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Study of stereochemical effect of galactoside mixture based on reaction time

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Abstract

Synthesis of palm kernel oil-based galactoside involves a three-step process: acetylation, glycosylation and deacetylation. Glycosylation reaction produced two stereoisomeric galactosides: α-anomer and β-anomer. The quantity of these anomers is directly dependent on the glycosylation time as each anomer is either kinetically or thermodynamically favoured. In this work, we studied the effect of time towards the production of predominating anomers. The quantity of the anomers is reported in terms of α/β ratio based on the integration of proton NMR peaks of the final product. From the result, it is found that the quantity of α-anomer increased by average of 1.15 %/h

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1.0 Introduction

Glycoside is considered a natural surfactant exists in nature as cell components of living organisms (Faivre & Rosilio, 2010). It can be extracted from natural resources, however, due to issues i.e. abundance and purity, synthetic glycosides are mostly used in large production. Alkyl polyglycoside is a commercial glycoside consists of glucose and other polysaccharide units, has been used in food and personal care products (von Rybinski & Hill, 1998). Recently, researchers are looking on applying synthetic glycosides as vectors in pharmaceutical and cosmeceutical products due to their excellent emulsifying and dermatological properties (Aripin, 2012, Mura, 2008, Mura, 2007).

Galactoside, a glycoside with galactose unit, has shown promising future in pharmaceutical formulations ever since it was discovered to have high affinity towards liver (Kiwada, 1985). Many researches on pure galactosides are done in order to understand the basic properties aiming for broader application. It is shown that different alkyl chain length as well as the stereochemical configurations could altered the thermal and surface activity of these glycosides (Chen, 2016, Vill, 1989).

In this work, we have synthesised a palm oil-based sugar surfactant from galactose and palm kernel oil. The aim is to observe the production of stereoisomers of this galactoside as they will determine the physico-chemical properties of these glycosides. The synthetic method is adopted from Vill et al. (Vill, Böcker, 1989) produced a pure technical galactoside consists of monoalkylated galactosides based on the fatty acid components of palm kernel oil which contains almost 80% saturated acids and less than 20% unsaturated acids (Pantzaris & Basiron, 2002).

2.0 Methodology

2.1 Materials

Palm kernel oil is obtained from Golden Jomaline Food Industries Sdn Bhd. Lithium Aluminium hydride, $LiAlH_4$ used as catalyst was bought from Sigma Aldrich (USA). Galactose, boron trifluoride (BF_3) and acetic anhydride are also from Sigma Aldrich (USA). Sodium methoxide, sodium acetate anhydrous, sodium hydrogen carbonate, Amberlite resin and most solvents i.e. diethyl ether, ethyl acetate, acetonitrile, hexane, methanol, and butanol were purchased from Merck. Chemicals are AR grade and used without further purification.

2.2 Synthesis

Acetylation: 20 g of sodium acetate and 100 ml of acetyl anhydride were mixed in a 1 L two-neck round bottom flask equipped with a condenser which is then heated to 120 °C with continuous stirring. Afterwards, 20 g of galactose is added in small portion using a spatula into the flask. Galactose was added in small portion to prevent uncontrollable exothermic reaction. The mixture was heated for an extra hour after all galactose was added into the flask to ensure the

completion of the reaction. After one hour, the hot mixture was poured into a separate container containing ice to solidify the acetylated galactose. The product was rinse with cold water several times until an off-white solid was formed. This solid was later recrystallised in ethanol for at least 48 hours. The crystallised acetylated galactose or galactose pentaacetate was filtered and washed with cold ethanol.

Glycosylation: 6 g of galactose pentaacetate was mixed with 3.2 g of reduced palm kernel oil in a 60 ml of dichloromethane into a round bottom flask. Approximately 2.3 ml of boron trifluoride (BF_3) is injected into the solution and left to stir for a specific period of time i.e. 12, 24, and 48 hours. At the end of the reaction time, concentrated sodium bicarbonate was added to neutralize BF_3 which consequently stopped the reaction. Excess reduced palm kernel oil is separated from the galactoside by hexane-acetonitrile separation. The presence of reduced palm kernel oil is checked using thin layer chromatography (TLC) and once it was completely removed, acetonitrile was evaporated from the galactoside solution to obtain the peracetylated galactoside.

Deacetylation: In the final step, peracetylated galactoside was dissolved in 50 ml methanol and a small amount of sodium methoxide was added to induced basicity to the solution. The mixture was left stirring overnight. Upon the completion of the reaction, a small amount of Amberlite resin was added to stop the reaction by neutralizing the solution. Prior to methanol evaporation, the solution was filtered to separate the Amberlite resin. Several butanol-water extractions were performed to purify the galactoside from free galactose. Finally, butanol was evaporated and the product, galactoside was dried in vacuum oven for 48 hours before further analysis.

2.3 Nuclear Magnetic Resonance (NMR) analysis

The palm kernel oil-based galactosides (and all the intermediates) were analysed using NMR. Galactoside samples were prepared by dissolving galactoside in deuterated methanol, methanol-d4 while the intermediate samples were prepared in chloroform-d solutions and measurements were performed at room temperature.

3.0 Results and discussion

Palm kernel oil-based galactoside (GalPKO) is synthesized using a previously reported method by Hashim et al. (2006), which produced two stereoisomers; the α-, and the β- anomers. The α-anomer forms glycosidic bond at axial position of C1 whereas β-anomer is at equatorial position, see Fig. 1. The configurations at C1 are determined by the reaction time and catalyst strength since α-anomers are thermodynamically favoured, while β-anomers are more kinetically stable (Lindhorst, 2007). The stereoselectivity occurred when acetyl group at C2 is shielding the α position at C1 which consequently produced more β-anomers than α-anomers (Lindhorst, 2007). In this work, we have selected BF_3 as catalyst for all glycosylation reactions to observe the effect of reaction time on the production of GalPKO. The BF_3 is preferred over other catalyst simply because of it is easier to handle since it does not complicate later chemical work-ups in obtaining the product.

