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Synthesis of 2-Hydroxydodecyl Starch Ethers: Importance of the Purification Process

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Abstract: 2-hydroxydodecyl starch ethers were synthesized by reaction of 1,2-epoxydodecane with potato starch in aqueous alkaline medium. A careful attention has been given to the purification steps and more precisely to the identification and the quantification of the impurities. The purification by Soxhlet extraction compared to the process by grinding required less steps but a longer time. The values of the MS were always around 1.1, but the recovery yields were higher for the treatment by grinding compared to Soxhlet (85% vs 63%).

Keywords: Aqueous medium; Etherification; Starch modification

1. INTRODUCTION

Starch is one of the most abundant polysaccharides on earth and is found in cereals (wheat, corn, rice), legumes (pea) and tuber (potato, cassava) as semi-crystalline granules.^{1,2} It is mainly composed of two polymers of D-glucose, which are amylose and amylopectin. The former is mainly linear with α -1,4 bonds while the latter is branched with 5% of α -1,6 bonds. Starch has been widely used in its native form (*i.e.* not chemically modified) or physically modified mainly for food applications.^{1, 3-5} Starch derivatives have been developed to overcome some drawbacks of native starch used in food such as gel texture, retrogradation or syneresis. Such derivatives included starch esters (mainly phosphate, acetate and octenyl succinate),⁶⁻⁸ starch ethers (mainly hydroxyethyl, hydroxypropyl or carboxymethyl),⁹⁻¹¹ reticulated starch⁷ and combination of these derivatizations.^{4,7,12-18} Due to the nature of the reagent that is employed and the used conditions, the granular structure of starch was usually preserved and the purification steps are fairly easy to proceed, the modified starch staying in suspension and thus being easily recovered by filtration.^{1,9,10,19} Other methods including dry or semi-dry reactions^{20,21} and reactions in a medium where the starch did not swell (typically alcohols like ethanol or isopropanol, acetone or mixture of these solvents with water)^{22,23} led to a higher degree of substitution.¹ The synthesis of starch esters and ethers of high degree of functionalization and with different alkyl chain length allowed the obtainment of mechanical and thermal properties suitable for a plastic use²⁴⁻³⁰ but also implies the loss of the granular structure.¹ Purification process in that case was hindered due to the paste-like structure of the crude material and the difficulty of filtration of the product. Purification usually implied the use of mechanical energy to break the crude (like grinding or blending) or the dissolution in an appropriate solvent followed by precipitation. Works around starch etherification

mainly concerned short chains where the granular structure was kept intact. Nevertheless, some publications described experiments with gelatinized/destructured starch and fatty epoxides in DMSO^{30,31} or in water.^{28,29,32} More precisely, in 2001 the groups of Lindhauer and Warwel simultaneously described the production of higher starch ethers in an aqueous alkaline medium with 2-hydroxyalkyl chains possessing 8 to 18 carbons.^{28,29} The experimental conditions were relatively similar but the group of Warwel used in addition sodium sulfate as co-catalyst. Compared to the classical processes performed in organic solvent, water was considered as green solvent leading these two processes to ecological favorable experimental conditions. In both cases, the starch ethers were recovered by several washings in water and organic solvents (ethanol, isohexane or diethyl ether) or by Soxhlet extraction with petroleum ether. Nevertheless, there were no details on the purification conditions and on the nature of the impurities. In this context, we described in this article two detailed methods for the purification of 2-hydroxydodecyl potato starch ethers synthesized using alkaline conditions in water. 1,2-epoxydodecane was chosen for its industrial availability and its low price. In addition, to limit the quantity of co-products and so to reduce the environmental impact, the workup without sodium sulfate issued from the publication of Lindhauer was chosen. A special attention has been given to the optimisation of the purification conditions in order to facilitate this complicated step. That is why the impurities extracted from the medium were, as far as possible, quantified and identified.

2. MATERIALS AND METHODS

2.1 Materials

Potato starch with water content of about 16% was kindly supplied by Roquette Frères SA, Lestrem, France. 1,2-epoxydodecane (90% of purity) and potassium hydroxide (85% of purity; 15% w/w of water) were obtained from Aldrich and Merck respectively. Petroleum ether (boiling point: 40-60°C (> 90%)) and ethanol (99% of purity) were purchased from Aldrich and were used as supplied without further purification.

2.2 Synthesis of starch hydroxydodecyl ethers

To a suspension of potato starch (2.14 g of starch containing 16% (w/w) of water *i.e.* 11.1 mmol of anhydroglucose unit (AGU)) in water (4.0 g) in a 25 mL autoclave with a mechanical stirring, potassium hydroxide (0.58 g of potash containing 15% (w/w) of water *i.e.* 8.9 mmol, 0.8 eq. mol/AGU) dissolved in water (0.9 g), was added at room temperature (Figure 1).

