acrylic resin-supported lipase (EC 3.1.1.3), ≥5000 U/g, recombinant, expressed in *Aspergillus niger*, was purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Solubility Test

A fixed amount of D-glucose was added to Eppendorf tubes containing a mixture of *tert*-BuOH, *tert*-BuOH/DMSO, 2M2B, 2M2B/DMSO, 2M2B/2MeTHF, or 2M2B/2MeTHF3one as solvent. Suspensions were stirred at 240 rpm and heated to 56 °C to reproduce the enzymatic reaction conditions described below. After 1 h heating, the supernatant was removed and the remaining DMSO was evaporated using a Speed vacuum RVC 2–18 CD-Plus (Martin Christ, Osterode am Harz, Germany) apparatus. Parameters for evaporation were 130 rpm, 40 °C. The mass variation allowed determination of the amount of D-glucose solubilized in the different solvent mixtures.

2.3. Enzymatic Synthesis

A molecular sieve 3 Å (10% *w*/*v*), D-glucose (0.18 g, 1 mmol, 1 eq.) and a fatty reagent (3 mmol, 3 eq.) were stirred together in 2M2B or *tert*-BuOH. For reactions involving a co-solvent, DMSO (20%, *v*/*v*) was then added. The reaction mixture was stirred at 240 rpm and heated to 56 °C in a ThermoFisher MaxQ4450 closed thermostatic apparatus. After 1 h heating, a homogeneous medium was obtained, and a sample was taken to carry out TLC kinetics and HPLC analysis (t_0). *Aspergillus niger* was finally added with a ratio of 1% (*w*/*v*). In parallel with the reaction, a reaction medium without enzyme was systematically used as negative control. For every synthesis, reaction mixture was filtered under vacuum, washed with 2M2B, and evaporated under reduced pressure. An extraction with water and dichloromethane was performed to remove the excess unreacted D-glucose. The organic layer was dried in $MgSO_4$ and evaporated under reduced pressure. Flash chromatographic purification was then performed using a petroleum ether/ethyl acetate gradient mixture as mobile phase, to remove the excess of unreacted fatty reagent. A methanol/ethyl acetate 1:4 (*v*/*v*) mixture was then used to recover the desired products.

6-*O*-lauroyl-(α/β)-D-glucopyranose was obtained as a white solid and characterized as follows [19,33,37]:

- 0.125 g, 34.6% isolated yield for initial synthesis conditions in 2M2B/DMSO.
- Rf 0.18 (AcOEt/petroleum ether 4:1 *v/v*).
- FTIR–ATR (v_{max}/cm^{-1}): 3300 (OH), 2852–2920 (aliphatic CH), 1730 (ester C=O), 1010 (–O), 952 (OH deformation), 722 ($(CH_2)_n$, $n \geq 4$).
- ^1H NMR (DMSO-d_6): δ ppm 5.08 (m, 1H), 4.90 (d, *J* = 4.6 Hz, 1H), 4.28 (dd, *J* = 13.5 Hz, 2.3 Hz, 1H), 3.97 (dd, *J* = 11.6 Hz, 6.3 Hz, 2H), 3.76 (m, 1H), 3.43 (m, 1H), 3.14 (m, 1H), 3.04 (t, *J* = 8,7 Hz, 1H), 2.27 (t, *J* = 7.2 Hz, 2H), 1.50 (m, 2H), 1.24 (m, 16H, alkyl chain), 0.85 (t, *J* = 6.7 Hz, 3H, CH_3).
- ^{13}C NMR (DMSO-d_6): δ ppm 97.35–92.76 (1C, α/β monoester), 173.4 (C=O), 76.58 (1C), 74.86 (1C), 73.02 (1C), 72.35 (1C), 64.35 (1C), 33.88–22.51 (10C, alkyl chain), 14.40 (1C, CH_3).
- DEPT analysis δ ppm 173.4, 64.35. The alkyl chain was identified from 33.88 to 22.5.
- MS(EI) = *m/z* 384.7 $[M + Na]^+$.

2.4. Analytical Methods

After product purification and SpeedVac sample drying, products were characterized by FT–IR spectroscopy (using Cary 630 purchased from Agilent). MS and NMR spectroscopy were performed on an Expression CMS (Advion) and on a Bruker 400 MHz spectrometer, respectively.

For every synthesis, reaction progress was followed by HPLC, using a LC-20ADSP pump (Shimadzu) and a Syncronis C18 column (150 mm × 4.6 mm, Lithuania), maintained at 40 °C. Detection was performed using a refractive index detector RID-20A. Methanol/water 9:1 (*v/v*) was used as mobile phase (flow rate 1.0 mL/min) for a variable duration, between 5 and 20 min depending on the fatty reagent [4]. After time reacting, the reactions were stopped by cooling the medium until room temperature. Samples were subjected to TLC (AcOEt/petroleum ether 4:1 *v/v*) and HPLC analysis.

