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Review article

Cationization of polysaccharides: A path to greener derivatives with many industrial applications

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ABSTRACT

Cationic polysaccharides are widely used in diverse areas such as water treatment, papermaking, chemical, food, cosmetic, and petroleum industries. The combination of cationic polysaccharides with anionic polymers can lead to interpolyelectrolyte complexes with hydrogel-like structures further expanding the application of the former. The aim of the present review is to fill a gap on the literature about cationization reactions of different polysaccharides and to offer a systematic and up-to-date analysis on the subject. Polysaccharides such as starch, dextran, cellulose and its derivatives, hemicellulose, pectin, chitosan, and seaweed polysaccharides among others are considered. Cationized polysaccharides can be prepared by reaction with various reagents. The main focus is on the substitution with dialkylamino hydroxypropyl and trialkylammonium hydroxypropyl ethers, being that the most common modifications involve the introduction of the 2-hydroxy-3-(trimethylammonium)propyl group by reaction of the polysaccharide with 2,3-epoxypropyltrimethylammonium chloride in an alkaline solution. An alternative to this method involves generation of the reagent *in situ* from 3-chloro-2-hydroxypropyltrimethylammonium chloride. In addition, polysaccharides substituted with other type of cationic groups and amphoteric derivatives are presented. Different methods of analysis, toxicological studies and applications of the modified polymers are also included.

Contents

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1. Introduction

Cationic polysaccharides with amino or ammonium functional groups are very useful in a wide range of applications. This fact has led not only to the production of an extensive scientific literature but also to the granting of numerous patents. Some cationized polysaccharides are available in the market in various grades depending on their specific application; such is the case of starch, cellulose, chitosan and guar gum, among others.

As a consequence of their properties in addition to their low cost, biodegradability and low toxicity, these cationic polyelectrolytes derived from natural products have found a place in areas as diverse as effluent treatment, papermaking, chemical, food, cosmetic, pharmaceutical, petroleum and textile industries, as well as in analytical chemistry and molecular biology. For example, cationic polysaccharides are being used as colloid flocculants instead of cationic polyacrylamides since toxicity of the latter has brought increasing legal restrictions on their use. In Germany, disposal of sludges treated with polyacrylamides will not be allowed in areas under cultivation from 2014 [1]. The combination of cationic polysaccharides with anionic polymers can lead to interpolyelectrolyte complexes (IPECs) with hydrogel-like structures further expanding the application of the former.

A review on cationic synthetic polyelectrolytes has been published a few years ago [2]. Despite the enormous amount of publications on polysaccharide cationization, as far as we know, no systematic revision of the literature on this subject has been performed to date.

Given the variety of cationic groups introduced in polysaccharides, this article will be mainly focused on the modification with dialkylamino hydroxypropyl ethers and trialkylammonium hydroxypropyl ethers, being these substitutions the more employed; the substitution with betaine esters and other groups will also be covered. Relevant applications of the different products will be considered.

2. Substitution with dialkylamino hydroxypropyl ethers, trialkylammonium hydroxypropyl ethers and related reactions

2.1. General description

In the late fifties, Montégudet working with cellulose [3,4] and later Wood and Mora, using a branched synthetic

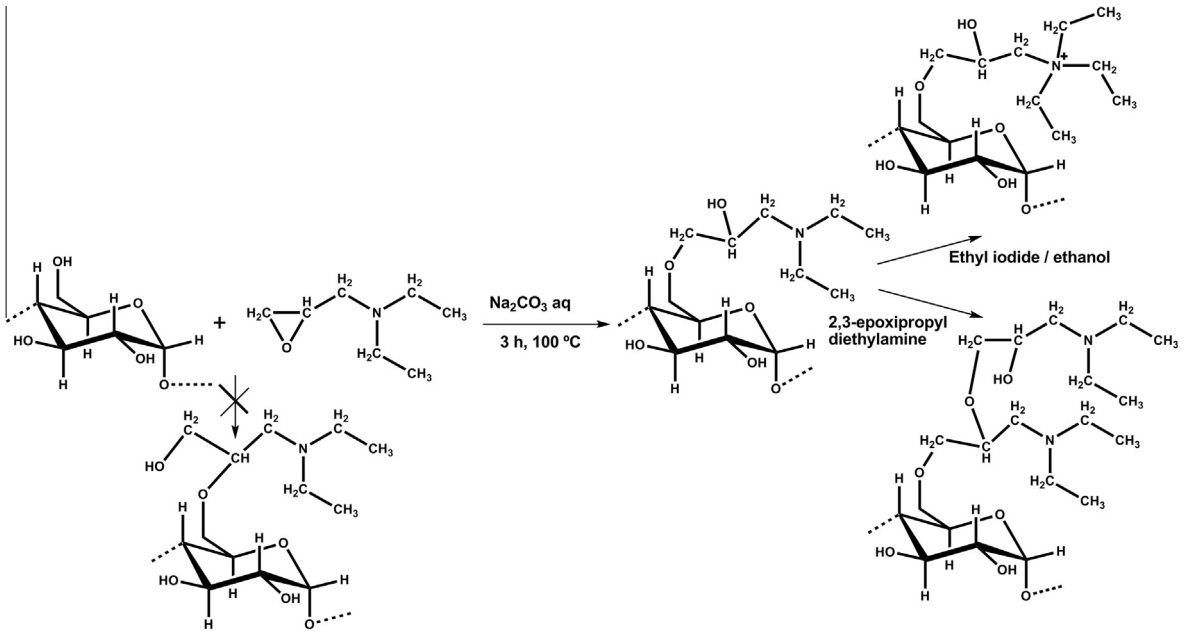

Fig. 1. Synthesis of the cationized derivative from a α-d-glucan.

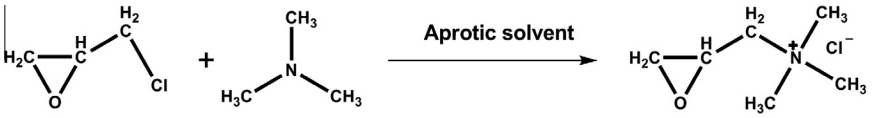

Fig. 2. Synthesis of EPTAC.

α-glucan [5] and amylose, amylopectin and dextran [6], published the synthesis of cationic derivatives employing 2,3-epoxypropyldiethylamine as reagent. Montégudet employed NaOH solution while Wood and Mora used concentrated Na_2CO_3 aqueous solution. The latter authors did not obtain satisfactory results with $NaHCO_3$ solution. In the next step, Wood and Mora treated the product of the first reaction with ethyl iodide in ethanol to obtain the corresponding quaternary ammonium iodide and later the free base by treatment with an anion exchange resin (Fig. 1). *DS* (degrees of substitution: the number of substituent groups attached per monosaccharidic unit) between 0.1 and 1.6 were reported. Wood and Mora raised the possibility of obtaining two isomeric derivatives: 3-diethylamino-2-hydroxy-1-propyl ether and 3-diethylamino-1-hydroxy-2-propyl ether, depending on how the opening of the epoxide ring occurred [5]. Nowadays it is known that epoxide opening in alkaline medium usually occurs through a S_N2 mechanism and therefore the less substituted carbons are attacked preferentially forming only the 3-dietylamino-2-hydroxy-1-propyl ether product [7]. The possibility that the hydroxyl of the side chain of the dialkylamino hydroxypropyl ether reacted with another epoxide, and was substituted in that position was also raised. This was observed in small quantities by Wilke and Mischnick in 1997 [8]. Excluding the aforementioned authors, 2,3-epoxypropyldiethylamine was rarely used, it is worth mentioning the heterogeneous cationization of cellulose activated with NaOH [9] and the reaction of cellulose acetates, that suffered deacetylation and cationization [10].

In recent years, the group most commonly introduced in polysaccharides to achieve cationization is the etherification with the 2-hydroxy-3-(trimethylammonium)propyl group, which can be obtained by the reaction of the polysaccharide with 2,3-epoxypropyltrimethylammonium chloride (glycidyltrimethylammonium chloride, EPTAC). This reagent is available commercially or can be synthesized from the reaction of epiclorohydrin with trimethylamine in an aprotic solvent (Fig. 2), employing an excess of epiclorohydrin as solvent [11], or by reacting epiclorohydrin with trimethylamine hydrochloride in water with the addition of NaOH [12]. Being EPTAC unstable [13,14], toxic [15] and expensive, the commonest alternative, particularly at industrial level, is to generate the reagent *in situ* from 3-chloro-2-hydroxypropyltrimethylammonium chloride (CHPTAC), also commercially available. Besides CHPTAC and EPTAC, similar reagents are available in the market. They show variations in one of the alkyl chains linked to the quaternary ammonium, among them we can quote CHPDLAC (3-chloro-2-hydroxypropyldimethyldodecylammonium chloride), CHPCDAC (3-chloro-2-hydroxypropylcocoalkydimethylammonium chloride, being cocoalkyl a mixture of hydrocarbon chains between 12 and 14 C) and CHPDSAC (3-chloro-2-hydroxypropyldimethylstearylammonium chloride [16]. Cationic polysaccharides containing long hydrocarbon chains show amphiphilic properties.

The cationization reaction begins with the formation of and alkoxide from a hydroxyl group of the polysaccharide in NaOH (or other base) aqueous solution, this alkoxide attacks the epoxide added as such or formed *in situ* by the alkaline medium, and it opens the epoxide to form the hydroxyether (Fig. 3). It was observed that *DS* and reaction efficiency are lower with CHPTAC than with EPTAC [17,18]. The epoxide can suffer as a secondary reaction the formation of a diol, unable to react with the polysaccharide, which decreases reaction efficiency [19]. The degradation of the epoxide to the diol depends on temperature, medium pH and reaction time. In Table 1 the stability of the epoxide at pH 11.5 (a pH commonly used in the process of cationization) is presented. EPTAC commercial reagent is reported to degrade on storage 3.5% a month at 20 °C and as a result a storage temperature between 2 and 8 °C is advised [13]. Fig. 4 shows stability data generated over a pH range from 10.5 to 12.5 and for temperatures between 20 °C and 50 °C. The equation resulting from a kinetic model of this system may be used to estimate half-life values within the specified pH and temperature limits [14]. Kavaliauskaite et al. described besides diol formation, the formation of soluble oligomers of EPTAC [18]. Hellwig et al. suggested that the hydrolysis of EPTAC predominated in water, whereas formation of 3-hydroxy-1-propen-1-trimethylammonium chloride was found in reaction media when the reaction was performed above room temperature, in alkaline conditions [20] (Fig. 5). Goclick et al. developed a determination method for EPTAC, CHPTAC and the residual diol by capillary electrophoresis (CE) and compared that method with a high performance liquid chromatography (HPLC) method with ion pairing [21].

