Structure Design of Polysaccharides by Selective Conversion: Old Hat or Topical?

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The functionalization pattern in polysaccharide derivatives is an important factor that determines their properties and, thus, their functions in applications. Regioselectively functionalized polysaccharide derivatives are used in material science because they may form lamellar structures in microscale by self-assembling. Intrinsically chiral polysaccharide derivatives are used for the separation of enantiomers by chromatography, and the separation efficiency is influenced by the regioselective distribution of substituents attached. Due to the multi-functionality of polysaccharides, their derivatization reactions usually yield products with random distribution of substituents. Thus, establishment of unambiguous structure-property relationships cannot be achieved. This review article summarizes recent developments in this topic. In addition to the blocking group techniques, synthesis methods applying activating substituents will be summarized. Moreover, the reaction medium itself may direct the substituent in a certain position without laborious multistep reactions.

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INTRODUCTION

It is generally accepted that the properties of polysaccharide derivatives depend not only on the type of substituent and its degree of substitution (DS) but also on the functionalization pattern within the repeating unit and along the polymer chain, which is of crucial importance. As it is depicted in Fig. 1, the repeating unit of the polysaccharide may bear three hydroxyl groups, considering the most available glucans. The hydroxyl groups are primary or secondary hydroxyl moieties located on different positions within the sugar repeating unit. Therefore, both reactivity and accessibility of these reactive sites are different, provided that the polymer is dissolved and reactivity is not influenced by presence of crystalline- and amorphous phases. A reagent of low steric demand is capable of reacting with each of those hydroxyl groups but to a different extent. Thus, up to eight differently functionalized repeating units can be detected in a polysaccharide derivative with a degree of substitution lower than three. In addition to non-functionalized and fully functionalized (*e.g.*, 2,3,6-tri-*O*-units) repeating units, there are three mono-functionalized (2-mono-*O*-, 3-mono-*O*-, and 6-mono-*O*-units) and three di-functionalized (2,3-di-*O*-, 2,6-di-*O*-, and 3,6-di-*O*-units) units for polysaccharides like cellulose or starch. Considering the entire polymer chain, the polymer can consist of uniformly functionalized repeating

units or differently functionalized repeating units that are blockwisely or randomly distributed along the polymer chain. These "blocks" may be constituted from differently functionalized units (Fig. 1B).

The structure of a glucan derivative becomes more complicated if two or more substituents are present. For hydroxyalkylations, generating a new hydroxyl group in the side chain, the structure becomes even more complex. Thus, the number of differently functionalized groups will further increase.

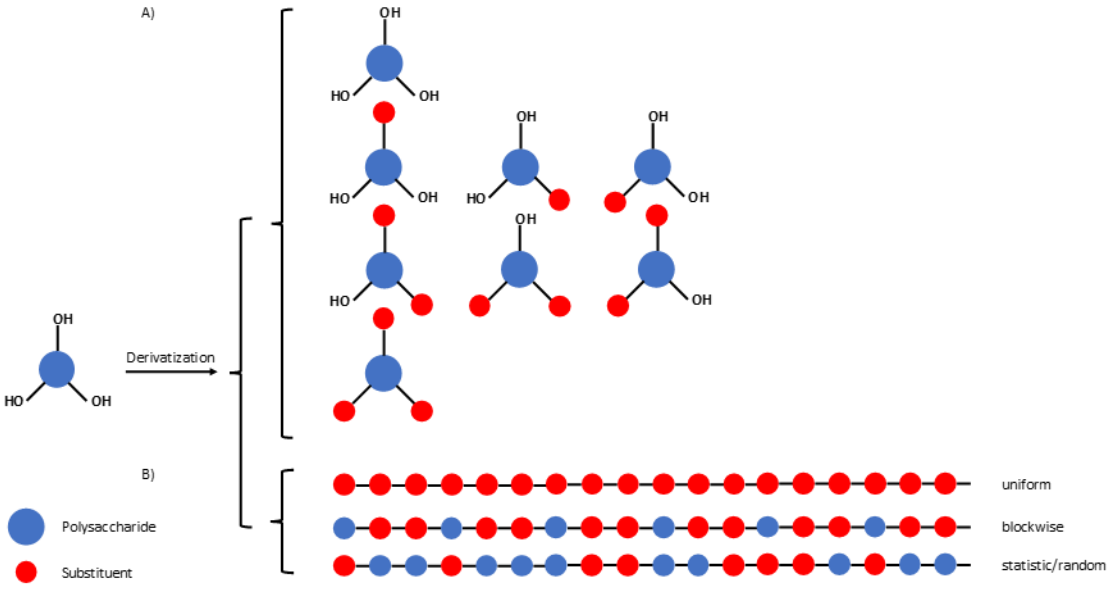

Fig. 1. Functionalization pattern in polysaccharide derivatives within the repeating unit (A) and along the polymer chain (B)

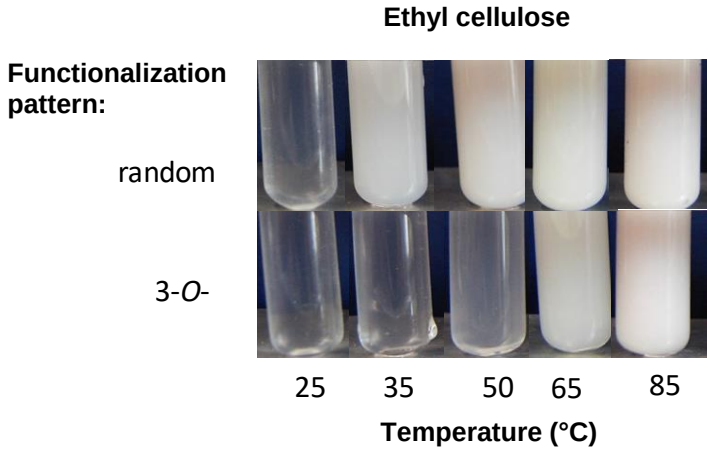

Fig. 2. Comparison of ethyl cellulose of different functionalization patterns dissolved in water at different temperatures; Adapted from Sun *et al.* (2009)

The establishment of structure-property relationships is a crucial issue in polysaccharide research. However, the huge number of differently functionalized repeating units makes the structure analysis difficult or even impossible. It is indispensable to know the structure of the polymers to understand their properties. In other words, there is a need of structures that can be analyzed; *i.e.*, the compound must be as uniform and controllable

as possible. Figure 2 depicts the impact of functionalization pattern on the thermal behavior of ethyl cellulose of comparable DS in aqueous solution. Both randomly and selectively functionalized ethyl cellulose are water soluble at room temperature. Through increasing the temperature, the conventional cellulose ether becomes insoluble starting at 30 °C, while the regioselectively functionalized derivative is still dissolved and starts to flocculate at 60 °C.

Several pathways for controlled functionalization have been developed so far:

- Selective blocking of reactive sites and use of orthogonal protecting groups;
- Selective activation of hydroxyl groups;
- Chemoselective conversion

This review intends to discuss the synthesis methods mentioned above. Moreover, recently published achievements are summarized. However, papers dealing with enzymatic reactions using lytic polysaccharide monooxygenases (Forsberg *et al.* 2020; Sun *et al.* 2022) are not in the focus of this particular review article. Moreover, topochemical reactions, where a discrimination between better and less accessible OH groups must be taken into account or where surface effects occur, are not considered here (Mann *et al.* 1998; Sobhanadhas *et al.* 2018; Vliegenthart *et al.* 2000).

SELECTIVE BLOCKING OF REACTIVE SITES

The utilization of blocking groups takes advantage of the steric demand of bulky reagents. As mentioned in the introduction, the accessibility of hydroxyl groups within the repeating unit is different, with the primary hydroxyl group being more accessible compared with the secondary ones. Thus, a bulky reagent will react preferably with the most accessible reactive site.

Blocking Groups

There are two main classes of blocking groups that have been established in regioselective functionalization of polysaccharides. They are based on (i) triphenylmethyl (trityl) ethers and (ii) trialkylsilyl ethers bearing at least one bulky substituent. An intriguing advantage of both types is that they show different selectivity, possess different stability towards reaction conditions, and they can be cleaved off under different conditions. However, it must be noted that the blocking group technique is quite laborious and involves several reaction steps: (i) introduction of the blocking group, (ii) functionalization of the remaining hydroxyl groups, and (iii) deprotection of the functionalized polysaccharide derivative. An indispensable prerequisite is that the functionalization reaction of the protected derivative can be conducted without affecting the blocking groups and that the deprotection occurs without affecting the functional groups introduced. Nevertheless, a certain polymer degradation due to this multistep reaction must be considered.

Triphenylmethyl ethers

One of the first papers describing "Ethers of triphenylcarbinol with cellulose and starch" was published in 1924 (Helferich and Koester 1924). The limitation of the DS_{Trityl} as well as a proposed regioselectivity were recognized by Hearon *et al.* (1943). It took nearly a half century before trityl ethers were employed for the synthesis of 2,3-*O*-methyl

cellulose (Kondo and Gray 1991). The most convenient way for the preparation of trityl ethers is the conversion of cellulose dissolved in *N*,*N*-dimethyl acetamide (DMA)/LiCl. It has been found that activating substituents attached to the benzene moiety lead to an increase of both formation and cleavage of the trityl ether (Fig. 3, Table 1) (Gömez *et al.* 1996).