To clearly analyze the different products and reagents detected in HPLC, a calibration was performed using C12, C12Et, and C12V as standard, with and without the presence of DMSO, to observe the effect of DMSO on retention times. Standards were also performed in negative control reactions containing the C12Et or C12V and the enzyme. For the runs performed at the end of the reactions, post-HPLC collected fractions were concentrated using a Speed vacuum RVC 2-18 CDPlus (Martin Christ, Osterode am Harz, Germany) apparatus for further mass spectrometry analysis.

A quantification of the 6-*O*-lauroyl-D-glucopyranose produced was carried out during the reactions. An external calibration was carried out using 6-*O*-lauroyl-D-glucopyranose, the structure of which was confirmed by NMR spectroscopy, as standard. Aliquots for quantification were made after the filtration and evaporation steps of 2M2B. A 100 µL measure of the residual medium containing DMSO was taken and mixed with methanol. For reactions without DMSO, the filtered reaction medium was evaporated and the residue was dissolved in DMSO and mixed with methanol to analyze under the same conditions.

2.5. Statistical Analyses

Results are expressed as the mean ± standard deviation (SD). All statistical analyses were performed using GraphPad Prism v6 software. Comparisons of more than two groups with each other were analyzed with two-way ANOVA and Tukey's test. * $p < 0.05$, **** $p < 0.0001$.

3. Results and Discussion

In the initial stage of our investigation, 6-*O*-lauroyl-D-glucopyranose was selected as the reference synthesis for setting parameters with *Aspergillus niger* lipase. This lipase has a specific activity ≥5000 U/g and therefore presents interesting features. Regarding the D-glucose ester studied, lauric acid has an intermediate size compared with conventional fatty acids (C8–C18). In addition, this fatty acid is widely described in the literature for the applicative aspect of sugar amphiphiles, with interesting critical micelle concentration (CMC) and minimum inhibitory concentration (MIC) [38,39].

The kinetics of lipase-catalyzed reactions are affected by various factors [15]. A large volume of research describes tertiary alcohols as optimal solvents for glucose ester synthesis [27]. The most widely used for these syntheses are tert-BuOH and 2M2B [40]. These solvents are generally combined with solubilizing agents such as DMSO, pyridine, or DMF because of their capacity to dissolve almost all molecules [41]. The use of mixtures of 2M2B or *tert*-BuOH with DMSO as solvent instead of pure 2M2B or *tert*-BuOH has been shown in the literature [19] to improve enzymatic reaction yields of the of D-glucose with fatty acid since they are able to increase D-glucose solubility. Moreover, 2M2B, *tert*-BuOH, and DMSO have a respective logP of 0.89, 0.35, and −1.35 [42]. For example, a mixture of 2M2B + DMSO (20% *v/v*) gives a logP of 0.44, while solubilizing more D-glucose than 2M2B alone. The starting experimental conditions were established based on protocols described in the literature with immobilized *Candida antarctica* lipase [19,43,44] and are:

- reaction volume of 20 mL
- 1 g of 3 Å molecular sieve
- ratio of 1 molar equivalent (eq) of glucose (180 mg) to 3 eq of fatty acid
- 1% lipase (*w/v*)
- 56 °C, 240 rpm, 72 h.

The effective yields, i.e., those obtained after purification, of 6-*O*-lauroyl-D-glucopyranose, confirmed by analysis (FT–IR, MS), were slightly better in 2M2B (22%) than in *tert*-BuOH (20%). In addition, the addition of DMSO as a co-solvent with 2M2B improved the obtained 6-*O*-lauroyl-D-glucopyranose yields (35%) (Figure 2).

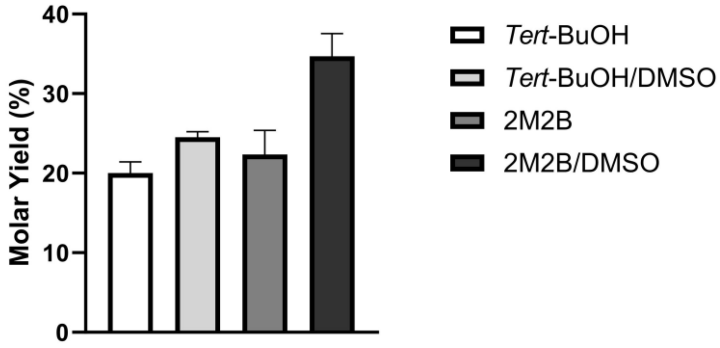

Figure 2. Effect of reaction medium for 6-*O*-lauroyl-D-glucopyranose synthesis. Results are expressed as the mean ± SD.

We performed total D-glucose solubility measurements in *tert*-BuOH/DMSO and 2M2B/DMSO mixtures containing 20% (*v/v*) DMSO (Table 1). The solubility of D-glucose at 56 °C is initially greater in 2M2B (2.1 g/L) than in *tert*-BuOH (1.8 g/L). 2M2B is a first-choice solvent, better than *tert*-BuOH. When DSMO is used as 20% co-solvent with 2M2B or *tert*-BuOH, the solubility of D-glucose at the beginning of the reaction is 5.73 g/L and 6.56 g/L, respectively (Table 1). Therefore, DMSO as a co-solvent increases D-glucose solubility and so improves its bioavailability.