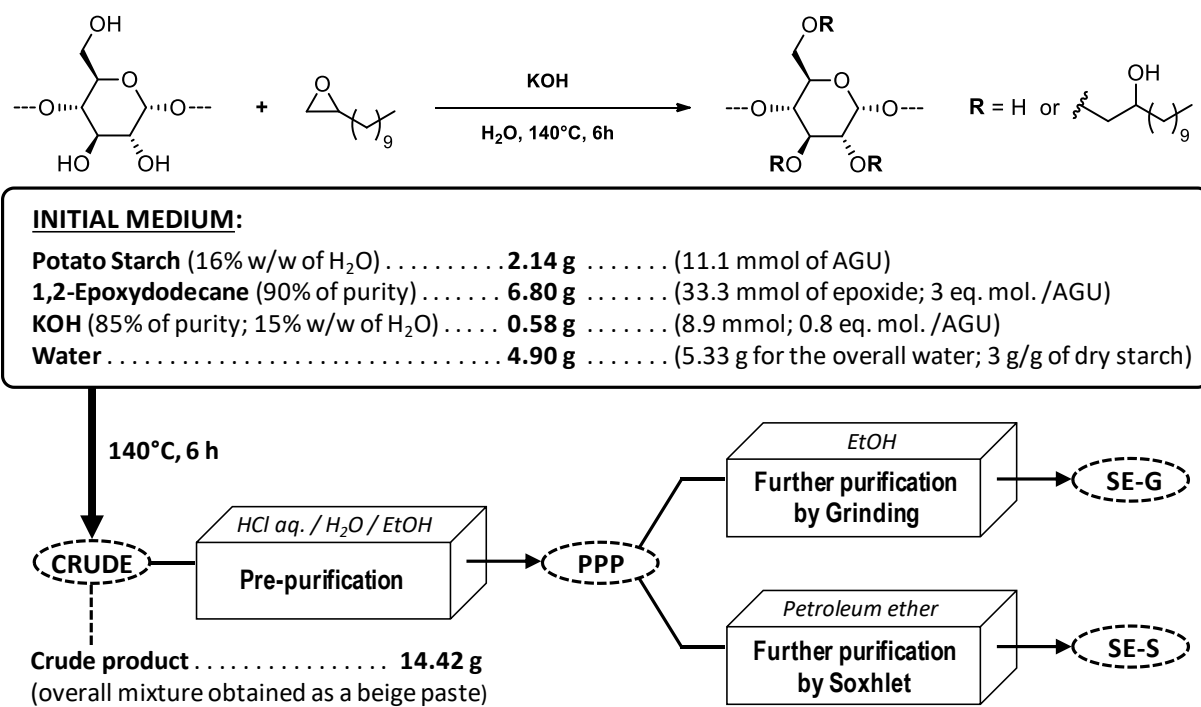


Figure 1: 2-hydroxydodecylstarch synthesis and purification modes conducted after etherification (**CRUDE**: crude product; **PPP**: Pre-Purified Product, *i.e.* prepurified starch ether; **SE-G**: Starch Ether purified by Grinding; **SE-S**: Starch Ether purified by Soxhlet).

The thick and clear starch gel obtained was stirred for 15 minutes. To this gel was added the 1,2-epoxydodecane (6.80 g, purity (90%), 33.3 mmol, 3 eq. mol/AGU). The autoclave was closed and the medium was then heated at 140°C for 6h under stirring. At the end of the reaction, the autoclave was cooled down to room temperature. The solid reaction product (a beige pasty crude product named crude) was extracted from the autoclave. Note that no liquid phase was present. As described in detail afterwards in this publication, the isolation of the starch product was performed by the following procedures (Figure 1). Pre-purification steps were done on the crude product by several washings by a mixture of water/ethanol (1/2). The product purified by this pre-purification

step was named **PPP** (pre-purified product). After this step, the remaining solid was purified either by grinding in ethanol or by Soxhlet in petroleum ether. The products purified by Soxhlet or grinding were named **SE-S** (Starch Ether – Soxhlet) and **SE-G** (Starch Ether – Grinding), respectively.

2.3 Characterisation

Elemental analysis was used to determine the molar substitution (MS) of the product and was carried out on a Thermo Scientific FlashEA 1112. The samples were oven-dried at 100°C for 24h before the analysis to remove water.

NMR analyses were recorded on a Bruker DPX300 Avance spectrometer. ¹H-NMR and ¹³C-NMR analysis were recorded at 25°C at 300.13 MHz and at 75.5 MHz respectively. The sample was dissolved in an appropriate solvent (CDCl₃ or DMSO-d₆, purchased from Eurisotop (99.5% and 99.8% of isotopic purity, respectively)).

Infrared spectra were recorded on a Bruker Vector 22 FTIR spectrometer with a diamond/Zr crystal under attenuated total reflectance. The spectra were recorded by the accumulation of 100 scans between 700 and 4000 cm⁻¹ at a resolution of 4 cm⁻¹.

MALDI-TOF spectra were realized with a Bruker Daltonics Ultraflex II spectrometer in the positive reflectron mode.

3. RESULTS AND DISCUSSION

2-Hydroxydodecyl ethers of starch were synthesized from potato starch and 1,2-epoxydodecane in alkaline medium. The isolation of starch products was performed in two steps: (i) a pre-purification procedure followed by a purification by grinding in ethanol or by Soxhlet in petroleum ether.

The pre-purification procedure of the crude was performed as described in the Figure 2.