To control *DS*, cationizing reagent:monosaccharide unit molar ratio, NaOH:cationizing reagent molar ratio, medium volume, temperature and time can be varied. In general it is observed that an increase in the cationizing reagent produces an increase in *DS*, this can be explained in terms of increased availability of reagent molecules in the vicinity of

Table 1
Percentaje of the remaining epoxide in different conditions.

Temperature (°C)	Time	% Remaining
20	3 days	90
25	2 days	90
50	4 h	90
50	1 day	50

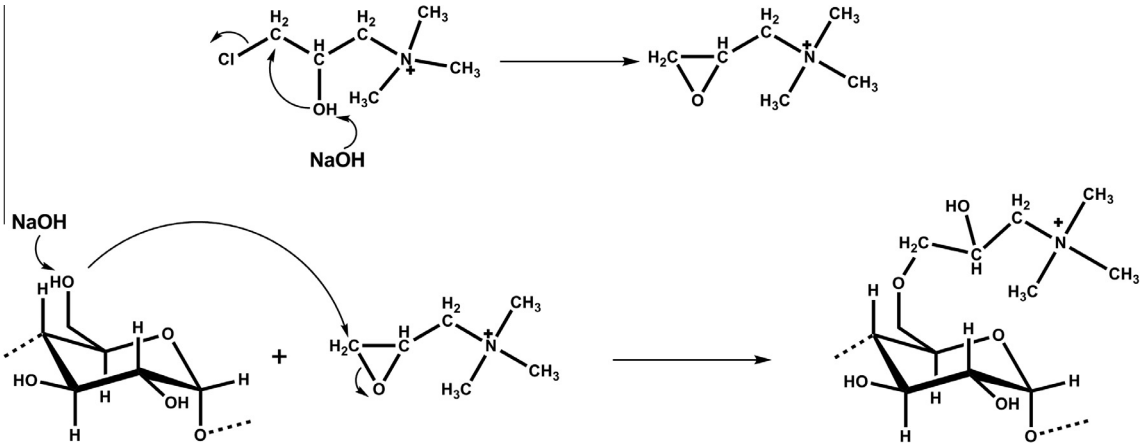

Fig. 3. Formation of the epoxide and nucleophilic attack of the alkoxide to the epoxide.

the polysaccharide. The increase occurs up to a certain limit, and if it is not accompanied by an increase in NaOH, the alkali may become the limiting reagent. The increase in NaOH to some extent, also increases *DS*; as one equivalent of NaOH is necessary to generate the epoxide EPTAC from the chlorohydrin CHPTAC, in the case that the latter reagent is used (that amount is called stoichiometric alkali and is consumed in the reaction), an additional amount of NaOH is also required to activate hydroxyls of the polysaccharide forming alkoxides (catalytic alkali). An excess of NaOH, however, favors polysaccharide degradation and epoxide degradation towards the diol. The effect of temperature on *DS* is controversial: Kavaliauskaite et al. employing the epoxide EPTAC in the range 35–85 °C, reported that the activation energy of the main reaction of starch cationization was lower than that of the secondary reactions, as a result efficiency was higher at lower temperatures [18]. In contrast, Kuo and Lai, working with starch and CHPTAC in the range 26–53 °C informed an increase in *DS* with an increase in temperature [22]. Meanwhile, Ren et al. found an increase and a subsequent decrease in the *DS* in the cationization of celluloses with CHPTAC (range 50–80 °C). The increase in the temperature of reaction, in a first step, would increase *DS*, due to the beneficial effects of temperature in the compatibility of reagents and their kinetic energy; further increase, on the other hand, would favor the degradation of both the polysaccharide and the cationizing reagent, reducing the *DS* [23]. The raise in reaction time follows similar trends, initially increasing the *DS*, whereas longer times would not produce further improvement, and can produce lowering in the *DS* by degradation [23,24]. Some researchers, working with starch, considered that long reaction times could also favor deetherification of the polysaccharide and thereby diminish the *DS* [22,24].

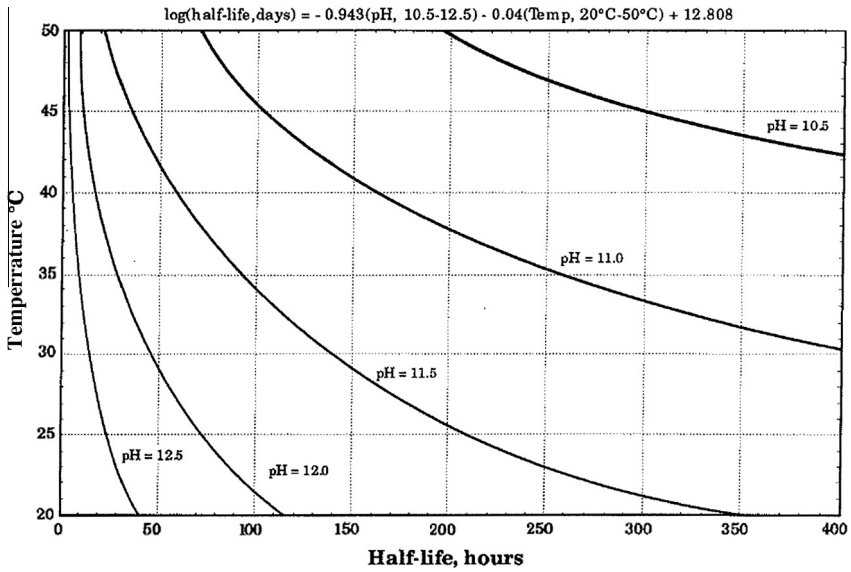

Fig. 4. Stability of EPTAC as function of pH and temperatures.

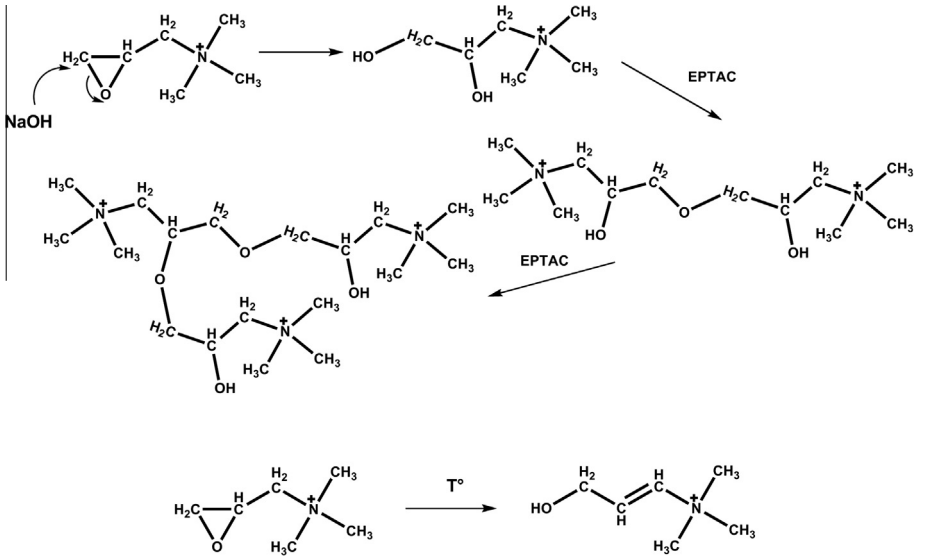

Fig. 5. Secondary products of EPTAC.

Therefore, it is necessary to determine optimum reagent concentrations, temperature and time for each case.

Usually, a $DS < 0.2$ is considered as low degree of substitution, and a $DS \geqslant 0.2$ is considered as high [19,25,26]. In general homogeneous conditions are sought because the efficiency of these systems is higher that that of heterogeneous systems. This can be explained by the fact that in the case of heterogeneous reactions, the charged groups accumulate in the external surface of the polysaccharide particles, and diffusion of other reagent molecules to the inner parts is increasingly hindered. Instead, in homogeneous processes the polysaccharide dissolves, and reactions are less hindered [19,27]. If it is an objective to preserve the structure of polysaccharide particles, heterogeneous processes are preferred.

Below are presented, the most relevant works that appear in the scientific literature on the cationization of different polysaccharides.

2.2. Starch

Starch is a major polysaccharide cationized with these reagents, aproximately 95% of CHPTAC consumed in the European Union (23,695 tons) in 2001 was used for starch cationization [15]. Starch cationization processes can be classified in extrusion, semidry and wet. This classification can be extended to other polysaccharides. In an extrusion process, the reagent is added to the dry starch during extrusion, and glycerol is usually added to the mixture as a plasticizer [28–32]. In the semidry process, reagents are sprayed over dry starch and the resulting mixture is exposed to thermal treatment [20,26,33]. In the wet process, the reactions are carried out homogeneously in DMSO or heterogeneusly in an aqueous or alcoholic suspension (mainly ethanol although methanol and isopropanol were also tested) in alkaline conditions [17,19,25,34–36]. Both the extrusion and semidry method benefit from the convenience in preparation, which does not require washing or filtration, thus avoiding the loss of starch and water pollution [20], but can be troublesome due to the presence of residual salts, reagents or intermediate products [37]. From this point of view, the election of the wet process seems to promise better product quality, whereas homogeneous phase cationization can be complicated by the high viscosity of starch paste. On the other hand, the use of heterogeneous systems preserves better starch granules' structure [38] and it was shown that cationized starches that maintained the structure of native starch were better adsorbents [39] and flocculants [25]. The common addition of swelling inhibiting salts such as sodium chloride [40], sodium sulfate [34,41], and calcium chloride [42] to reaction media in the heterogeneous process, that allows the use of more concentrated suspensions, causes problems in treatment of effluents and unfavorable inhibition of granule swelling [43,44]; these problems can be partially overcome by addition of alcohols instead of salts, however in these conditions the reaction becomes slower [45]. Recently glucose and especially sucrose have been investigated as alternative swelling inhibitors with results comparable to sodium sulfate for low *DS* (0.07) [46].

As starch is less expensive than the cationizing reagent, the cost of the latter can mainly influence the price of cationized starch, and thus it is essential to maximize reaction efficiency in order to turn this product competitive with regard to synthetic polymers. Kavaliauskaite et al., managed to improve previous efficiency values and obtained cationized starches, precrosslinked or not, with *DS* between 0.2 and 0.85 and reaction efficiencies between 82 and 93%. Reactions were carried out in heterogeneous conditions, with preservation of granule structure, employing monosaccharide units: EPTAC: NaOH: H_2O = 1: (0.3–2): (0–0.175): (0–11) molar ratios [18]. Kuo and Lai performed the homogeneous cationization of starch in aqueous medium free of salts or swelling inhibitors, by controlling temperature, pH and other reaction conditions to avoid gelatinization of starch granules; they applied response

surface methodology (RSM) to optimize reaction conditions [22,47]. Pi-xin et al. cationized starch by a wet heterogeneous method, employing EPTAC and mixtures of organic solvents with aqueous alkaline solutions, and obtained *DS* up to 1.37 with 1:4 dioxane/water and up to 1.19 with tetrahydrofurane/water [24]. Wang and Xie, applying a green chemistry approach, employed 1-butyl-3-methylimidazolium chloride, a room-temperature ionic liquid as cationization solvent. These homogeneous conditions allowed *DS* up to 0.99, after 2 h at 80 °C [48].