Table 1. D-glucose solubility (g/L) with (+) or without (−) DMSO in *tert*-BuOH or 2M2B.

	DMSO 20% (*v/v*)	
	−	+
tert-BuOH	1.8	5.73
2M2B	2.1	6.56

3.1. Optimization of Key Parameters

The key parameters of enzymatic reaction were then optimized for the synthesis of glucose esters. More specifically, the aim was to optimize the synthesis on various points:

- types of substrates
- ratio between the different reagents
- reaction time
- temperature
- stirring speed.

An alternative to the esterification of fatty acids is transesterification. It uses alcohol esters, which are more reactive than fatty acids, and whose co-product is the corresponding alcohol. This alcohol has less impact on the enzymatic equilibrium than the water generated by esterification reaction.

In our study, esterification and transesterification were therefore compared using reference conditions (2M2B/DMSO 20% (*v*/*v*), 1 g 3 Å sieve, and 1% *Aspergillus niger* lipase (*w*/*v*), 56 °C, 240 rpm, 72 h). Lauric acid (C12), for esterification, and ethyl laurate (C12Et) and vinyl laurate (C12V), for transesterification, were studied depending on two D-glucose/acyl chain ratio, 1:2 and 1:3 (Figure 3a).

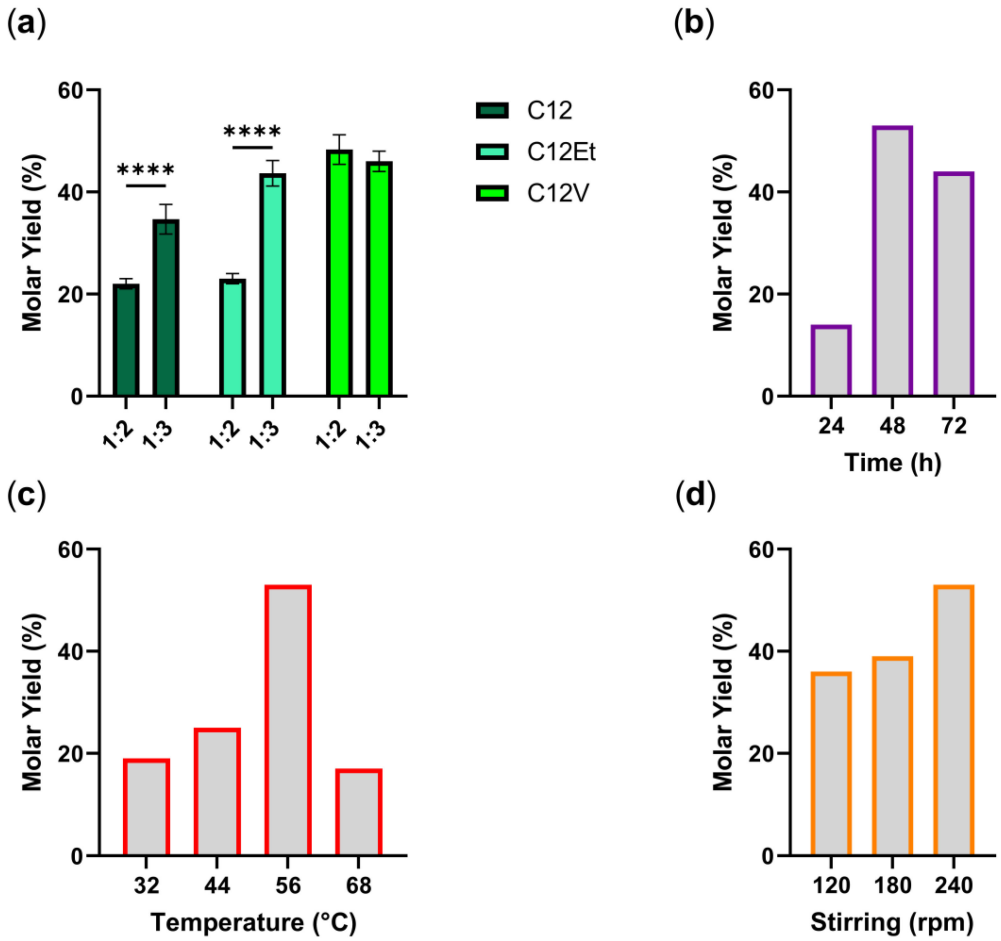

Figure 3. Optimization of some parameters for 6-*O*-lauroyl-D-glucopyranose synthesis: (**a**) D-glucose/acyl donor ratio, (**b**) time reaction, (**c**) temperature reaction, and (**d**) stirring speed. Results are expressed as the mean ± SD. Statistical significance was determined by two-way ANOVA and Tukey's test. **** $p < 0.0001$.

