Solubility Measurements of Fatty Acid Glucose and Sucrose Esters in 2-Methyl-2-butanol and Mixtures of 2-Methyl-2-butanol with Dimethyl Sulfoxide

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Solubility measurements of fatty acid esters of glucose and sucrose in pure 2-methyl-2-butanol and mixtures of 2-methyl-2-butanol with dimethyl sulfoxide are presented. For glucose esters the increase of the fatty acid chain length from C8 to C12 leads to an about 3-fold solubility decrease in 2-methyl-2-butanol at 30 °C and 60 °C, while a slight increase is observed for sucrose monoesters. The presence of dimethyl sulfoxide increases the solubility of the esters in 2-methyl-2-butanol. Sucrose dilaurates were 4-fold more soluble than the corresponding monoesters in 2-methyl-2-butanol and in the mixture of 2-methyl-2-butanol with dimethyl sulfoxide.

Introduction

Sugar fatty acid esters are nonionic surfactants consisting of a sugar (e.g. glucose or sucrose) as the hydrophilic group and a fatty acid as the lipophilic group. Sugar fatty acid esters have broad applications in the food industry, cosmetics, detergents, oral-care products, and medical supplies.[1] They are tasteless, odorless, nontoxic, a nonirritant to the eyes and skin, and biodegradable.[2]

Sugar esters can be synthesized either by chemical or enzymatic processes. Current chemical production of sugar esters is usually base-catalyzed at high temperatures and has a low selectivity, forming colored derivatives as side-products.[3] In contrast, the enzyme-catalyzed synthesis of sugar esters provides regio- and stereoselective products.[4]

Methodologies for sugar acylation need to find a medium where a polar substance (the carbohydrate) and an apolar reagent (the fatty acid donor) are able to react in the presence of the biocatalyst. Although sugar acylations have been achieved in solvents such as dimethylformamide or pyridine, these are not very convenient due to their toxicity. Several processes have been recently reported using more benign solvents such as tertiary alcohols or ketones, that dissolve the carbohydrate only partially.[5−8] This strategy has been very fruitful for monosaccharides; for example, the acylation of glucose and fructose has been successfully achieved in *tert*-butanol,[6] 2-methyl-2-butanol (*tert*-pentanol),[7] or acetone.[8] Recently we have developed a new procedure for di- and trisaccharides acylation in which two miscible solvents were employed: a tertiary alcohol as bulk solvent and dimethyl sulfoxide (DMSO) as cosolvent.

For the proper modeling of the reaction thermodynamics and kinetics, which is required for the design of bioreactors and the development of processes for the separation of the products from the reaction mixture, accurate knowledge of reactant and product solubilities in the reaction medium is needed. Unfortunately, solubility data for sugar esters in organic media are very limited.[8,9]

Among the sugar esters, derivatives of glucose and sucrose esters are the only ones industrially commercialized.[10] This work presents glucose and sucrose fatty acid esters solubility measurements in *tert*-pentanol and in mixtures of *tert*-pentanol with DMSO. These solvent mixtures are especially useful for disaccharide acylation, because they represent a compromise between sugar solubility and enzyme stability.[11,12] More specifically, measurements are presented for (a) α-D-glucose-6-*O*-octanoate and α-D-glucose-6-*O*-laurate in *tert*-pentanol at 30 and 60 °C; (b) a mixture of α-D-glucose-6-*O*-laurate and *β*-D-glucose-6-*O*-laurate in *tert*-pentanol and *tert*-pentanol + DMSO (80/20 vol %) at 40 °C; (c) sucrose-6-*O*-laurate and sucrose-6-*O*-palmitate in *tert*-pentanol and *tert*-pentanol + DMSO (80/20 vol %) at 40 °C; and (d) sucrose-6,1′-di-*O*-laurate and sucrose-6,6′-di-*O*-laurate in *tert*-pentanol and *tert*-pentanol + DMSO (80/20 vol %) at 40 °C.

Experimental Section

Materials. 2-Methyl-2-butanol (99% purity) and dimethyl sulfoxide (>99% purity) were purchased from Aldrich. Pure α-D-glucose-6-*O*-octanoate and α-D-glucose-6-*O*-laurate were kindly provided by Novozymes A/S. The purity of the samples was at least 95% as analyzed by HPLC. Samples were proven by NMR to be pure anomers.

