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RECENT ADVANCES IN CELLULOSE CHEMISTRY

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1.1 INTRODUCTION

The chemical modification of polysaccharides is still underestimated regarding the structure and hence property design of materials based on renewable resources. At present, the cellulose derivatives commercially produced in large scale are limited to some ester with C_2–C_4 carboxylic acids, including mixed esters and phthalic acid half-esters as well as ethers with methyl-, hydroxyalkyl-, and carboxymethyl functions. In general, organic chemistry of cellulose opens a wide variety of products by esterification and etherification. In addition, novel products may be obtained by nucleophilic displacement reactions, unconventional chemistry like "click reactions," introduction of dendrons in the cellulose structure, and regiocontrolled reactions within the repeating units and along the polymer chains. The aim of this chapter is to highlight selected recent advances in chemical modification of cellulose for the synthesis of new products with promising properties as well as alternative synthesis paths in particular under homogeneous conditions, that is, starting with dissolved polymer considering own research results adequately.

1.2 TECHNICAL IMPORTANT CELLULOSICS

The application of the glucane cellulose as a precursor for chemical modifications was exploited extensively even before its polymeric nature was determined and well

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understood. Cellulose nitrate (commonly misnomered nitrocellulose) of higher nitrogen content was one of the most important explosives. Its partially nitrated ester was among the first polymeric materials used as a "plastic" well known under the trade name of Celluloid. Today, cellulose nitrate is the only inorganic cellulose ester of commercial interest (Balser et al., 1986). Further cellulose products like methyl-, ethyl-, or hydroxyalkyl ethers or cellulose acetate, and, in addition, products with combinations of various functional groups, for example, ethylhydroxyethyl and hydroxypropylmethyl cellulose, cellulose acetopropionates, and acetobutyrates are still important, many decades after their discovery. Ionic cellulose derivatives are also known since a long time. Carboxymethyl cellulose, up to now the most important ionic cellulose ether, was first prepared in 1918 and produced commercially in the early 1920s in Germany (Brandt, 1986). Various cellulose derivatives are produced in large quantities for diversified applications. Their properties are primarily determined by the type of functional group. Moreover, they are influenced significantly by adjusting the degree of functionalization and the degree of polymerization (DP) of the polymer backbone (Table 1.1).

1.3 NUCLEOPHILIC DISPLACEMENT REACTIONS (S_N)

It is well known from the chemistry of low molecular alcohols that hydroxyl functions are converted to a good leaving group for nucleophilic displacement reactions by the formation of the corresponding sulfonic acid esters (Heinze et al., 2006a). Moreover, cellulose derivatives obtained by S_N reactions are suitable starting materials for the preparation of novel products by unconventional chemistry like "click reactions." Even selectively dendronized celluloses could be prepared.

1.3.1 Cellulose Sulfonates

Typical structures of sulfonic acid esters used in polysaccharide chemistry are shown in Figure 1.1. The synthesis of sulfonic acid esters is realized heterogeneously by reaction of cellulose with sulfonic acid chlorides in aqueous alkaline media (NaOH, Schotten–Baumann reaction), or is most efficiently completely homogeneous in a solvent like *N,N*-dimethylacetamide (DMA)/LiCl. The main drawback of heterogeneous procedures is a variety of side reactions, including undesired nucleophilic displacement reactions caused especially by long reaction times and high temperatures required. In contrast, the homogeneous process using cellulose dissolved in DMA/LiCl yields well soluble sulfonic acid esters (McCormick and Callais, 1987).

The *p*-toluenesulfonic (tosyl) and the methanesulfonic (mesyl) acid esters of cellulose are the most widely used sulfonic acid esters, due to their availability and hydrolytic stability (Heinze et al., 2006a). The homogeneous reaction of cellulose in DMA/LiCl with *p*-toluenesulfonyl chloride permits the preparation of cellulose tosylate with defined degree of substitution (DS) easily controlled by the molar ratio reagent to anhydroglucose unit (AGU) with almost no side reactions (McCormick and Callais, 1986, 1987; Rahn et al., 1996; Siegmund and Klemm, 2002).