Under a 1:2 D-glucose/carbon chain ratio condition, transesterification with vinyl laurate (C12V) as the acyl donor gave better yields (48%) than transesterification with ethyl lau-

rate (C12Et) as the acyl donor (23%) and esterification (22%). When the D-glucose/carbon chain ratio was 1:3, the molar yield significatively increased, with molar yields of 35% and 44%, respectively, with lauric acid and ethyl laurate as acyl donor. Comparable results were obtained by transesterification with vinyl laurate (C12V) at a ratio of 1:3 (46%) (Figure 3a). Even if the use of vinyl esters gave better yields, it led to acetaldehyde as a co-product (and therefore to a non-reversible reaction), but this neo-formed acetaldehyde could react with the free amino groups of the lysine residues, resulting in lipase inactivation [35]. Thus, the synthesis of compound was optimized using ethyl laurate as an acyl donor with 1:3 D-glucose/acyl chain ratio. Indeed, the yields were systematically better for transesterification reactions and ethyl laurate leaves less doubt concerning the effect of the released co-product compared with vinyl laurate.

The optimal conditions generated thus far are repeated, i.e., a 2M2B/DMSO 20% (*v*/*v*) mixture and a ratio of 1 molar equivalent of glucose to 3 molar equivalents of C12Et.

Reaction time, temperature, and stirring parameters were subsequently optimized (Figure 3b–d). The best condition obtained was retained to vary the next one.

First, we studied the effect of different reaction times, i.e., 24 h, 48 h and 72 h, on lauric ester of D-glucose molar yields (Figure 3b). A 24 h reacting period led to 14% yield, 48h to 53%, and 72h to 44% yield (Figure 3b). A possible explanation for why 48h led to better yields is the denaturation or conversion of the neo-formed product, the monoester of glucose, during synthesis. Monoester could become the preferred substrate for lipase instead of D-glucose and thus lead to the diester. Another explanation could be the inability of lipase to avoid, as much as possible, hydrolysis reactions in the presence of an excess of esterification substrates over time [45]. In conclusion, the reaction time will therefore be set at 48 h for the rest of the study.

Temperature also plays an important role in reaction synthesis, by affecting two aspects: enzymatic activity and substrate solubility. There are no data on the use of this commercial lipase from *Aspergillus niger* for the synthesis of sugar esters, hence the interest in learning more about this lipase. Here, we evaluated 6-*O*-lauroyl-D-glucopyranose synthesis yields under various reaction temperatures: 32 °C, 44 °C, 56 °C, and 68 °C (Figure 3c).

The ester lauric of D-glucose yields obtained at 56 °C (53%) are higher than those obtained at 32 °C, 44 °C, and 68 °C (19%, 25%, and 17%, respectively) (Figure 3c). For the synthesis of D-glucose ester lauric, *Aspergillus niger* lipase displayed an optimum range of catalytic activity around 56 °C. The drop in yield, observed here at 68 °C, can be explained by protein denaturation, which generally occurs at temperatures above 60 °C [46].

Stirring efficiency is an important parameter to evaluate during enzyme synthesis, because it homogenizes the heterogeneous reaction medium containing the solvents, enzymes, substrates, and molecular sieve. The effect of stirring (120 rpm, 180 rpm, and 240 rpm) on ester lauric of D-glucose yields was studied (Figure 3d). Interestingly, stirring has a very significant effect on reaction efficiency. With stirring at 120 rpm and 180 rpm, the monoester yields were similar (36% and 38%), while at 240 rpm yields were much higher (53%) (Figure 3d). This is mainly due to an increase in the probability of the enzyme, immobilized on the resin, encountering the reagents.

Optimization studies show the benefits of using DMSO to improve D-glucose solubilization. Transesterification gives higher yields than esterification. The parameters optimized for the synthesis of 6-*O*-lauroyl-D-glucopyranose are, therefore, in the case presented here:

- 1% *Aspergillus niger* lipase (*w*/*v*)
- co-solvent reaction medium, 2M2B/DMSO 20% (*v*/*v*).
- ratio of 1 molar equivalent of glucose to 3 equivalents of ethyl laurate
- 48 h, 56 °C, 240 rpm, 1 g 3 Å sieve.

3.2. Enzyme Selectivity

The advantages of producing amphiphiles by enzymatic catalysis are energy savings, and reduced use of petroleum-based solvents during the reaction and the processing

stages, particularly purification, due to the high selectivity. In classical chemistry, there is considerable heterogeneity in the obtained molecules, linked to polydispersity and/or polysubstitution but also due to the lack of reaction stereoselectivity. To specifically obtain monoester by chemical means, it is necessary to carry out steps to protect the hydroxyls upstream and deprotect the glucose downstream, making synthesis more complex. In this section, we focused on the grafting selectivity using immobilized *Aspergillus niger* lipase as a catalyst under the previously optimized conditions.

