Lipase-catalyzed syntheses of sugar esters in non-aqueous media

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Abstract The lipase-catalyzed reaction is useful to obtain sugar esters with chemically defined structures. The synthesis of sugar esters in non-aqueous media has been attempted for a quarter century. To facilitate the reactions, they have been performed either in an organic solvent with/without a polar adjuvant or in an ionic liquid, or by using a hydrophobic sugar derivative. In this review, the following points are discussed: 1) various synthetic methods of sugar esters; 2) role of the solvents or adjuvants; and 3) improvement in the productivity.

Keywords Lipase · Non-aqueous medium · Productivity · Sugar derivative · Sugar ester

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Introduction

Daily necessities such as foods, cosmetics or medicines contain many esters. One of the more famous ones is triacylglycerol in olive oil, but there are many other esters including sugar esters which are dealt with in this review. In general, a sugar ester is used as an emulsifier. Because the types of constitutive fatty acid and sugar moieties of the sugar esters can be easily changed, their properties can widely vary; e.g., each sugar ester has a different critical micelle concentration (CMC) and hydrophilic-lipophilic balance (HLB) over a wide range.

There are various methods to efficiently synthesize esters, and the enzymatic syntheses of sugar esters are described in this review. The lipase-catalyzed synthesis of sugar esters by dehydrative condensation or transesterification can be relatively easily applied for food processing in comparison with the general organic ones from the viewpoint of safety because one of the organic ones is performed by adding acyl chloride into the mixture of a sugar, *N,N*-dimethylformamide (DMF), and pyridine. This synthesis also has an advantage that the product may be accepted by customers as a 'natural product'. Furthermore, the enzymatic method theoretically has characteristics that can introduce a fatty acid into a specific position of the sugar by taking advantage of the high substrate specificity.

Sugar esters used in industries are currently being manufactured by chemical syntheses. However, the current methods generally afford several isomers that have the different degrees of acylation and different acylated positions. Many trials have been done to synthesize the sugar esters with chemically defined structures. As one of these trials, the lipase-catalyzed synthesis is expected to be a promising method. In addition, the lipase-catalyzed synthesis can be performed under mild conditions and requires a fewer number of separating and refining steps.

Sugar esters synthesized by lipase-catalyzed reaction

In many cases, the aim of the addition of a fatty acid to sugars is the improvement of the compatibility between the sugar and fat. Based on these concepts, lipase-catalyzed syntheses have been performed to produce various sugar esters and related compounds (Table 1). The fatty acid ester of a monosaccharide or sugar alcohol attracted attention during the first decade of the lipase-catalyzed syntheses (Chopineau et al. 1988; Ikeda & Kilbanov 1993; Khaled et al. 1991; Therisod & Klibanov 1986). In these cases, glycerol or glucose, galactose, xylitol, sorbitol, etc., were mainly used as the sugar substrate. Whereas, an unsaturated fatty acid such as oleic acid or linoleic acid, a medium or long chain saturated fatty acid was often used as

Table 1 Sugar esters synthesized by lipase-catalyzed reaction in nonaqueous media.

