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Glycosidation of fructose-containing disaccharides using MCM-41 material as the catalyst

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

Abstract

Glycosidation of saccharides combines the essential characteristics of two major renewable classes, viz. triglycerides and carbohydrates, leading to biofriendly surfactants and emulsifiers. The development of the alkylglycosides derived from reducing disaccharides has lagged, because no efficient synthesis was available. We have found that ordered mesoporous materials of the MCM-41 type are active and selective catalysts for the glycosidation of disaccharides containing fructose at the reducing end, i.e., isomaltulose, lactulose and leucrose. No alcoholysis or hydrolysis of the glycosidic bond was observed, demonstrating the mildness of the MCM-41 catalyst. Leucrose was found to be less reactive than the two other disaccharides, in accordance with the absence of furanose forms in leucrose.

Keywords: Isomaltulose; Lactulose; Leucrose; Glycosidation

1. Introduction

Direct glycosidation of carbohydrates with aliphatic alcohols has recently been reviewed by Corma and Iborra.[1] Homogeneous catalysts for the glycosidation of aldohexoses and aldopentoses include hydrochloric acid,[2] sulfuric acid, *p*-toluenesulfonic acid and heteropoly acids. As heterogeneous catalysts acid clays,[3] zeolites H-Y[4] and H-Beta[5] and sulfonic acid resins[6] have been investigated.

Industrially, glucose is glycosylated by long chain alcohols (C_{12}, C_{14}) in processes operated by Henkel (nowadays Cognis) applying homogeneous sulfonic acid catalysis. The non-ionic surfactants obtained are named alkyl polyglycosides (APGs) and actually consist of a mixture of glycosylated glucose oligomers.[7] APGs display favourable surfactant properties together with excellent biodegradability.

Chemocatalytic direct glycosidation generally leads to mixtures of isomers (α/β, furanose/pyranose rings). By contrast, biocatalytic direct glycosidation using glycosidases[8] leads to anomerically pure glycosides, but is more expensive.

Ketohexoses are more vulnerable towards strong homogeneous and heterogeneous Bronsted acids, due to easy conversion of furanose forms to furan systems, e.g., fructose to hydroxymethylfurfural. Here mild acids like oxalic acid,[9] silica–alumina[10] or MCM-41 material[11,12] are preferred for 2-O-alkylation. MCM-41 is an ordered mesoporous silica alumina with parallel channels of 3 nm diameter.

We reasoned that MCM-41 could also be used in the glycosidation of disaccharides which contain a fructose unit at the reducing end and a glucose or galactose unit at the non-reducing end. Examples of these types of disaccharides are isomaltulose[13] (6-*O*-α-D-glucopyran-

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osyl-D-fructofuranose), leucrose[14] (5-*O*-α-D-glucopyranosyl-D-fructose), and lactulose (4-*O*-β-D-galactopyranosyl-D-fructose) (see Scheme 1). The fructose unit in isomaltulose can only be in the furanose form, whereas in leucrose it only exists in the pyranose form and in lactulose the unit can be in both the furanose and pyranose forms.

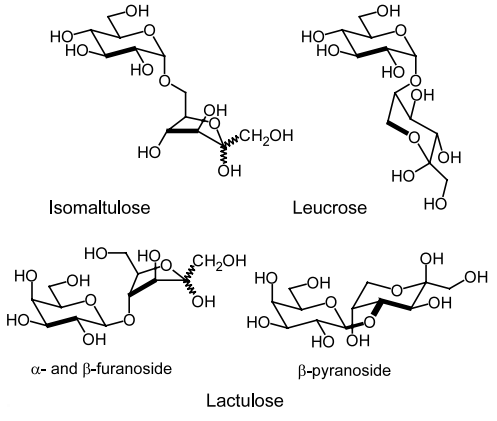
2. Experimental

Materials.—Methanol, ethanol, 1-propanol and 1,2-dimethoxyethane were purchased from Acros Chemicals, 1-butanol and 1-octanol were obtained from J.T. Baker Chemicals and zeolite 3A (KA) from Aldrich.

Leucrose was a gift from Pfeiffer & Langen (Dormagen), lactulose from Solvay Pharmaceuticals (Weesp) and isomaltulose from Südzucker (Mannheim).