Grafting selectivity under our reference conditions (56 °C–48 h–240 rpm in 20 mL of 2M2B, with a 1:3 D-glucose/carbon chain ratio and 1 g of 3 Å sieve), for esterification reactions (with lauric acid) and transesterification reactions (with ethyl laurate or vinyl laurate) was determined (Figure 4). Negative control syntheses (Figure 4, CTL), without lipase, were systematically carried out simultaneously with lipase-catalyzed reactions. These syntheses allowed confirmation (or not) that the reaction products resulting from the syntheses were only due to the lipase activity.

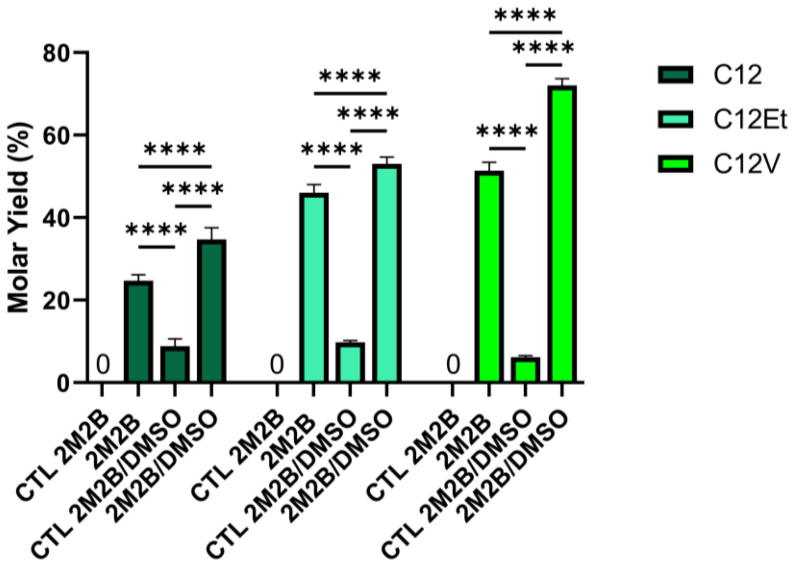

Figure 4. Molar yields (after purification) for the synthesis of 6-*O*-lauroyl-D-glucopyranose (by esterification and enzymatic transesterification) (CTL: negative control conditions without enzyme). Results are expressed as the mean ± SD. Statistical significance was determined by two-way ANOVA and Tukey's test. **** $p < 0.0001$.

In 2M2B solvent, in the absence of the enzyme (CTL), there is no lauric ester of D-glucose synthesis. Thus, 2M2B had no synthesis activity. When the enzyme was added, molar yields after purification were 24% with C12, 47% with C12Et, and 49% with C12V. DMSO, as cosolvent with 2M2B, seems to have a significant positive impact. Indeed, by esterification, molar yields were increased to 35% and to 53% and 72% by transesterification with C12Et and C12V, respectively. This represented an increase of 40%, 15%, and 41%, respectively, compared to the 2M2B condition (Figure 4).

The analyses and characterizations carried out (FT-IR, MS, and NMR) on the synthesis products have shown that 6-*O*-lauroyl-D-glucopyranose is obtained with the three starting "fatty" derivatives. MS analyses for each synthetic route identified lauroyl-D-glucopyranose with a peak at *m/z* 384.6 corresponding to $[M + Na]^+$. 6-*O*-lauroyl-D-glucopyranose obtained by esterification with C12 or by transesterification with C12Et and C12V exhibits the same characteristic signals in ^{1}H NMR, in particular the peak at 4.64 ppm (d, 1H), characteristic of the free anomeric carbon of D-glucose [47].

In the ^{13}C NMR spectra, the single peak obtained at 173.4 ppm (C=O) demonstrates the specificity and binding selectivity of this enzymatic reaction, enabling only 6-*O*-lauroyl-D-glucopyranose to be obtained (Figure 5).

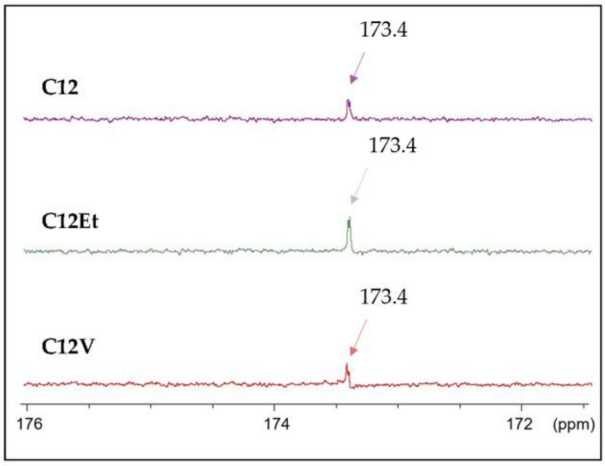

Figure 5. Superposition of ester carbon zone (C=O) for ^{13}C NMR spectrum for the synthesis of 6-*O*-lauroyl-D-glucopyranose, using C12, C12Et, and C12V.