Sugar(s) (alcohol(s))	Fatty acid(s) (carboxylic acid(s))	Origin(s) of lipase	Solvent(s)	Yield (%)	Reference(s)
D-Glucose	Myristic acid	*Candida antarctica*	TAA[a]		Cauglia & Canepa, 2008
D-Glucose, D-mannose, D-galactose	Linoleic acid	*Candida antarctica*	TBA[b]+pyridine		Chen et al. 2005
D-Glucose, sucrose, D-glucosamine	Vinyl acrylate	*Pseudomonas* sp.	TBA[b], acetonitrile		Ikeda & Klibanov 1993
D-Glucose	L-Alanine, L-leucine, L-phenylalanine	*Rhizomucor miehei*, porcine pancreas	DMF[c]+dichloromethane	99	Vijayakumar et al. 2004
Hexoses, pentoses, disaccharides	L-Alanine	*Rhizomucor miehei*	Dichloromethane+DMF[c], hexane+chloroform+DMF[c]	8-56	Somashekar & Divakar 2007
Xylitol	Fatty acids	*Candida antarctica*	TBA[b]+pyridine		Cramer et al. 2007
Trehalose	Fatty acids	*Candida antarctica*	TBA[b]+pyridine		Chen et al. 2007
Sucrose, maltose, glucose	Vinyl laurate, vinyl palmitate	*Thermomyces lanuginosus*, *Candida antarctica*	TAA[a]+DMSO[d]	>95	Ferrer et al. 2005
Maltose, leucrose, maltotriose	Fatty acid vinyl esters	*Humicola lanuginosa*	TAA[a]+DMSO[d]		Ferrer et al. 2000
n-Alkyl alcohol	D-Glucuronic acid	*Candida antarctica*	TBA[b]		Moreau et al. 2004
n-Alkyl glucoside	4-Phenylbutyric acid	*Candida antarctica*	TBA[b]	21	Otto et al. 1998
n-Butyl lactoside	Methyl oleate	*Candida antarctica*	TAA[a]	65	Coulon et al. 1998
n-Octyl glucoside	Cinnamic acid, *p* (*o*)-coumaric acid, ferulic acid, *p*-hydroxyphenyl propionic acid	*Candida antarctica*, *Rhizomucor miehei*	TBA[b]		Stamatis et al. 2001
Methyl glucoside, lactose, galactose	2-Bromomyristic acid, decanedioic acid	*Candida antarctica*	TBA[b]		Gao et al. 1999
Acetal of D-glucose	Palmitic acid	*Candida antarctica*	Acetone+TBA[b]	70	Kobayashi et al. 2010
Acetals of lactose and maltose	Fatty acids	*Rhizomucor miehei*	no	48-77	Sarney et al. 1994
Acetals of D-xylose, D-glucose and D-galactose	Fatty acid methyl ester	*Rhizomucor miehei*, *Pseudomonas* sp.	no	50-90	Fregapane et al. 1991

Table 1 (continued)

Sugar(s) (alcohol(s))	Fatty acid(s) (carboxylic acid(s))	Origin(s) of lipase	Solvent(s)	Yield (%)	Reference(s)
Diglycerol	Conjugated linoleic acids	*Penicillium camembertii*	no	93	Yamauchi-Sato et al. 2005
Glycerol	Conjugated linoleic acids	*Penicillium camembertii*	no		Watanabe et al. 2005
Glycerol	Fatty acids	*Penicillium camembertii*	no		Pinsirodom et al. 2004
Glycerol	Ferulic acid	*Candida antarctica*	no	75	Matsuo et al. 2008
Arbutin	Fatty acid vinyl esters	*Penicillium expansum*, *Candida antarctica*, *Thermomyces lanuginosus*	THF[e]	99	Yang et al. 2010
Rutin	Palmitic, lauric acid	*Candida antarctica*	Acetone	70-77	Lue et al. 2010
Rutin, esculin	Fatty acids、dicarboxylic acids, ω-substituted fatty acids	*Candida antarctica*	TAA[a]	>70	Ardhaoui et al. 2004
Salidroside	Carboxylic acids	*Candida antarctica*	1,4-Dioxane, acetonitrile, acetone, TBA[b], TAA[a]		Yu et al. 2008
Naringin, isoquercetin	Cinnamic acid, phenylpropionic acid, palmitic acid	*Candida antarctica*	TBA[b]		Stevenson et al. 2006
Arbutin, isoquercetin, rutin, naringin	Vinyl cinnamate, vinyl *p*-coumarate	*Candida antarctica*, *Pseudomonas aeruginosa*	Acetone, acetonitrile, acetonitrile+pyridine		Nakajima et al. 1999
D-Glucose	Vinyl laurate	*Candida antartica*	[Bmim][TfO], [Bmim][Tf_2N]	86	Lee et al. 2008
Salicin, helicin, esculin, naringin	Vinyl butyrate	*Candida antarctica*	[bmim]BF_4, [bmim]PF_6		Katsoura et al. 2007
Methyl-6-*O*-trityl-glycosides	Vinyl acetate	*Candida rugosa*	$[BMIM]^+PF_6^-$, $[MOEMIM]^+PF_6^-$	20-95	Kim et al. 2003