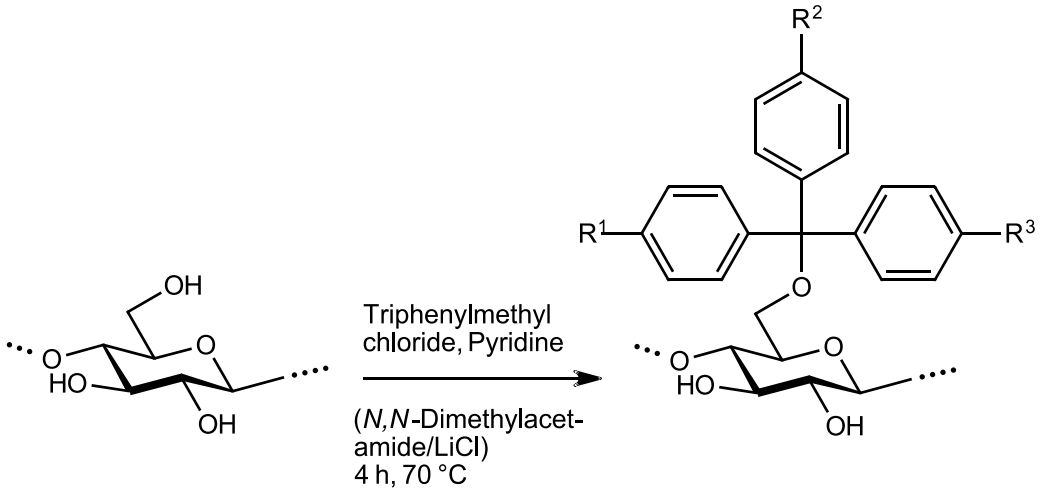

Fig. 3. Synthesis of triphenylmethyl ethers by conversion of cellulose with triphenylmethyl chlorides in presence of pyridine under homogeneous conditions; R means H or OCH_3

Table 1. Conversion of Cellulose Dissolved in *N*,*N*-dimethylacetamide/LiCl with Substituted Triphenylmethyl Chlorides in Presence of Pyridine for 24 h at 70 °C

Triphenylmethyl Ether			DS	Reaction Rate	
R^1	R^2	R^3		Formation	Cleavage
H	H	H	0.41	1	1
H	H	H	1.05[a]		
OCH_3	H	H	0.96	2	18
OCH_3	OCH_3	H	0.97	$2 \cdot 10^5$	100
OCH_3	OCH_3	OCH_3	0.96	$6 \cdot 10^6$	590
DS: Degree of substitution [a] After 48 h at 70 °C					

Notes: Selected values taken from Gömez *et al.* (1996)

Already one methoxy group increases the reaction rate by the factor of 2 for formation and by the factor of 18 for the cleavage. However, the price of the reagent increases by one magnitude per methoxy group. Considering this, monomethoxytrityl chloride was found as the reagent of choice. The resulting monomethoxytrityl ethers of the polysaccharide are soluble in solvents such as dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF), and the trityl ethers tolerate aqueous alkaline conditions without being lost. Deprotection by acidic cleavage is favored by the high stability of the intermediately formed trityl cations. This can be achieved under both heterogeneous and homogeneous conditions by the treatment of the protected polymer with HCl in THF (Gömez *et al.* 1996), HCl in ethanol (Heinze *et al.* 1999), or with HBr in glacial acetic acid (Iwata *et al.* 1992).

Trialkylsilyl ethers

Trialkyl silyl ethers are formed by conversion of cellulose with the corresponding chlorosilanes (Schuyten *et al.* 1951; Klebe 1968; Klebe and Finkbeiner 1969) or hexamethyldisilazane (Cooper *et al.* 1981; Mormann and Wezstein 2009). However, the steric demand of the trimethylsilyl group is low and, hence, no regioselectivity of silylation is observed. Even the synthesis of almost fully trimethylsilylated cellulose derivatives is possible (Kostag *et al.* 2010). However, such derivatives bear the advantage of shaping and regenerating cellulose due to the lability of the silyl ether under acidic conditions. This has been applied for the preparation of nanoparticles (Kostag *et al.* 2010), thin films (Jones *et al.* 2019; Reishofer *et al.* 2022), and melt-spun fibers (Cooper *et al.* 1981).

The steric demand of the silyl reagents is tremendously increased by replacing one of the methyl groups by a bulky alkyl moiety like tert.-hexyl or tert.-butyl. Both tert.-hexyldimethylchlorosilane (TDMS-Cl) and tert.-butyldimethylchlorosilane (TBDMS-Cl) react regioselectively and can even be controlled by the state of dissolution and activation state of the polysaccharide (Fig. 4).

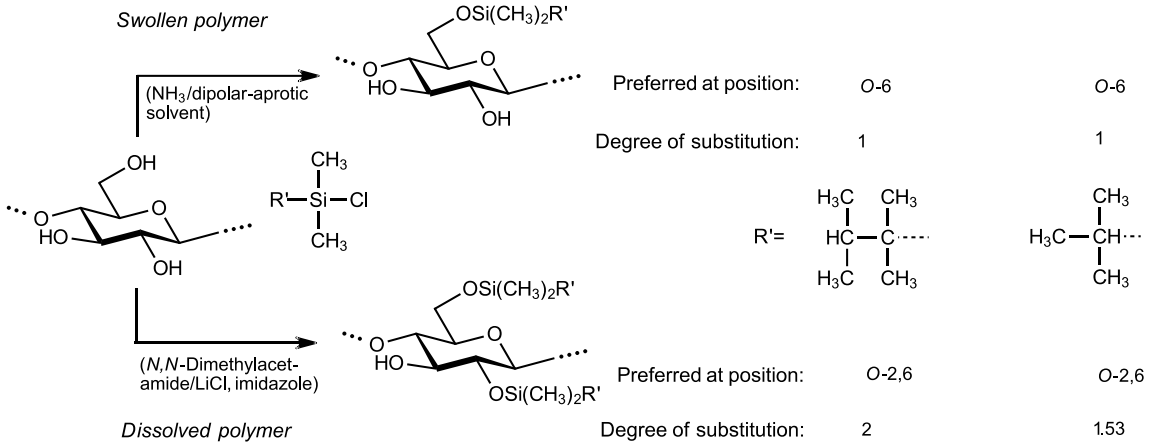

Fig. 4. Regioselectivities of trialkylchlorosilanes depending on the activation state of cellulose. References: Thexyldimethylsilyl ether (Klemm and Stein 1995; Koschella and Klemm 1997), tert-butyldimethylsilyl ether (Heinze *et al.* 2008)

Selected Examples

The following subsections summarize selected examples for the utilization of blocking groups in the field of regioselective polysaccharide functionalization.

2,3-O-Functionalized polysaccharide derivatives

The trityl group has been applied for the preparation of "cellulosic bottlebrushes". In this context, the 6-*O*-protected cellulose was allowed to react with 2-bromoisobutyryl bromide (Sakakibara *et al.* 2018). The DS values of up to 0.90 could be realized. The ester obtained is used as atom transfer radical polymerization initiator to polymerize styrene. Thus, polystyrene grafts are regioselectively attached to positions 2 and 3, while position 6 remains unaffected. Other derivatives such as polyethyleneglycol chains at those positions are described as well. In this regard, position 6 has been reacted with 4-pentynylcarboxylic acid after detritylation, which can be further treated by click chemistry (azide/alkyne cycloaddition). This concept can also be applied for the synthesis of mixed derivatives bearing polystyrene and poly(ε-caprolactone) (Sakakibara *et al.* 2021). The

products were shaped to films. The polymers form a lamellar microdomain structure by self-assembling with an interlamellar distance of 30 nm (Fig. 5).

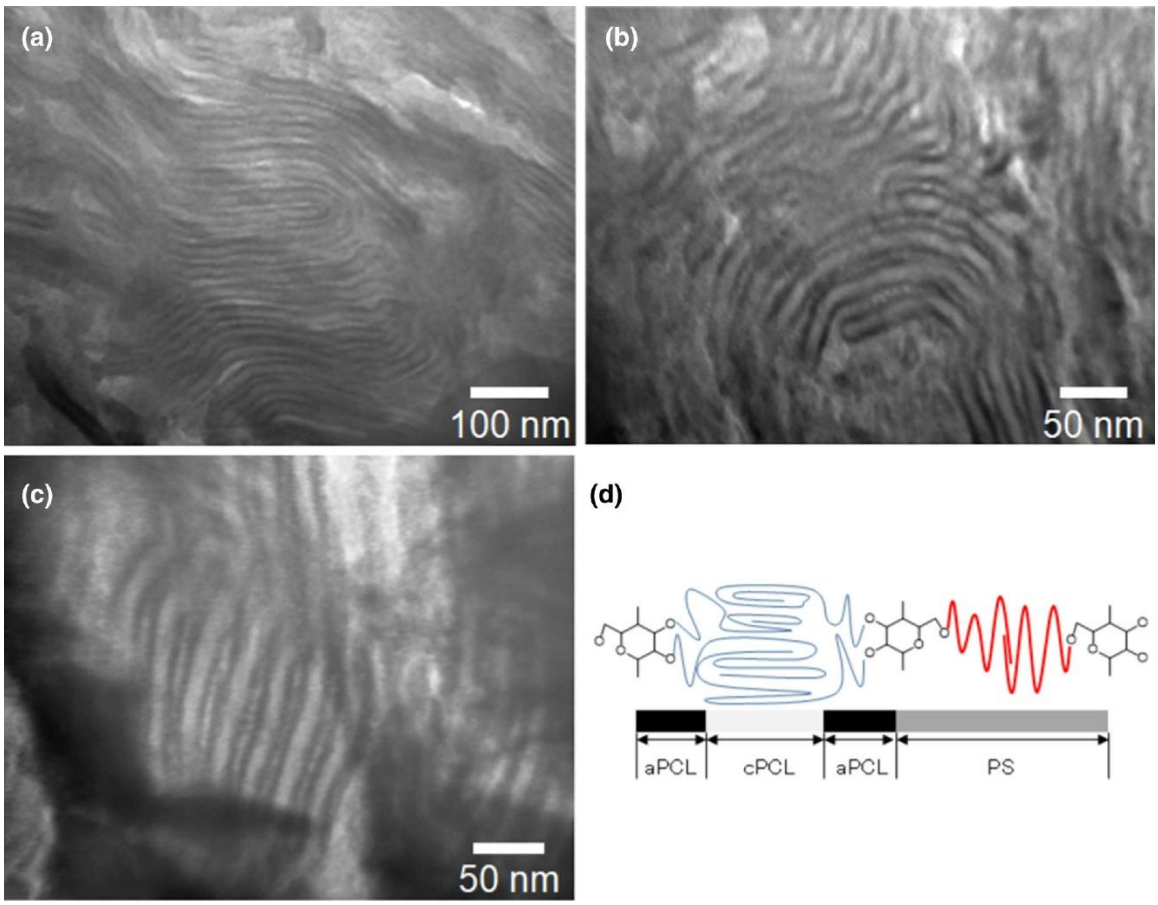

Fig. 5. Transition electron microscopic images of bulk films from mixed derivatives bearing polystyrene and poly(ε-caprolactone) (PCL) annealed at 120 °C for 24 h (a through c); d: Schematic illustration of the packing of the Janus bottlebrush with stained regions (cPCL: crystalline PCL; aPCL: amorphous PCL) ((Reprinted from Sakakibara *et al.* 2021 with permission from Springer Nature)

Long-chain ethers with exclusive etherification of positions 2 and 3 were prepared *via* 6-*O*-monomethoxytrityl cellulose followed by deprotection with *p*-toluenesulfonic acid (Saito *et al.* 2012). Subsequent conversion to phthalocyanine-containing cellulose derivatives afforded products that can be shaped to monolayer films on indium tin oxide by Langmuir-Blodgett technique that generates a photocurrent upon light irradiation (Saito *et al.* 2014; Saito *et al.* 2017).

