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Catalyst-Free Synthesis of Alkylpolyglycosides Induced by High-Frequency Ultrasound

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The irradiation of concentrated feeds of carbohydrates in alcoholic solution by high-frequency ultrasound (550 kHz) induces the formation of alkylpolyglycosides (APGs). This work is distinct from previous reports in that it does not involve any (bio)catalyst or activating agent, it takes place at only 40 °C, thus avoiding degradation of carbohydrates, and it selectively yields APGs with a degree of polymerization in a window of 2–7, an important limitation of the popular Fischer glycosylation. This ultrasound-based technology proved successful with a range of different valuable carbohydrates and alkyl alcohols. The elucidation of the structure of all the produced glycosides strongly suggests that 1,6-anhydrosugars formed in situ are key intermediate species.

Alkylpolyglycosides (APG) are chemicals of utmost importance with applications in cosmetics, food, pharmaceutical, and detergents industries.[1] APGs are used as bio-based hydrotropes or surfactants, depending on the nature of the alkyl alcohol,[2] and also serve as bio-based building blocks in the manufacture of more complex chemicals.[3] Industrially, APGs are produced by the acid-catalyzed Fischer glycosylation of carbohydrates with alkyl alcohols,[4] which results in a mixture of different glycosides, owing to partial monosaccharide oligomerization. APGs may also contain reducing oligosaccharides, their proportion depending on the reaction conditions. On average, APGs have one alkyl chain per 1.1–1.5 glucose units. Increasing the degree of polymerization (DP) of APGs to 2–8 is of huge interest, since it enables (i) an increase in the solubility of APGs in water at ambient temperature and (ii) improvement of their physicochemical properties, including their biocompatibility, thus upgrading their global performances.[5] Unfortunately, increasing the DP of APGs to 2–8 is currently not feasible by the traditional Fischer glycosylation reaction. So far, APGs with a DP > 2 were successfully obtained by enzymatic reactions but the high cost of enzymes and low space-time yield represent important limitations.[6] Finding an alternative technology to produce APGs with a DP of 2–8 and high space-time yield is an important scientific challenge, which we address herein.

Ultrasound, which has in the past been employed for echography, surface cleaning, welding, and telemetry, is now attracting growing interest as a clean energy activation technology among the organic chemistry community; the term *sonochemistry* has thus been coined.[7] The implosion of cavitation bubbles generated by ultrasound locally induces high temperatures (up to 5000 K), pressures (up to 1000 bar), shockwaves, microjets (up to 100 m s^{-1}), radical formations, and solvated electrons.[8] In contrast to the popular low-frequency ultrasound (20–80 kHz), which mainly induces physical effects,[9] sonication at high frequency (> 150 kHz) produces large quantities of small-sized cavitation bubbles and their implosion releases enough energy to break chemical bonds.[10] For instance, the homolytic cleavage of molecular oxygen inside the collapsing bubble was proven feasible at high ultrasonic frequency.[11]

To date, high-frequency ultrasound (HFUS) has been essentially employed for the total catalyst-free oxidation of aqueous pollutants at low concentrations.[12] The mechanism involves several reaction pathways, such as pyrolysis inside the cavitation bubbles and hydroxyl radical-mediated reactions. Pyrolysis of methane and polymers mediated by HFUS has also been reported.[13]

Until now, the energy released on implosion of cavitation bubbles created by HFUS has been scarcely used for the synthesis of specialty chemicals. The effect of HFUS (611 kHz) on the rate of cellulose enzymatic hydrolysis has been reported previously, but with only a minor improvement in comparison to the silent conditions.[14] Very recently, we reported that diluted feeds of hexoses were selectively oxidized to uronic acids (up to 94% yield) at room temperature under HFUS irradiation (550 kHz), thanks to the in situ sonolysis of water, generating HO$^{\bullet}$ and HOO$^{\bullet}$ radical species.[15]

Herein we report that, in alcoholic media, HFUS selectively activates the anomeric position of unprotected carbohydrates at only 40 °C, without assistance of any catalyst or activating agent, resulting in the quantitative formation of APGs with DPs