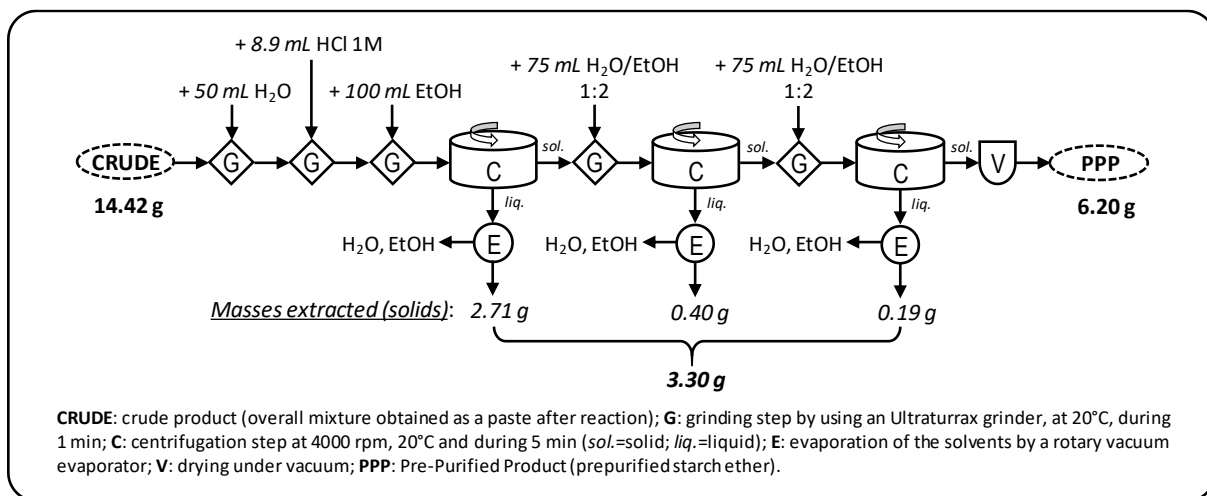


Figure 2: Pre-purification steps of the 2-hydroxydodecylstarch from the crude reaction product obtained in the 2-hydroxydodecylstarch synthesis.

This step consisted in neutralising the alkaline medium with aqueous HCl solution and then to remove the created potassium chloride. The crude extracted from the autoclave (14.42 g) was put in 50 mL of water and grinded by the mean of an Ultra-Turrax® (1 min) until only small particles could be observed. The alkaline medium was neutralized with 1 M aqueous hydrochloric acid under stirring by an Ultra-Turrax® (1 min). 100 mL of ethanol was then added (giving a ratio 1:1

to water). This mixture of water/ethanol (1/2) was used to solubilize KCl and the potential organic impurities. The suspension was grinded for 1 min by Ultra-Turrax® and centrifuged. The solid and liquid phases were separated by centrifugation. The liquid phase containing impurities was evaporated for identification and a mass of 2.71 g was extracted. The solid phase was washed by grinding in 75 mL of a mixture of water/ethanol (1/2) and recovered by centrifugation. This step was repeated once. After evaporation of the two liquid phases, masses of 0.40 g and 0.19 g were extracted. The solid phase recovered after the third centrifugation was dried under vacuum and a **PPP** mass of 6.20 g was obtained. In order to optimize the purification, the three extracted solids obtained during the pre-purification step were analysed. The two first solids contained KCl as demonstrated by formation of a AgCl precipitate by addition of aqueous AgNO₃. So, KCl was extracted during the two first washings. A sample of each solid was dissolved in CDCl₃ and analysed by ¹H NMR (Figure 3).