[a] *t*-Amyl alcohol
[b] *t*-Butyl alcohol
[c] Dimethylformamide
[d] Dimethylsulfoxide
[e] Tetrahydrofuran

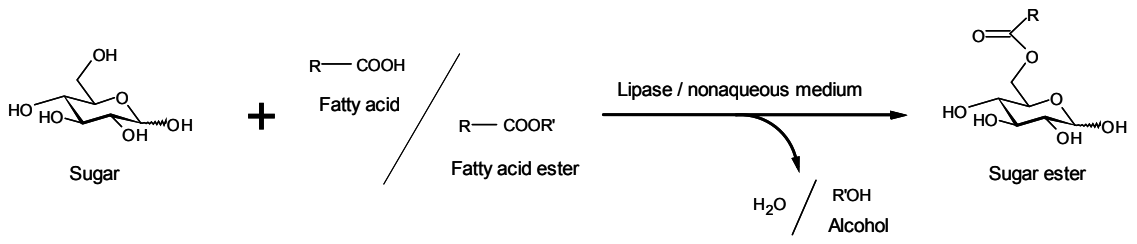
an acyl substrate.

In the first half of 1990s, investigations emerged that synthesized sugar esters containing a disaccharide such as sucrose or lactose, maltose, an oligosaccharide such as maltotriose as a sugar moiety (Ferrer et al. 2000; Sarney et al. 1994; Sarney et al. 1996). The background for the trials using these syntheses suggested that sugar esters with a big carbohydrate moiety may have more desirable properties as an emulsifier. Relatively recently, polyphenolic glycoside esters have also been synthesized to improve the lipophilicity of the glycosides. In these cases, there is a trend to exploit the functionality of the glycosides by solubilizing the less soluble functional compounds in oil. In addition, there are many reports that adopted the lipase-catalyzed reactions as a part of the chemo-enzymatic synthesis, in which most of the reactions were often used for the purpose of taking advantage of the substrate specificity or that of planning an "improvement in productivity".

Synthesis of esters in non-aqueous media

When a sugar ester is synthesized by dehydrative condensation from a fatty acid and sugar, water is formed as a by-product (Scheme 1). To suppress the inverse reaction, i.e., hydrolysis, it is effective to perform the reaction in an environment containing little water, namely in a non-aqueous medium. In addition, for the transesterification, the reaction in a non-aqueous medium is also effective from the viewpoint of hydrolysis control; if water exists in a reaction system, hydrolysis also occurs in parallel with the transesterification.

Some researchers reported that certain enzymes show their catalytic activity in some organic solvents with a low water content (Klibanov, 1986; Klibanov, 1989; Therisod & Klibanov 1986), and then the non-aqueous enzymatic reactions became noteworthy. Thereafter, the lipase-catalyzed synthesis has been tried in organic solvents for a quarter century. In addition, the synthesis of esters in an ionic liquid, the property of which is quite different from that of a general organic solvent, has also attracted attention in relatively recent years.



Scheme 1 Lipase-catalyzed synthesis of sugar ester in a non-aqueous medium

Synthesis in an organic solvent

The synthesis in an organic solvent has the advantage that a high yield can be anticipated. However, there is a problem that the lipase easily inactivates. This problem limits the origin of the lipase and also makes its selection difficult at the same time. Lipases from *Candida antarctica* (fraction B; CALB), *Rhizomucor miehei*, *Burkholderia cepacia*, etc., are usually selected.

