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Improved Method for the Synthesis of 2-Alkylamino-2-deoxy-D-glucopyranose and 1,2-Dialkylamino-1,2-dideoxy-D-(*N*)-*β*-glucoside

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Abstract: An improved method for the synthesis of two types of carbohydrate-based, pH-sensitive surfactants has been developed. The surfactants are formed in almost quantitative yields from D-fructose and suitable alkylamines, when using a zinc halide salt as catalyst. The reaction proceeds via an initial Amadori reaction, and the 1,2-dialkylamino-1,2-dideoxy-D-(*N*)-*β*-glucoside precipitates out of the reaction. The product can easily be hydrolyzed to the more water-soluble, surface-active, and pH-sensitive monoalkyl derivative 2-alkylamino-2-deoxy-D-glucopyranose. Products from several amines can be prepared.

The ecological impact of surfactants is of general concern. Sugar-based surfactants, comprising sugar esters, sugar amides, glycosides, and similar sugar-based compounds, are of interest because they offer suitable surfactant properties in combination with environmental advantages. Therefore, new or enhanced methods of production of such surfactants are of interest.

The products formed by reactions between D-fructose and aromatic[1] and aliphatic amines[2−6] have previously been investigated. It was found that D-fructosyl alkylamines (also called *N*-fructosides) are formed, which by addition of acetic acid as a Lewis acid can be slowly rearranged to the corresponding 2-deoxy-2-alkylamino-D-glucopyranoses via an Amadori-like rearrangement reaction.[6,7] The products were obtained in relatively low total yields (ca. 10−20%), and the reaction required very long reaction times (ca. 7−30 days). The products were difficult to purify. In this note, we present an improved method for the synthesis of 1,2-dialkylamino-1,2-dideoxy-D-(*N*)-glucosides (**1**) in high yields (Figure 1). 2-Alkylamino-2-deoxy-D-glucopyranoses (**2**) can also be prepared in high yields. The compounds **1** and **2** possess useful surfactant properties.[8,9] The surfactants are formed in almost quantitative yields from D-fructose and suitable alkylamines, when using zinc halide salts as catalyst. The reaction proceeds via an initial Amadori reaction, and the 1,2-dialkylamino-1,2-dideoxy-D-(*N*)-*β*-glucoside precipitates out of the reaction (see Scheme 1). The product can easily be hydrolyzed to the more water-soluble, surface-active, and pH-sensitive monoalkyl derivative 2-alkylamino-2-deoxy-D-glucopyranose (see Scheme 1). The hydrolysis proceeds readily using ultrasound. A wide array of products from amines, including *N*-*n*-hexylamine, *N*-*n*-octylamine. and *N*-benzylamine can be prepared. Zinc chloride was proven to be an effective catalyst, while zinc bromide was also useful. The synthetic principle has been previously described, using hydrochloric acid as catalyst, but provided products in low yields and with extended reaction times.[1−6] 2-Alkylamino-2-deoxy-D-glucopyranose is a nonionic surfactant in basic media but possesses a functional group that can be charged at neutral or lower pH-levels.

Under dehydrating conditions, D-fructose will effectively react with amines to produce the corresponding imine product. The imine will assume the more thermodynamically stable chair form by ring-closure into the *N*-fructoside. It is clear from mechanistic considerations that, by applying electronic pull on the imine nitrogen, an Amadori rearrangement will occur. This rearrangement transforms the sugar from a ketohexose to an aldohexose. It is clear from previous results that using a strong acid for this electron-pulling effect will give rise to a number of undesired side reactions, including polymer formation and Maillard reactions. We anticipated that the use of a softer Lewis acid should provide the product in higher yields. It was found that zinc salts are suitable for this particular rearrangement. Zinc chloride or zinc bromide efficiently provides the product with short reaction times at room temperature and in almost quantitative yields. The lack of any major amounts of byproducts enables the compound to easily be purified by recrystallization. We suggest that the reaction sequence, as evidenced from reaction products, is as outlined in Scheme 1. As noted in the scheme, there are two possible energetically favorable reaction paths leading to the same product. These mechanisms are indistinguishable by considerations of the structures of the formed products alone. The crucial step of the rearrangement reaction is the intermediate complex between the zinc and the monoimine of D-fructose. The cyclic intermediate can be either six-membered (**3**) or five-membered (**4**) as shown in Scheme 1. The rearrangement reaction may proceed by an Amadori-like reaction via either intermediates **3** or **4** or via a hydride shift from intermediate **4**.