Dai *et al.* applied 6-*O*-protected amylose for the preparation of mixed carbamates (Dai *et al.* 2019). Positions 2 and 3 were carbamoylated with an isocyanate, followed by deprotection and carbamoylation of position 6 with another isocyanate (Fig. 6). Tests of the enantioseparation ability revealed that the chiral recognition of the amylose derivatives was significantly influenced by the structure and electronic properties of substituents.

Bui and Rosenau used a 6-*O*-protected cellulose derivative for the preparation of novel chiral selectors for the separation of enantiomers by high performance liquid chromatography (HPLC) (Bui *et al.* 2023a). The resulting cellulose 2,3-bis(3,5-dimethylphenyl carbamate) was further reacted with phenyl chloroformate, which

underwent aminolysis with enantiopure α-methylbenzylamine affording cellulose 2,3-bis(3,5-dimethylphenyl carbamate)-6-(R/S-α-phenylethyl carbamate). The chiral selectors were then coated onto silica and packed into HPLC columns. These new derivatives have shown a medium dependence on the performance of separation of enantiomers. However, clear trends could not be identified up to now and further evaluation with a bigger set of chiral analytes is necessary.

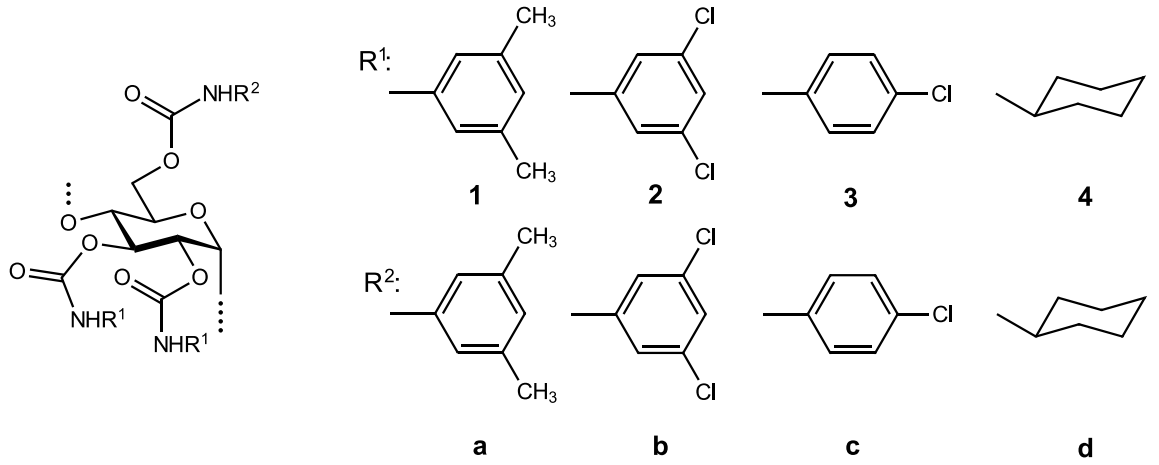

Fig. 6. Structures of amylose derivatives (redrawn from Dai *et al.* 2019)

Guar gum has been subjected to tritylation; a degree of substitution of trityl groups of 0.71 was achieved (Niu *et al.* 2013). Further conversion with phosphoryl chloride in pyridine and subsequent detritylation with dichloroacetic acid afforded products with a degree of substitution of around 0.4. Phosphorylation of positions 2 and 3 increases the antioxidant activity compared with non- and randomly phosphorylated guar gum.

3-O-Functionalized cellulose derivatives

The intriguing 2,6-di-*O*-selectivity of the TDMS group has drawn attention towards the preparation of 3-*O*-functionalized cellulose derivatives. A broad variety of differently substituted derivatives has been prepared (Table 2).

The methylation can be used to selectively switch-off of intra- and intermolecular hydrogen bonds that prevent, *e.g.*, the dissolution of cellulose. The hydrogen bond systems of regioselectively methylated polysaccharide derivatives have been investigated by deconvolution of the band of remaining OH groups in the Fourier transform infrared (FTIR) spectra as well as by X-ray diffraction (XRD)- and ^{13}C-cross polarization/magic angle spinning (CP/MAS) nuclear magnetic resonance (NMR) experiments (Kondo *et al.* 2008). A recent approach to obtain insight in such well-defined polymers is the utilization of dynamic nuclear polarization MAS NMR to characterize these derivatives, giving a much higher resolution compared with standard ^{13}C-CP/MAS- or solution-NMR techniques (Fig. 7) (Berruyer *et al.* 2021). This sophisticated technique gains information on spatial distribution of functional groups, which can be helpful for the establishment of structure-property relationships in the field of commercially relevant cellulose ethers (Berruyer *et al.* 2022).

Table 2. Properties of Different 3-*O*-Functionalized Cellulose Derivatives

Substituent	Solubility[a]					Comment[b]	Reference
	EtOH	DMSO	DMA	H_2O			
				< 20 °C	rt		
Methyl	-	-	-	-	-	Hydrogen bonding	(Koschella *et al.* 2001)
Ethyl	-	+	+	+	+	LCST	(Koschella *et al.* 2006a)
Hydroxyethyl	-	+	+	+	+	No LCST	(Fenn and Heinze 2009)
Methoxyethyl	-	+	+	+	+	No LCST	(Heinze and Koschella 2008)
3'-Hydroxy-propyl	-	+	+	+	+	No LCST	(Schumann *et al.* 2009)
Allyl	-	+	+	-	-	Reactive	(Koschella *et al.* 2001)
Propyl	+	+	+	+	-	LCST	(Heinze *et al.* 2011)
Propargyl	-	+	+	-	-	Reactive	(Fenn *et al.* 2009)
Butyl	+	+	+	-	-		(Illy 2006)
n-Pentyl	+	+	+	-	-	n_A 82	(Petzold *et al.* 2004)
iso-Pentyl	+	+	+	-	-	n_A 6.5	(Petzold *et al.* 2004)
Dodecyl	-	-	-	-	-	n_A 1[c]	(Petzold *et al.* 2004)
Oligo(ethylene glycol)	-	-	-	-	-		(Bar-Nir and Kadla 2009)

[a] Ethanol (EtOH), dimethyl sulfoxide (DMSO), *N,N*-dimethylacetamide (DMA), room temperature (rt), soluble (+), insoluble (-)
[b] Lower critical solution temperature (LCST), aggregation number (n_A) measured by light scattering
[c] Molecularly dispersed at c < 2 g/L

It became obvious that a strong hydrogen bond network must be present in 3-*O*-methyl cellulose because it dissolved in DMSO only after addition of LiCl (Koschella *et al.* 2001).

Longer chains attached to position 3 render the polymer soluble in solvents of different polarity including water. It is known that water soluble cellulose ethers exhibit the phenomenon of lower critical solution temperature (LCST), which is helpful for product purification during the production of cellulose ethers in industrial scale. The LCST of 3-*O*-propyl cellulose is in the range of room temperature. It could be noticed that the solubility test conducted at room temperature was negative, but a positive test was achieved with the chilled mixture of the same sample (Heinze *et al.* 2011). Other 3-*O*-ethers like allyl- (Koschella *et al.* 2001) and propargyl moieties (Fenn *et al.* 2009) bear selectively introduced reactive sites for further functionalization. In particular, the propargyl ether is of interest in the field of azide/alkyne chemistry (Huisgen reaction (Fenn *et al.* 2009).