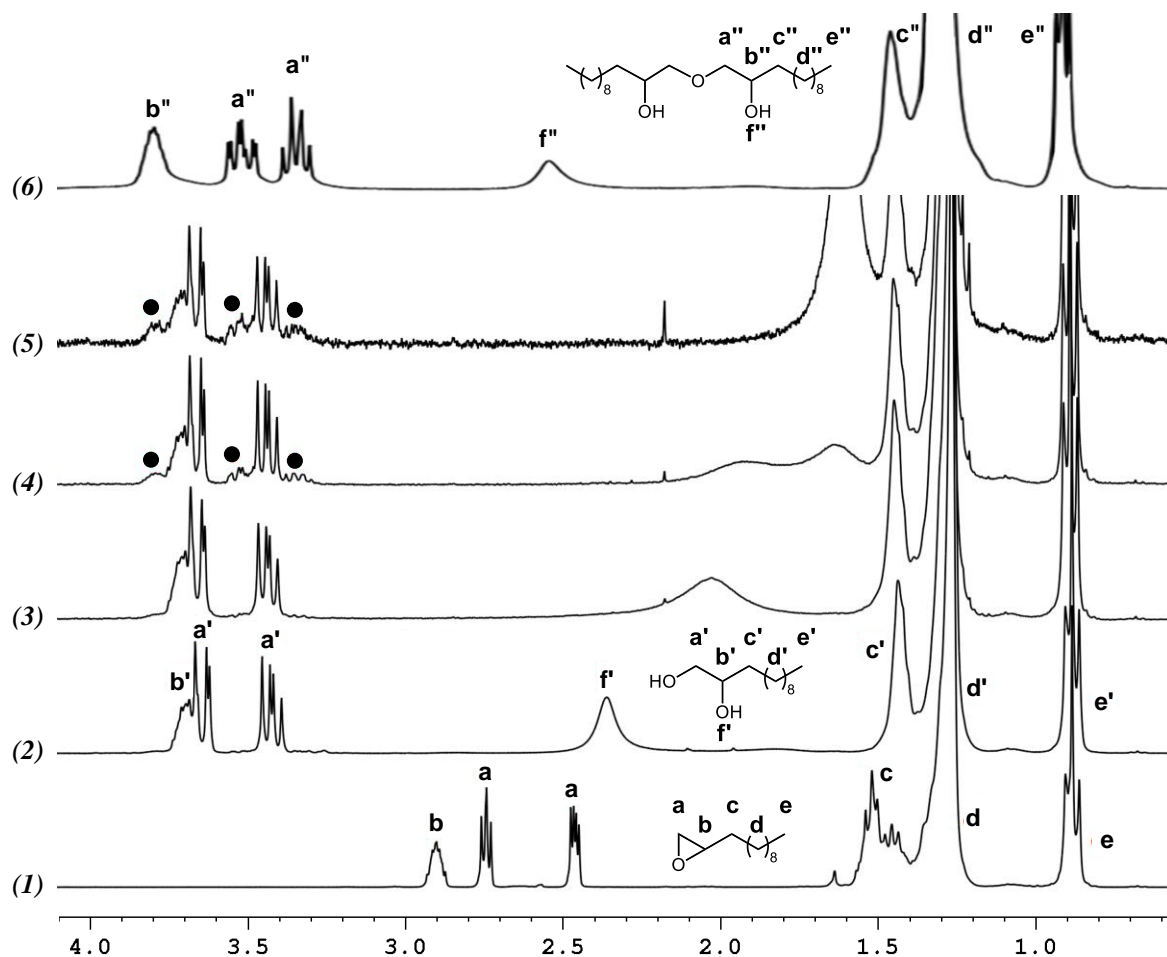


Figure 3: $^1\text{H-NMR}$ spectrum of (1) 1,2-epoxydodecane, (2) 1,2-dodecanediol, (3) first solid issued from the first washing performed during the pre-purification of the crude product, (4) second solid, (5) third solid, (6) bis-(2-hydroxydodecyl)oxide isolated from the combined second and third washings (300 MHz, CDCl_3 , 25°C).

The spectra of 1,2-epoxydodecane and 1,2-dodecanediol were presented as reference (Figure 3, spectra 1 and 2). No traces of 1,2-epoxydodecane was observed in the three filtrates, confirming its total consumption. The presence of 1,2-dodecanediol, as hydrolysis product of the epoxide, was clearly showed in the three filtrates (Figure 3, spectra 3, 4 and 5). However, some peaks in these

spectra did not match with the 1,2-epoxydodecane (black dots on spectra 4 and 5 in Figure 3). To determine the nature of the residual impurities, the solids issued from the washings 2 and 3 were gathered and washed with small quantities of ethanol to remove the 1,2-dodecanediol. Indeed, the solubility of 1,2-dodecanediol in ethanol at 25°C was determined to be 300 g/L. The washing left an insoluble product after solubilisation of 1,2-dodecanediol. This insoluble product was dried, dissolved in CDCl₃ and analysed by ¹H NMR (Figure 3, spectrum 6), ¹³C NMR, 2-dimensional NMR experiments and MALDI-TOF-MS (see supporting information; Figures S1, S2 and S3). Bis-(2-hydroxydodecyl)oxide was clearly identified. This dimer was issued from the reaction of 1,2-dodecanediol on 1,2-epoxydodecane. The symmetry of the obtained oxide was probably due to the preference of the less hindered primary alcohol of 1,2-dodecanediol to attack the less substituted site of the epoxide. It seemed important to notice that this kind of by-product was never reported during the synthesis of 2-hydroxyalkyl starch ethers.

To resume, at the end of the pre-purification steps and after drying under vacuum, **PPP** was recovered ($m(\mathbf{PPP}) = 6.20 \text{ g}$). So, from a crude mass of 14.42 g (containing 5.33 g of an initial mass of water), 6.20 g of **PPP** was obtained by having removed 3.30 g of impurities. The observed enhancement of 0.41 g ($14.42 \text{ g} - 5.33 \text{ g} - 3.30 \text{ g} - 6.20 \text{ g}$) was attributed to the medium neutralisation by KOH (the weight of KOH was replaced by the weight of KCl formed) and to the consumption of water in the formation of 1,2-dodecanediol. **PPP** was not totally soluble in classical NMR solvents preventing analysis. However, when CDCl₃ was added on **PPP**, the NMR analysis clearly showed the presence of soluble impurities such as 1,2-dodecanediol and dimer. In addition, the last purification by the mixture water/ethanol (1/2) allowed to only extract 6% ($=0.19/3.30 \times 100$) of impurities (compared to the values of 82% ($=2.71/3.30 \times 100$) and 12%

(=0.40/3.30x100) extracted during the first and the second washings, respectively). So, the impurities seemed deeply included inside the modified starch and so an enhanced purification was necessary. So, to be further purify, **PPP** was submitted to two different subsequent treatments either by an Ultra-Turrax® apparatus (Grinding) or by a Soxhlet extraction (Soxhlet). The treatment by an Ultra-Turrax® allowed to stir, disperse, homogenize and grind the modified starch in order to remove impurities by further washings. The extraction by Soxhlet allowed to remove impurities from modified starch by repeated washings with an organic solvent at higher temperature. In order to obtain two samples of **PPP** (one for the purification by grinding and another for the purification by Soxhlet; 2 x 6.20 g), the synthesis and the pre-purification steps were performed twice with high reproducibility.

In order to remove the residual impurities, the first choice felt on a purification by further grinding on **PPP**. To find the best solvent to extract the impurities, the solubility of 1,2-dodecanediol and bis-(2-hydroxydodecyl)oxide was determined in various solvents at 25°C (table 1).