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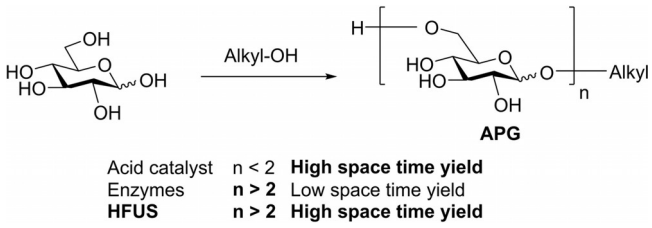

Scheme 1. Contribution of the present work: case of glucose.

of 2–7, together with a space-time yield up to 876 kg m^{-3} h^{-1} (Scheme 1).

A concentrated methanolic solution of mannose (40 wt%) was subjected to ultrasonic irradiation at 550 kHz (0.44 W L^{-1}, cup horn system) under air, and maintained at 40 °C (see the Supporting Information, Figure S1). At this concentration, mannose was not soluble in methanol but progressively dissolved during the reaction. Conversions and yields were determined by HPLC and size-exclusion chromatography (SEC). After 3 h of irradiation, 81% of mannose was consumed and formation of molecules with a high molecular weight was observed by SEC (Figure 1). After the removal of methanol under reduced pressure, the as-obtained crude product was completely soluble in water at ambient temperature. Analysis by electrospray ionization mass spectrometry (ESI-MS) confirmed the formation of APGs, with a degree of polymerization (DP) ranging from 1 to 12 (average DP = 7), as measured by SEC. No peak stemming from mannose oxidation was detected, either by ESI-MS or by ^{13}C NMR spectroscopy, indicating that anhydromannosyl units were not chemically damaged during the HFUS irradiation (Figures S2 and S3). The recovered mass of APGs corresponded to 97% of the amount of mannose initially introduced into the reactor, confirming that no gaseous products were formed.

Analysis of the monosaccharide fraction confirmed the glycosylation reaction (Figure S4). In addition to unreacted mannose (19%), methyl mannosides (MeMan) and 1,6-anhydromannoses accounted for 39% of the product mass. α/β-MeMan represented over 95% of this fraction (i.e., 37% yield; Table 1, entry 1), with 1,6-anhydromannoses (pyranose/furanose ratio = 6.4) formed as minor components (2% yield). Overall, the pyranose derivatives were the major products (pyranose/furanose ratio = 7:1) as well as the α-anomer (α/β ratios = 4.6:1 and 3.6:1 for the pyranose and furanose forms, respectively; Figure S5). Importantly, no product incorporating a methoxy group at a position other than the anomeric one was observed, supporting a selective activation of the anomeric position of mannose by HFUS.

Table 1. Impact of the experimental parameters on the HFUS efficiency.[a]

Entry	T [°C]	Mannose conc. [wt%]	Gas	Mannose conv. [%]	Yield [%] 1,6-anhydro-mannose	MeMan	Me-alkylpoly-mannoside[b]
1	40	40	air	81	2	37	42
2	20	40	air	58	1	26	31
3	0	40	air	6	0	2	4
4	40	40	Ar	70	1	35	34
5	40	40	O_2	50	0	21	29
6	40	80	air	73	1	6	66

[a] Ultrasonic irradiation at 550 kHz for 3 h. (0.44 W L^{-1}). [b] DP ≥ 2; also includes terminal free oligomannosides.

The disaccharide fraction accounted for 12% of the product mass, with an estimated Me(Man)$_2$/Man$_2$ ratio of 1.9:1, similar to the MeMan/Man ratio (2:1) found in the monosaccharide fraction (Figure S6). APGs with a DP higher than 3 represented the largest fraction (30% of the product mass) and the overall yield of APGs with a DP ≥ 2 was 42% (Table 1, entry 1).