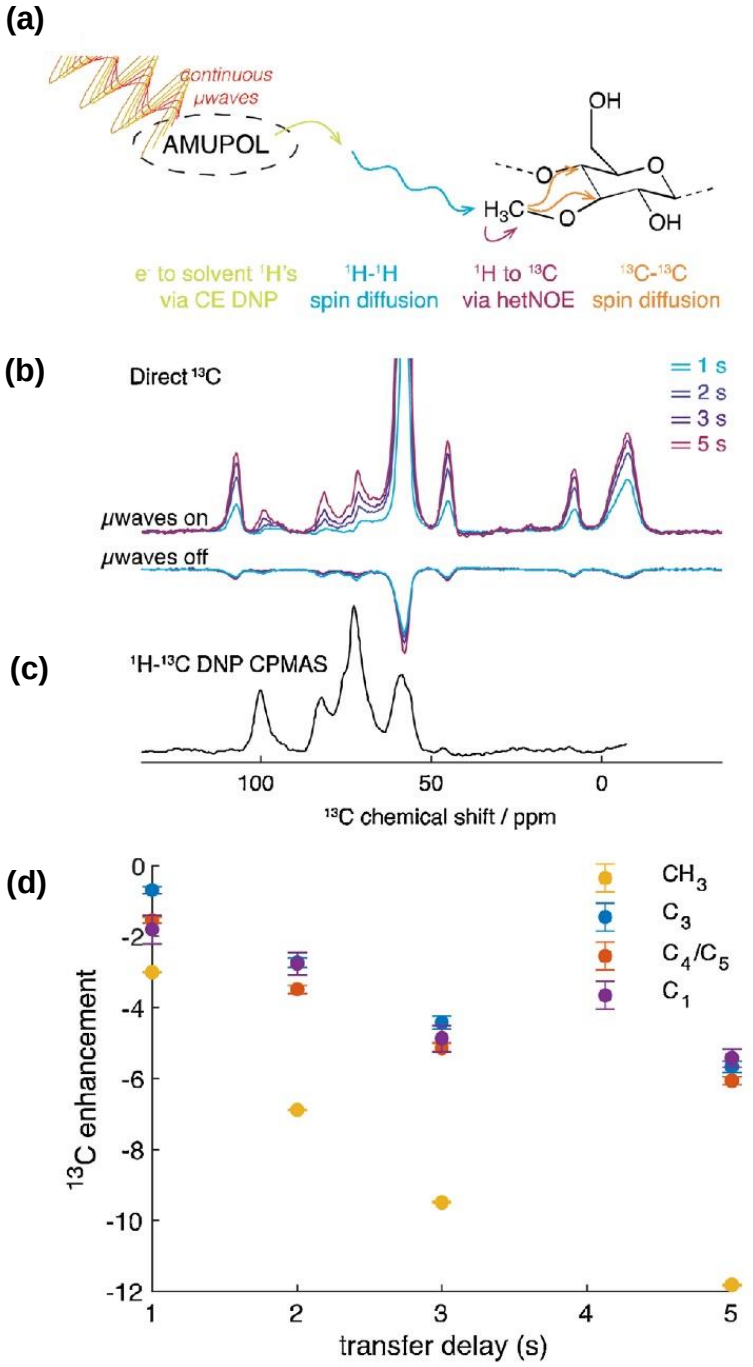

Fig. 7. (a) Principle of substitution site identification for the reference sample 3-*O*-methyl cellulose by combining dynamic nuclear polarization magic angle spinning (DNP MAS) with hNOE and ^{13}C-^{13}C spin diffusion. (b) Direct ^{13}C NMR spectra with (plain line) and without (dashed line) μwave irradiation, and with recycle delays varying from 1 to 5 s and (c) ^{1}H-^{13}C DNP CPMAS of 3-*O*-methyl cellulose impregnated with 10 mM AMUPOL in D_2O:H_2O 9:1 v/v at 5 kHz MAS, at *ca.* 100 K. (d) ^{13}C enhancement (from direct ^{13}C NMR) as a function of the recycle delay and for the different resolved and detectable signals (Reprinted from Berruyer *et al.* 2021; with permission from Elsevier)

Consequent utilization of blocking group technique including so-called orthogonal blocking groups enabled the preparation of all functionalization patterns (Fig. 8).

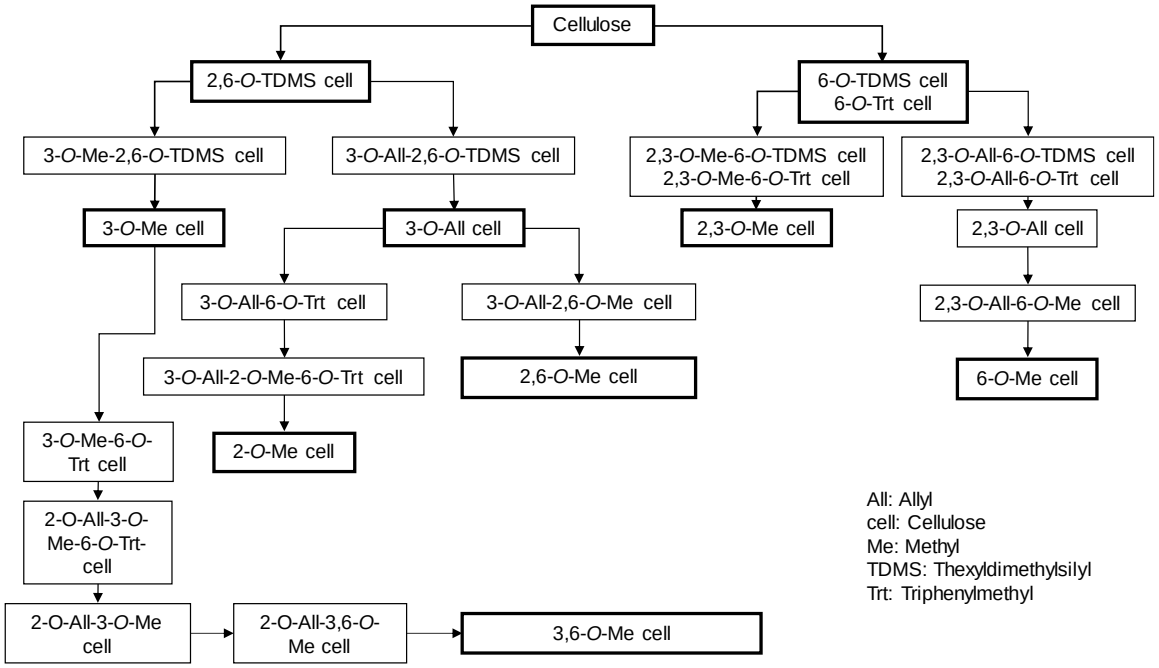

Fig. 8. Synthesis scheme for the preparation of a toolbox of differently functionalized methyl celluloses using multiple blocking groups. References: 2-O- (Nakagawa *et al.* 2012), 3-O- (Koschella *et al.* 2001), 6-O- (Kondo 1993), 2,3-O- (Kondo and Gray 1991; Koschella *et al.* 2006b), 3,6-O- (Nakagawa *et al.* 2012), and 2,6-O- (Kamitakahara *et al.* 2008)

It has been found that the length of the alkyl chain determines the LCST of the 3-*O*-alkyl cellulose, *i.e.*, 3-*O*-ethyl cellulose possesses a LCST of *ca.* 60 °C (Koschella *et al.* 2006a), while the LCST of 3-*O*-propyl cellulose is around room temperature (Heinze *et al.* 2011). Attempts of controlling the LCST by simply mixing both cellulose ethers failed thus far because the LCST in a physical mixture of two different cellulose ethers is always governed by the component with the lowest LCST (Fig. 9A). Therefore, the drop of transmittance always starts in a similar temperature range.

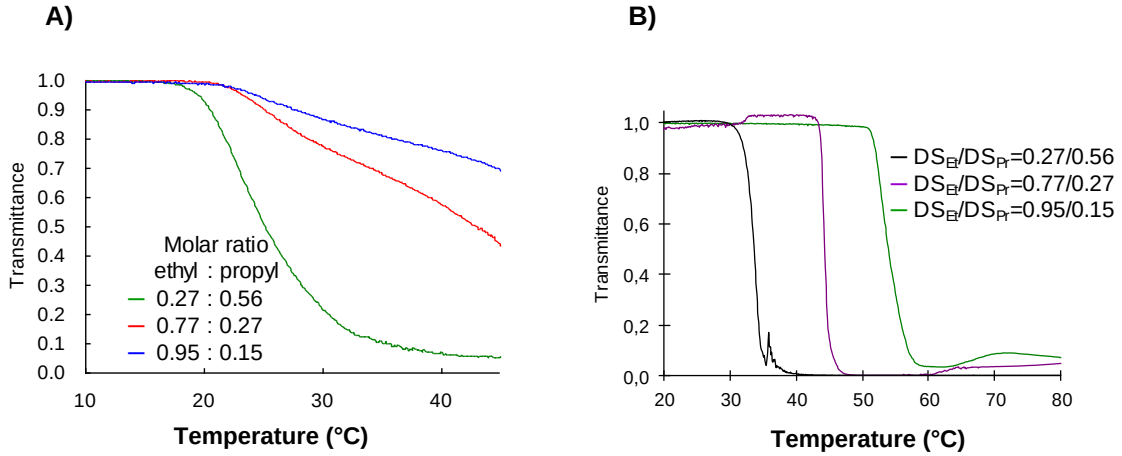

Fig. 9. Transmittance of aqueous solutions (1% w/w) of (A) physical mixtures of 3-*O*-ethyl (Et)- and 3-*O*-propyl (Pr) cellulose and (B) 3-*O*-Et/Pr cellulose of different DS of the particular ether moiety (redrawn from Heinze *et al.* (2012))

In contrast, the LCST of 3-*O*-ethers bearing two different alkyl moieties clearly depends on the ratio of both groups (Fig. 9B). Microcalorimetric- and rheological studies revealed that the clusters rather than single molecules aggregate at LCST (Sullo *et al.* 2013). Both the number and structure of such aggregates as well as the transition temperature are influenced by the ratio of the alkyl moiety. Clearly, the propyl group is more hydrophobic, because of the undesirable entropy decrease of water surrounding the hydrophobic moieties that is proportional to the size of the hydrophobic moieties (Privalov and Gill 1989).

The approach of 2,6-di-*O*-blocking has been used by Shen *et al.* (2016) for the preparation of amylose derivatives bearing different phenylcarbamate substituents at position 2, 6, and 3. The resulting products were used as a stationary phase in a HPLC column. Separation of enantiomers was better compared with commercially available products. However, the chiral separation ability depends on the aromatic substituents.