Table 1: Solubility of the two impurities in different solvents at 25°C

Solvent	Solubility of 1,2-dodecanediol (g/L)	Solubility of bis-(2-hydroxy-dodecyl)oxide (g/L)
Chloroform	380	150
THF	300	120
Ethanol	300	15 ^a
Isopropanol	160	10
Diethyl ether	70	20
Acetone	40	5
Ethyl acetate	40	5
Heptane	Insoluble	Insoluble
Petroleum ether	Insoluble	Insoluble
Water	Insoluble	Insoluble

^a the solubility of bis-(2-hydroxy-dodecyl)oxide in ethanol at 50°C is equal to 300 g.L⁻¹

According to these results, heptane, petroleum ether or water were inappropriate solvents since the impurities were insoluble. The impurities were only slightly soluble in isopropanol, diethyl ether, acetone or ethyl acetate. The best options appeared to be available for chloroform or THF since both impurities were highly soluble. Unfortunately, the crude product swelled in those solvents and cannot be recovered afterwards, either by filtration or by centrifugation. Ethanol is therefore the best solvent among the remaining solvents to extract these impurities by considering their solubility.

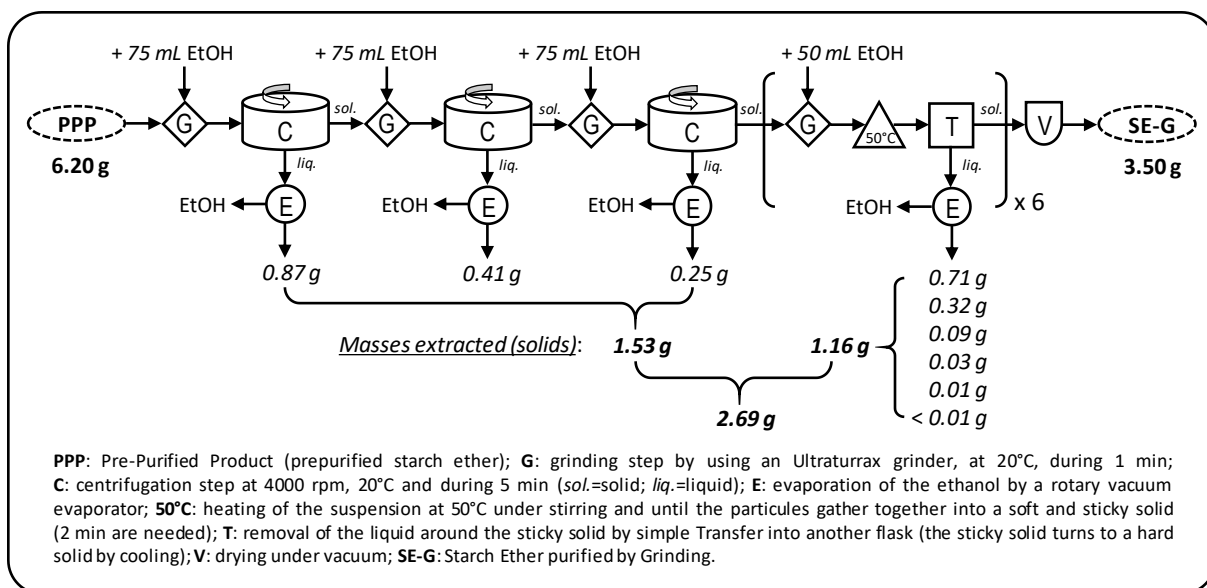


Figure 4: Further washings done by Grindings of the pre-purified product (**PPP**) and leading to a purified 2-hydroxydodecylstarch (**SE-G**) in the 2-hydroxydodecylstarch synthesis.

PPP (6.20 g) was grinded for 1 minute in pure ethanol (75 mL – Figure 4). The solid and the liquid phase were separated by centrifugation. The liquid phase was evaporated and the residual solid (0.87 g) was analysed by $^1\text{H-NMR}$. The presence of 1,2-dodecanediol and bis-(2-hydroxydodecyl)oxide was demonstrated. This procedure was repeated twice and 0.41 g and 0.25 g of residual solids containing 1,2-dodecanediol and bis-(2-hydroxydodecyl)oxide were respectively obtained. At the 3rd extraction, $^1\text{H NMR}$ analysis demonstrated that the dimer was more and more difficult to extract. The dimer has a limited solubility in ethanol at room temperature ($15 \text{ g}\cdot\text{L}^{-1}$) but its solubility in ethanol at 50°C was higher ($300 \text{ g}\cdot\text{L}^{-1}$). Therefore, to extract the remaining impurities, the solid was grinded in 50 mL of ethanol and then the suspension was heated at 50°C under stirring. The solid did not stay in this dispersed form when heating but became soft and sticky. The warm solvent is thus removed by transfer. The product needed to be

cooled down with cold ethanol (50 mL) to make it hard enough to be again grinded. This process was repeated until no impurity was observed in the filtrate (five times). At the end, the final product **SE-G** was obtained after drying under vacuum ($m(\mathbf{SE-G}) = 3.50$ g). Some assays were performed to determine the molar substitution (MS). MS was defined as the molar ratio of 2-hydroxydodecyl substituents to anhydroglucose units of the starch molecules. The first attempts for its determination were realized by NMR but unfortunately this modified starch was not soluble in the traditional solvents (water, chloroform, DMSO, acetone, pyridine, methanol or ethanol) even after being heated for 24h. Hence, the molar substitution was determined by the mean of elemental analysis (Table 2, entry 1- see supporting information). The MS value for **SE-G** was equal to 1.11. A reaction efficiency of 37% and a yield of 85% were also determined. The FT-IR spectra of native starch and **SE-G** were shown in supporting information (Figure S5). The structure of etherified starch was mainly confirmed by the intensity increase of the carbon-hydrogen bonds elongation bands (ν_{C-H}) compared to native starch.