Hebeish et al. informed for the case of starch that *DS* and reaction efficiency follow the order: aqueous medium > aqueous/nonaqueous medium > semidry method > nonaqueous medium. These authors also tested different bases for the reaction and found that effectiveness followed the order NaOH > Na_2CO_3 > $NaHCO_3$. Evaluating different organic amines as bases, the effectiveness order was diethylamine > ethylamine > methylamine. Diethylamine was as effective as NaOH, not causing as much alkaline hydrolysis of the epoxide as NaOH. These results also apply to carboxymethylcellulose [49]. Organic bases such as benzyltrimethylammonium hydroxide or tertiary amines triethylamine and dimethylbenzylamine were compared in the reaction of crosslinked starch with EPTAC. *DS* from 0.18 to 1.05 were achieved in the preserved granules. When benzyltrimethylammonium hydroxide was used as a catalyst instead of NaOH, the reaction proceeded slightly slower and with a lower efficiency. Dimethylbenzylamine unexpectedly showed similar catalyst efficiency as benzyltrimethylammonium hydroxide. It was suggested that the reason for such phenomena is the reaction of EPTAC with tertiary amines and the subsequent formation of quaternary ammonium hydroxides. These strong bases would actually catalyze starch cationization. Dimethylbenzylamine was more active in this reaction in comparison with triethylamine. It was shown that, due to a higher amount of quaternary ammonium hydroxides in the liquid phase of the reaction mixture, the yield of starch cationization decreased. Cationization in the presence of organic bases provided higher sorption capabilities to the modified polysaccharide [50].

Microwave assisted methods were employed in the cationization of starch with 2,3-epoxypropyloctyl dimethylammonium chloride, 2,3-epoxypropyldodecyldimethylammonium chloride, and 2,3-epoxypropyltetradecyldimethylammonium chloride [51] and in the cationization of a polyacrylic acid grafted amilopectin with CHPTAC to obtain amphoteric products [52]. Reaction time is reported to be reduced around one to two orders of magnitude for microwave assisted reactions, compared to conventional conditions [51,52], while cationizing agent requirements were reduced around one order of magnitude [51]. The products prepared via microwave irradiation showed better flocculation performance [51,52].

Cationized starch (with $DS < 0.2$), is employed in big quantities as additive in papermaking to improve mechanical resistance, promote fines, pigments and loads retention, allow a rapid drainage of paper sheet and slip into the machine, and reduce the biological oxygen demand of pulp mills effluents. It is also used as flocculant ($DS \geq 0.2$), as an additive in textiles, adhesives and detergents and in petroleum recovery [2,17,53–64]. It has been employed in the formulation of cosmetic and pharmaceutical products [19,22,47]. Cationized starches, previously subjected to benzylation reaction, were amphiphilic presenting tensioactive properties [65]. Crosslinked cationic starches were evaluated as iodophores for potential antiseptics [66].

Cationic starch with *DS* of 0.29 or 0.36, were succinylated to a *DS* of 0.11–0.34, to obtain amphoteric products. These were investigated in the flocculation of kaolin suspensions and the sedimentation of wastewater sludge. Amphoteric starch presented the advantage of a broader range of efficient phase separation (flocculation "window") when compared to cationic starch [67].

Cationized amylopectin has been successfully employed in capillary electrophoresis (CE) to modify the fused-silica inner surface, by directly adding the modified polysaccharide to the running solution. Thus, a rapid and stable electroosmotic inverse flow was achieved, with batch to batch reproducibility. Proteins adsorption was avoided and an efficiency of 560.000 theoretical plates m^{-1} was reached for the analysis of α-quimotrypsinogen [68].

Starch crosslinking with epichlorohydrin is regarded to be the most common method used in polysaccharide chemistry, a modification of this reaction with the addition of NH_4OH allowed the preparation of crosslinked insoluble weak basic ion exchangers [69,70] (Fig. 6). In another publication, to the aforementioned reaction mixture, CHPTAC was also added [71]. Maltodextrins crosslinked with epichlorohydrin, cationized with EPTAC and associated with phospholipids were used as Ionic Amphiphile Biovectors (ABV), a new type of drug carrier, and were evaluated for amphotericin B release [72]. Native corn starch was crosslinked with phosphorus oxychloride ($POCl_3$) before and after cationization, with potential applications as adhesive and in paper industry [73]. Semi-interpenetrating polymer networks (semi-IPN) were prepared based in cationized starch and acrylic polymers [74].

2.3. Dextrans

Nichifor et al. have extensively published about the preparation of amphiphilic cationic dextrans (Fig. 7), previously crosslinked with epichlorohydrin or not, by substituting them with groups similar to the described ones

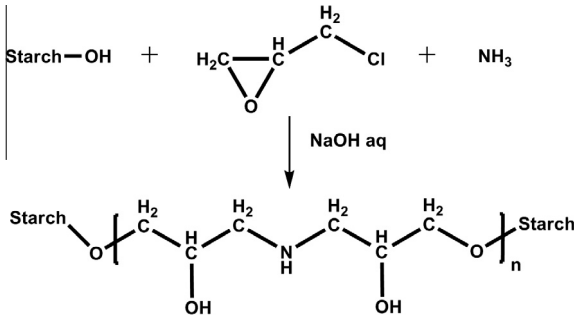

Fig. 6. Starch crosslinked with epichlorohydrin in the presence of NH_4OH.

but in which one of the quaternary ammonium substituents was an alkyl chain between C2 and C16 instead of methyl [75]. In this case the reagent employed for cationization was a 2,3-epoxypropylalkyldimethylammonium chloride obtained from epichlorohydrin and a dimethylalkylamine [76]. Products with a *DS* between 0.18 and 0.94 were obtained.

The kinetic of the reaction of polysaccharides (dextran, crosslinked dextran or pullulan), with epichlorohydrin and different tertiary amines was studied [77] (Fig. 8), by quantification of reagents and products in the reaction mixture with or without the presence the polysaccharide, at regular intervals. They found that the use of cyclic amines such as 1-methyl-imidazol or 1,4-diazabicyclo[2,2,2]octan as "catalysts" together with another tertiary amine, used for the substitution, was not necessary (as was reported earlier for the case of cellulose by Gruber and Ott [78]), and led to a cationic polysaccharide with mixed and uncontrolled chemical composition. After 30 min of reaction at 40 °C, 80% of epichlorohydrin had reacted with the amine, reaching a 94% after 3 h. Initially, the original epoxy groups remained unchanged, but they started to decrease at 24 h. The best solvent for this reaction was water and an equimolar amine: epichlorohydrin ratio gave adequate results.

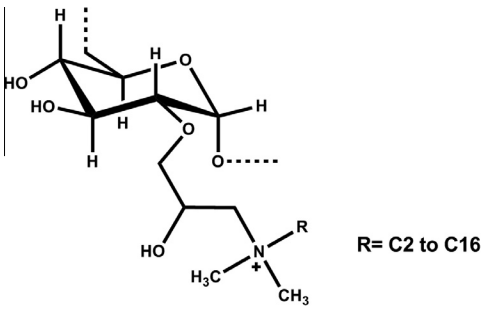

Fig. 7. Modified dextran with cationic substituents that present alkyl chains of different length.

In the conditions tested no further crosslinking was informed. The authors also compared the reaction of polysaccharides with different reagents and found that efficiency followed the order EPTAC > epichlorohydrin + tertiary amine > CHPTAC. The better performance of the polysaccharide plus EPTAC method was valid only for amines with short substituents (mainly CH_3), for longer alkyl substituents the best results were obtained by the method epichlorohydrin plus tertiary amine, possibly by the contribution of the reaction of the polysaccharide with epichlorohydrin and then with the amine or by a better compatibility/ solubilization of the step-wise formed epoxide derivative of more hydrophobic tertiary amines [77].

The autoaggregation phenomenon of cationic dextrans was studied [76,79]. Results from fluorescent techniques suggest that the intermolecular hydrophobic association of alkyl substituents takes place at a very low concentration of amphiphilic polymers [80]. These polysaccharides effectively interacted with biological surfactants such as biliar salts, and thus presented potentiality as hipocolesteremic agents [77,81]. The cationized polysaccharides also interacted with different sodium alkyl sulfates [79,82–84], and with cationic surfactants [85]; the electrical conductivity and viscosity properties in different solvents [86–91], the thermodinamic interaction with water [92], as well as their applications in clay flocculation were evaluated [93–95]. The interaction between hydrophobically modified cationic polysaccharides based on dextran and a flavonoid drug (rutin) was studied in view of drug delivery applications [80]. Cationized dextrans-DNA intepolyelectrolyte complexes were successfully employed for gene delivery [96]. Cationic dextrans were studied as potential novel heparin antagonists [97].

2.4. Cellulose, hydroxyethylcellulose and carboxymethylcellulose

Cellulose is a polysaccharide difficult to process in normal aqueous solutions due to its strong intra and intermolecular hydrogen bonds that make it insoluble. For this

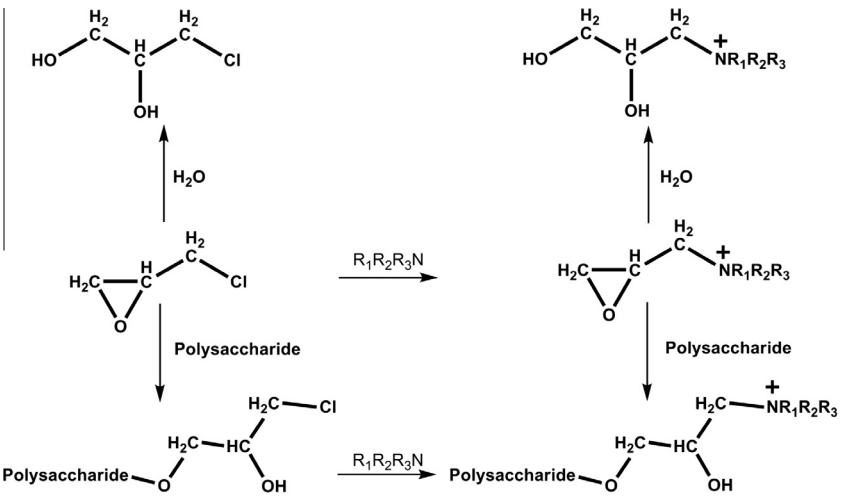

Fig. 8. Synthesis of cationized polysaccharides with epichlorohydrin and tertiary amines.