Regioselective esterification using blocking groups

The regioselective esterification of polysaccharides by means of blocking group technique is much more challenging compared to the formation of ethers. This can be explained as due to the sensitivity of the ester bond towards the reagents used for cleavage of the Si-O bond; tetra-n-butylammonium fluoride trihydrate (TBAF) is usually used. Xu and Edgar (2012) studied the synthesis of 2,6-*O*-esters of cellulose *via* a 3-*O*-protected derivative. Both allyl- and benzyl groups have been introduced to position 3 *via* a 2,6-di-*O*-TDMS cellulose followed by deprotection with TBAF. Subsequent acylation with acetic- and propionic acid anhydride afforded the fully functionalized cellulose derivatives. The benzyl group is prone to be cleaved by hydrogen in presence of palladium hydroxide. It turned out that the benzyl group attached to position 3 could not be removed, neither under mild nor under harsh conditions. Computational analysis revealed a very low reactivity of the benzyl ether in combination with steric issues that prevent the debenzylation. In contrast, the treatment of the allyl ether with $PdCl_2$ in methanol/ chloroform afforded the completely deprotected 2,6-*O*-acyl celluloses with negligible loss of acyl groups.

REGIOSELECTIVE ESTERIFICATION WITHOUT BLOCKING GROUPS

Some synthesis pathways for the regioselective esterification without the utilization of laborious blocking group techniques have been developed. These techniques take advantage of the bulkiness of the carboxylic acid derivative or they utilize the dissolution- or activation state of the polymer in solution to direct the ester substituent in a certain position.

Regioselective esterification by self-selective reagents

Bulky carboxylic acids have been reacted with cellulose under homogeneous conditions in different solvents (Xu *et al.* 2011). Pivaloyl-, adamantoyl-, and 2,4,6-trimethylbenzoyl chlorides were applied and DMA/LiCl, DMSO/TBAF, and 1-allyl-3-methylimidazolium chloride ([Amim]Cl) were chosen as the solvent. The acid chlorides studies exhibit different reactivities with pivaloyl chloride as the most reactive one followed by adamantoyl chloride. The DS values of around 1.7 were achieved using 3 mol reagent per mol repeating unit (Fig. 10). Clearly, the aromatic carboxylic acid derivative is

much less reactive (DS 0.6) under comparable conditions. The inherent water content of DMSO/TBAF and [Amim]Cl lowers the DS accordingly. A preferred but not exclusive acylation of position 6 could be achieved.

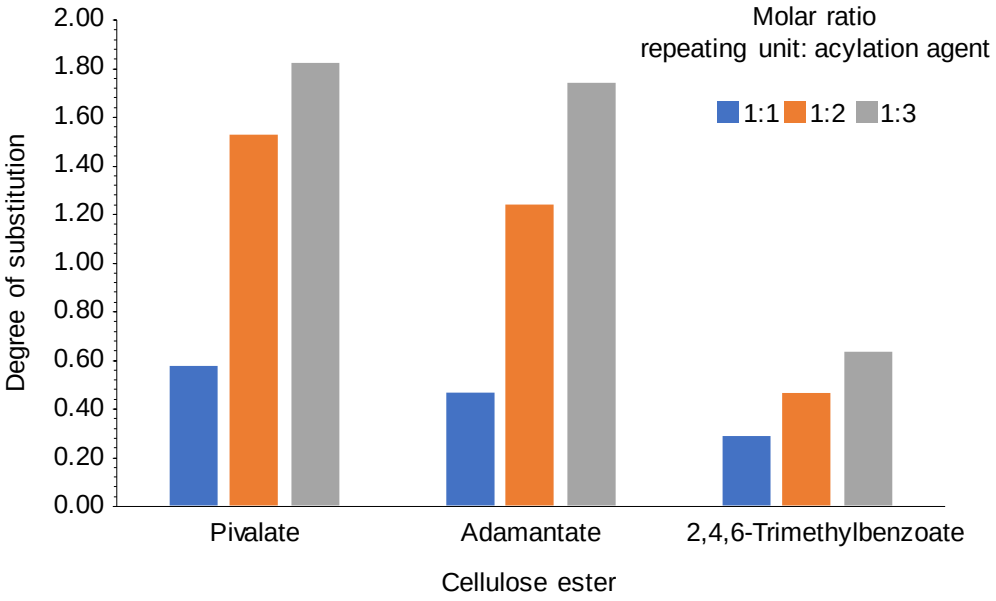

Fig. 10. Relative efficiencies of cellulose acylation using the three bulky acid chlorides (synthesized in *N,N*-dimethylacetamide/LiCl, 72 h, 20 °C) redrawn from (Xu *et al.* 2011)

The benzoylation of cellulose under homogeneous conditions in [Amim]Cl was studied in detail by Chen *et al.* (2015). Here, substituted benzoyl chlorides bearing activating, deactivating, and bulky groups were included in the studies. It was found that benzoyl chlorides with activating substituents reacted with cellulose by a unimolecular ionization mechanism, and benzoyl chlorides with deactivating substituents by a bimolecular addition–elimination mechanism. A synergistic effect of appropriate reaction rate, moderate steric effect, and reaction mechanism of benzoyl chlorides could be identified. At total DS of 1, a selectivity > 90% at position 6 was found based on ^{13}C-NMR experiments (Fig. 11).

Conversion of cellulose dissolved in DMA/LiCl with hydroxycinnamic acids in presence of triphenylphosphine and diisopropyl azodicarboxylate afforded cellulose esters with DS up to 0.5 and preferred esterification of position 6 (Mitsunobu esterification; Elschner *et al*. 2021).

It has been found that chloroformate-based reagents exhibit a certain regioselectivity that depends on both reagent and polysaccharide. Conversion of dextran with ethyl chloroformate afforded dextran ethyl carbonate with DS 0.47. A regioselective functionalization of position 2 was concluded from HMBC NMR spectra (Elschner *et al*. 2013). An exclusive formation of dextran 2-*O*-*p*-nitrophenyl carbonate with DS 1.02 was realized (Elschner *et al.* 2013b). Phenyl chloroformate reacts with dissolved cellulose with a certain selectivity towards the primary hydroxyl group. A 6-*O*-functionalized cellulose phenylcarbonate with DS 1.0 without affection of the secondary OH groups was synthesized (Elschner *et al.* 2016). Bui and Rosenau applied this for the preparation of mixed derivatives without the laborious use of blocking groups (Bui *et al.* 2023b). Cellulose 2,3-bis(3,5-dimethylphenyl carbamate)-6-(phenyl carbonate) has been

synthesized in a one-pot two-step method by treating dissolved cellulose first with 1.5 eq phenylchloroformate for 12 h followed by conversion with 3,5-dimethylphenyl isocyanate in presence of pyridine. The phenylcarbonate undergoes aminolysis with enantiopure α-methyl-benzylamine to obtain cellulose 2,3-bis(3,5-dimethylphenyl carbamate)-6-((R/S)-α-phenylethyl carbamate). The selectivity of the conversions was concluded from NMR data. The DS of 3,5-dimethylphenyl carbamate was 2.05 and the DS of the phenyl carbonate was 0.93. Studies of the enantioseparation revealed that mixtures of enantiomers could be separated by HPLC, but no clear trend could be identified.

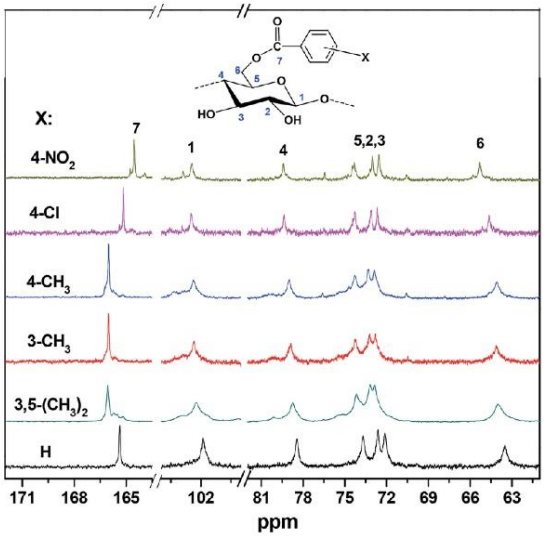

Fig. 11. ^{13}C-NMR spectra of cellulose benzoate (degree of substitution, DS = 0.99), cellulose 3,5-dimethyl benzoate (DS = 0.94), cellulose 3-toluoyl benzoate (DS = 0.98), cellulose 4-toluoyl benzoate (DS = 1.03), cellulose 4-chlorobenzoate (DS = 1.11), and cellulose 4-nitrobenzoate (DS = 1.06) (reprinted from Chen *et al.* 2015 with permission from Royal Society of Chemistry)

Regioselective esterification by medium-controlled selectivity

The most convenient way for regioselective esterification is the so-called medium-controlled selectivity. Here, a reagent of comparably low steric demand is used that might react with all hydroxyl groups within the repeating unit. Its regioselectivity is controlled by the solvent and, hence, the dissolution state of the polymer.

The conversion of starch dissolved in DMSO with vinyl acetate in the presence of inorganic salts affords 2-*O*-acetyl starch with DS up to 1 (Dicke 2004). Formation of gaseous ethanal is the driving force of this conversion. It must be noted that this pronounced regioselectivity is observed only in the presence of neutral as well as weak acidic or basic salts (*e.g.* Na_2HPO_4, NH_4Cl, NaCl). A preferred but not exclusive transesterification is observed for alkaline salts (*e.g.*, K_3PO_4, K_2CO_3, CH_3COONa), while strongly acidic salts such as hydrogensulfate or dihydrogenphosphate do not catalyze the conversion.

Clearly, this selectivity is somehow affected by the size of the starch molecule. Transesterification of dextrin with vinyl carboxylates in presence of lipases occurs at position 6, which is in contradiction with the transesterification in presence of salts (Lee *et al.* 2018). Polar solvents are necessary to obtain high DS values, while hydrolysis of the reagent becomes predominant in water. The highest DS obtained was 1.3, which indicates that secondary OH groups react as well after complete esterification of position 6. The reaction rate decreases with increasing chain length of the vinyl carboxylate but the final

DS increased, which is explained with the increased hydrophobicity. The regioselectivity of the esterification was assessed by ^{13}C-NMR spectroscopy of the mixed peracetylated derivatives (Fig. 12).