Table 2: Experimental results obtained for the synthesis of 2-hydroxydodecylstarch

Entry	Product	MS ^a	MS ^b	MS ^c	RE ^d (%)	Yield (%)
1	SE-G	1.13	1.09	1.11	37	85
2	SE-S	1.15	1.08	1.12	37	63
3	SE-G-S	1.12	1.09	1.10	37	70
4	SE-S-G	1.15	1.08	1.12	37	63

^a calculated from the percentage of C determined by elemental analysis; ^b calculated from the percentage of H determined by elemental analysis; ^c Mean of the two values; ^d RE (reaction efficiency) = experimental MS / theoretical MS

To find the best way for the purification, another method was performed to extract the impurities. Thus, a Soxhlet extraction was performed on **PPP** (6.20 g) with petroleum ether (40-60°C fraction) as solvent since this one is usual to purify modified starch (Figure 5).²⁸

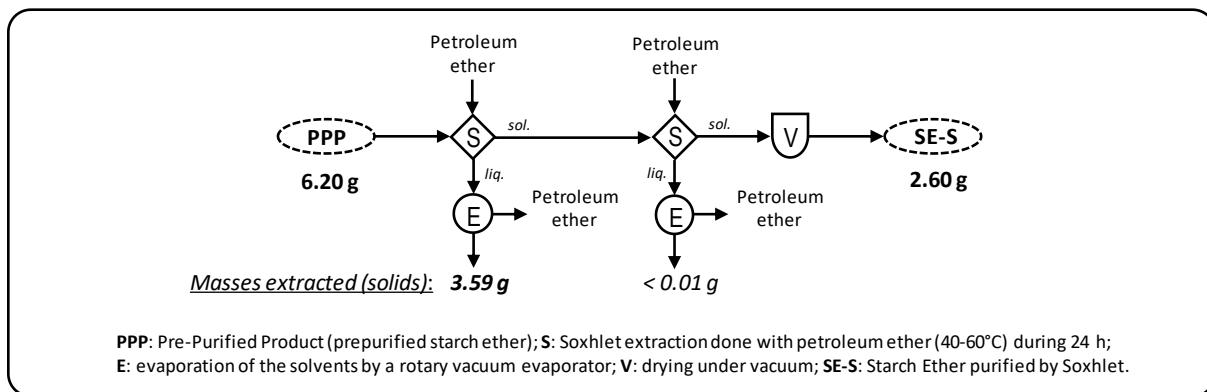


Figure 5: Further washings done by Soxhlet extractions on the pre-purified product (**PPP**) and leading to a purified 2-hydroxydodecylstarch (**SE-S**) in the 2-hydroxydodecylstarch synthesis

1,2-dodecanediol and bis-(2-hydroxydodecyl)oxide were soluble enough in warm petroleum ether. Note that other solvents (such as ethanol, chloroform) were assayed but they were inappropriate for a purification by Soxhlet (product stuck on the cartridge, leak across the cartridge). After 24 h of extraction with petroleum ether, the product in the cartridge was found as an aggregated uniform solid instead of its initial powder form. The liquid phase (solution in petroleum ether) was evaporated leading to a residual solid (3.59 g). The analysis by ¹H-NMR allowed to identify the presence of 1,2-dodecanediol and bis-(2-hydroxydodecyl)oxide. A second Soxhlet was performed and no supporting impurities were extracted. After drying under vacuum, the final product **SE-S**

was obtained ($m(\mathbf{SE-S}) = 2.60 \text{ g}$). The MS, reaction efficiency and yield were equal to 1.12, 37% and 63%, respectively (Table 2, entry 2). As already described in the case of **SE-G**, the FT-IR spectrum of **SE-S** showed the intensity increase of the carbon-hydrogen bonds elongation bands ($\nu_{\text{C-H}}$) compared to native starch (see supporting information; Figure S5).

Although the masses of **PPP** were the same at the beginning of both further purifications (6.20 g for each), each method of purification gave a different quantity of final product. Indeed, the purification by grinding and Soxhlet gave 3.50 g and 2.60 g, respectively. Note that a same value of MS (around 1.1) was determined for the two products (**SE-G** and **SE-S**). In order to ensure of the specificity of each purification method, the samples **SE-G** and **SE-S** were purified by Soxhlet (Figure 6) and grinding (Figure 7), respectively. **SE-G** was suspended in petroleum ether and a Soxhlet extraction was performed during 24 h. The liquid phase (solution in petroleum ether) was evaporated leading to a residual solid (0.63 g). A second Soxhlet extraction was performed and no supporting solid was extracted ($< 0.01 \text{ g}$). After this purification, the MS and the reaction efficiency remained constant whereas the overall yield decreased to 70% (Table 2, entry 3).