Next, more attention is paid to the type of organic solvents as the reaction medium. The available organic solvents are rather limited for the lipase-catalyzed reaction; hydrocarbons or nitriles, tertiary alcohols, ethers, ketones, aromatic solvents, etc., are usually used. Among them, relatively polar solvents have been used for the synthesis of the sugar esters; e.g., tertiary alcohols, nitriles, ketones. Use of these solvents is due to the low solubility of the sugars in the less polar solvents; e.g. the solubilities of glucose, fructose, and galactose in acetonitrile are 92.7, 978, 211 μmol/L (Watanabe et al. 2000). On the other hand, a polar solvent tends to easily inactivate a lipase. Based on these reasons, CALB is often practically used in many reactions because of the high activity in and the high tolerance toward polar solvents (Table 1).

However, even by using an approach of solvent selection, it is very difficult to synthesize the sugar esters of disaccharides and oligosaccharides at a practical level. The main reason is that the solubility of these sugars in these organic solvents becomes extremely low when the saccharide chain length increases. Therefore, an idea has been proposed using a highly polar solvent which easily dissolves both the fatty acid and saccharide, in which the use of dimethylsulfoxide (DMSO), DMF, pyridine, etc., has been tried. However, most lipases easily inactivate in these solvents in a pure form even if CALB is used. The reason may be due to the unfolding of the protein (Klyosov et al. 1975) or the removal of water to maintain the minimum catalytic activity of the lipase (Krishna et al. 2001).

To prevent inactivation of the lipase, it has been suggested that a small amount of these highly polar solvents is added to *t*-butyl alcohol (TBA) or to *t*-amyl alcohol (TAA) as an adjuvant (a co-solvent). Plou et al. (2002) reported that inactivation of the lipase is suppressed when the concentration of DMSO is below 20-30% in TAA. There are other reports adopting the mixed solvent system including a highly polar solvent such as TBA+pyridine or TAA+dimethylacetamide (Chen et al. 2005; Ferrer et al. 1999; Ferrer et al. 2005; Nakajima et al. 1999).

Synthesis in an ionic liquid

When a sugar ester is synthesized by a lipase in a general organic solvent, it is necessary to use an adjuvant

to dissolve the sugars in some cases. In addition, organic solvents usually have a high volatility and are also harmful. To overcome these problems, the lipase-catalyzed reaction in an ionic liquid has attracted attention. An ionic liquid is formed as an asymmetric organic salt and is in liquid state below 100°C or close to room temperature. It also has the following characteristics: i) it is suitable for green chemistry because the vapor pressure is approximately zero, i.e., it is nonvolatile, ii) each ionic liquid has different properties because it is easy to change the combination of the cation and anion species of the ionic liquid, and iii) good choice of an ionic liquid contributes to both the high stability of the enzyme and the high dissolution of sugars (Diego et al. 2005; Kaar et al. 2003; Lozano et al. 2004; Zhao et al. 2008). Based on these characteristics, an ionic liquid has been studied as the reaction medium; e.g., Kim et al. (2003) performed the acetylation of the monoprotected glycosides, while Zhao et al. (2008) succeeded in the acylation of glucose and cellulose.

Solvent-free reaction

The reaction systems above introduced include a certain type of solvent or liquid as the adjuvant. However, it is possible to perform a reaction without any adjuvant under limited conditions (solvent-free system). For example, glycerol, a simple sugar alcohol, can be easily converted to acylglycerols by mixing with a fatty acid or an aromatic carboxylic acid in the presence of lipase (Matsuo et al. 2008; Pinsirodom et al. 2004; Watanabe et al. 2002; Watanabe et al. 2005). In addition, the ester of diglycerol can also be synthesized by mixing the substrates and lipase (Yamauchi-Sato et al. 2005). Although some esters can be synthesized in a solvent-free system, it is necessary to adopt another strategy to obtain other sugar esters when this reaction system is selected.

Improvement in productivity

It is necessary to achieve a higher productivity, namely, a high reaction rate and high product concentration, to facilitate the production of sugar esters. Various methods have been tried to achieve a high productivity. The first one is to improve the equilibrium yield. The second one is to raise the product concentration by increasing the substrate concentration, and the last one is to improve the reaction rate.