MCM-41 materials with Si/Al ratios 30, 60 and 100 were home made[12] and coded MCM-41/30, MCM-41/60 and MCM-41/100. The materials were brought in the H^+-form by refluxing in aq 1 M NH_4NO_3 followed by calcination at 450 °C. Before use, the materials were recalcinated at 400 °C and subsequently aged at rt for 1 week.

Analytical methods.—Analysis of the glycosyl disaccharides was performed by gas chromatography (GC) on a Hewlett–Packard (HP) 5890, Series II chromatograph, equipped with a 7673 auto injector and a Chrompack 50 m × 0.32 mm CP-Sil 5 CB, 0.12 μm column. The carrier gas was nitrogen at a flow of 1.5 mL min^{-1}. Temperature program: 60 °C (5 min) to 300 °C (10 °C min^{-1}). Peaks were detected using flame ionisation detection (FID) and were integrated on a HP 3396A integrator. Tetradecane was used as internal standard. Samples were prepared by withdrawing 20 μL samples of the reaction mixture and treating them with 0.5 mL of a mixture of pyridine (104 mL), *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (26 mL), and trimethylsilyl chloride (13 mL). Comparative retention times were: isomaltulosides: β-furanoside < α-furanoside, lactulosides: β-furanoside < α-furanoside < β-pyranoside.



Scheme 1. Structures of fructose-containing disaccharides.

Separation of the reaction products was performed by using a Millipore-Waters Delta Prep 4000 preparative chromatography system equipped with two 25 × 100 mm 7 μm Symmetry C18 cartridges in a 25 × 10 radial Compression unit and an extension tube, or with two 40 × 100 mm 6 μm Nova-Pak C18 cartridges on a 40 × 10 PrepPak RCM Base unit and an extension tube, a Waters differential refractometer R401 and a Waters fraction collector.

NMR spectra were recorded using a 300 MHz Varian Unity Inova spectrometer or a 400 MHz Varian-VXR 400S spectrometer.

Glycosidation of disaccharides with short chain alcohols (up to 1-butanol).—Disaccharide (3 g, 8.3 mmol), alcohol (100 mL) and catalyst (0.3 g) were refluxed in a round-bottomed flask equipped with a Soxhlet apparatus containing zeolite KA (10 g). The reactions were monitored by taking samples and analysing them with GC. For isomaltulose, MCM-41 was used with a Si/Al ratio of 100, for lactulose a catalyst with Si/Al 60 and for leucrose catalysts with a ratio of 30 and of 60.

After 24 h, the catalyst was removed by filtration and the excess of alcohol was removed by evaporation under vacuum. Different anomers were obtained pure by separation with preparative HPLC, using a Nova-Pak C18 column with water as eluent at 20 mL min^{-1}. Comparative retention times were: isomaltulosides: β-furanoside < α-furanoside; lactulosides: β-furanoside < α-furanoside < β-pyranoside.

The following ^{13}C NMR data were obtained:

Propyl α-isomaltulofuranoside. The ^{13}C NMR spectra of the propyl isomaltulosides are obtained from the mixture: ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 10.58 (CH_3), 22.86 (CH_2), 60.02 (Cα), 60.75, 61.82, 66.83 (C-6′, C-1, C-6), 70.02 (C-4′), 71.80, 72.45 (C-2′, C-3′), 73.18 (C-5′), 76.96 (C-5), 80.32, 80.82 (C-3, C-4), 98.86 (C-1′), 107.26 (C-2).

Propyl β-isomaltulofuranoside. ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 10.58 (CH_3), 22.98 (CH_2), 60.48 (Cα), 60.75, 62.01, 69.52 (C-6′, C-1, C-6), 70.02 (C-4′), 71.80, 72.33 (C-2′, C-3′), 73.08 (C-5′), 75.70, 75.87 (C-3, C-4), 79.40 (C-5), 98.86 (C-1′), 104.18 (C-2).

Ethyl α-lactulofuranoside. ^{13}C NMR (75 MHz, D_2O): δ 16.24 (CH_3), 60.26 (Cα), 62.66, 64.22, 68.38 (C-6′, C-1, C-6), 70.28 (C-4′), 72.35, 74.15, 74.20 (C-2′, C-3′, C-5′), 78.05 (C-5), 81.24, 82.75 (C-3, C-4), 99.67 (C-1′), 109.77 (C-2).