All types of glycosidic linkages, namely (1→2), (1→3), (1→4), (1→5) and (1→6), were formed between mannosyl units. The (1→6) linkages, with the primary hydroxy as the acceptor, were formed preferentially (39% of the linear units; Figure 2). The proportion of glycosidic linkages involving secondary alco-

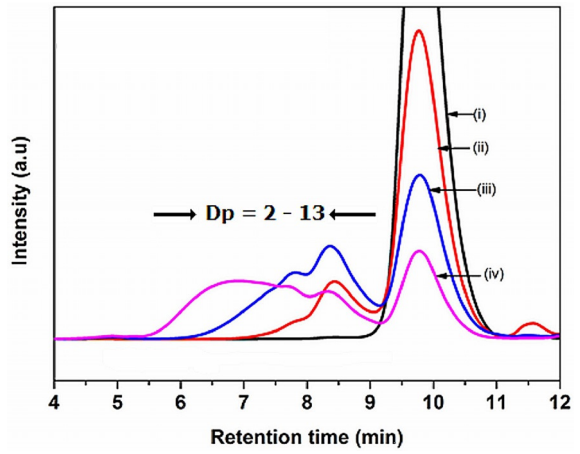

Figure 1. Monitoring of the reaction progress by HPLC-SEC (40 wt% of mannose in methanol, 40 °C, 550 kHz). i) Standard mannose; ii) t = 1 h; iii) t = 2 h; iv) t = 3 h.

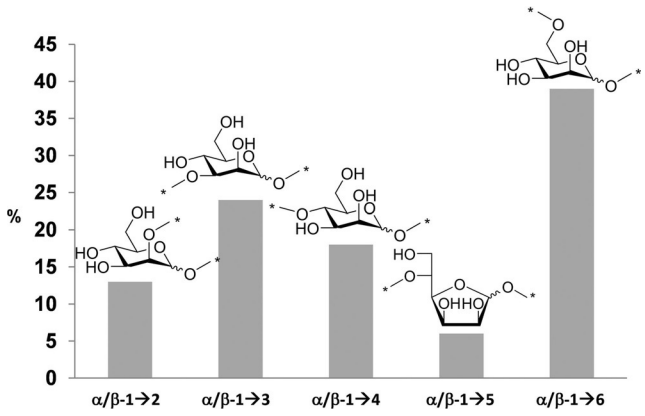

Figure 2. Relative proportions of the substitution patterns in linear regions of the product obtained after HFUS irradiation of D-mannopyranose in methanol. For the sake of clarity, only the pyranoside form was represented except for the 1,5 linkage, which implies the furanoside form.

hols was also significant [13, 24, 18, and 6% of (1→2), (1→3), (1→4), (1→5) glycosidic linkages, respectively]. Peaks corresponding to [(1→6),(1→2)]-, [(1→6),(1→3)]- and [(1→6),(1→4)]-branched di-*O*-substituted mannosyl units were also observed. Overall, 15% of the mannosyl units were branched. A general structure of the as-obtained APGs is presented in Figure S7. Although no further evidence about the stereochemistry of the glycosidic bonds present in the higher DP fraction was obtained, it seems reasonable to assume that the α/β ratio for these glycosidic linkages will be close to that determined for MeMan, that is, about 7:1.[16] No other linkage than glycosidic bonds was observed, indicating that the oligomannoside chain grows exclusively through the anomeric position.

Lowering the temperature from 40 °C to 20 °C and 0 °C decreased the conversion of mannose from 81% to 51% and 6%, respectively, but without any change in the reaction selectivity (Table 1, entries 1–3). Additionally, the nature of the gas used impacted the rate of the reaction, presumably by affecting the cavitation phenomenon as previously reported in other applications (Table 1, entries 1, 4, and 5).[17] For instance, after 3 h, the conversion of mannose was decreased from 81% under air to 70% and 50% under bubbling of Ar and O_2, respectively.

Pleasingly, the concentration of mannose in methanol could be increased to 80 wt% (Table 1, entry 6). Under these conditions, 73% conversion of mannose was obtained without altering the selectivity to APGs, affording an unprecedented space-time yield of 876 kg m^{-3} h^{-1}. The chemical composition of APGs was also favorably impacted, with the formation of a higher proportion of APGs with DP 2–7 (66% yield).