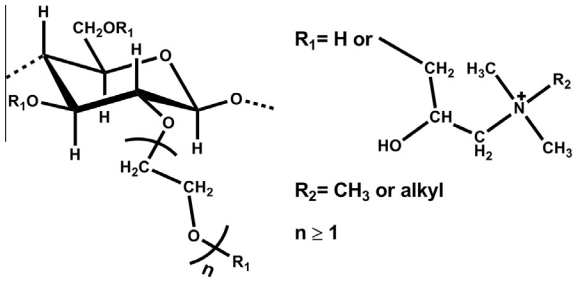

Fig. 9. Cationized derivatives of hydroxyethylcellulose.

reason, cationic celluloses are currently obtained by cationization of water soluble hydroxyethylcelluloses. In hydroxyethylcellulose, the quaternary ammonium group can be directly linked to the hydroxyls of the cellulose backbone or to the polyethylene glycol substituents present (Fig. 9).

Cellulose cationization in dimethylacetamide/LiCl in homogeneous conditions is reported [98]. Recently, synthesis of cationized cellulose has been published by Song et al. using CHPTAC as reagent in homogeneous medium of aqueous NaOH through the addition of urea to allow polysaccharide solubilization [99]. *DS* between 0.2 and 0.63 were obtained. Yan et al. [100] also employed urea to solubilize cellulose and perform cationization, but used the epoxide EPTAC directly instead of the chlorohydrin CHPTAC in the reaction. Yan et al. reported a decrease in cationized cellulose solution viscosity with an increase in *DS*, attributing this fact to an increase in the hydrophilicity of the polymer and to the decrease in the molecular weight of the polysaccharide by degradation, in the alkaline conditions. Song et al., meanwhile, did not found degradation of the polysaccharide by size exclusion chromatographic (SEC). This is noteworthy as reaction conditions in the paper of Yan et al. were slightly softer than those in the one of Song et al.

Cationized celluloses were synthesized by Rodriguez et al. for controlled drug release applications, crosslinked or not with ethylene glycol diglycidil ether (EGDE) (Fig. 10) [101–103]. The same group studied the formation of interpolyelectrolyte complexes of cationic celluloses with anionic acrylic polymers [104].

Cationized cellulose has found applications in colloid flocculation for water treatment [100] and in paper, textile, food, cosmetic, chemical and pharmaceutical industries [99]. The rheological behavior of an interpolyelectolyte complex of cationized cellulose and an anionic acrylamide derivative was characterized [105]. Cationic hydroxyethylcellulose or cationic cellulose complexes with DNA succesfully transfected genes in cell lines [99,106,107]; a ternary complex of DNA, schyzophyllan and cationized hydroxyethylcellulose was also studied [108]. The reversible precipitation of casein with cationized hydroxyethylcellulose was used to prepare low casein foods [109].

Carboxymethylcellulose (CMC) was cationized with CHPTAC by Hashem et al., to improve its textile properties [110]. Both Hashem et al. [111], and Hebeish et al. [49], found that a higher substitution with the carboxymethyl

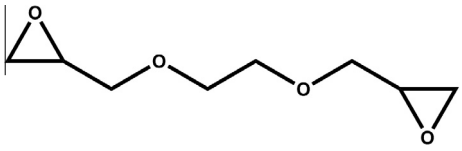

Fig. 10. Ethylene glycol diglycidil ether (EGDE).

group led to obtaining a higher *DS* with regard to the cationizing group. Cationized CMC, of amphoteric character, was tested in the flocculation of ferric laurate [49].

2.5. Hemicelluloses and pectins

Hemicelluloses are branched noncellulosic heteropolysaccharides, with a degree of polymerization in the range 80–200, consisting on various different sugar units, arranged in different proportions and with different substituents. The main constituting monosaccharides are D-xylose, D-glucose, D-galactose, D-mannose, D-glucuronic acid, D-galacturonic acid, and in a smaller proportion, L-rhamnose, L-fucose and various *O*-methylated neutral monosaccharides.

Ebringerová et al. cationized xylans with CHPTAC and characterized the products [111]. More recently Schwikal et al. performed the cationization of xylans employing EPTAC, and obtained products with *DS* up to 1.6. The reaction was carried out in heterogeneous phase employing NaOH aq/1,2-dimetoxyethane. The heating of the xylan under reflux before the addition of NaOH increased *DS*. EPTAC was added drop by drop. Due to the presence of uronic acids in the xylan the products were amphoteric [112].

Ren et al. cationized hemicelluloses from sugar cane bagasse in aqueous alkaline solution, obtaining *DS* in the range 0.01–0.54. These researchers found that in order to increase *DS* it was desirable to add NaOH in two stages, in an initial stage to activate the polysaccharide and in a second stage together with the cationizing reagent. The use of EPTAC gave products with higher *DS* and less reduction in molecular weight than with CHPTAC, and thus the former was preferably used [113]. In order to reduce the substantial degradation of the hemicelluloses, the cationization was performed with CHPTAC in aqueous ethanol, under relatively low concentrations of alkali. Products with *DS* between 0.063 and 0.19 were obtained [23]. To further reduce polysaccharide degradation they extensively decreased alkali concentration and performed a homogeneous cationization with EPTAC in aqueous DMSO, the products presented *DS* in the range 0.16–0.23 [27].

The glucuronogalactoarabinoxylans from corn fiber were cationized with CHPTAC, in a water suspension and then extracted with alkaline aqueous solutions by Šimkovic et al. *DS* between 0.16 and 0.31 are reported, for a CHPTAC: monosaccharide unit molar ratio of 0.7: 1. Two bases were used for cationization (NaOH or KOH) as well as two conditions (ambient pressure or 60 °C in a rotary evaporator) [114]. Mixtures of arabinogalactans and rhamnogalacturonans from sugar beet pulp were cationized and fractionated by the same research group in classical alkaline medium [115] and even in acidic conditions (at pH

1.5 adjusted with trifluoroacetic acid, H_3PO_4 or HCl) [116]. Xylans from beech holocellulose were the polysaccharide most recently cationized by this group and their film properties were studied [117].

Polygalacturonic acids (pectins) were crosslinked and cationized [118] or only cationized [119]. Glucurono(arabino)xylans from barley husks were cationized by Köhnke et al. [120].

Cationized hemicelluloses have been studied as flocculants and adhesives [121], and as papermill additives [111,122–124]. Antimicrobial activity was also found [125]. Crosslinked cationized products present potentiality as ion exchangers [118,126].

2.6. Chitosan

Chitosan is a polysaccharide obtained by deacetylation of chitin, the second most abundant polysaccharide in nature after cellulose. Chitin is extracted from the exoskeletons of arthropods and from the cell walls of fungi; chitosan can be found as such in some fungi but in limited quantities and this makes commercial chitosan a derivative of chitin. Chitosan has a linear structure, formed by β-(1→4)-2-amino-2-deoxy-D-glucose units. One disadvantage of chitosan is its insolubility at pHs above 6.5 by deprotonation of its amino group. As a result its known antimicrobial activity limits to acid pHs. Cationized chitosan presents better properties of higroscopicity, moisture retention, actibacterial activity, mucoadhesivity and as a dermal permeation enhancer of drugs [127–131]. The most obvious cationization of chitosan: the permethylation of the amino group in C-2 generates an expensive product due to the costs of reagents such as sodium borohydride and methyl iodide [132].

Seong et al. [133] treated trisaccharides derived from chitosan, dispersed in water, with EPTAC and studied the effect on *DS* of time and reaction temperature, EPTAC: monosaccharide unit molar ratio and the use of 1% acetic acid as catalyst. The optimum values were 18 h and 50 °C, not significantly increasing *DS* after that period or employing higher temperatures. The use of 1% acetic acid significantly increased the *DS*. Products with *DS* up to 1.04 were obtained. Later the same reaction was performed, but in this case using chitosan as such and 0.5% acetic acid [134,135]. The use of small quantities of acetic acid caused the epoxide group to open more easily, increasing reaction rate. It also assured chemoselectivity towards substitution in the amino group [134,135].

Some variations in the synthesis were reported: the reaction with EPTAC in neutral medium [136–139] or in slightly alkaline medium (pH 9) [140–144] and 0.1% $Zn(BF_4)_2$ was employed as catalyst for epoxide opening [145]. The cationization of chitosan was also performed in isopropanol [146].

Substitution is reported to occur only in the amine group of chitosan (Fig. 11) since in the conditions employed hydroxyl groups are not sufficiently nucleophilic to induce EPTAC ring opening [147,148]. Most authors did not discuss reaction regioselectivity.

Cationized chitosan has been employed as a biomedical material for a broad range of applications, including wound healing [143], also for gene, drug and protein release [131,134,135,137–139,144,149,150]. Besides, it is known by its bioadhesive properties as other cationic polysaccharides. The important antimicrobial activity of cationized chitosan interested to the textile industry, for applications as fiber additive [133,142,145]. Hybrid organic–inorganic materials have been developed constituted by cationized chitosan with silicate (rectorite) with antimicrobial activity [141]. The antioxidant activity of cationized chitosan is also important [132]. Cationized chitosan was employed for removal of Mo^{IV} [151] and Cr^{VI} [136]. Among other varied applications are included: membranes of cationized chitosan crosslinked with glutaraldehide for fuel cells [152]; from cationized chitosan a crosslinked anion exchange resin with borohydride as counterion was prepared, useful in organic synthesis for reduction of carbonyls to alcohols, with high chemoselectivity and easy sample handling [153]. Cationized chitosan was tested as flocculant agent in papermaking and presented a better efficiency than cationized starch, the polysaccharide most used for those purposes [140].

An IPEC formed between an *N*-carboxyethyl chitosan and chitosan cationized with CHPTAC, was prepared and used in protein controlled release [154].

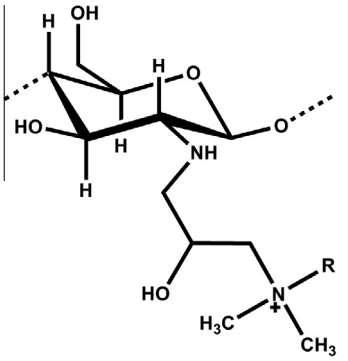

Fig. 11. Cationized chitosan.