TABLE 1.1 Examples of Important Cellulose Esters and Ethers Commercially Produced

Product	Worldwide Production (*t/a*)	Functional Group	Degree of Functionalization	Examples of Solubility
Cellulose acetate	900,000	$-C(O)CH_3$	0.6–0.9	Water
			1.2–1.8	2-Methoxyethanol
			2.2–2.7	Acetone
			2.8–3.0	Chloroform
Cellulose nitrate	200,000	$-NO_2$	1.8–2.0	Ethanol
			2.0–2.3	Methanol, acetone, methyl ethyl ketone
			2.2–2.8	Acetone
Cellulose xanthate	3,200,000	–C(S)SNa	0.5–0.6	Aqueous NaOH
Carboxymethyl cellulose	300,000	$-CH_2COONa$	0.5–2.9	Water
Methyl cellulose	150,000	$-CH_3$	0.4–0.6	4% Aqueous NaOH
			1.3–2.6	Cold water
			2.5–3.0	Organic solvents
Ethyl cellulose	4,000	$-CH_2CH_3$	0.5–0.7	4% Aqueous NaOH
			0.8–1.7	Cold water
			2.3–2.6	Organic solvents
Hydroxyethyl cellulose	50,000	CH_2CH_2OH	0.1–0.5	4% Aqueous NaOH
			0.6–1.5	Water

Adapted from Heinze and Liebert (2001).

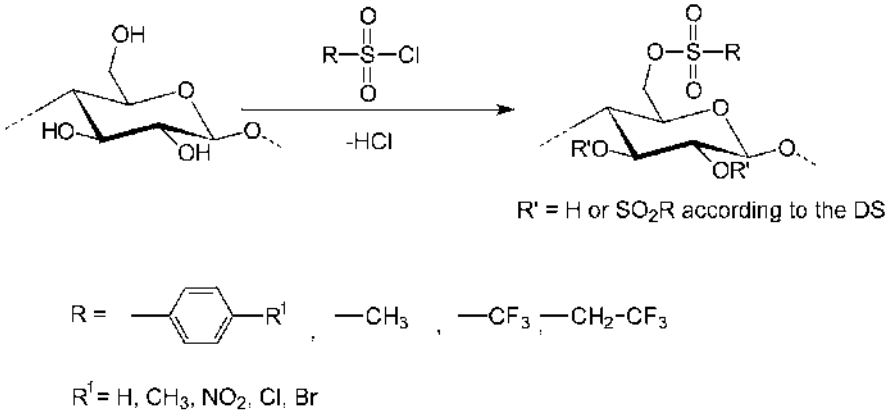


FIGURE 1.1 Typical sulfonic acid esters of cellulose.

The structure of the product may depend on both the reaction conditions and the workup procedure used (McCormick et al., 1990). The tosyl chloride may react with DMA in a Vilsmeier–Haak-type reaction forming the *O*-(*p*-toluenesulfonyl)-*N,N*-dimethylacetiminium salt, which attacks the OH groups of the cellulose depending on the reaction conditions used. For a higher efficiency of tosylation of cellulose, stronger bases such as triethylamine (pK_a 10.65) or 4-(dimethylamino)-pyridine (pK_a 9.70) are necessary, which react with the *O*-(*p*-toluenesulfonyl)-*N,N*-dimethylacetiminium salt building a quaternary ammonium salt and hence lead to the formation of tosyl cellulose without undesired side reactions (Figure 1.2) (McCormick et al., 1990). On the contrary, the use of a weak organic base like pyridine (pK_a 5.25) or *N,N*-dimethylaniline (pK_a 5.15) for the reaction with cellulose yields a reactive *N,N*-dimethylacetiminium salt, which may form chlorodeoxy celluloses at high temperatures or cellulose acetate after aqueous workup (Heinze et al., 2006a).

Various cellulose materials with degree of polymerization in the range of 280–1020 were transformed to the corresponding tosyl esters (Rahn et al., 1996). DS values in the range of 0.4–2.3 with negligible incorporation of chlorodeoxy groups were obtained at reaction temperatures of 8–10°C for 5–24 h (Table 1.2).

Cellulose tosylates are soluble in various organic solvents; beginning at DS of 0.4, solubility in aprotic dipolar solvents like DMA, *N,N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO) occurs. The cellulose tosylates become soluble in acetone and dioxane at a DS value of 1.4 and solubility in chloroform and methylene chloride appears at DS of 1.8. Position 6 reacts faster compared to the secondary OH groups at positions 2 and 3, which can be characterized by means of FTIR and NMR spectroscopy of cellulose tosylate (Rahn et al., 1996).