The control synthesis without the lipase in presence of DMSO co-solvent generated a lauroyl-D-glucopyranose in low yields, around 9% for C12, 10% for C12Et, and 6% for C12V (Figure 4). MS analyses correspond to lauroyl-D-glucopyranose, with a peak at *m/z* 384.6 corresponding to $[M + Na]^+$. These results highlight the ability of DMSO to catalyze D-glucose esterification and transesterification reactions in small quantities. NMR analysis shows the absence of selectivity, demonstrated by the presence, on ^1H NMR spectra, of weak signals between 4 ppm and 5.5 ppm, and of signals between 170 ppm and 173 ppm (C=O) on ^{13}C NMR spectra in both reaction routes whatever the acyl donor was, demonstrating variability in the ester formation site. In the literature, DMSO has been shown to catalyze the formation of sugar esters, with palmitic and oleic acids [48,49], but not during transesterification.

HPLC was used to detect the products formed during the reaction. The desired 6-*O*-lauroyl-D-glucopyranose, used as standard, had a retention time of about 3.40 min and allowed identification of the 6-*O*-lauroyl-D-glucopyranose formed during the reaction. Lauric acid or its ester derivatives were also used as standards according to the reaction studied. In reaction kinetics, under the reaction conditions without DMSO, it was possible to detect the monoester at 3.40 min, and C12 fatty acid at 5.3 min, or C12Et at 9.93 min or C12V at 11.31 min, according to a synthetic condition.

Conversely, in the syntheses using DMSO and lipase, the retention times of the peak identified previously as acyl donors saw its retention time slightly decreased to 5.32 min to 5.11 min for C12, from 5.33 to 5.17 min for C12Et, and from 5.31 to 5.11 min for C12V. This can be explained by the stronger eluting power of the solvents, due to the polar effect of DMSO already present in the injected sample. After HPLC elution, fractions were collected, concentrated with a Speed vacuum, and analyzed by mass spectrometry to correlate the molar mass to the products detected by HPLC (Figure 6).

For the conditions without DMSO (Figure 7, full line), mass analysis identified the unique presence of the carbon chain. Conversely, for the fractions containing DMSO (Figure 7, dotted line), di-lauroyl-D-glucopyranose was detected.

Indeed, mass spectrometry clearly indicates the presence, in these fractions, of a mixture of lauric acid $[M + K]^+$ at *m/z* 239 and diester, identified by $[M + Na]^+$ at *m/z* 566.5 (Figure 7).

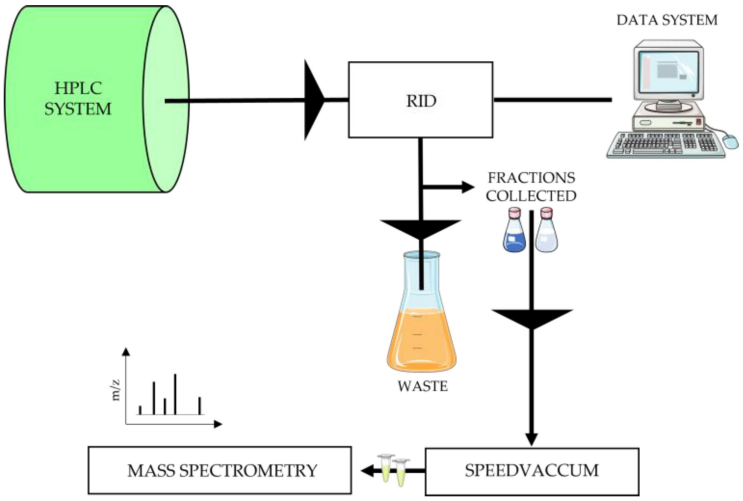

Figure 6. HPLC technique used. Fractions are collected at the output of the RID (refractor index detector) before waste collection. The fractions were then concentrated with a Speed vacuum and analyzed by mass spectrometry.