2.7. Seaweed polysaccharides

Unlike other polysaccharides (see previous sections) there are very few references in the literature on the use of algal polysaccharides as substrates for cationization. Geresh et al. employed the extracellular polysaccharides of the red microalgae *Porphyrium* sp., using as a reagent CHPTAC in aqueous alkali in heterogeneous conditions. These polysaccharides were composed of about 10 different monosaccharides, of which xylose (40%), galactose (18%) and glucose (15%) were the most abundant. The polysaccharides were anionic due to the presence of glucuronic acid and sulfate groups. The group investigated the effect of the reaction mixture dilution on the *DS*, and found that a higher *DS* was obtained when the reaction occurred in small volumes of water in a gel-like phase. In this article the N% were reported instead of *DS*, the maximum obtained was 3.00% which would correspond to a *DS* of 0.52 in the case of a polysaccharide composed solely of hexoses.

They also concluded that there was no degradation of the polysaccharide because phenol-sulfuric acid assay of the native and modified polysaccharide was identical, although this is a very nonspecific method for total sugars that does not provide information on molecular weight decrease [155].

Wang et al., in search of new column packing materials for the purification of antibodies, coated glass beads (63–106 μm in diameter) with an agarose film which was crosslinked with epichlorohydrin. Then, the coated beds were equilibrated with aqueous EPTAC and filtered. Later, they added more EPTAC solution and 10 M NaOH. The reaction was maintained at 32 °C with stirring up to 24 h. The authors achieved densities in the range of 119–374 mol mL^{-1} gel and reported that they could obtain different functionalization densities of agarose changing reaction conditions. The functionalization density obtained with the only condition tested was not specified, neither were the process variables that yielded other densities. The authors did not characterize the functionalized product but focused on the permeability and compressibility of the beds formed with the spheres and their application in the purification of monoclonal antibodies [156].

Prado et al., our group, cationized agaroses with CHPTAC and obtained different degrees of substitution (0.04–0.77). The influence of different reaction parameters on the substitution degree and molecular weight was evaluated. The investigated parameters were concentration of reagents, temperature, time and addition of sodium borohydride. The products were characterized by means of scanning electronic microscopy, infrared spectroscopy, viscosimetry and NMR. Products of methanolysis were studied by electrospray ionization mass spectrometry (ESI-MS). The higher the concentration of CHPTAC employed, the higher degree of substitution obtained, when the optimum concentration of NaOH in each case was employed. Insufficient quantities of NaOH reduced epoxide formation and the reacting alkoxides of the polysaccharide, whereas an excess of NaOH favored epoxide degradation and a decrease in the molecular weight of the product. A reaction time of 2 h was sufficient to obtain products with the maximum degree of substitution for each case. The addition of $NaBH_4$ gave products with a slightly higher molecular weight, but the extra cost involved should not justify its use for large-scale application [157]. Two cationized agaroses (*DS* = 0.19 and *DS* = 0.58), presented colloid flocculation performance comparable to commercial cationic polyacrylamides [158]. Cationized agaroses with *DS* = 0.19 and *DS* = 0.77, were combined with the sulfated agarans extracted from the seaweed *Polysiphonia nigrescens* to prepare IPECs and used as matrices for controlled drug release [159].

2.8. Other polysaccharides

Konjac gum is obtained from the tubercles of a plant that grows in Japan, China and Korea (*Amorphophallus konjac* K. Koch). It is formed by β-1,4 linked glucose and mannose units, with about 1 in 19 units being acetylated. Yu et al. cationized this glucomannan in homogeneous conditions, with the polysaccharide in water and the addition of NaOH and CHPTAC. It was necessary to control NaOH concentrations in order to avoid deacetylation of the polysaccharide that led to an insoluble product that did not react with the cationizing reagent [160]. Tian et al. cationized konjac gum by a semi-dry process that involved the addition of a certain amount of grinded solid NaOH with a small amount of water to maintain suitable moisture content and EPTAC, the reaction time was 15 min with mechanical stirring [161]. Cationic konjac gum has incipiently been applied to food preservation because of its antimicrobial and film forming propeties [160] and for colloid flocculation [161].

Guar gum, obtained from the endosperm of the seeds of leguminous *Cyamopsis tetragonolobus* L., is a galactomannan formed by linear β-1,4 linked D-mannose units with β-1,6 linked D-galactose single stubs. Levy et al. cationized guar gum, previously fragmented with ammonium persulfate, employing EPTAC, and obtained a more efficient bentonite flocculant than native guar gum [12]. More recently, guar gum was cationized with CHPTAC in homogeneous conditions (50% aqueous NaOH), with 2 h of stirring before reagent addition. *DS* of 0.35 was obtained for an approximate CHPTAC: monosaccharide unit molar ratio of 5:1. Cationized guar gum formed hydrogels with opposite charge polymers with controlled drug release applications [162]. Native galactoglucomannans, which were isolated from thermomechanical pulping waters of Norway spruce, were modified through cationization with EPTAC and were used as a retention and dry strength aid in papermaking [163].

Cationic polysaccharides are very effective as conditioning agents in cosmetic, due to their attachment to the specific substrate (hair or skin), which is directly attributable to the electrostatic interactions between negative charged sites on the surface of hair or skin with the polymer. Native or hydroxypropylated guar gum, cationized with EPTAC or CHPTAC is the polysaccharide more widely used as conditioner in the cosmetic industry formulary [16,164].

Glycogen cationization was published by Pal et al., together with that of amylose, amylopectin, guar gum and starch. These authors employed CHPTAC in aqueous NaOH, and found a better charcoal flocculation performance than other cationized polysaccharides and even than other commercial flocculants evaluated; this was attributed to the high molecular weight and branching of glycogen [165,166]. Tamarind kernel polysaccharide, derived from the seeds of the tree *Tamarindus indica*, is a xyloglucan which has β-1,4 linked D-glucan backbone that is partially substituted at the 6 position of its glucopyranosyl residue with α-D-xylopyranose. This polysaccharide was also cationized with CHPTAC and *DS* between 0.26 and 0.52 were obtained and tested in textile industry and wastewater treatment [167]. Hyaluronic acid was crosslinked and cationized with epichlorohydrin and $NaOH/NH_4OH$ solution [168]. The water-insoluble linear β-(1,3) D-glucan extract from the fruit body of *Ganoderma lucidum* was cationized using CHPTAC in 1 M NaOH aqueous solution at 60 °C. This product condensed DNA efficiently and was studied as gene carrier [169]

2.9. Complex agricultural products

Many other materials have been cationized with CHPTAC, among them, agricultural by-products that contain lignin together with polysaccharides, mainly cellulose and hemicelluloses. In 1980s, a series of ten articles with regard to the cationization of lignocellulosic materials such as beech sawdust, aspen wood and spruce wood meal were published [124,170–178]. The reaction of corn cob meal, allowed the extraction of modified arabinoglucuronoxylans [179]. The reaction has been used on stems of *Pisum sativum* L. cv Tyrkys (peas) to assist the fractionation of arabinogalactans and modified galacturonans [180]. Beech sawdust and wheat straw have also been cationized and crosslinked with epichlorohydrin to prepare insoluble anion exchangers, as the cationization alone tends to increase the solubility of the products [126]. Orlando et al., reacted rice hulls, sugarcane bagasse, coconut husks, pine barks, persimmon tealeafs, *Moringa oleifera* hulls and lauan sawdust with epichlorhydrin and dimethylamine in the presence of pyridine and *N,N*-dimethylformamide to create weak anion exchangers (the reacting amine is secondary which gives as a product a tertiary amine) [181,182]. Almond shells, corn cob, peanut shells, corn stover, oat hulls, cottonseed hulls, pecan shells, rice hulls, rice straw, soybean hulls, sugarcane bagasse and white oak chips were also treated [183]. It is believed that in these materials cellulose is the main component that reacts with CHPTAC and that high percentage of lignin hinders the access of the cationization reagent to the cellulose, thus decreasing cationization [170]. Because of this hindrance, Antal et al. found that in the case of sawdust the products more substituted were the hemicelluloses [171]. It was also found that the delignification of agricultural materials increased the efficiency of the reaction [124,181,182]. Cotton (80–90% cellulose, with smaller proportions of waxes and fats, proteins, hemicelluloses, pectins, etc.) was carboxymethylated and then cationized, obtaining in this way an amphoteric product capable of ionic crosslinking with improved textile fiber properties [110].

2.10. Analysis of cationized polysaccharides

Various analytical methods have been applied to cationized polysaccharides. One of the commonest tests is the determination of nitrogen to calculate the *DS* of the polysaccharide. This has been carried out by elemental analysis of nitrogen [48,76,157] or Kjeldhal method [25,62]. Less habitually, the determination of counteion was performed with silver nitrate (assuming chloride is the only counterion present) [76], or by a combustion method for the same purpose [17]. Infrared spectroscopy was also employed to confirm occurrence of reaction [26,99,100,157]. NMR spectroscopy was employed for that application and for the determination of the *DS* and less frequently to study the positions of substitution in the sugar unit [99,100,112,157,185]. Solid state NMR spectroscopy was also applied [184]. In this sense, Salomonsson et al. found that, in the conditions employed, amylopectin was more reactive than amylose [185].

Thermogravimetric analysis (TG) and differential scanning calorimetry (DSC) were used to study product stability with regard to native polysaccharide [23,27,100,113,157]. The rheological behavior of different cationic polysaccharides was also characterized [58,59,87–91,100,157,186–189].

In addition to *DS*, the substitution pattern within the monosaccharide unit and along the polysaccharide chain strongly influences product properties. Surprisingly, despite the number of publications on the cationization of polysaccharides, this has been barely studied by spectroscopic methods and even less by chemical methods. The group of Mischnick [8,21,190–194] developed a method to determine the substitution pattern of starch cationized with the group 2-hydroxy-3-(trimethylammonium)propyl ether. After cleavage of the glucosidic linkages by methanolysis and subsequent permethylation, the positively charged substituents were transformed to the neutral 2-methoxy-2-propenyl ethers through Hofmann elimination (Fig. 12, path A). These compounds could directly be separated by capillary gas liquid chromatography or after mild hydrolysis as the more stable 2-oxo-propyl derivatives. To halve the number of products, the methyl glycosides could be reduced to the corresponding 1,5-anhydroglucitols and then derivatized in the same way (Fig. 12, path B) [8,190]. Later an alternative approach of methanolysis, *N*-demethylation and *O*-trimethylsilylation was proposed. Two *N*-demethylation reagents were tested: thiophenolate, which gave high amounts of by-products, and morpholine with better results [194]. The reactivity order for starches cationized in homogeneous and heterogeneous conditions was $2 \gg 3 > 6$. Haack et al. applied the same method to their cationic starches and also found a higher reactivity of OH-2 [17]. The high selectivity, generally observed for reactions with low concentration of base reflects the highest acidity if the OH-2 next to the anomeric center. The disubstituted fraction followed the order $2,3 \gg 2,6 > 3,6$. Trisubstitution was only detected for $DS > 0.3$. Heterogeneous cationized samples show a higher amount of unsubstituted and disubstituted fraction than homogeneous ones. This shows uneven substitution of the starch molecule in hetereogeneous conditions [8]. In general, the proportion of monosubtituted units was higher, and that of unsubstituted and disubstituted units was lower when compared with those calculated with the model of Spurling [195]. This model takes into account the reactivities of the different substitution positions but assumes that the reactivities remain unchanged during the whole reaction. A conclusion is that the substitution with one cationic group has a negative intramolecular effect on new substitutions in the same unit, which can be attributed to electrostatic repulsions. The same group also applied enzymatic degradations and electrospray tandem mass spectrometry to substitution analysis [193]. Size exclusion chromatography coupled with with multi angle laser light scattering (SEC-MALLS) provided information about molecular weight distribution as different reaction conditions can result in more or less degradation [37,99,196].