Improvement of equilibrium yield

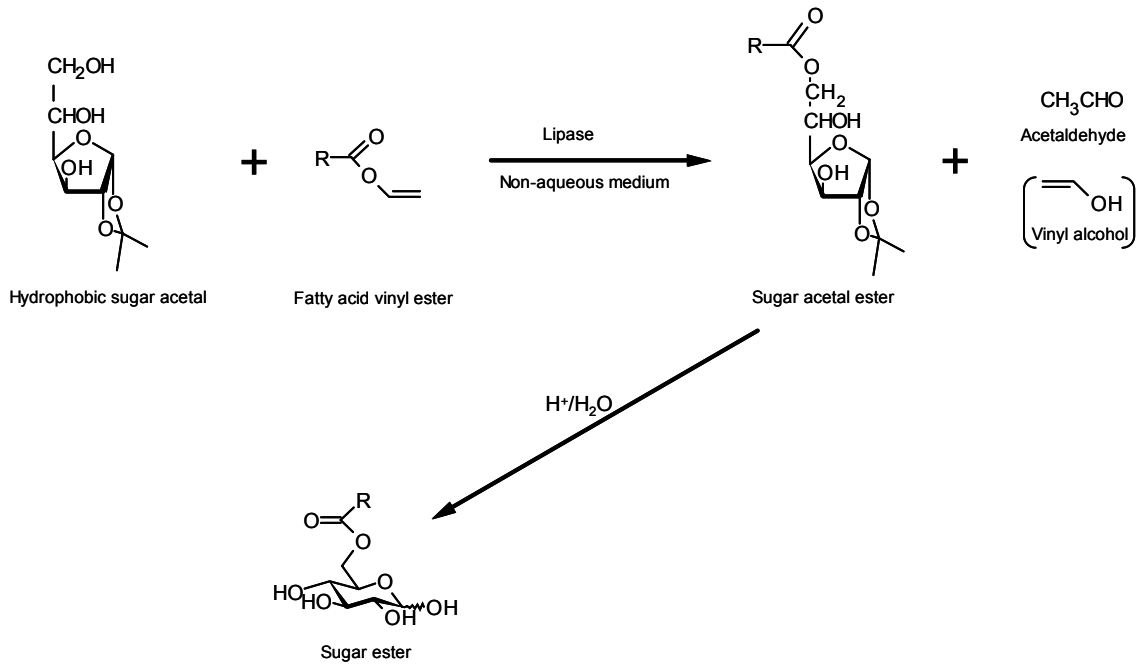
There are several techniques to raise the equilibrium yield. The synthesis of esters by a lipase requires two substrates. The yield can be effectively raised by adding one of the substrates in excess. If one of the

substrates is cheap and can be easily removed, this technique is the simplest and is often first evaluated in a general study. This technique is also effective for transesterifications.

The synthesis of esters by a lipase is a reversible reaction, and a by-product forms; i.e., water forms during dehydrative condensation, and an alcohol forms during transesterification. Therefore, the equilibrium yield can also be improved by removing these by-products from the reaction system. In these cases, methods are often adopted in which water or alcohol is removed in *vacuo* (Watanabe et al. 2002; Watanabe et al. 2005; Yamauchi-Sato et al. 2005) or by a desiccant such as molecular sieves (Ardhaoui et al. 2004; Cramer et al. 2007; Ferrer et al. 2005; Katsoura et al. 2007; Lue et al. 2010; Stamatis et al. 2001; Stevenson et al. 2006). Although the former one can be performed without any additive, its applications are limited only to a reaction involving a solvent-free system or in an ionic liquid.