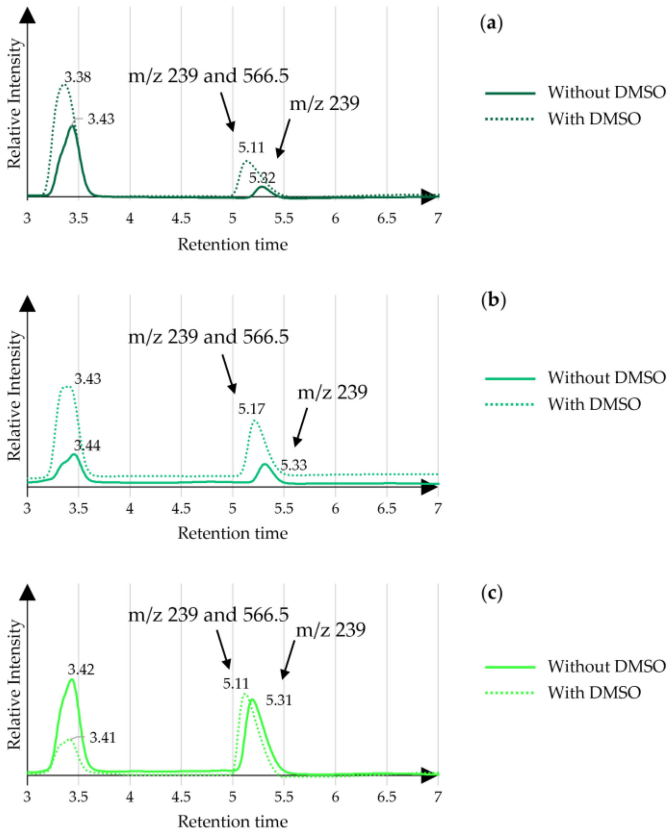

Figure 7. Comparison between chromatograms obtained for the enzymatic synthesis of 6-O-lauroyl-D-glucopyranose performed (**a**) with C12, (**b**) C12Et, and (**c**) C12V. Flat lines correspond to syntheses performed in 2M2B, dotted lines to those with 2M2B/DMSO mixture.

These analyses show the presence of diesters in syntheses carried out under the 2M2B/DMSO 20% conditions, whatever the acyl donor was. Even if the produced amounts of diester are low, this shows the loss of selectivity due to DMSO catalytic activity. This generated dispersity is therefore a problem, as it will limit the simplified application of the synthesized products and/or complicate purifications.

HPLC was also used to quantify the amount of synthesized 6-*O*-lauroyl-D-glucopyranose, confirmed by NMR analysis, at the end of the reaction (Table 2). It can be noted that the quantity of products lost during the purification steps is higher when DMSO is used.

Table 2. Comparison of the molar yields obtained by HPLC. Quantification is performed before and after treatment and purification for the synthesis of 6-*O*-lauroyl-D-glucopyranose without (−) or with (+) DMSO.

Fatty Reagent	DMSO *	Yield before Treatment %	Yield after Treatment %
Lauric Acid C12	−	24	23
	+	54	33
Ethyl Laurate C12Et	−	47	44
	+	66	52
Vinyl Laurate C12V	−	49	49
	+	93	71

* 20% of DMSO (*v*/*v*).

DMSO, therefore, increased monoester yields, but had negative aspects such as reduced selectivity, even though *Aspergillus niger* lipase is highly specific. In addition, DMSO also induces diester production, undesirable in the fraction. Furthermore, DMSO is described as a disproportionating agent and could therefore affect the stability of the product formed, in this case 6-o-lauroyl-d-glucpyranose. This last point remains to be determined. However, these studies do not concern sugar esters [50,51]. Moreover, in an industrial process, DMSO is more difficult to remove from the final product due to its high boiling point. These difficulties will limit the application of the product as DMSO. Then, considering its potential toxicity to organisms, particularly aquatic organisms, the DMSO introduction into the environment needs to be studied and monitored. In particular, biodegradability and cytotoxicity make DMSO, as a co-solvent, a limiting factor in the application of the produced molecules.

3.3. Greener Co-Solvents

Two biobased co-solvents were tested to replace DMSO: 2MeTHF and 2MeTHF3one. 2MeTHF is an agro-solvent, derived from furfural, itself derived from agricultural by-products, representing a sustainable alternative solvent [52]. The second choice, 2MeTHF3one is a food-grade solvent, GRAS (generally recognized as safe), derived from coffee furanone. It is applicable in the food industry and therefore 2MeTHF3one is easier to apply. These two solvents are also more easily removable from reaction media than DMSO, due to their lower boiling point, 78 °C and 138 °C, respectively, compared with 190 °C for DMSO.

First, the solubility of D-glucose was measured in 2M2B added with 20% of alternative co-solvent, using the same protocol as developed before. Thus, the 2M2B/2MeTHF (20% *v*/*v*) mixture solubilized 1.53 g/L of D-glucose at 56 °C, compared to 2.1 g/L in 2M2B at equivalent final volume. The 2M2B/2MeTHF3one (20% *v*/*v*) mixture solubilized an average of 3.2 g/L D-glucose at 56 °C, showing then an interest in using 2MeTHF3one as a co-solvent to increase the bioavailability of sugar at the beginning of the reaction. In addition, 2MeTHF3one has a logP of −0.563, a negative value, as with DMSO. In mixture, 2M2B/2MeTHF3one (20% *v*/*v*) has a logP of 0.59. Thereafter, syntheses were carried out by replacing DMSO by 2MeTHF3one. This mixture gives a logP close to that of 2M2B (0.89), while solubilizing more D-glucose. We thus performed 6-*O*-lauroyl-D-glucopyranose synthesis using 2M2B/2MeTHF3one (20% *v*/*v*) as solvent, using the reaction conditions established previously. The yields obtained in these conditions were compared to those from 2M2B/DMSO ones (Figure 8).