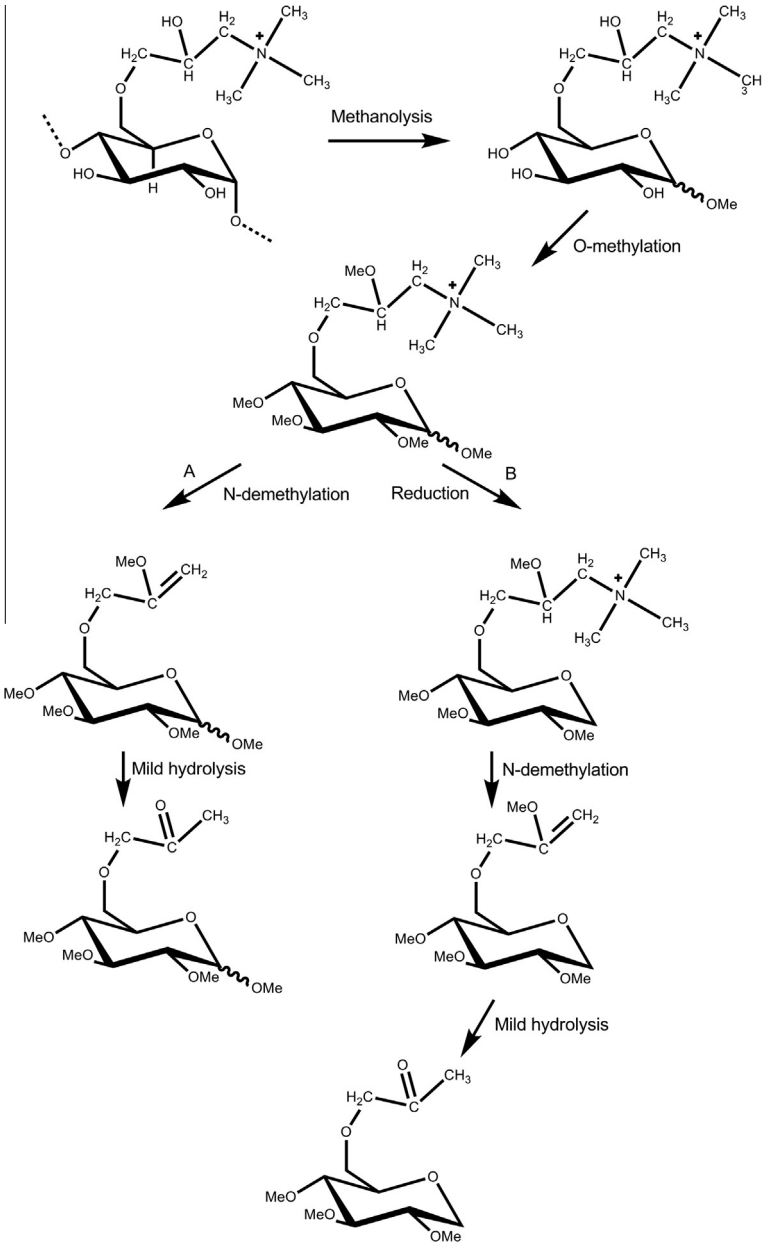

Fig. 12. Derivatization strategy of cationized polysaccharides for gas liquid chromatography analysis, as proposed by the group of Mischnick.

The mass-specific charge distribution in molar mass fractions of cationic starch derivatives was investigated by semi-preparative and analytical SEC-MALLS and from the consumption of anionic titrant solution using polyelectrolyte titration in combination with particle charge detection. The heterogeneity of substituent distribution decreased with increasing *DS* of the starch derivative. This was the case for samples from both the slurry and semi-dry processes. The heterogeneity of derivatization was highest for low *DS* samples up to *DS* 0.03, with the amylopectin-rich fraction incorporating more charges than the amylose-rich fraction. This was more pronounced for the sample from the slurry process than from the semi-dry process [196].

Another structural level of substitution analysis appears when the starting material presents a complex structure as starch granules, Vihervaara et al. concluded that in the cationization of starch by the wet method, granules are substituted homogeneously, whereas in semidry reactions the external regions of granules are preferentially modified [38]. Most authors agree that cationization by the wet method mainly occurs in amorphous regions of starch granules, as is evidenced by the unmodified X ray diffraction patterns [41,197] and the maintenance of the birefrin-

gence in polarized light microscopy [37]. Hamunen studied cationic starches prepared by different (dry or wet) methods by electron spectroscopy for chemical analysis (ESCA) and found that the differences in nitrogen distribution between the two methods was negligible, and that cationization took place more easily in the amorphous material of the inner parts of the granule than in the crystalline amylopectin layer of the surface [198]. However, the studies of Manelius et al., on cationized starch hydrolysates that were fractioned and analyzed, concluded that modification occurs throughout the granule [199]. Scanning electronic microscopy (SEM) provided information about the structure of the solid raw materials and the products, showing, for example if the structure of the starch granule was retained after cationization or not [22,24,26,41,157].

2.11. Toxicological studies

Toxicological evaluations of polysaccharides cationized with the 2-hydroxy-3-(trimethylammonium) propyl ether group were conducted with promising results. Cationized hydroxyethylcellulose administered orally in rats did not present toxicity at doses above 16 g kg^{-1}, three different mutagenicity assays gave negative results, as well as irritation and sensitization/fotosensitization assays [200]. When the citotoxicity of cationized celluloses was evaluated in embrionic human kidney cells (293T), employed for genes transfection, it was found that toxicity increased by increasing the concentration and the *DS*, even so toxicity was lower than polyethylenimine considered the "gold standard" in the field of transfection with cationic polymers [99]. Ito et al. evaluated the hemocompatibility of IPECs formed between celluloses or hydrohyethylcelluloses, cationized with EPTAC, as polycations and carboxymethylcellulose or cellulose sulfate as polyanions. The *in vitro* and *in vivo* assays revealed that according to the criteria employed, the cellulosic IPECs presented an excellent hemocompatibility. The experiments on the excess of charge in the IPEC (nonstoichometric IPECs) revealed that: (i) the relative coagulation time of whole blood is almost independent on the molar ratio polycation/polyanion within the ranges examined, in agreement with the *in vivo* studies, but (ii) platelet adhesion increased by increasing the polycation/polyanion molar ratio in the IPEC, and (iii) the activation of the intrinsic pathway of coagulation increased with decreasing molar ratio [201,202]. For applications as flocculants of colloids, the toxicity of cationized starches was studied, and it was concluded that starch with $DS = 0.28$ had no effect on mortality of chickens in the range of concentrations evaluated of 2–250 mg kg^{-1}. Despite toxicity slightly increased with increasing *DS*, this was lower than that of cationic polyacrylamides currently used for that purpose. Toxicity was independent of the botanical source of starch and the hydrolyzed cationic product presented a similar toxicity to that of the original cationic polysaccharides [1]. Cationized dextran presented good blood compatibility with no haemolysis, red blood cell or white blood cell aggregation. The citotoxicity of cationized dextran was very low and similar to native dextran [96].

3. Other substitutions

Similarly to the substitution with EPTAC and CHPTAC, in the 1950s and 1960s, the foundations of cationization with some other groups were laid. However, other substitutions are more recent. Among all the substitutions we can mention:

- Substitution with glycine betaine, forming an ester bond instead of an ether one. Granö et al., synthesized first betainyl chloride, which reacted in heterogeneous phase with starch; a disadvantage is the handling of the unstable betainyl chloride [203]. Auzély-Velty and Rinaudo employed starch, in the presence of *N*,*N*-dimethylglycine, diisopropylcarbodiimide and 4-dimethylaminopyridine in dry DMSO, to obtain the *N*,*N*-dimethylglycine ester. The modified starch was reacted with methyl iodide in dry DMSO to give starch betainate. The direct synthesis of starch betainate was also achieved, and consisted in the reaction of betaine hydrochloride in dry DMSO, diisopropylcarbodiimide and 4-dimethylaminopyridine (Fig. 13, path a) [204]. In two patents, Dubief et al. (together with Rinaudo) [205,206] presented the same reaction with the addition of hydroxybenzotriazole. This reagent is commonly employed in the synthesis of amide bonds to minimize the formation of the nonreactive *N*-acylurea [207] (Fig. 13, path b). Betaine was introduced in the amino group of chitosan, employing a five steps route that exploits a regioselective protection strategy. [208], or by reaction of *N*-chloroacyl-6-*O*-triphenylmethylchitosan with tertiary amines [209]. Chitosan *N*-betainates were applied as nonviral gene vectors [210], were employed in sublingual delivery of low solubility peptides [211] and showed low antimicrobial activity in neutral conditions [212]. Toxicity of chitosan *N*-betainates was rather low [213].
- Substitution with diethylaminoethyl and triethylaminoethyl groups through nucleophylic substitution of haloamines in alkaline medium on glucans, dextrans, amylose, amylopectin, cellulose, methylcellulose, hydroxyethylcellulose and pullulan [5,214–219]. In the case of pullulan the terciary amine was modified with alkyl bromides (of 10, 12 or 16 carbons of length) to achieve its quaternization and to obtain amphipatic products [220,221].
- In another aproach, Gonera et al. introduced the aminopropyl group in amylose and starch by a Wiliamson etherification with 3-bromine-propylamine protected with *N*-phthalyl group. The highest *DS* was achieved in dimethylsulfoxide with tetrabutylammoniumbromide as phase transfer catalyst and Li-dimsyl as base. The protecting group was removed by borohydride reduction and subsequent hydrolysis with acetic acid (Fig. 14) [222,223].
- Substitution with choline, in alkaline conditions similarly as the previous point. This reaction was performed with choline chloride and crosslinked starch in aqueous NaOH [70] or with chlorcholine chloride and cellulose in a deep eutectic solvent (chlorcholine chloride: urea 1: 2) (Fig. 15) [224].