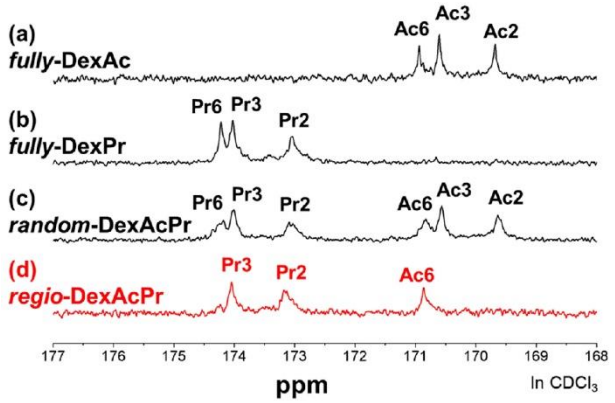

Fig. 12. ^{13}C NMR spectra of peracylated dextrin esters: fully-DexAc (DS = 3) (spectrum (a)), fully-DexPr (DS = 3) (spectrum (b)), random-DexAcPr (DS = 1.5/1.5) (spectrum (c)), and regio-DexAcPr (DS = 1.06/1.94) (spectrum (d)) (Reprinted with permission from Lee *et al.* 2018, Copyright American Chemical Society)

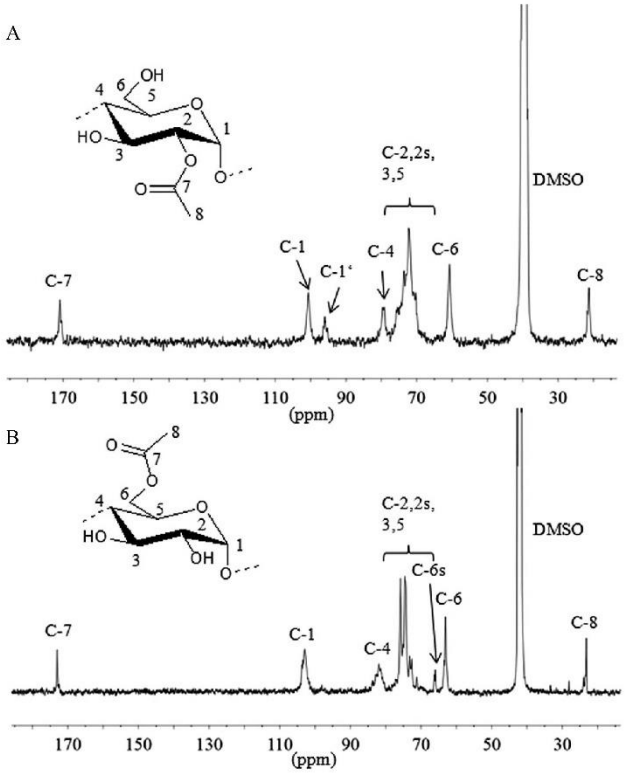

Fig. 13. ^{13}C NMR spectra of (A) 2-*O*-acetyl starch (DS 0.35) prepared in DMSO and (B) 6-*O*-acetyl starch (DS 0.34) prepared in molten imidazole (Reprinted from Hampe and Heinze 2014, with permission from Wiley)

Carboxylic acid anhydrides as activated carboxylic acid derivatives are usually converted with polysaccharides in presence of a base. With imidazole as base, reactive

carboxylic acid imidazolides are formed that enable esterification under mild conditions, *i.e.*, without liberation of HCl. It has been found that conversion of starch dissolved in DMSO with acetic anhydride and imidazole affords 2-*O*-acetyl starch (Hampe and Heinze 2014). Acetylation of position 6 starting at total DS > 0.5 is observed. In contrast, conversion of starch in molten imidazole with acetic anhydride affords starch esters with preferred acylation of the primary OH group. Secondary positions are not affected in samples with DS ≤ 0.5. The ^{13}C-NMR spectra clearly indicate the different selectivity of the acetylation by showing a signal for the acetylated position 6 at 63.8 ppm, which does not appear in a sample prepared in DMSO solution (Fig. 13).

Heterogeneous conversions may direct the ester group to position 6, as claimed (Chakraborty *et al.* 2005). Starch nanoparticles were incorporated in reversed micelles of anionic surfactant aerosol-OT/isooctane/water microemulsions and treated with vinyl carboxylates in presence of lipase enzyme. A preferred acylation of position 6 has been observed without affecting the dimension of the nanoparticles (Fig. 14). Clearly, the conversion rate is influenced by the chain length of the carboxylic acid derivative. The longer alkyl chain gives the higher conversion respectively DS, most likely due to their increased hydrophobicity. No reaction was observed in the case of vinyl acetate.

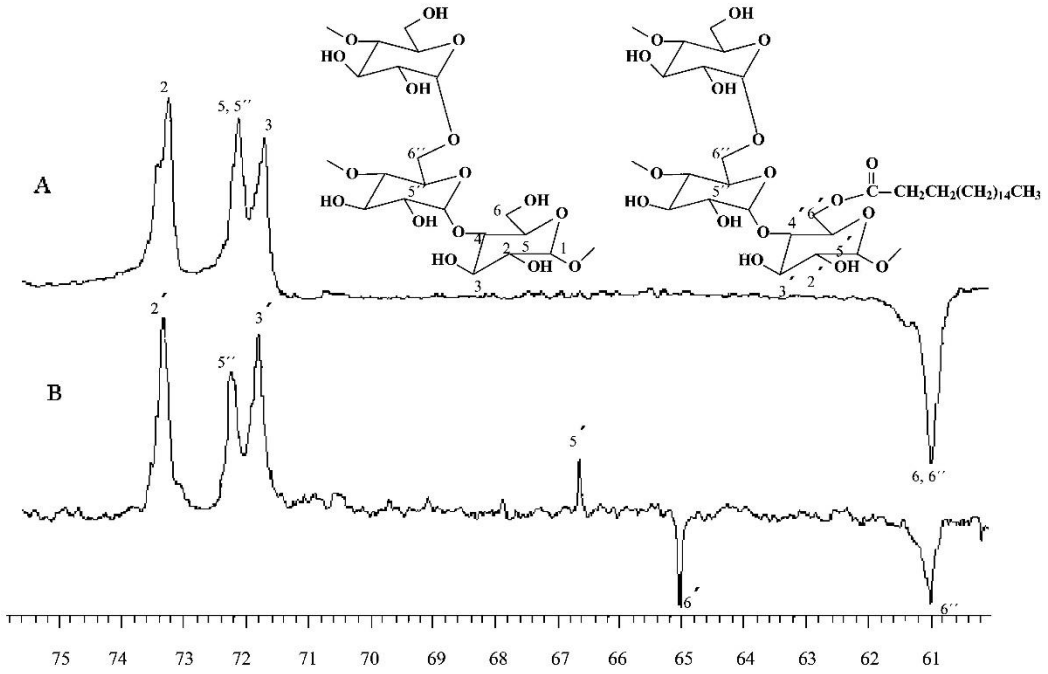

Fig. 14. Expanded region of DEPT-135 (75 MHz, δ in ppm, dimethyl sulfoxide-d_6) spectra that shows the carbon signals for the sugar units of (A) native starch nanoparticles and (B) vinyl stearate modified starch nanoparticles with DS = 0.8 (Reprinted with permission from Chakraborty *et al.* 2005, Copyright American Chemical Society)

SELECTIVE CLEAVAGE

An alternative way for the achievement of regioselective functionalization is the nonselective introduction of a substituent followed by partial cleavage in a selective manner.

Regioselective deesterification

Sulfuric acid half esters of polysaccharides possess certain bioactivities, and this activity depends on both content and distribution of sulfate groups. This desulfation can be chemically or enzymatically driven. Because of the vast number of publications, the reader may consult recent review papers (Bedini *et al.* 2017; Dimassi *et al.* 2018; Caputo *et al.* 2019; Arlov *et al.* 2021).

The regioselective synthesis of cellulose esters using the TDMS group failed so far because the TBAF removes not only the TDMS group efficiently but also cleaves the ester bond, due to its basic nature. Edgar and other researchers studied this finding in more detail (Xu and Edgar 2012; Zheng *et al.* 2013a,b, 2014). Conversion of cellulose triesters with TBAF leads to a preferred cleavage of esters at positions 2 and 3. Although, the mechanism is not fully understood yet, a faster E1cB elimination mechanism at positions 2 and 3 compared with a slower "general base-catalyzed" mechanism at position 6 was hypothesized. Similar results have been found for reactions with tetraalkylammonium hydroxides. The chelation of the cation by the carboxyl groups at positions 2 and 3 favors the deacetylation. Although no distinct deacetylation can be achieved, the reaction is insensitive towards solvents and their water content. Moreover, it works for benzoates lacking α-protons as well.

SELECTIVE ACTIVATION

Another approach for the selective introduction of functional groups is the use of functional groups that activate reactive sites for, *e.g.*, nucleophilic displacement reactions. The introduction of such groups can be, but is not necessarily, in a regioselective manner. However, the subsequent reaction may undergo regioselectively. The activating substituent can be used as a blocking group and further functional groups as, *e.g.*, solubilizing substituents, can be introduced (Fig. 15). However, it must be considered that the complete removal of the activating group might not be possible.

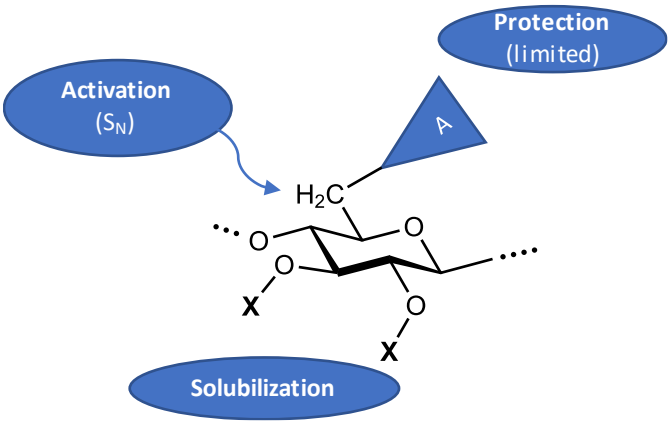

Fig. 15. Cellulose derivative bearing an activating group (A) and solubilizing substituents (X)

Two different approaches have been established in polysaccharide functionalization, namely sulfonic acid esters and 6-halogeno-6-deoxy groups.