The anomeric production was first monitored using the thin layer chromatography (TLC) during glycosylation step and later confirmed using the NMR. The ^{1}H-NMR shows the α-anomer gives a doublet at 4.7 ppm while β-anomer's peak is found at 4.2 ppm, see Fig. 2. By comparing the peaks integrations, amount of each anomer can be accurately estimated, considering the baseline is properly set. The information is obtained as α/β ratio.

Based on the NMR analysis of the GalPKO that were synthesized for 12, 24 and 48 hours, the α-anomer is produced more over the longer glycosylation time, as expected. Since α-anomer is thermodynamically favoured, longer glycosylation reaction will convert the more stable β-anomer into α -anomer, thus decreasing amount of β-anomer. The conversion rate is higher at the first 12 hours which is 1.4%/h which then is reduced to 0.9%/h.

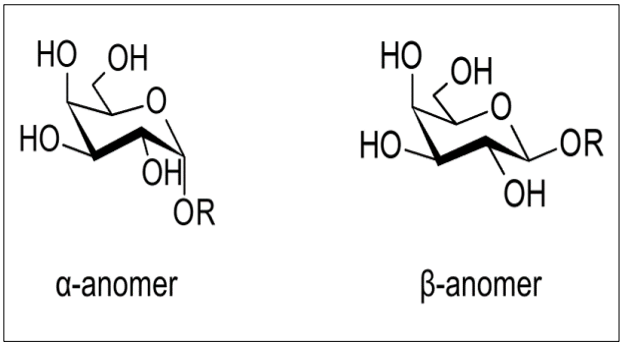

Fig. 1: Chemical structures of two stereoisomers of GalPKO.

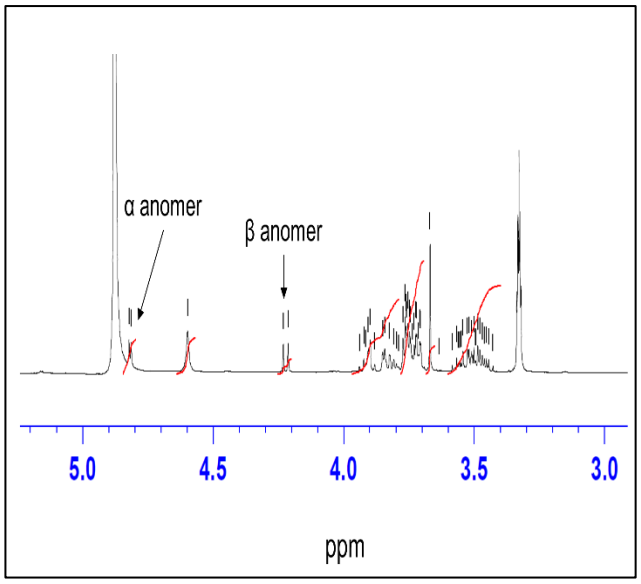

Fig. 2: 1H-NMR of GalPKO showing the stereoisomeric peaks, the α- and β- anomers.

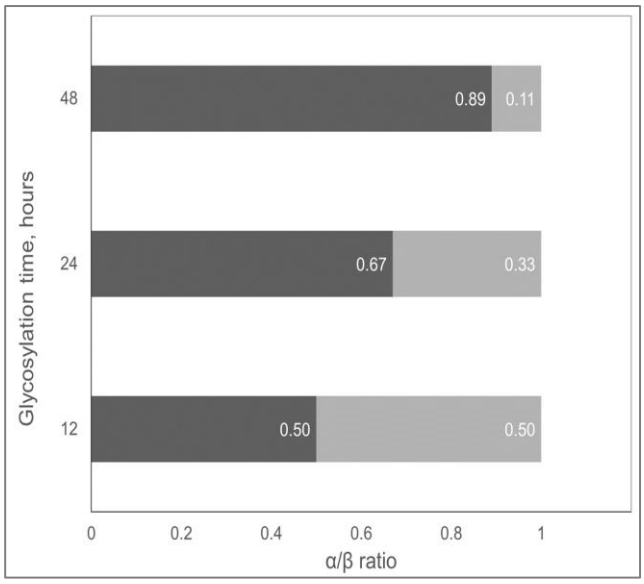

Fig. 3: Graph shows the α/β ratio of the palm kernel oil-based galactoside according to glycosylation time. The blue area represents the α anomer and orange area is β anomer.

Fig. 3 shows the α/β ratio of the palm kernel oil-based galactoside according to glycosylation time. In case of palm kernel oil-based glucoside, which is the analogue of GalPKO, differs by having hydroxy group at equatorial position on C4, the conversion rate is slightly higher at first 12 hours; 2.2%/h but afterwards, reduced by two-fold (unpublished). On the other hand, dodecyl lactoside is observed to have the initial conversion rate of 3.7%/h which then plummeted to three times much slower (Kamalul Aripin, 2009). From these results, it shows that the conversion rates of these glycosides vary despite in all cases, the acetyl group at C2 is at equatorial configuration, which indicates the glycosylation reactivity at C1 is influenced by another factor apart from the neighbouring group effect.

4.0 Conclusion

GalPKO produced two stereoisomers based on glycosylation reaction time. The α-GalPKO is produced at longer reaction time whereas β-GalPKO requires shorter reaction time since it is kinetically favourable. The average conversion rate of β-anomer to α-anomer is 1.15 %/h.

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