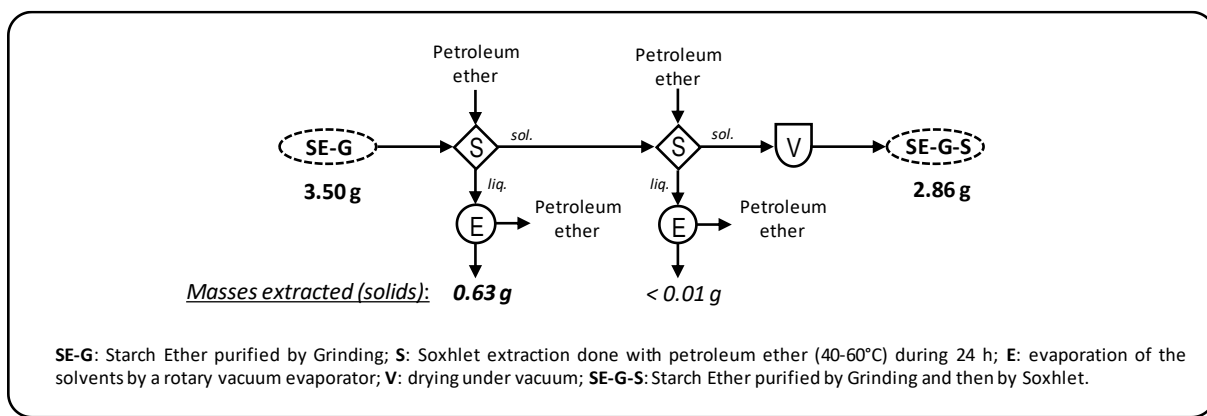


Figure 6: Further washings done by Soxhlet extractions on the 2-hydroxydodecylstarch obtained after washings of the prepurified product (**PPP**) by **Grindings (SE-G)** in the 2-hydroxydodecylstarch synthesis.

For the same purpose, by following a similar procedure than **SE-G**, **SE-S** was grinded twice in 50 mL of ethanol and then the suspension was heated at 50°C under stirring (Figure 7). The warm solvent is then removed by transfer. It is important to underline that no impurity was extracted. Logically, the values of the MS, reaction efficiency and yield remained constant (1.12, 37% and 63%, respectively - Table 2, entry 4).

In order to understand this difference in behavior between **SE-G-S** and **SE-S-G** samples, we noticed that the solid (0.63 g) extracted during the Soxhlet treatment of **SE-G** (Figure 6) was perfectly soluble in chloroform, contrary to all the obtained starch ethers samples. This unexpected property permitted to obtain a $^1\text{H-NMR}$ spectrum in CDCl_3 which showed the absence of 1,2-dodecanediol and of bis-(2-hydroxydodecyl)oxide but the presence of peaks relative to 2-hydroxydodecyl chains and to glucose units (see supporting information; Figure S4). Because of its solubility in chloroform and of the observed NMR signals, we think that this extracted solid was probably composed of low molecular weight starch ethers. This interpretation was confirmed by elemental analysis. Indeed, the extracted solid gave a MS value of 1.09, compared to 1.11 and 1.10 for **SE-G** and **SE-G-S** respectively, showing that the major difference of solubility observed came probably from smaller molecular sizes in the extracted solid and not from a possible higher degree of etherification.

The structural changes producing these low molecular weight starch ethers probably occurred during the synthesis at high temperature in strong alkaline conditions. Indeed, some publications described the degradation of starch chains in alkaline conditions.³³⁻³⁶

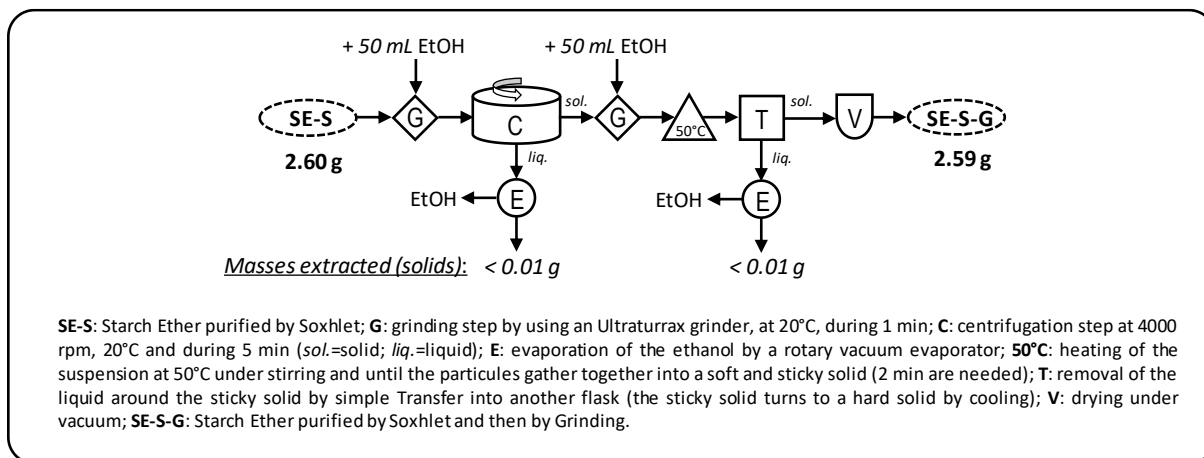


Figure 7: Further washings done by Grindings of the 2-hydroxydodecylstarch obtained after washings of the prepurified product (PPP) by Soxhlet extractions (SE-S) in the 2-hydroxydodecylstarch synthesis.

To give a global overview of the synthesis, figure 8 lists the various purification steps.