Sulfonic Acid Esters

Sulfonic acid esters have been employed in polysaccharide chemistry for a long time. They are prepared by conversion of cellulose with reactive sulfonic acid derivatives, usually anhydrides or chlorides. Cellulose tosyl esters can be readily prepared under homogeneous conditions in DMA/LiCl with tosyl chloride and a base (McCormick and Callais 1987; Dawsey *et al.* 1989). Later studies showed that tosyl cellulose can be easily prepared from a variety of cellulosic starting materials and having a broad range of DS values (Rahn *et al.* 1996). Thus, they can be referred to as platform compound. The derivatives are not limited to tosyl esters only; other aliphatic and aromatic sulfonic compounds are also used. The reactivity and the stability of the resulting sulfonic acid esters is governed by the type of sulfonic acid derivative (Petzold-Welcke *et al.* 2009). The same review paper summarizes typical subsequent reactions, namely nucleophilic displacement. However, a preferred conversion of the primary OH group at low DS is observed but secondary positions react as well. Different sulfonic acid chlorides possess different reactivities, but no distinct regioselectivity could be observed (Koschella *et al.* 2006c). In this regard, conversion with halides yields the corresponding 6-halogeno-6-deoxy compounds, which was also applied for analytical purposes to distinguish between primary and secondary sulfonic acid esters. The ease and completeness of the displacement depends on the strength of the nucleophile. Nucleophiles such as halides and amines do displace primary sulfonic acid groups while leaving the secondary ones unattached. In contrast, strong nucleophiles like azide ions are capable of replacing secondary sulfonic acid ester groups as well (Heinze *et al.* 2006). Thus, selectivity in terms of primary/secondary positions is limited in this case. The 6-azido-6-deoxy group can be reduced to the corresponding 6-amino-6-deoxy moiety by treatment with reducing agents. This can be accomplished with sodium borohydride (Matsui *et al.* 2005; Takano *et al.* 2007), sodium borohydride/metal complexes (Heinze *et al.* 2006), or with lithium tetrahydridoaluminate (Liu and Baumann 2002). The authors claimed that remaining sulfonic acid groups were completely removed (Liu and Baumann 2002). However, treatment of such leaving groups with hydride donors may also lead to the formation of 6-deoxycelluloses instead of liberating the OH group (Koschella and Heinze 2022).

Weaker amines displace primary sulfonic acid esters only, which leads to the regioselective formation of 6-amino-6-deoxy celluloses with a large variety of structural features (Heinze *et al.* 2016b). With respect to efficient synthesis of such derivatives, the amine can be used as both reagent and solvent (Heinze *et al.* 2016a).

6-Halogeno-6-Deoxy Derivatives

Different approaches for the preparation of 6-halogeno-6-deoxy polysaccharides have been developed. As described in the previous section, sulfonic acid ester moieties can be replaced by halide ions. However, sulfonic acid ester groups may remain in the product. Another approach consists in the direct introduction of the halide by either nucleophilic displacement of a labile sulfonic acid ester (*e.g.*, methanesulfonic acid ester) *in situ* or by direct halogenation of the polysaccharide with halides in presence of triphenylphosphan (Cimecioglu *et al.* 1994). This reaction is usually completed under homogeneous conditions in DMA/alkali metal halide.

The halide can then be replaced by, *e.g.*, azide leading to 6-azido-6-deoxy cellulose. Approaches for the direct introduction of the azide moiety have been developed as well. Thus, treatment of curdlan with lithium azide in DMF, triphenylphosphan, and tetrabromomethane afforded the 6-azido-6-deoxy curdlan directly without isolation of the

6-halogeno-6-deoxy derivative (Borjhan *et al.* 2001). The two-step method developed by Hasegawa *et al.* consists of the formation of the 6-bromo-6-deoxy curdlan, which was isolated and subsequently subjected to nucleophilic displacement with sodium azide (Hasegawa and Abe 2011).

The 6-azido-6-deoxy group can be used as a reactive site for azide/alkyne reactions forming triazoles (Meng and Edgar 2016; Kemmer *et al.* 2022). The conversion of 6-azido-6-deoxy polysaccharides with triphenylphosphan affords the corresponding 6-amino-6-deoxy derivatives. In the course of this "Staudinger reaction", an iminophosphorane is formed in an almost quantitative yield under nitrogen release. The second step consists of the rapid hydrolysis of the intermediate yielding the primary amine and triphenyl-phosphanoxide (Liu and Edgar 2015). However, it is hard to completely remove the triphenylphosphanoxide, and traces persist in the samples. Nevertheless, this method is versatile and has been applied to different polysaccharides such as amylose (Cimecioglu *et al.* 1994), cellulose (Fox and Edgar 2012), curdlan (Zhang and Edgar 2014, 2015; Zhang *et al.* 2016; Liu *et al.* 2018), and pullulan (Pereira and Edgar 2014). It is possible to convert the primary amine of the 6-amino-6-deoxy polysaccharide to a secondary amine by conversion with an aldehyde and reduction of the imine formed (Zhang *et al.* 2017).

Conversion of the 6-azido-6-deoxy cellulose with carbon disulfide in presence of triphenylphosphan yields a 6-isothiocyanato-6-deoxy cellulose that can be further converted to thiocarbamate derivatives (Shibano *et al.* 2013).

The 6-bromo-6-deoxy moiety can be replaced by amines and alkylphosphanes leading to 6-ammonium/phosphonium-6-deoxy cellulose derivatives (Marks *et al.* 2016). The DS is limited due to accumulation of positive charges along the polymer backbone; DS (Et_3N^+) ~ 0.47 and DS (Et_3P^+) ~ 0.73 were achieved for charged derivatives, while neutral derivatives with DS ~ 0.9 could be synthesized.

Both cationic- and zwitterionic *N*-heterocyclic cellulose ionomers were prepared by nucleophilic displacement of 6-bromo-6-deoxy cellulose with pyridine, imidazole, and *N*-methylimidazole (Liu *et al.* 2016). Up to 83% of the leaving groups were replaced. The resulting products are water-soluble, thermally stable up to 251 °C, and adsorb on self-assembled monolayers that bear carboxyl groups.

Nucleophilic displacement with cyanide ions is scarcely described in the literature. The synthesis of 6-cyano-6-deoxy cellulose esters was reported by reaction of 6-bromo-6-deoxy-2,3-*O*-propionyl cellulose with sodium cyanide (Fox and Edgar 2011). The DS of 6-cyan-6-deoxy groups of up to 0.68 could be realized. However, hydrolysis of the nitrile to the carboxylate failed due to the pronounced alkaline degradation of the polymer instead of the intended saponification.

6-Bromo-6-deoxy cellulose was converted with primary- and secondary amines and carboxy-protected amino acids to prepare polysaccharide-amino acid conjugates (Zhou and Edgar 2022). Proline tert-butyl ester afforded a higher conversion (96%), while tyrosine methyl ester is apparently less reactive (77% conversion).

Trimethylsilyl Ethers

Trimethylsilyl ethers do not possess a distinct regioselectivity, and a complete silylation can be achieved. However, it was found that sulfur trioxide inserts in the O-Si-bonds of primary silyl ethers, *i.e.*, activating this position for subsequent reactions. The sulfur trioxide is usually added as a complex with DMF, pyridine, or triethylamine. Those complexes are solids, which are commercially available and much easier to handle compared with the extremely hygroscopic sulfur trioxide. It was found that the

regioselectivity depends on the sulfur trioxide complex used (Richter and Klemm 2003). Cellulose sulfates with preferred sulfation at position 6 were obtained the complex with DMF, while the triethylamine complex promotes sulfation of position 2.

This approach was used for the preparation of differently functionalized sulfuric acid half esters of a β-1,3-glucan from *Ganoderma lucidum* (Fig. 16) (Zhang *et al.* 2020). Thus, sulfation of the polysaccharide afforded the randomly functionalized product, while sulfation of the dimethoxytriphenylmethyl ether yielded the 2,4-*O*-sulfated derivative after deprotection. It was found that *O*-6 sulfation is essential to anticoagulant activity.