The scope of the HFUS technology was then assessed with glucose and xylose, two important sugars used in industry (Table 2). Under standard conditions (3 h of ultrasonic irradiation at 550 kHz), 40% of glucose and 65% of xylose were converted into APGs (average DP = 2) and alkylpolyxylosides (APXs; average DP = 3), respectively. The conversions were improved to 82 and 86%, respectively, by increasing the reaction time to 6 h. Further ESI-MS and GC analyses confirmed that methylation also occurred exclusively at the anomeric position in both cases.

Table 2. Application of the HFUS process to different monosaccharides.[a]

Entry	Sugar	Conv. [%]	DP	Glycosidic linkages [%]			
				1→6	1→4	1→3	1→2
1	mannose	81	7	52	16	19	13
2	glucose	40	2	53	16	21	10
3	xylose	65	3	–	80	20	–

[a] Ultrasonic irradiation at 550 kHz (0.44 W L^{-1}) for 3 h at 40 °C. Concentration of carbohydrate in alcoholic solution = 40 wt%.

Analysis of the monosaccharide fraction of APGs obtained from glucose indicated that methyl glucopyranosides were the major component (99%, α/β ratio = 1.5:1); the remaining 1% was 1,6-anhydro-α/β-D-glucopyranoside. Similar to mannose, α/β (1→6) glycosidic linkages were preferentially formed (53%), followed by (1→3) (21%), (1→4) (16%), and (1→2) (10%) linkages (Table 2, entry 2). For APXs, the monosaccharide fraction analysis revealed the formation of methyl xylopyranosides (α/β ratio = 1:1) and xylofuranosides (α/β ratio = 1:10) in a 10:1 ratio. In APXs, branched units represented less than 1% and the (1→4) glycosidic linkages accounted for 80% of glycosidic bonds followed by the (1→3) linkage (20%; Table 2, entry 3).

Various other alkyl alcohols, including ethanol, *n*-propanol and *n*-butanol, were also tested with mannose (Table 3) and all led to the selective formation of APGs. In ethanol, *n*-propanol and *n*-butanol, mannose conversions were 70, 66, and 87%, respectively, and no other products than APGs were detected. When moving to *n*-dodecanol, the reaction failed, owing to the low solubility of mannose in this fatty alcohol. Notably, amphiphilic APGs could be produced by transglycosylation of butylpolyglycosides with *n*-dodecanol under HFUS irradiation, yielding amphiphilic APGs with 20% yield and an average DP of 2 (see the Supporting Information).

Table 3. Application of the HFUS process to different alkyl alcohols.[a]

Entry	Carbohydrate	Alkyl alcohol	Conv. [%]	Average DP[b]
1	mannose	ethanol	70	3
2	mannose	*n*-propanol	66	3
3	mannose	*n*-butanol	87	4

[a] Ultrasonic irradiation at 550 kHz (0.44 W L^{-1}) for 3 h at 40 °C. Concentration of carbohydrate in alcoholic solution = 40 wt%. [b] Measured by SEC.

Analysis of mannose-derived APGs by MALDI-TOF revealed, in addition to the expected peaks for APG pseudomolecular ions, the presence of a minor series of oligomannosides that was tentatively attributed to the formation of oligomannosides incorporating a terminal 1,6-anhydrosugar unit at the reducing end (Figure S8). Together with the detection of 1,6-anhydromannose in the monosaccharide fraction, these data strongly suggest that 1,6-anhydromannose and its mannosylated derivatives are key intermediate species in this HFUS process. To test these findings, commercially available 1,6-anhydroglucose, the C2 epimer of 1,6-anhydromannose, was subjected to HFUS irradiation under the reaction conditions mentioned in Table 1, entry 1, leading to APGs with a chemical composition similar to that obtained from glucose (Figure S9).