The compounds **1a**−**c**, being *N*-glucosides, are rather easily hydrolyzed. The hydrolysis product is the corresponding monoalkyl amino derivative, such as compound **2**. It was found that the hydrolysis proceeds smoothly in

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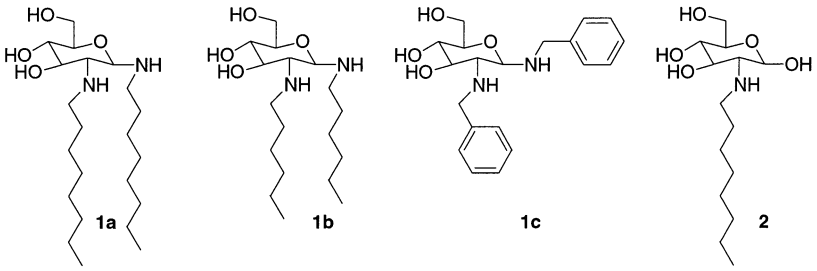
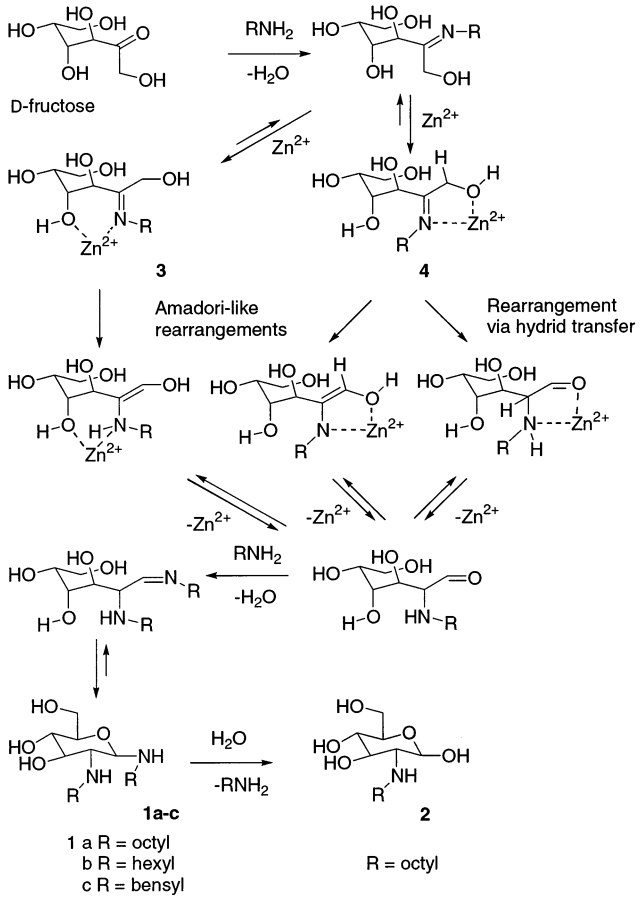


FIGURE 1. Synthesized surfactants using the new method.

SCHEME 1



an acidic aqueous solution promoted by ultrasound. In a water medium, without the application of ultrasound, the starting material will tend to flocculate, giving a heterogeneous reaction mixture, and colored byproducts are formed. The pure hydrolysis product could not easily be isolated from such a mixture. It has been reported that hydrophobic *N*-glucosides are more resistant toward hydrolysis than hydrophilic ones.[6,10] We assume that the increased level of hydrophobicity of the compounds will result in shielding of the reactive site.

1-*n*-Alkylamino-1-deoxy-D-glucitols are known to exhibit strong and useful surfactant properties.[8,9,11] Thus it is reasonable to assume that the 2-alkylamino-2-deoxy-D-glucopyranose (**2**) has a similar activity. The latter type of compounds (**2**) possesses a ring-closed headgroup instead of the open headgroup of 1-*n*-alkylamino-1-deoxy-D-glucitols. Therefore, it was of interest to prepare compounds of the type for studies of their surfactant properties.

The surface activity of **1a**−**c** and **2** were studied and compared to other compounds, and although promising, they were not generally as active as the previously reported 1-deoxy-1-octylamino-D-glucitol. The difference in activity probably stems from the structural difference of the headgroup. Our compounds **1a**−**c** are very insoluble and compound **2** has a ring-closed headgroup, whereas the reference substance is an open sugar. More detailed surface measurements data can be found elsewhere.[8,9] The dialkyl amino products, such as **1a**−**c**,[4,6] can be considered as potential pH-sensitive surfactants if the R groups are large enough.