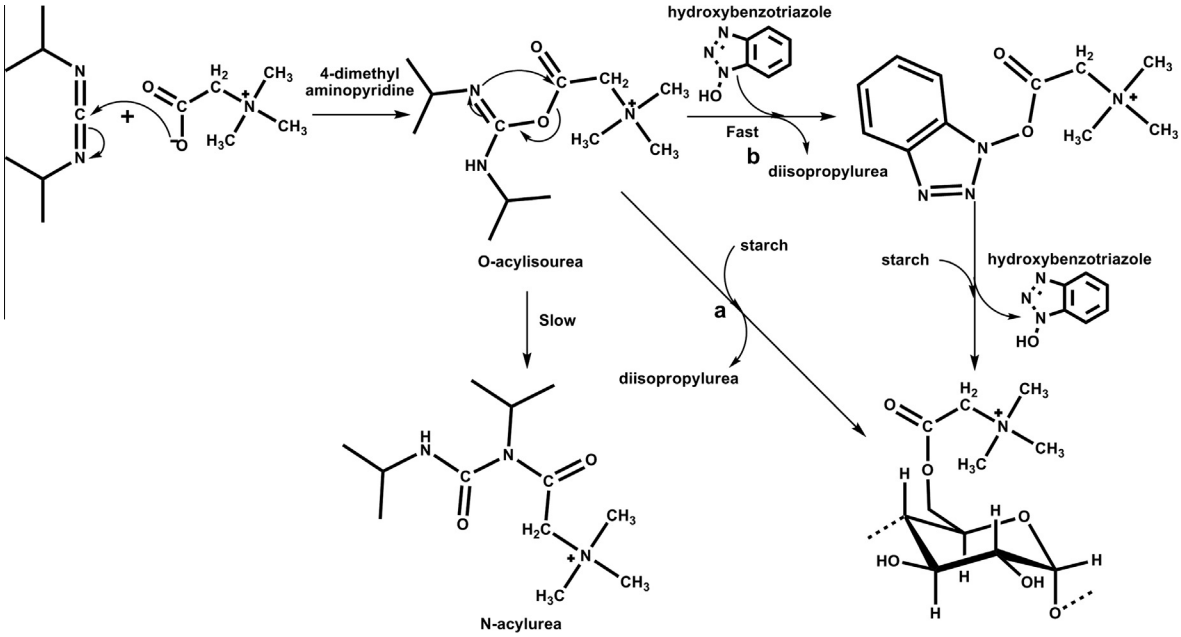

Fig. 13. Formation of the esther by carbodiimide coupling (a), use of hydroxybenzotriazole to minimize the formation of non reactive N-acylurea (b).

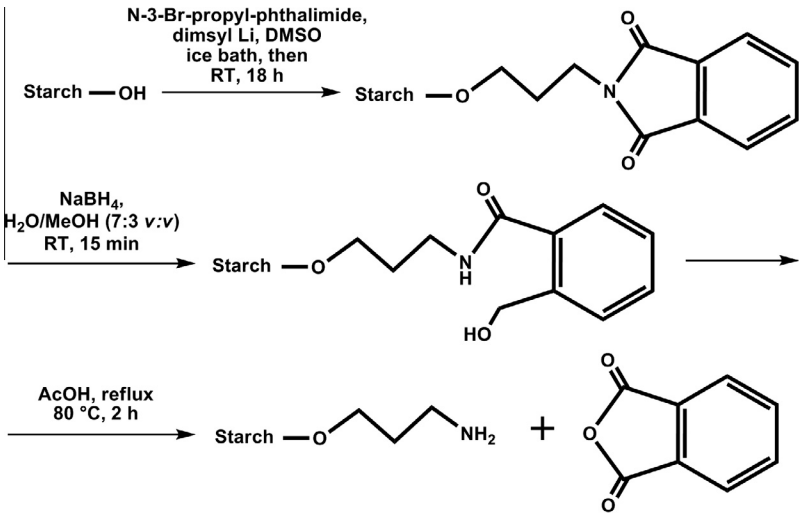

Fig. 14. Williamson etherification and removal of the protecting group.

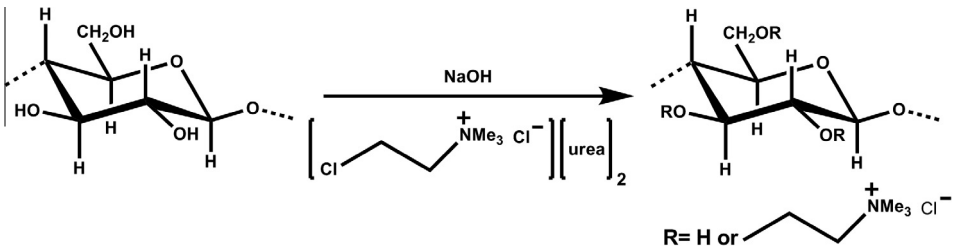

Fig. 15. Substitution of cellulose in a deep eutectic solvent (chlorcholine chloride: urea 1: 2).

- Reaction of glucans or starch with ethylenimine (aziridine). *DS* in the range 0.1–0.2 were obtained. When more vigorous conditions were applied the product presented lower *DS*, possibly because of ethylenimine polymerization with itself [5,225].
- Tamarind kernel polysaccharides were treated with ethylene diamine in aqueous medium at 30 °C for 6 h. This was followed by slow addition of reducing agent sodium borohydride ($NaBH_4$) for a period of 2 h until the formation of a thick gel. This product presented bioadhesive properties with applications in drug delivery [226].
- Nucleophilic substitution of the tosyl polysaccharide derivative with different aliphatic and aromatic amines, working on glucans, starch and cellulose [5,227–230].
- Cellulose or starch were treated in homogeneous phase with phenyl chloroformate in *N*,*N*-dimethylacetamide and pyridine with the addition of LiCl for cellulose or dimethylsulfoxide for starch. Resulting polysaccharide phenyl carbonates were treated with *N*,*N*-diethylaminopropylamine in tetrahydrofuran to obtain *N*,*N*-diethylaminopropyl carbamate polysaccharides. Quaternization was achieved by reaction with ethyl bromide in dimethylformamide (Fig. 16). The potential of basic polysaccharide derivatives as green and selective catalysts in Knoevenagel reaction was investigated [231].
- Reaction of the polysaccharide (glucan, cellulose, inulin, starch or amylose) with acrylonitrile in aqueous NaOH and subsequent reduction of the nitrile to amine. This prevents tandem reactions and reagent polymerization, which occur when using alkyl amine halides [5,221,232–236] (Fig. 17).
- Introduction of the nitro group and subsequent reduction. Various 2-nitroalkyl ether derivatives of polysaccharides (pullulan, agarose, inulin, poliglucuronates and hydroxyethylcellulose) were synthesized by reaction with 2-nitro-alquenes (2-nitro-1-propene and 2-nitro-1-butene) formed *in situ* from nitroalkyl acetates. The reduction of the two 2-nitroalkyl polysaccharides with $Na_2S_2O_4$ or $Na_2S_2O_4/NaBH_4$, unfortunately resulted in mixtures with the starting materials, nitroso compounds, hydroxylamines, hydroxypropyl ethers and sulfamates [237].
- Substitution of the hydroxyl in 6 position of the amylose with a halogen, followed by the substitution with azide and finally reduction to amine [238]. "Click chemistry" philosopy has been applied to synthesize curdlan cationic derivatives from an azide group introduced in 6-position [239].
- Block copolymers between dextrans and polylysine were synthesized, linked through reductive amination [240]. L-lysine amphoteric derivatives of cellulose were prepared by means of the reaction of a Cu(N6-(4,6-dichloro-1,3,5-triazin-2-yl)-L-lysine)$_2$ complex with cellulose (Fig. 18) [241].
- Partial oxidation of dextrans with periodate, to form a dialdehyde in the oxidized sugar unit and subsequent reductive amination employing different polyamines of interest such as spermine or quaternary monoammonium derivatives; these products were employed for gene delivery [242–250] (Fig. 19). An analogous synthesis is reported for schizophyllan, a β-(1→3)-glucan [251]. Employing a similar strategy, the hydroxyl in the 6 position of a β-glucan from oat (*Avena sativa* L.) was oxidized with paraformaldehide and then underwent a reductive amination with ammonium acetate and $NaBH_4CN$ [252].
- The reaction of starch or polygalacturonic acid with 1,3-bis(3-chloro-2-hydroxypropyl)imidazolium hydrogen sulfate, in aqueous NaOH results in crosslinking with

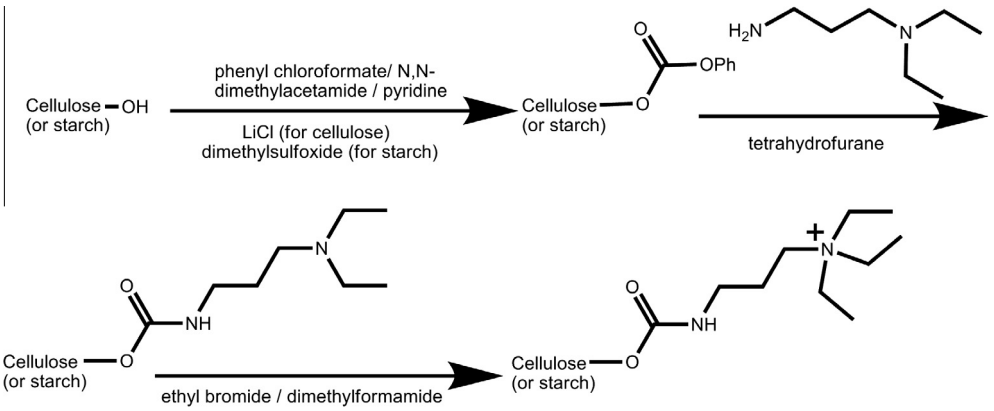

Fig. 16. Synthesis of soluble *N*-functionalized polysaccharide derivatives from cellulose or starch using phenyl carbonate precursor.

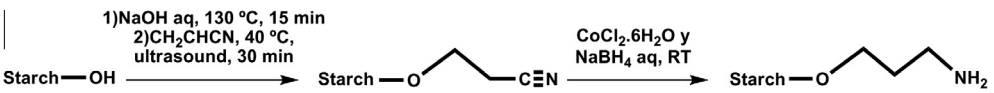

Fig. 17. Reaction of starch with acrylonitrile and subsequent reduction.