Propyl α-lactulofuranoside. ^{13}C NMR (75 MHz, D_2O): δ 11.51 (CH_3), 24.08 (CH_2), 60.36 (Cα), 62.06, 64.84, 68.26 (C-6′, C-1, C-6), 71.05 (C-4′), 72.92, 73.51 (C-2′, C-3′), 74.61 (C-5′), 78.53 (C-5), 81.75, 82.72 (C-3, C-4), 100.12 (C-1′), 109.69 (C-2).

Propyl β-lactulofuranoside. The ^{13}C NMR spectrum was obtained from the spectrum of the mixture of the propyl α- and β-lactulofuranoside by subtraction: (75 MHz, D_2O): δ 11.47 (CH_3), 24.18 (CH_2), 60.35 (Cα), 61.73, 61.83, 64.79 (C-6′, C-1, C-6), 70.88 (C-4′), 72.85, 73.64 (C-2′, C-3′), 74.49 (C-5′), 76.85, 77.80 (C-3, C-4), 80.64 (C-5), 99.93 (C-1′), 105.41 (C-2).

Propyl leucroside. ^{13}C NMR (75 MHz, D_2O): δ 11.53 (CH_3), 24.15 (CH_2), 62.14, 62.72, 64.16 (Cα, C-6′, C-1, C-6), 70.12, 71.47, 73.53, 74.43 (C-2′, C-3′ C-4′ C-5′, C-3, C-4), 80.70 (C-5), 102.02 (C-1′, C-2′).

Butyl leucroside. ^{13}C NMR (75 MHz, D_2O): δ 14.65 (CH_3), 18.36 (CH_2), 19.90 (CH_2), 58.91 (Cα), 62.24, 62.67, 64.16 (C-6′, C-1, C-6), 70.04, 71.13, 73.44, 74.37 (C-2′, C-3′ C-4′ C-5′, C-3, C-4), 80.85 (C-5), 101.88, 101.96 (C-1′, C-2′).

Glycosidation of disaccharides with 1-octanol.—For the direct glycosidation, the disaccharide (3 g, 8.3 mmol) and 1-octanol (50 mL) were stirred in a round-bottomed flask at 110 °C under diminished pressure. The catalyst (0.3 g) was added and the reaction was monitored by GC.

For the trans-acetalation, 1-octanol (50 mL) was added to the reaction mixture of the butyl saccharides. 1-Butanol was evaporated under diminished pressure. The reaction was monitored by GC.

Synthesis of octyl isomaltuloside using 1,2-dimethoxyethane as solvent.—Isomaltulose (3.0 g, 8.3 mmol) and 1-octanol (50 mL) were added to 100 mL 1,2-dimethoxyethane with eicosane as internal standard and heated to reflux (83 °C). MCM-41/100 (0.3 g) was added and water was scavenged using zeolite KA in a Soxhlet apparatus. The reaction was monitored using GC. After 24 h the reaction was stopped and the catalyst was removed. Analysis of the reaction mixtures showed the rapid formation (initial reaction rate 1.7 g g^{-1} h^{-1}) of octyl isomaltulosides with a maximum yield of 25% after 7 h.

Synthesis of octyl leucroside using 1,2-dimethoxyethane as solvent.—Leucrose (3.0 g, 8.3 mmol) and 1-octanol (50 mL) were added to 100 mL of 1,2-dimethoxyethane with eicosane as internal standard and heated to reflux. MCM-41/100 (0.3 g) was added and water was scavenged using zeolite KA in a Soxhlet apparatus. The reaction was monitored using GC for 20 h but no formation of octyl leucroside was shown.

Synthesis of methyl leucrosides under pressure at elevated temperature.—Leucrose (3.0 g, 8.3 mmol) and MeOH (100 mL) were put in a Hastelloy C-276 reaction vessel of 160 mL (Parr 4564) equipped with a mechanical stirrer, pressure control and a reversed Dean–Starke unit which was filled with zeolite KA (10 g) to withdraw water. The catalyst (MCM-41/30, 0.3 g) was added and the mixture was heated under pressure (1 MPa) to 120 °C. When the reaction mixture reached the desired temperature, the pressure was lowered to 0.4 MPa to obtain a refluxing reaction mixture. After 24 h, the reaction was stopped and the mixture was monitored by GC. The yield of methyl leucrosides was 90%.