It should be noted that the pure 1,2-dialkylamino-1,2-dideoxy-D-(*N*)-*β*-glucosides are resistant toward air-oxidation, and the 2-alkylamino-2-deoxy-D-glucopyranoses tend to darken in time. The previously reported hydrochloride salt form[6] appears to be more stable.

In conclusion, we have developed a useful method for preparing both 1,2-dideoxy-1,2-dialkylamino-D-(*N*)-*β*-glucosides and 2-deoxy-2-alkylamino-D-glucopyranoses in high yields. Such compounds appear to have useful properties as surfactants. The synthetic procedure is effective, fairly cheap, and simple.

Experimental Section

General Methods. Water was distilled by standard procedures. Unless otherwise stated, solvents or reagents were used without further purification**.** All melting points are measured in open glass capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra are measured at 400 or at 500 MHz; solvent was $CDCl_3$ for all compounds and served as reference in all measurements. For accurate interpretation of the NMR spectra ^{1}H−^{1}H, ^{1}H−^{13}C 2D-NMR and ^{13}C-DEPT experiments were performed with the 500 MHz instrument. IR spectra were recorded on samples prepared with KBr. TLC analyses were performed on standard silica plates and developed with phosphomolybdic acid (10% w/v) and concentrated sulfuric acid (1% w/v) in ethanol.

1,2-Dideoxy-1,2-di-*n*-octylamino-D-(*N*)-*β*-glucoside (1a). To a 250-mL round bottle were added D-fructose (30.0 g, 167 mmol, 1 eq) and *n*-octylamine (78.99 g, 611,2 mmol, 3.66 eq). The bottle was thoroughly shaken until most of the fructose was dissolved. Molecular sieves (4 Å, 5 g) and catalytic amounts (2−4 mg) of $ZnBr_2$ were added. After 2 days of stirring at room temperature the stirrer and molecular sieves were removed. Approximately 15 mL of the excess *n*-octylamine was evaporated, at room temperature, using a rotary evaporator, after which acetone (140 mL) was added. The solution was kept at −20 °C for 1 day and then at 4 °C for 3 more days. The crystals thus formed consisted of compound **1a** contaminated with some

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unreacted amine (as shown by TLC using methanol as the eluent). To obtain an analytically pure sample, the crude product was filtered and washed with cold acetone (15 mL). It was then washed with diethyl ether and ethyl acetate until the washing liquid became colorless and the crystals became clearly white. The product was dried in a vacuum desiccator, yielding 1,2-dideoxy-1,2-dioctylamino-D-(*N*)-*β*-glucoside (**1a**): yield 67 g (∼100%); mp 98.0−99.0 °C (from acetone), lit.[6] mp 99−100 °C; IR (KBr) $\bar{\nu}$ 3300, 3200, 1510, 1500, 1470, 1275, 1225, 1180, 715 cm^{-1}; ^1H NMR δ 0.90 (t, 6 H, J = 6 Hz), 1.20−1.30 (m, 20 H), 1.40−1.50 (m, 4H), 2.30−2.85 (m, 6H), 3.25 (s, 1H), 3.55 (t, 2H, J = 7 Hz), 3.7 (s, 1H), 3.85 (t, 2H, J = 7 Hz), 3,95 (d, 1H, J = 9 Hz); ^{13}C NMR δ 14.5, 23.1, 27.3, 27.8, 29.8, 30.0, 30.4, 30.8, 30.9, 32.3, 33.8, 46.4, 47.2, 62.2, 63.3, 70.2, 71.3, 75.8, 90.2.

Alternative Method. The reactants were mixed and reacted just as previously described, but using $ZnCl_2$ instead as the catalyst. After 2 days of stirring at room temperature, the solution has became a light orange solid. According to TLC (using methanol as eluent) this crude product was composed of the product **1a** and unreacted amine, indicating a quantitative yield. The product was isolated according to the following procedure. Acetone (50 mL) was added, and the bottle was kept at −20 °C for 1 day. The solution was warmed to room temperature, and the crystals were filtered and washed with acetone. The yellow-white raw product was recrystallized from acetone, and the filtered product was washed with further acetone. The product was then recrystallized from acetone (200 mL) and water (25 mL), yielding a powder that was washed with acetone and cold water. The product was dried in a vacuum desiccator for 1 day and then washed with acetone again. The solid material was grinded and dried in a vacuum desiccator to yield a fine, analytically pure, white powder: yield 67 g (∼100%).