To determine the electronic nature of the process, 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), a radical scavenger, was added into the methanolic solution of mannose during HFUS irradiation. A complete inhibition of the reaction was observed, suggesting a radical mechanism. Analysis of the reaction mixture by electron paramagnetic resonance (EPR) spectroscopy using the spin trap procedure with DMPO confirmed the formation of a $CH_3O^{\bullet}$ radical with typical coupling constants of 1.36 mT (A_N), 0.79 mT G ($A_{H\beta}$) and 0.15 mT ($A_{H\gamma}$; Figures S10 and S11). No formation of DMPO–H, the pendent adduct of DMPO–OCH_3, was observed, which is not surprising given its poor stability.[18] Other radical species, presumably derived

from mannose, were also trapped with DMPO. Unfortunately, elucidation of their precise structures was beyond the possibilities of this technique (Figure S12).

From these data, the HFUS-assisted synthesis of APGs is proposed to occur via a radical mechanism leading to the formation of anhydrosugars, which next polymerize, as also observed in the pyrolysis of biomass.[19] The polymer chain growth might then be terminated by reaction with methanol, which is dissociated to give $CH_3O^{\bullet}$ and $H^{\bullet}$ radicals under HFUS. In methanol, the activation energy for the conversion of glucose to levoglucosan is 37 kcal mol^{-1},[17] a level of energy that can be easily obtained by HFUS.[20] When the reaction was performed under silent conditions or by using low frequency ultrasound (20 kHz), no reaction occurred, further highlighting the groundbreaking nature of HFUS for the synthesis of APGs.

Our attempts to reach a conversion higher than 81% and DPs higher than 10, in particular by prolonging the sonication time, failed, suggesting that in situ-released water may hydrolyze APGs. To test this claim, the as-obtained oligomannosides were subjected to HFUS irradiation in neat water. Under these conditions, oligomannosides were hydrolyzed to a large extent, demonstrating the reversible nature of the reaction in the presence of water under the action of HFUS irradiation.

In conclusion, we have shown that the anomeric position of unprotected mannose, glucose, or xylose, can be selectively activated at only 40 °C by HFUS in an alcoholic solution, without need for any catalyst or activating agent, leading to the selective formation of APGs. Conversely to the classical Fischer glycosylation, water soluble APGs with average DPs of 2–7 were obtained, thus addressing significant unmet needs. Importantly, the absence of catalyst or activating agent and the possibility to convert highly concentrated feeds of carbohydrates (up to 80 wt%) with this technology is of high interest as regards reactor productivity (up to 876 kg m^{-3} h^{-1}) and workup procedures. The transposition of this process to cellulose, which would open an access to APGs from a non-edible source of sugar, is now the topic of investigation in our group and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylpolyglycosides · carbohydrates · glycosylation · surfactants · ultrasound