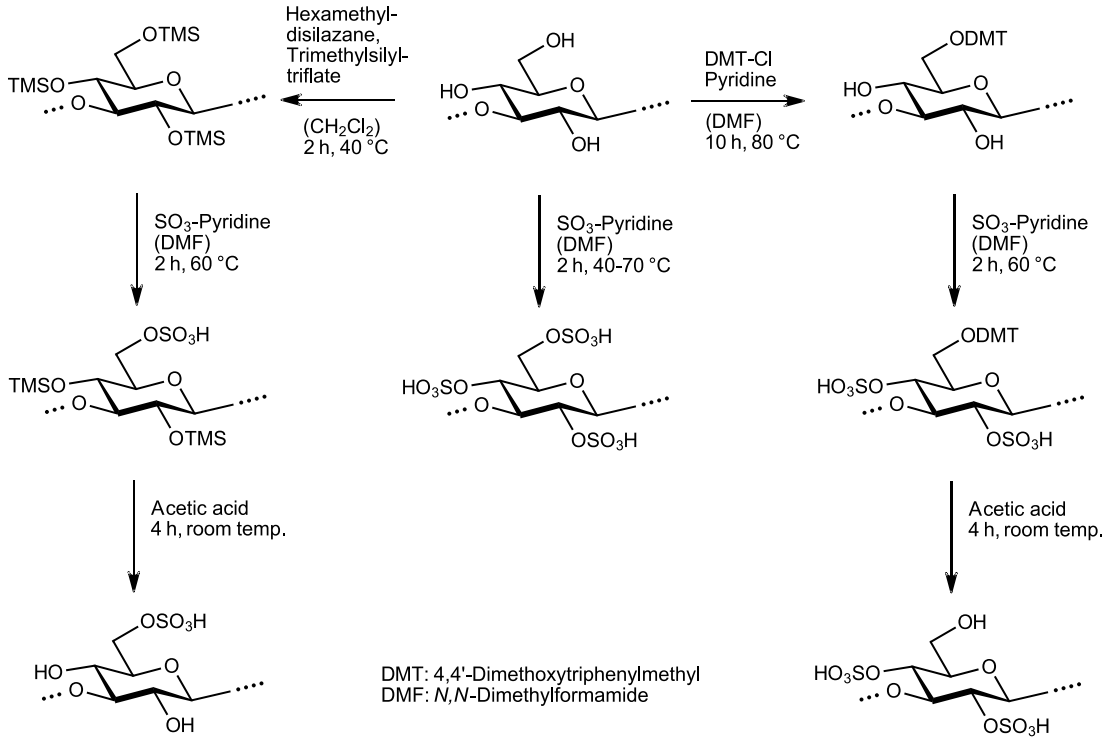

Fig. 16. Synthesis procedures of direct sulfation and regioselective sulfation of *Ganoderma lucidum* polysaccharide. Redrawn from Zhang *et al.* (2020)

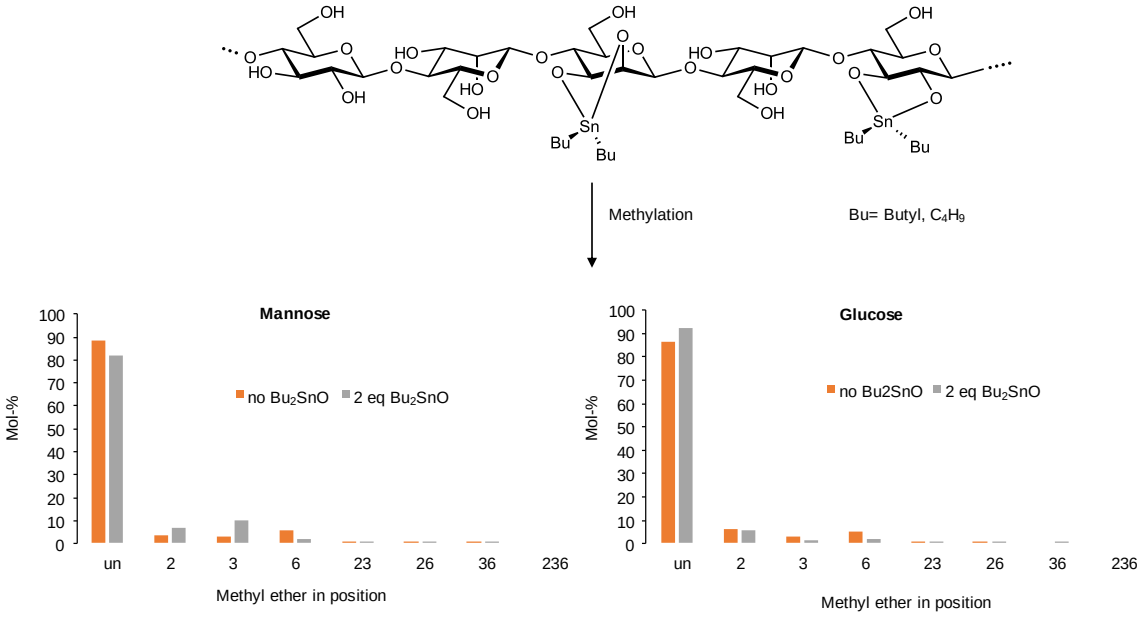

Fig. 17. Methyl pattern obtained by tin-mediated methylation of konjac glucomannan (M-KGM 2) in comparison with a reference experiment under the same conditions, but without Bu_2SnO (M-KGM 1, see Online Resource Table A1). Molar portions are given separately for mannose (a) and glucose (b), both normalized to 100 % (redrawn from Raßloff *et al.* 2018)

Stannylene Acetals

Stannylene acetals are described as activating substituents that are used in carbohydrate chemistry (Traboni *et al.* 2020). However, they are scarcely described in polysaccharide research. Recently, it was shown that the distribution of methyl groups in glucomannan can be influenced by a dibutylstannylene acetal (Raßloff *et al.* 2018). The acetal is formed by conversion of the glucomannan with dibutyltin oxide in methanol/pyridine and methylation was accomplished by conversion with methyl iodide in presence of tetrabutylammonium bromide and potassium carbonate/diisopropylethyl-amine. A maximum degree of substitution of methyl groups of 0.28 was achieved. Detailed structure characterization by means of GLC revealed preferred methylation at *O*-3 (Mannose, cis-diol) and *O*-2 (Glucose, trans-diol, Fig. 17).

MISCELLEANEOUS CONVERSIONS

Tri-*O*-methyl cellulose oligomers bearing either azide- or a propargyl group at position 1 were prepared (Kamitakahara *et al.* 2016). These could be achieved by solvolysis of, *e.g.*, methyl cellulose with unsaturated alcohols like allyl alcohol and 4-pentene-1-ol in presence of methanesulfonic acid (Chen *et al.* 2020a). The polymer chain is randomly cleaved under formation of oligomeric blocks bearing an allyl- or 4-pentenyl acetal at position 1. These oligomers are capable of undergoing olefin cross-metathesis in the presence of Hoveyda-Grubbs second generation catalyst. This mild, highly efficient, tolerant, and flexible synthesis route can be applied for the preparation of block-copolymers.

Azide moieties are prone to react with alkynes under formation of triazoles. For chitosan, the amino group can be selectively converted in an azide group without affecting the hydroxyl groups (Kulbokaite *et al.* 2009). Imidazole-1-sulfonyl azide hydrochloride possesses the highest efficiency (content of azide moieties 64.4%), followed by trifluoromethane sulfonyl azide (content of azide moieties 40.3%).

DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride) is an efficient coupling agent that is commercially available. The organic triazine derivative activates carboxyl groups for amide formation. The activation mechanism is similar to that of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/*N*-hydroxysuccinimide condensation, *i.e.*, a triazine ester is formed that is attacked by the amine as nucleophile. The DMTMM does not react with aliphatic OH groups but with phenolic hydroxyl groups. It is stable in water, insensitive to pH, and it can be recovered (Kunishima *et al.* 1999; Farkaš and Bystrický 2007; Labre *et al.* 2018).

The conversion of cellulose acetate with a DS of 1.75 with methanesulfonyl chloride in DMF was described (Gao *et al.* 2018). The acetyl groups act as blocking groups, while the educts react in a Vilsmeier-Haack-type reaction. The DS of 6-chloro-6-deoxy moieties agrees with the available hydroxyl groups at position 6 (0.5). This approach uses cheap reagents, and no phosphanes are necessary. Thus, the difficulties of complete removal of the phosphanoxide are circumvented.

Recently, dextran was converted with triphenylphosphan and *N*-bromosuccinimide in dimethyl sulfoxide (Chen *et al.* 2020b). The primary hydroxyl group at position 6 of the repeating unit at the nonreducing end had been exclusively converted into a 6-bromo-6-deoxy group, while secondary- and the anomeric hydroxyl groups remained unaffected. Thus, a selective end-group functionalization could be achieved. A two-step pathway led from native linear dextran *via* end-functional dextran derivatives to dextran-based block copolymers, which exhibit self-association in solution (Fig. 18). This kind of selective introduction of a single leaving group can be used for the selective impartment of biological activity, *e.g.*, by attaching single amino acids (Zhou and Edgar 2022).

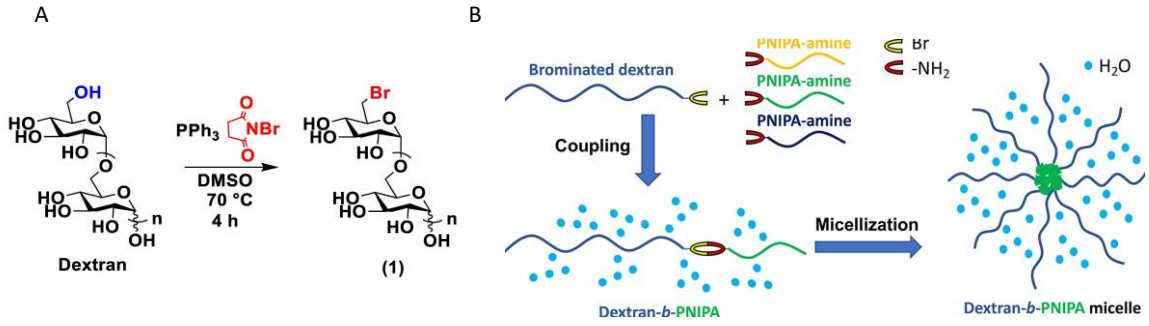

Fig. 18. *N*-bromosuccinimide/triphenylphosphine bromination of dextran (A) and (B) micellization of dextran-branched-poly(*N*-isopropylacrylamide) (PNIPA) (Reprinted with permission from Chen *et al.* 2020b, Copyright American Chemical Society)

CONCLUSIONS

A review of papers mainly published in the last decade led to the conclusion that the exploration of structure-property-relationships and material science issues are of great

importance. Applications such as separation of enantiomers by polysaccharide-based stationary phases are state of the art. However, there are only slight developments in the field of regioselective functionalization, *e.g.*, novel blocking or deblocking methodologies. Moreover, reliable explanations for known phenomena such as medium-controlled selectivity still have not been provided. Nevertheless, regiochemistry of polysaccharides is an interesting research field and novel (biotechnologically produced) polysaccharides should be included in the studies. Moreover, novel and innovative reaction paths must be studied and established. Maybe enzymes can be engineered that enable the selective introduction of functional groups.

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