Synthesis of octyl leucrosides under pressure at elevated temperature.—Leucrose (1.5 g, 4.2 mmol), 1-octanol (25 mL) and 1,2-dimethoxyethane(75 mL) were put in a Hastelloy C-276 reaction vessel of 160 mL (Parr 4564) equipped with a mechanical stirrer, pressure control and a reversed Dean–Starke unit that was filled with zeolite KA (10 g). The catalyst (MCM-41/30, 0.15 g) was added and the mixture was heated under pressure (1 MPa) to 120 °C. When the reaction mixture reached the desired temperature the pressure was lowered to 0.175 MPa to obtain a refluxing reaction mixture. After 24 h the reaction was stopped and the mixture was monitored by GC. The yield of octyl leucrosides was 5%.

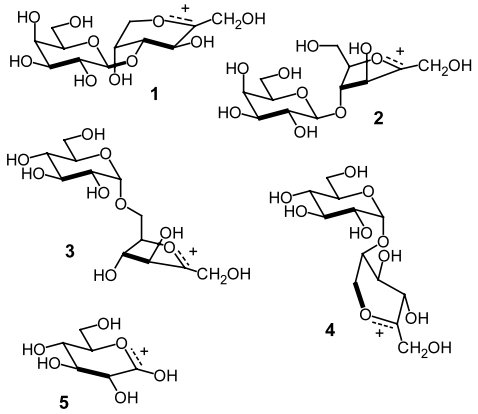
Dissolution rate.—1-Octanol (50 mL) and heptadecane (100 μL, internal standard) were heated to 80 °C and the disaccharide (leucrose or isomaltulose) was added. The concentration of carbohydrate in solution was monitored by GC. For the dissolution rate in 1,2-dimethoxyethane, 50 mL of the solvent containing 0.50 g of eicosane was heated to reflux (83 °C) and the carbohydrate was added.

For the dissolution rate in a mixture of 1-octanol and 1,2-dimethoxyethane, 15 mL 1-octanol and 30 mL of the 1,2-dimethoxyethane–eicosane mixture were mixed and heated to reflux and the carbohydrate was added. The concentration of the carbohydrate in solution was monitored by GC.

3. Results and discussion

Previously we have shown[12] that MCM-41 catalysts with a Si/Al ratio from 30–100 efficiently catalyse the glycosidation of fructose, mainly via the furanose isomers. The isomerisation of the initial furanosidic product to the more stable pyranoside was slower with the MCM-41/100 catalyst. Accordingly, we found that the glycosidation of isomaltulose, in which the fructose unit is furanosidic, was catalysed by MCM-41/100. When catalysts with a higher concentration of aluminium were used, partial decomposition of the isomaltulose occurred. In leucrose, the fructose unit is only present in the less reactive pyranose form and a catalyst with a relatively high concentration of protonic sites such as MCM-41 with a Si/Al ratio of 30 or 60 was required. This phenomenon can be explained by the reaction intermediates (cf. Scheme 2).

During the reaction, the anomeric centre of the fructose unit will be protonated and subsequently dehydrated to the tertiary fructosyl cation (**1**–**4**). The planar structure of the fructofuranosyl cations (**2** and **3**) will favour delocalisation of the positive charge by the ring



Scheme 2. Reaction intermediates required for glycosidation of lactulopyranose (1), lactulofuranose (2), isomaltulose (3), leucrose (4) and glucopyranose (5).