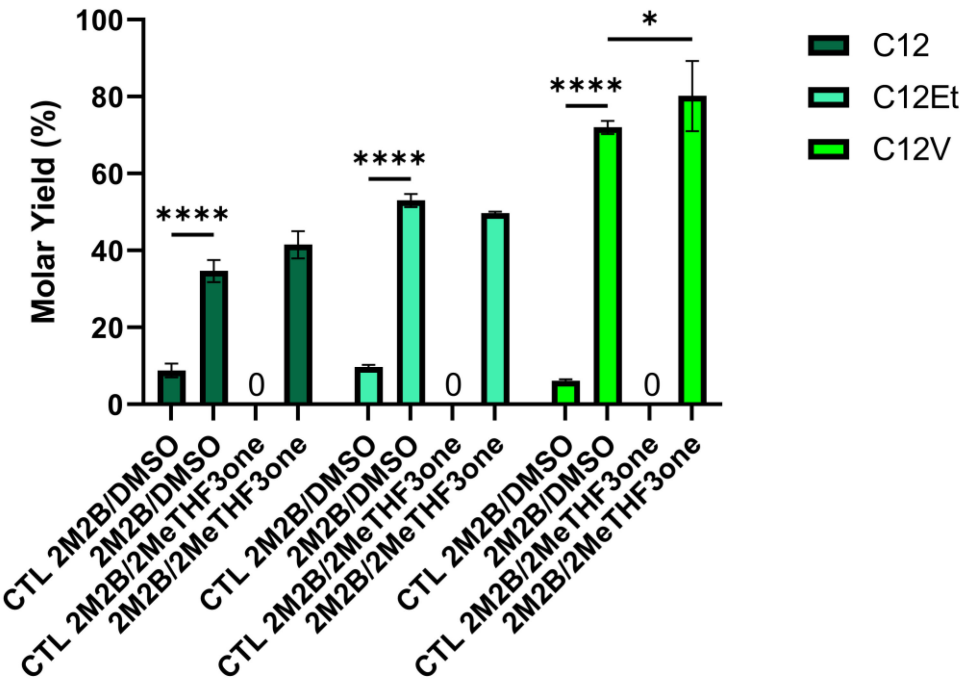

Figure 8. Comparison of molar yields for the synthesis of 6-*O*-lauroyl-D-glucopyranose according to co-solvent mixture, in absence (CTL) or using *Aspergillus niger* lipase. Results are expressed as the mean ± SD. Statistical significance was determined by two-way ANOVA with Tukey's test. * $p < 0.05$, **** $p < 0.0001$.

No catalytic activity was reported in the control syntheses performed without lipase in the 2M2B/2MeTHF3one mixture (Figure 8). Only 6-*O*-lauryl-D-glucopyranose was detected, recovered, and analyzed. After purification, MS and NMR confirmed its structure. 2MeTHF3one as co-solvent allows obtaining of yields like those obtained in the presence of 20% DMSO.

The yields obtained are 42% for the esterification reactions with lauric acid, which is higher (27% increase in yield) than the syntheses performed with DMSO co-solvent (33%). By transesterification with ethyl laurate, we obtained 49% yield, not significantly different to that obtained in the presence of the co-solvent DMSO (52%). For the syntheses performed with vinyl laurate, the yields were much higher, with 80% average yields after purification, and significantly increased compared to the 2M2B/DMSO condition (71% yield) (Figure 8). This shows not only the potential for 2MeTHF3one to replace DMSO but also the ease of the post-synthesis treatment steps.

4. Conclusions

We determined the kinetic parameters of 6-*O*-lauroyl-D-glucopyranose synthesis with *Aspergillus niger* lipase: 56 °C, 48 h, 240 rpm, D-glucose/acyl chain 1:3. We observed a greater efficiency by transesterification. Moreover, this lipase exhibits very high grafting selectivity with the specific synthesis of 6-*O*-lauroyl-D-glucopyranose. As expected, the use of DMSO as a co-solvent at 20% (*v*/*v*) increases reaction yields. However, DMSO is also able to catalyze D-glucose esterification and transesterification, which to our knowledge has never been reported before. In our experiments, the use of DMSO as co-solvent also allow the synthesis of diesters in addition to monoesters, leading to a loss of selectivity of enzyme-catalyzed synthesis. Moreover, purification steps in the presence of DMSO are very energy-consuming and do not necessarily lead to an eco-efficient process. An alternative to DMSO has been proposed, 2MeTHF3one, as a co-solvent for 2M2B. 2MeTHF was also tested but did not increase substrate bioavailability. The 2M2B/2MeTHF3one (20% *v*/*v*) mixture enabled greater D-glucose solubilization than in 2M2B alone, and thus

higher yields without selectivity problems. As 2MeTHF3one presents no difficulties for its removal, its use as a solvent alone is also possible [33]. Nevertheless, the price of this solvent remains high (538 EUR/kg) and does not currently allow its use as a green solvent on a large scale. Therefore, its use as a co-solvent in enzymatic synthesis offers a possibility to envisage a rational application of 2MeTHF3one. This last point reinforces the interest of this food-grade solvent as a co-solvent.

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