Synthesis of Sugar Esters. Synthesis of glucose-6-*O*-laurate (mixture of α- and *β*-isomers), sucrose-6-*O*-laurate, sucrose-6-*O*-palmitate, sucrose-6,1'-di-*O*-laurate, and sucrose-6,6'-di-*O*-laurate was carried out according to a method previously developed.[11,13] In all cases, the acylation was carried out in *tert*-pentanol containing a low percentage (0 to 20 vol %) of DMSO. The lipase from *Thermomyces lanuginosus* (formerly *Humicola lanuginosa*) immobilized on diatomaceous earth (Celite) was used as biocatalyst.

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Reactions were performed in the presence of molecular sieves at 40 °C with magnetic stirring. The products were isolated by column chromatography and/or solvent precipitation and were fully characterized by chromatography and spectroscopic techniques (HPLC, NMR, IR, HRMS). Their purity was found to be greater than 99%.

Solubility Measurements. The experimental apparatus used for the solubility measurements of α-D-glucose 6-*O*-octanoate and α-D-glucose 6-*O*-laurate in *tert*-pentanol has been presented elsewhere.[13,14] The temperature is set at the desired level, and the solvent (15 mL) is added to the vessels. Once the desired temperature is reached, excess glucose ester (considering the expected solubility) is added to the solution. The solution is stirred at (600 to 800) rpm with a magnetic stirrer, until equilibrium is reached. Samples of the solution are withdrawn at intervals using pipets with a slightly higher temperature than the solution temperature in order to avoid any precipitation. The samples are then filtered with prewarmed 0.22 μm Nylon filters (polypropylene housing) and analyzed gravimetrically. Experiments were performed in triplicate.

For solubility determination of glucose-6-*O*-laurate (mixture of α- and β-isomers), sucrose-6-*O*-laurate, sucrose-6-*O*-palmitate, sucrose-6,1′-di-*O*-laurate, and sucrose-6,6′-di-*O*-laurate, the ester (90 to 700 mg, depending on the compound, in excess compared with the expected solubility) was added to 0.5 mL of *tert*-pentanol or *tert*-pentanol + DMSO (80/20 vol %). The mixture was kept at 40 °C with magnetic stirring (600 to 800) rpm until equilibrium was reached. Samples of the solution were taken at various intervals, centrifuged, and filtered using prewarmed 0.45 μm Ultrafree-MC filter devices (Millipore). Experiments were performed in triplicate. Samples were analyzed by reverse-phase high-performance liquid chromatography (HPLC).

Analytical Methods. (a) Gravimetric Method. Gravimetric solubility measurements were performed by drying the solvent mixture from a previously weighed sample of solution (0.5 to 1) mL in a vacuum oven (80 °C, 800 mbar) and by weighing the precipitated sugar ester regularly until a constant value is achieved. The uncertainty of the method is less than 1 mass %.

(b) HPLC Analysis. A system equipped with a Spectra-Physics pump, a 4.6 mm × 250 mm Nucleosil 100-C18 column (Sugelabor, Spain), and a refraction-index detector (Spectra-Physics) was employed. Methanol + water (90/10 vol %) was used as mobile phase (flow rate 1.0 mL/min). The temperature of the column was kept constant at 40 °C. Integration was carried out using the Varian Star 4.0 software. The uncertainty of the method is less than 2 mass %.

Results and Discussion

Solubility of Glucose Esters. Table 1 presents the solubility of α-D-glucose-6-*O*-octanoate and α-D-glucose-6-*O*-laurate in *tert*-pentanol at (30 and 60) °C and that of glucose-6-*O*-laurate (mixture of α- and β- isomers) in *tert*-pentanol and *tert*-pentanol + DMSO (80/20 vol %) at 40 °C. The following comments summarize the observations on the obtained results:

(a) Glucose esters are much more soluble in *tert*-pentanol than pure glucose. Notice that the solubility of α-glucose in *tert*-pentanol is 0.6 g L^{-1} at 30 °C while at 60 °C it is 2.4 g L^{-1}.[13]

(b) As the chain length of the fatty acid increases from C8 to C12, the solubility in *tert*-pentanol decreases about 3-fold, which may be attributed to the incompatibility of the fatty acid chain with *tert*-pentanol. In this context, Cao *et al.*[9] reported a very low solubility (1.6 g L^{-1}) of glucose palmitate in *tert*-pentanol at 25 °C that fits well with the tendency we have observed. Furthermore, the behavior in *tert*-pentanol is similar to the one reported by Yan *et al.*[8] for the solubility of glucose esters in acetone.