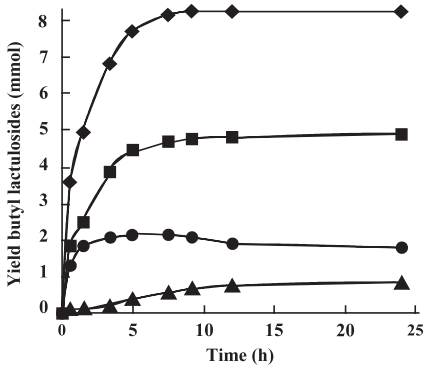


Fig. 1. Course of the H-MCM-41/60 catalysed reaction of lactulose (3.0 g, 8.3 mmol) with 1-butanol (100 mL). ■ butyl α-lactulofuranoside, ● butyl β-lactulofuranoside, ▲ butyl β-lactulopyranoside, ◆ total yield of butyl lactulosides.

oxygen, hence these will be formed faster than the non-planar pyranosyl cations (**1** and **4**). The latter in turn will be formed faster than the secondary carbocation obtained for glucose (**5**). The fructofuranosyl cation easily undergoes dehydration to a furan system which explains the degradation of the isomaltulose when catalysts are used with a higher concentration of protonic sites.

Glycosidation with short chain alcohols.—The reactions with short chain alcohols up to 1-butanol were carried out under reflux. This is possible because the boiling point of the alcohols is lower than the melting point of the disaccharides. When methanol was used as the alcohol, no reaction took place which is probably due to its relatively low boiling point (64 °C). The reaction of fructose with methanol was also relatively slow.[12] The reaction with ethanol resulted in good conversions for isomaltulose and lactulose but leucrose showed no conversion.

Since leucrose is only present in the pyranose form, it requires more energy to achieve the reaction intermediate (a partially planar six-membered ring form (4)) than for lactulose and isomaltulose. The boiling point of ethanol (78 °C) is apparently too low for the alkylation of leucrose. The reactions of the three disaccharides with 1-propanol (bp 97 °C) and 1-butanol (bp 117 °C) showed high conversions and yields (see Table 1).

From the reaction course of lactulose with 1-butanol (Fig. 1) it becomes clear that the butyl lactulofuranosides are formed first followed by the slow formation—by isomerisation—of the butyl lactulopyranoside. After 15 h, all lactulose has been converted.

Glycosidation of disaccharides with 1-octanol.—In the glycosidation reaction of leucrose and isomaltulose with 1-octanol, the conversion dramatically dropped to 5%. This is attributed to the low solubility (see Table 2) of the disaccharides and the higher viscosity of the reaction mixtures. These problems also arose during the alkylation of fructose with 1-octanol,[11,12] and can be solved by using a trans-acetalation technique. Then, the butyl saccharides are synthesised first (which can be done essentially quantitatively) followed by trans-acetalysation with 1-octanol. In this way, the yields are 60% for the octyl isomaltulosides and the octyl leucroside which are the same as obtained for the octyl fructosides.[12]

Table 1
Glycosidation of disaccharides [a]

Disaccharide	MCM-41	Yield [b] of alkylated disaccharide (%) upon reaction with		
	Si/Al	Ethanol	1-Propanol	1-Butanol
Isomaltulose	100	20/69/0	26/61/0	25/74/0
Lactulose	60	36/41/3	28/65/6	24/65/19
Leucrose	60			0/0/89
Leucrose	30	0/0/1	0/0/73	0/0/91

[a] Reaction conditions: 3 g (8.3 mmol) disaccharide, 100 mL alcohol, 0.3 g catalyst, 24 h reflux over zeolite KA.
[b] Yield as detected by GC in percentage β-furanoside/α-furanoside/β-pyranoside form.

Table 2
Dissolution rate and solubility of isomaltulose and leucrose

Disaccharide	Solvent (Temperature)	Dissolution rate (mg mL^{-1} h^{-1})	Solubility (mg mL^{-1})
Isomaltulose	1-octanol (80 °C)	111	3.4
	1,2-dimethoxyethane (83 °C)	29	0.63
	1-octanol and 1,2-dimethoxyethane[a]	320	1.44
Leucrose	1-octanol (80 °C)	104	3.0
	1,2-dimethoxyethane (83 °C)	<1	<0.01
	1-octanol and 1,2-dimethoxyethane [a]	14	1.84

[a] 1:2 v/v, reflux.

Synthesis of octyl isomaltuloside and leucroside using dimethoxyethane as solvent.—The problems of the high viscosity and the lack of solubility might be solved by the use of an inert solvent as is used for the glycosidation of fructose.[12] When 1,2-dimethoxyethane was used as solvent for the synthesis of octyl isomaltulosides, the reaction rate increased substantially and the yield of isomaltulosides was already 10% after 35 min. Apparently, some dissolution synergy plays a role. Unfortunately the yield after 7 h was only 25% and decreased subsequently because of the formation of di-isomaltulosides.