1,2-Dideoxy-1,2-di-*n*-hexylamino-D-(*N*)-*β*-glucoside (1b). Synthesis was performed in the same way as described above for the preparation of the *n*-octylamine derivative (**1a**) using $ZnCl_2$ as catalyst, but with the use of *n*-hexylamine as the amine. The product was filtered off after 2 days at −20 °C. TLC (using methanol as eluent) indicated a quantitative reaction. For obtaining an analytically pure sample the following procedure was followed. The crude product was washed with cold diethyl ether. The product was then boiled in diethyl ether and placed at −20 °C for 1 h. The compound was filtered, washed with cold diethyl ether, and dried, yielding a pure sample. The yield of the product was almost 100%: mp 99.0−100.0 °C (from diethyl ether), lit.[6] mp 99−100 °C; IR (KBr) $\bar{\nu}$ 3300, 3200, 1510, 1500, 1470, 1275, 1225, 1180, 715 cm^{-1}, cf. lit.;[6] ^1H NMR δ 0.90 (t, 6 H, J = 6 Hz), 1.20−1.30 (m, 12 H), 1.40−1.50 (m, 4H), 2.30−2.85 (m, 6H), 3.25 (s, 1H), 3.55 (t, 2H, J = 7 Hz), 3.7 (s, 1H), 3.85 (t, 2H, J = 7 Hz), 3.95 (d, 1H, J = 9 Hz).

1,2-Dibenzylamino-1,2-dideoxy-D-(*N*)-*β*-glucoside (1c) was prepared according to the procedure presented for compound **1b**, but using benzylamine as the amine. According to TLC (using methanol as eluent) the yield of the product was quantitative. ^1H NMR of the crude product indicated that all D-fructose had been transformed into the product, **1c**. The product was purified according to the description given for compound **1b**. Yield was almost 100%: mp 119−120 °C, lit.[4] mp 119−120 °C; IR (KBr) $\bar{\nu}$ 3300, 3200, 3050, 1600, 1510, 1500, 1470, 1275, 1225, 1180, 730, 715 cm^{-1}; ^1H NMR δ 2.30−2.85 (m, 6H), 3.25 (s, 1H), 3.61 (s, 2H), 3.7 (s, 1H), 3.81 (s, 2H), 3.95 (d, 1H, J = 9 Hz), 7.06−7.14 (m, 10H).

2-Deoxy-2-*n*-octylamino-D-glucose (2). The dialkylamino-sugar **1a** (0.3 g) was placed in a 50-mL round bottle together with water (20 mL). The reaction was started by addition of hydrochloric acid (12 N, 2.5 mL), and the round bottle was fully immersed in an ultrasound water bath (2.5 L) and was treated with ultrasound (90/180 W, 40 kHz) for effectively dissolving the starting material. After 1.5 h the ultrasound was turned off, although a shorter reaction time would also be sufficient. To the clear solution was added solid sodium hydroxide in small portions until the pH becomes clearly basic (approximately pH 9). The solution becomes oblique white. The alkylamine that was produced was removed by washing the solution with diethyl ether (4 × 10 mL). The product surfactant was isolated by careful extraction with $CHCl_3$, which was evaporated, yielding the 2-deoxy-2-*n*-octylamino-D-glucose (**2**). According to the ^1H NMR spectrum of the crude product, the alkylamine substituent of the anomeric carbon was selectively and quantitatively removed, giving the monoalkyl amino sugar derivative in 95% yield: mp 130−131 °C, lit.[6] mp 130−131 °C; IR (KBr) $\bar{\nu}$ 3300, 3200, 1470, 1275, 1230, 1200, 1170, 710 cm^{-1}; ^1H NMR δ 0.90 (t, 3 H, J = 6 Hz), 1.20−1.30 (m, 10 H), 1.40−1.50 (m, 2H), 2.20−2.85 (m, 6H), 3.25 (s, 1H), 3.55 (t, 2H, J = 7 Hz), 3.70 (s, 1H), 3.95 (s, 1H), 4.55 (s, 1H), 4.75 (d, J = 9 Hz, 1H).

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