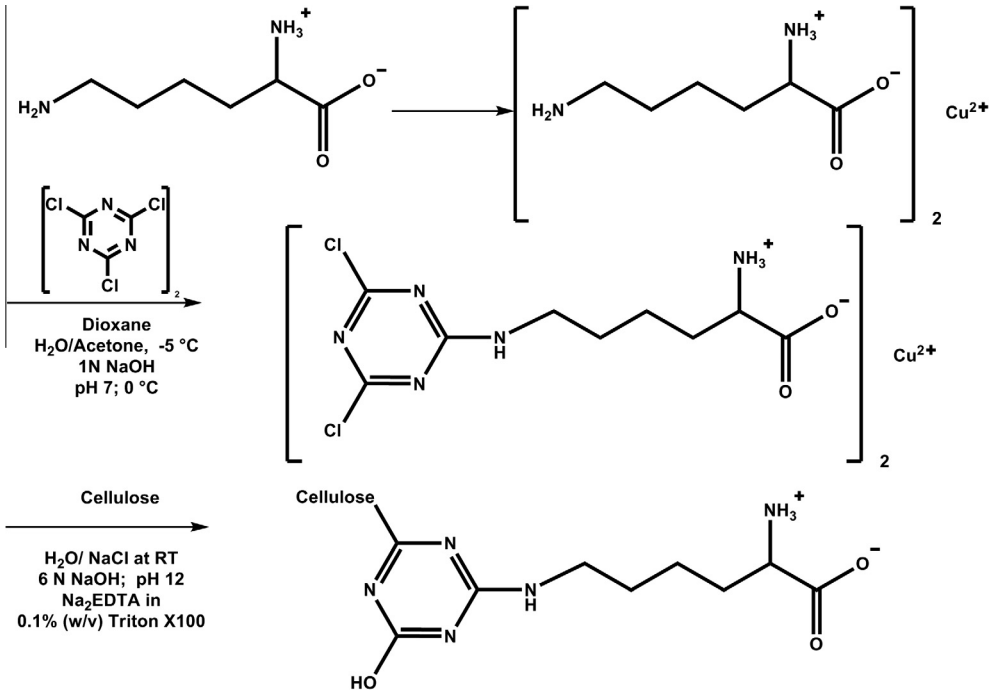

Fig. 18. Synthesis of the L-lysin cellulose derivative.

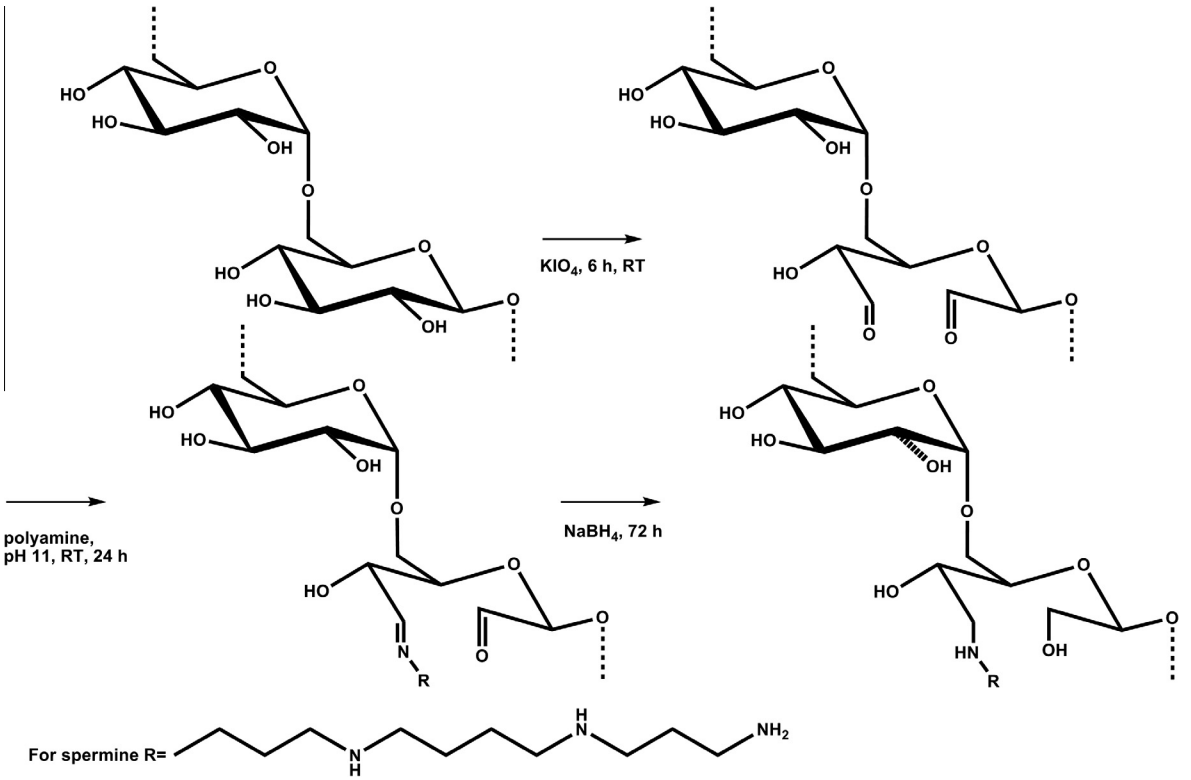

Fig. 19. Periodate partial oxidation and subsequent reductive amination of dextran.

the mentioned bifunctional cationic group, the insoluble product presents potentiality as ion exchanger [253] (Fig. 20). Microcrystalline cellulose was also treated with 1,3-bis(3-chloro-2-hydroxypropyl)imidazolium hydrogen sulfate together with CHPTAC in alkaline medium [254]. The cationic cellulose was employed as a carrier capable of quantitative removal of heparin from blood plasma samples [255].

- Hydroxypropylcellulose was cationized with (3-acrylamidopropyl)-trimethylammonium chloride and benzoyl peroxide and evaluated as potential heparin antagonist [97]. Pullulan was also grafted with (3-acrylamidopropyl)-trimethylammonium chloride in aqueous solution using potassium peroxydisulfate [256]. Another thermosensitive cationic pullulan polysaccharide was synthesized by graft-polymerization of p(*N*-isopropylacrylamide) (pNIPAAm) onto pullulan using Ce^{IV} ion as initiator [257]. Cationic pullulan was used as biodegradable flocculant agents [256,257]. Acrylamide was grafted onto starch using Ce^{IV} ion as initiator. Starch-graft-polyacrylamide was then modified through Mannich reaction using formaldehyde and diethylamine to give poly(*N*,*N*-[(diethylamino) methyl]-acrylamide) derivative. The modified-graft copolymer was quaternized using different reagents; methyl iodide, *N*-butylbromide, sodium chloroacetate and propane sultone to give cationic and amphoteric graft materials, with swelling properties [258].

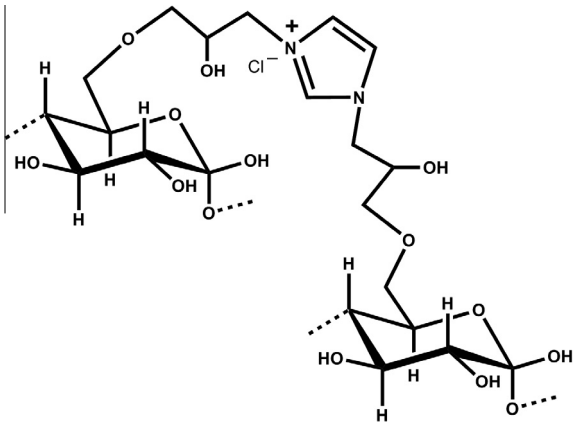

Fig. 20. Starch crosslinked with 1,3-bis(3-chloro-2-hydroxypropyl)imidazolium hydrogen sulfate.

- Rosol et al., in search of cationic polyelectrolytes that associate with oppositely charged surfactants, prepared a cationic derivative from hydroxypropylcellulose by the reaction with *N*-vinylformamide and benzoyl peroxide as initiator of the radical reaction in dimethylformamide, then hydrolyzed the amide group to release the amino [259].
- Photoactive derivatives were prepared by a mild esterification of cellulose with 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetic acid via the activation of the carboxylic acid with *N*,*N*′-carbonyldiimidazole. The product was esterified with the cationic carboxylic acid (3-carboxypropyl)trimethylammonium chloride to obtain a water soluble product [260].
- Trimethyl chitosan was synthesized by various authors. A typical method of *N*-trimethylation is the dispersion of chitosan in *N*-methylpyrrolidone that contains sodium iodide and methyl iodide in the presence of NaOH as a base (Fig. 21). The iodide counterion of the reaction product is interchanged with chloride, to obtain a more stable salt. The varied chemistry of chitosan led to some revisions [131,261,262].

4. Conclusions

The reaction most frequently used for polysaccharide cationization is the etherification with the 2-hydroxy-3-(trimethylammonium)propyl group. This reaction has proved its versatility and robustness, allowing the derivatization of all kinds of polysaccharides. Its advantages are high speed, compatibility with aqueous media, the fact that it does not require imperatively heating, and the possibility of *DS* modulation in an ample range varying reaction conditions. While it is true that a certain degree of degradation occurs by the alkaline medium, this can be kept to a minimum choosing the right conditions. All the aforementioned, coupled with the low toxicity of the products, have made the above reaction very adequate for multiple applications at industrial scale.

The substitution with glycine betaine seems atractive for the biodegradability of the ester bond that leads to the original polysaccharide and to betaine. The latter is a nontoxic natural product found in many plants (including seaweeds), animals, fungi and bacteria [263]. However, the advantages of the substitution with this group are partially offset by the need to use organic solvents instead of water and other technical difficulties. This is reflected in the low number of publications on this substitution. Other modifications have found applications in specific fields, as the substitution with polyamines (for example spermine)

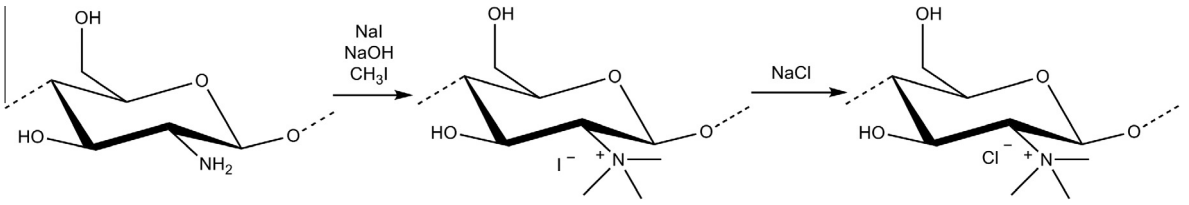

Fig. 21. Quaternization of the nitrogen of chitosan.

to form interpolyelectrolyte complexes with DNA in cell transfection.

Research on the cationization of polysaccharides and its applications is a bet on an enviromentally friendly future, where modified natural macromolecules would replace petroleum derived polymers. One area particularly promising for the replacement of synthetic materials is that of stimuli-sensitive drug delivery [264]. Paraphrasing the title of an article by Šimkovic in 2008, what could be greener than polysaccharides? [265].

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