1,2-Dimethoxyethane was also used as solvent for the synthesis of octyl leucroside, but in this experiment no product was formed. This is caused by the low dissolution rate and solubility of leucrose in the reaction mixture (see Table 2). Moreover the reaction temperature is only 83 °C which is apparently too low for the protonation and dehydration of the pyranosidic fructose moiety in leucrose (cf. the reaction of leucrose with ethanol).

Synthesis of alkyl leucrosides under pressure.—To solve the problem of the too low reaction temperature for the synthesis of short chain alkyl leucrosides, the boiling point of the alcohol can simply be enhanced by increasing the pressure. When methanol and leucrose were reacted at a temperature of 120 °C and a pressure of 0.42 MPa, the yield of methyl leucroside was 90%.

A reaction of leucrose and 1-octanol in 1,2-dimethoxyethane was carried out at 120 °C and a pressure of 0.18 MPa. The yield of octyl leucroside was only 5% after 24 h, indicating that the low dissolution rate and/or solubility of leucrose in dimethoxyethane is the major obstacle in this case.

4. Conclusion

MCM-41 can be used as catalyst for the glycosidation of three fructose-containing disaccharides without hydrolysis of the glycosidic bond. The catalyst is not effective at low temperatures, but at temperatures > 95 °C yields of 80–99% can be obtained.

The yields of the octyl disaccharides are higher when a trans-acetalation is used while the use of an inert solvent only improves the reaction rate when the boiling point is high enough for the reaction to proceed and the disaccharide has a sufficient solubility.

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References

1. Corma, A.; Iborra, S. In *Fine Chemicals through Heterogeneous Catalysis*; Sheldon, R. A.; van Bekkum, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 257–274.
2. Fischer, E. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400–2412.
3. Brochette, S.; Descotes, G.; Bouchu, A.; Queneau, Y.; Monnier, Y.; Petrier, C. *J. Mol. Catal. A* **1997**, *123*, 123–130.
4. Chapat, J. F.; Finiels, A.; Joffre, J.; Moreau, C. *J. Catal.* **1999**, *185*, 445–453.
5. Camblor, M. A.; Corma, A.; Iborra, S.; Miguel, S.; Primo, J.; Valencia, S. *J. Catal.* **1997**, *172*, 76–84.
6. Straathof, A. J. J.; van Bekkum, H.; Kieboom, A. P. G. *Starch/Stärke* **1988**, *40*, 229–234.
7. (a) *Alkyl Polyglycosides*: Hill, K.; Rybinski, W. von; Stoll, G. Eds.; VCH, Weinheim, 1997;
(b) von Rybinski, W.; Hill, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 1328–1345.
8. van Rantwijk, F.; Woudenberg-van Oosterom, M.; Sheldon, R. A. *J. Mol. Catal. B: Enzym.* **1999**, *6*, 511–532.
9. de Goede, A. T. J. W.; van Rantwijk, F.; van Bekkum, H. *Starch/Stärke* **1995**, *47*, 233–237.
10. de Goede, A. T. J. W.; van Deurzen, M. P. J.; van der Leij, I. G.; van der Heijden, A. M.; Baas, J. M. A.; van

Rantwijk, F.; van Bekkum, H. *J. Carbohydr. Chem.* **1999**, *18*, 131–147.
11. de Goede, A. T. J. W.; van der Leij, I. G.; van der Heijden, A. M.; van Rantwijk, F.; van Bekkum, H. WO 96/36640, 1996.
12. van der Heijden, A. M.; van Rantwijk, F.; van Bekkum, H. *J. Carbohydr. Chem.* **1999**, *18*, 131–147.
13. Schiweck, H.; Munir, M.; Rapp, K. M.; Schneider, B.; Vogel, M. In *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed.; VCH: Weinheim, 1991; pp 57–94.
14. Schwengers, D. In *Carbohydrates as Organic Raw Materials*; Lichtenthaler, F. W., Ed.; VCH: Weinheim, 1991; pp 183–195.