The next example is a reaction using fatty acid vinyl esters (Table 1). The fatty acid moiety of the vinyl ester is incorporated into a target ester by transesterification, and vinyl alcohol forms as a by-product. Vinyl alcohol is a tautomer of acetaldehyde, but its existence mostly leans to the keto form (acetaldehyde) at normal temperature. Therefore, almost all of vinyl alcohol is virtually removed from the reaction system (Scheme 2). Because other enols having a longer alkyl chain also have their keto forms, a similar technique may theoretically improve the yield. However, there are few studies using the esters of these enols maybe due to the cost and acquisition of the ester as a raw material.

The properties of an organic solvent are next focused on. Equilibrium yields usually depend on the



Scheme 2 Synthesis of sugar ester using sugar acetal and fatty acid vinyl ester

properties of, i.e., the type of organic solvents (Castillo et al. 2003; Kobayashi et al. 2003b; Watanabe et al. 2001). An equilibrium yield is high in hydrocarbons such as hexane, but becomes lower in nitriles, ketones, and tertiary alcohols in this order. The equilibrium yield in TBA+DMSO tends to be much lower. These tendencies are quantitatively related to the difference in the polarity of the solvents in the pure or mixed form (Castillo et al. 2003; Kobayashi et al. 2003b). These facts mean that a change in the type and mixing ratio of the solvents enables us to freely control the equilibrium yield, which Castillo et al. (2003) called 'solvent engineering approach'.

Improvement of reaction rate

Although dehydrative condensation has the merit that the by-product is water, its reaction rate is not always fast. Therefore, to increase the reaction rate, transesterification is instead often adopted. However, depending on the molecular structure of the substrate, the reaction rate may be sometimes very low. If a carboxylic acid has a carboxyl group with a conjugated double bond (e.g., acrylic acid), its reactivity is much lower than that without a conjugated double bond (Kobayashi et al. 2003a). A similar phenomenon was observed when methacrylic, benzoic, or cinnamic acid was used as the substrate. Therefore, the synthesis of the sugar esters of these carboxylic acids may usually produce a very low yield within a practical reaction period by conventional techniques because of the low solubility of the sugar and the low reactivity of the carboxylic acid.

There are several techniques, such as using an ionic liquid or adding an adjuvant to overcome these drawbacks by improving the solubility of the sugar. Now, the other method is introduced that uses the sugar derivatives as sugar substrates. The solubility of a sugar in an organic solvent can be raised using a hydrophobic sugar derivative instead of an unmodified sugar. There are several hydrophobic derivatives of the sugars: i) phenylboronic acid esters, ii) sugar acetals, and iii) *n*-alkyl glycosides. Phenylboronic acid esters and sugar acetals are usually used for the protection of the hydroxyl groups in sugars. In addition, these protecting groups are also effective to improve the solubility in an organic solvent. Many reports have dealt with the synthesis of sugar esters using hydrophobic sugar derivatives (Table 1, Scheme 2), and some of them succeeded in the production with a high reaction rate and high concentration.

Meanwhile, there are some reports using a polyphenolic glycoside, such as arbutin, rutin, or naringin, which itself has some bioactivities and is a relatively less polar glycoside (Table 1). To further increase the lipophilicity of these compounds, a medium or long chain fatty acid was incorporated into the glycoside

(Lue et al. 2010; Stevenson et al. 2006; Yang et al. 2010). In addition, the creation of a new bioactivity may be expected when a functional carboxylic acid, such as cinnamic acid, is used as an acyl substrate for esterification of the glycosides (Nakajima et al. 1999; Stevenson et al. 2006).

Conclusion

The synthesis of a sugar ester using a lipase has been tried for a quarter century, and various kinds of synthetic processes have been suggested. The most important and difficult problem has been how to couple a hydrophobic fatty acid with a hydrophilic sugar at a practical level. To overcome this, improvement in the productivity has been performed by optimizing the types of lipase and the reaction medium based on the solvent engineering, and using hydrophobic sugar derivatives. As a result, it becomes relatively easily to synthesize the target sugar ester on a laboratory scale. The industrialization and further creation of functional sugar esters will be expected by the lipase-catalyzed reaction.

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