Table 1. Solubility of Glucose Esters in *tert*-Pentanol and *tert*-Pentanol + DMSO at Different Temperatures

ester	solvent	*t*/°C	s/ g L^{-1}	±SD[a]/ g L^{-1}
α-D-glucose-6-*O*-octanoate	*tert*-pentanol	30	42.1	0.1
	tert-pentanol	60	276.4	0.7
α-D-glucose-6-*O*-laurate	*tert*-pentanol	30	13.0	0.1
	tert-pentanol	60	102.1	0.2
glucose-6-*O*-laurate[b]	*tert*-pentanol	40	23.0	0.9
	tert-pentanol + DMSO (80/20 vol %)	40	100.1	3.4

[a] SD is the standard deviation of the experimentally measured solubility. [b] Mixture of α-D-glucose-6-*O*-laurate and β-D-glucose-6-*O*-laurate.

Table 2. Solubility of Sucrose Mono- and Diesters in *tert*-Pentanol and *tert*-Pentanol + DMSO (80/20 vol %) at 40 °C

ester	solvent	*s*/ g L^{-1}	±SD/ g L^{-1}
sucrose-6-*O*-laurate	*tert*-pentanol	135	5
	tert-pentanol + DMSO	820	31
sucrose-6-*O*-palmitate	*tert*-pentanol	155	6
	tert-pentanol + DMSO	1005	37
sucrose-6,1′-di-*O*-laurate	*tert*-pentanol	515	25
	tert-pentanol + DMSO	765	28
sucrose-6,6′-di-*O*-laurate	*tert*-pentanol	670	23
	tert-pentanol + DMSO	995	34

(c) As temperature increases, solubility increases considerably. Yan *et al.*[8] reported that the solubility of a series of glucose fatty acid esters significantly increases at temperatures above (50 to 60) °C.

(d) DMSO is a much better solvent for glucose esters than *tert*-pentanol. So, the use of 20 vol % DMSO in *tert*-pentanol increases the solubility of glucose-6-*O*-laurate (mixture of α- and β- isomers) about 5-fold with respect to the case of pure *tert*-pentanol.

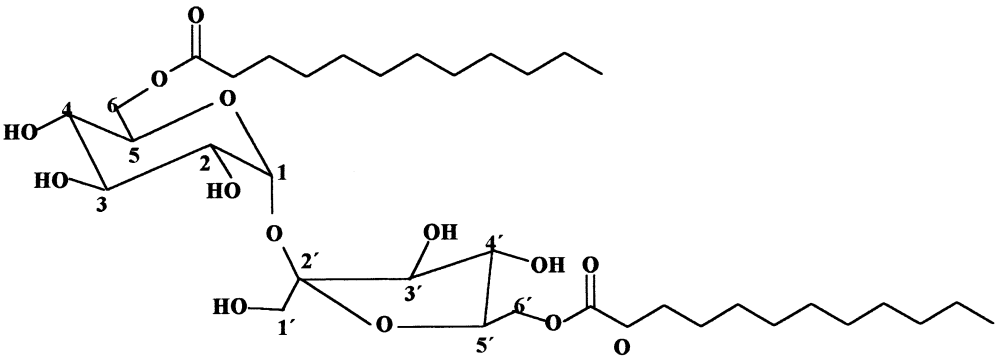
Solubility of Sucrose Esters. Table 2 presents the solubility of sucrose-6-*O*-laurate, sucrose-6-*O*-palmitate, sucrose-6,1′-di-*O*-laurate, and sucrose-6,6′-di-*O*-laurate at 40 °C in *tert*-pentanol and the *tert*-pentanol + DMSO mixture (80/20 vol %). The following comments summarize the observations on the obtained results:

(a) Similarly to glucose esters, sucrose esters are much more soluble in *tert*-pentanol than pure sucrose. It must be noted that the solubility of sucrose in *tert*-pentanol is 0.21 g L^{-1} at 30 °C while at 60 °C it is 0.42 g L^{-1}.[14]

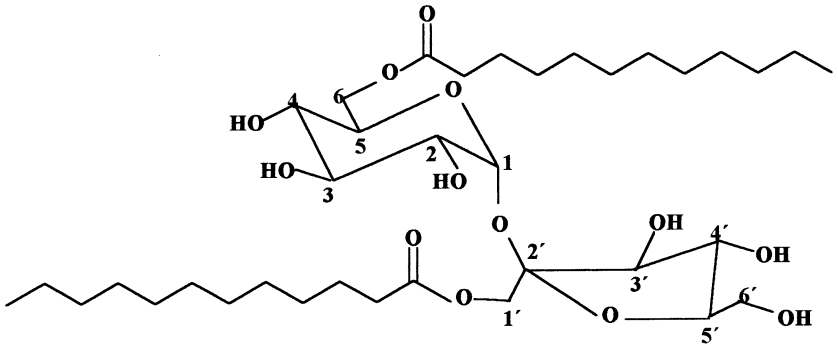
(b) Although sucrose is less soluble than glucose in *tert*-pentanol, sucrose monoesters are more soluble than the corresponding glucose monoesters, as indicated by the comparison of results for glucose-6-*O*-laurate and sucrose-6-*O*-laurate.

(c) As the chain length of the fatty acid increases, the solubility in *tert*-pentanol and in the mixture *tert*-pentanol + DMSO increases slightly. This is opposite of what would be expected from the aforementioned case of glucose esters.

A first explanation of this behavior would be micellization of the sucrose esters. In particular, the formation of normal micelles would be more consistent with our results, that is, alkyl chains in the interior of the micelle. However, formation of normal micelles is driven by solvophobic effects on the surfactant tails, which are not supposed to



sucrose 6,6'-di-*O*-laurate



sucrose 6,1'-di-*O*-laurate

Figure 1. Spatial disposition of sucrose-6,6′-di-*O*-laurate and 6,1′-di-*O*-laurate.

be in alcohols.[15] Such effects have been observed only in special solvents such as polyols, formamide, and water.

Another explanation would be related to differences in the thermophysical properties (melting point temperature and heat fusion) of the related derivatives. It has been observed that melting points of surfactants often behave quite anomalously, because of crystal packing problems. We attempted to measure the melting points of sucrose laurate and sucrose palmitate, and it was observed that a first phase transition occurred at 136 °C for sucrose laurate and at 124 °C for sucrose palmitate, while a second phase transition, which is the melting point, occurred at 160 °C for laurate and 196 °C for palmitate. In the Fluka catalog is reported for commercial sucrose caprate (a complex mixture of regioisomers, as observed by HPLC) a melting point of (133 to 135) °C, and for sucrose laurate, also a mixture of monoesters, (150 to 152) °C, which seems to be consistent with our results.

(d) An approximately 4-fold increase of the solubility in *tert*-pentanol is observed when moving from sucrose monolaurate to sucrose dilaurates.

(e) DMSO is a better solvent for sucrose esters than *tert*-pentanol, especially for sucrose monoesters. So, the use of 20 vol % DMSO increases the solubility of sucrose monoesters about 6-fold with respect to their solubility in pure *tert*-pentanol. On the other hand, the increase of the solubility of sucrose diesters is only 1.5-fold.

(f) The solubility of the 6,6′-diester is slightly higher as compared to that of the 6,1′-diester. This may be a consequence of the different spatial dispositions of the two lauric acid chains in both isomers shown in Figure 1.

Conclusions

Solubility measurements of glucose and sucrose fatty acid esters were performed in pure *tert*-pentanol and mixtures of *tert*-pentanol with dimethyl sulfoxide. The results show that for glucose esters the increase of the fatty acid chain length leads to a solubility decrease in *tert*-pentanol, while the opposite is the case for sucrose monoesters. Furthermore, sucrose esters are more soluble in *tert*-pentanol than glucose esters. Finally, the presence of dimethyl sulfoxide increases esters' solubility, especially in the case of glucose and sucrose monoesters.

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