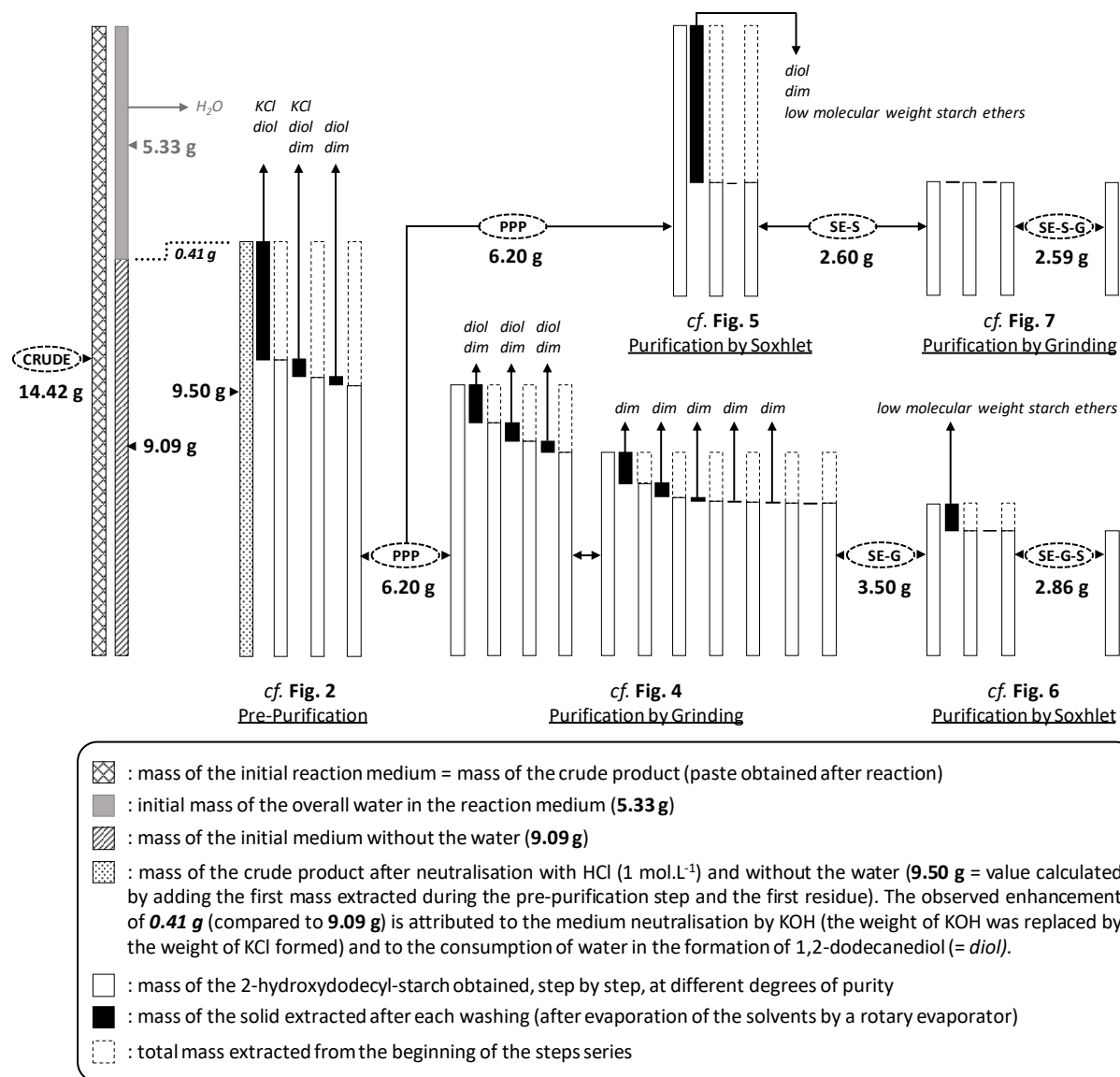


Figure 8: Mass follow-up done during the purification of the 2-hydroxydodecylstarch and identification of the major impurities extracted at each step (diol = 1,2-dodecanediol; dim = diol dimer = bis-(2-hydroxydodecyl)oxide)

Finally, four different samples of 2-hydroxydodecylstarch were produced: **SE-G**, **SE-S**, **SE-G-S** and **SE-S-G**. The process by Soxhlet extraction compared to the process by grinding required less steps for the purification (1 vs 8) but a longer time (24h vs 80 minutes). It can be noted that whatever the method of purification, the values of the MS were around 1.1. However, there is a gap in the recovery yield of the products by comparing **SE-G**, **SE-S**, **SE-G-S** and **SE-S-G** (85%, 63%, 70% and 63%, respectively). The difference was probably due to the extraction of low molecular weight starch ethers when the treatment by Soxhlet was performed. Finally, it would be very interesting to find a method to determine a potential degradation of the starch molecular structure during the synthesis. Unfortunately, classical methods required a solvent to solubilize the modified starch but, in our case, 2-hydroxydodecyl starch ethers were insoluble in usual solvents.

4. CONCLUSIONS

2-hydroxydodecyl starch ethers were synthesized by reaction of 1,2-epoxydodecane with potato starch in aqueous alkaline medium. A careful attention has been given to the purification steps and, more precisely, to the identification and the quantification of the co-products. In addition to classically observed 1,2-dodecanediol, bis-(2-hydroxydodecyl)oxide was extracted from the crude. This dimer issued from the reaction of the diol on the epoxide has never been described during the synthesis of 2-hydroxyalkyl starch ethers. The purification by Soxhlet extraction compared to the process by grinding required less steps but a longer time. The values of the MS were always around 1.1 in the used conditions, but the recovery yields were higher for the treatment by grinding compared to Soxhlet (85% vs 63%). Finally, in term of industrial

development, the recycling of the washing solvents is possible in the both cases. Nevertheless, the technologies available at industrial scale are more in line with the transposition of the grinding process that can provide better productivity through the use of existing and scalable equipment to handle both grinding of the crude product and extraction of soluble by-products in relevant solvent.

Supporting Information.

The characterizations of bis-(2-hydroxydodecyl)oxide and the determination of the molar substitution (MS) of the 2-hydroxydodecyl potato starches by elemental analysis were presented.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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