[1] R. Eskuchen, M. Nitsche in *Alkyl Polyglycosides: Technology, Properties and Applications* (Eds.: K. Hill, W. von Rybinski, G. Stoll), Wiley-VCH, Weinheim, **1997**, Chapter 2.
[2] I. Johansson, C. Strandberg, B. Karlsson, G. Karlsson, K. Hammarstrand in *Progress in Colloid and Polymer Science, vol 116: Surface and Colloid Science* (Eds.: V. Razumas, B. Lindman, T. Nylander), Springer, Heidelberg, **2000**, pp. 26–32.
[3] V. Kren, L. Martínková, *Curr. Med. Chem.* **2001**, *8*, 1303–1328.
[4] a) W. von Rybinski, K. Hill, *Angew. Chem. Int. Ed.* **1998**, *37*, 1328–1345; *Angew. Chem.* **1998**, *110*, 1394–1412; b) *Nonionic Surfactants: Alkyl Polyglucosides* (Eds.: D. Balzer, H. Lüders), CRC Press, Boca Raton, FL, **2000**.
[5] a) C. A. Ericsson, L. C. Ericsson, V. Kocherbitov, O. Söderman, S. Ulvenlund, *Phys. Chem. Chem. Phys.* **2005**, *7*, 2970–2977; b) S. Ulvenlund, M. Andersson, P. Adlercreutz, M. Viloria-Cols, N. Barchan, T. Halthur, C. Salomonsson, *Household Pers. Care Today* **2016**, *2*, 03/04.
[6] a) D. Svensson, S. Ulvenlund, P. Adlercreutz, *Biotechnol. Bioeng.* **2009**, *104*, 854–861; b) U. Ackelid, M. Svensson in *Proceedings of Materials Science and Technology Conference*, Pittsburgh, PA, USA, **2009**, Vol. 2529.
[7] a) D. R. Raichel, *The Science and Applications of Acoustics*, Springer, Heidelberg, **2006**; b) *Synthetic Organic Sonochemistry* (Eds.: H. Fillion, J. Luche), Plenum Press, New York, NY, **1998**; c) G. Cravotto, E. C. Gaudino, P. Cintas, *Chem. Soc. Rev.* **2013**, *42*, 7521–7534.
[8] a) T. J. Mason, D. Peters, *Practical Sonochemistry: Power Ultrasound Uses and Applications*, Woodhead Publishing, Cambridge, **2002**; b) G. Chatel, *Sonochemistry: New Opportunities for Green Chemistry*, World Scientific, Singapore, **2016**.
[9] *Advances in Sonochemistry, Vol. 4* (T. J. Mason), Elsevier, Amsterdam, **1996**.
[10] a) K. S. Suslick, Y. Didenko, M. M. Fang, T. Hyeon, K. J. Kolbeck, W. B. McNamara, M. M. Mdleleni, M. Wong, *Philos. Trans. R. Soc. London Ser. A* **1999**, *357*, 335–353; b) T. Leong, M. Ashokkumar, S. Kentish, *Acoust. Aust.* **2011**, *39*, 54–63; c) D. Kirpalani, K. McQuinn, *Ultrason. Sonochem.* **2006**, *13*, 1–5; d) S. I. Nikitenko, R. Pflieger, *Ultrason. Sonochem.* **2017**, *35*, 623–630.
[11] a) B. Babgi, M. Zhou, M. Aksu, Y. Alghamdi, M. Ashokkumar, *Ultrason. Sonochem.* **2016**, *29*, 55–59; b) R. Pflieger, T. Chave, G. Vite, L. Jouve, S. I. Nikitenko, *Ultrason. Sonochem.* **2015**, *26*, 169–175.
[12] a) H. Hao, M. Wu, Y. Chen, Y. Yin, Z. Lü, *Environ. Toxicol.* **2003**, *18*, 413–417; b) T. Y. Wu, N. Guo, C. Y. Teh, J. X. W. Hay, *Advances in Ultrasound Technology for Environmental Remediation*, Springer, Heidelberg, **2012**.
[13] A. Henglein, *Ultrason. Sonochem.* **1995**, *2*, S115–S121.
[14] Y. G. Adewuyi, V. G. Deshmane, *Energy Fuels* **2015**, *29*, 4998–5006.
[15] P. N. Amaniampong, A. Karam, Q. T. Trinh, K. Xu, H. Hirao, F. Jérôme, G. Chatel, *Sci. Rep.* **2017**, *7*, 40650.
[16] R. Das, B. Mukhopadhyay, *ChemistryOpen* **2016**, *5*, 401–433.
[17] A. Henglein, *Ber. Bunsen-Ges.* **1989**, *93*, 1150–1151.
[18] Z. Wei, F. A. Villamena, L. K. Weavers, *Environ. Sci. Technol.* **2017**, *51*, 3410–3417.
[19] a) D. Mohan, C. U. Pittman, P. H. Steele, *Energy Fuels* **2006**, *20*, 848–889; b) F.-X. Collard, J. Blin, *Renewable Sustainable Energy* **2014**, *38*, 594–608; c) L. Chen, J. Zhao, S. Pradhan, B. E. Brinson, G. E. Scuseria, Z. C. Zhang, M. S. Wong, *Green Chem.* **2016**, *18*, 5438–5447.
[20] a) Y. T. Didenko, K. S. Suslick, *Nature* **2002**, *418*, 394–397; b) G. Mark, A. Tauber, R. Laupert, H.-P. Schuchmann, D. Schulz, A. Mues, C. von Sonntag, *Ultrason. Sonochem.* **1998**, *5*, 41–52.

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