1.3.2 S_N Reactions with Cellulose Sulfonates

Cellulose sulfonates are studied for a broad variety of S_N reactions, as discussed in various review papers (Belyakova et al., 1971; Hon, 1996; Siegmund

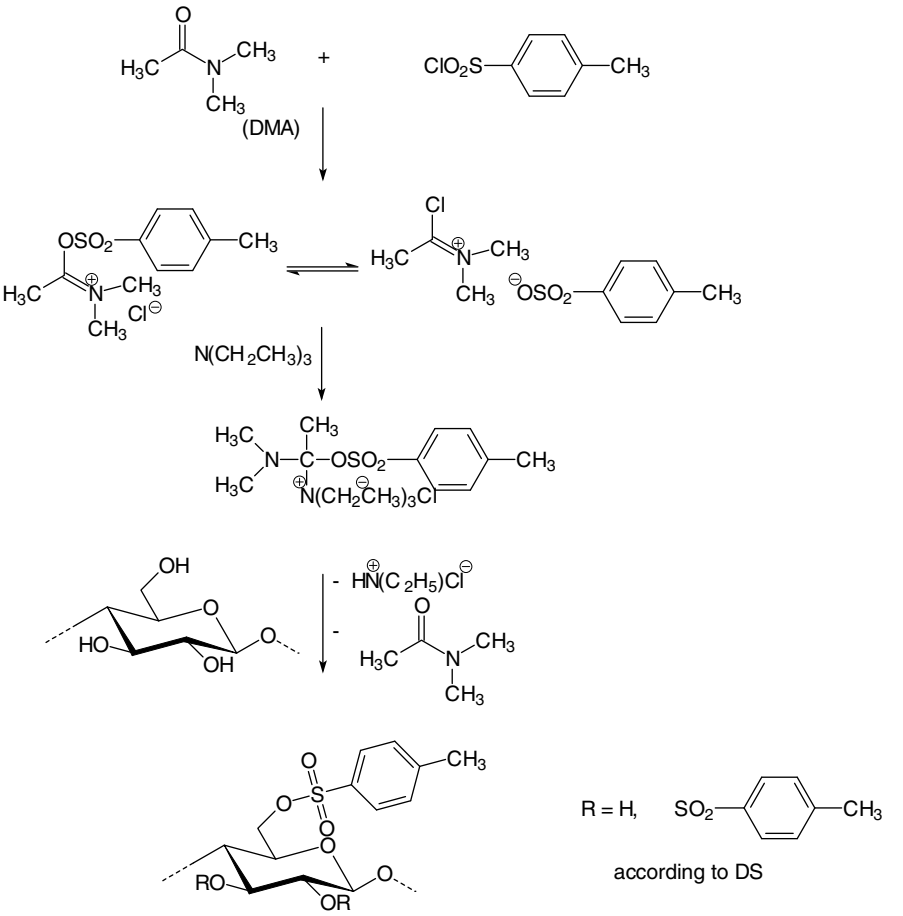


FIGURE 1.2 Mechanism of the reaction of cellulose with *p*-toluenesulfonyl chloride in DMA/LiCl in the presence of triethylamine. Adapted from McCormick et al. (1990).

and Klemm, 2002). Usually the S_N reaction occurs selectively at the primary sulfonates. The mechanism (S_N1 versus S_N2) of nucleophilic substitution reaction of cellulose derivatives is still a subject of discussion. A remarkable finding is that a treatment of partially substituted cellulose tosylates (DS 1.2–1.5) with strong nucleophiles like azide or fluoride ions leads to a substitution of both primary and secondary tosylates (Siegmund and Klemm, 2002; Koschella and Heinze, 2003).

Water-soluble 6-deoxy-6-*S*-thiosulfato celluloses (Table 1.3) form S–S bridges by oxidation with H_2O_2—in analogy to nonpolymeric compounds of this type (Milligan and Swan, 1962)—leading to waterborne coatings (Klemm, 1998).

Water-soluble 6-deoxy-6-thiomethyl-2,3-carboxymethyl cellulose forms self-assembled monolayers at a gold surface (Wenz et al., 2005). The insoluble products yielded by S_N reactions of cellulose tosylate with iminoacetic acid have high water

TABLE 1.2 Results and Conditions of the Reaction of Cellulose with *p*-Toluenesulfonyl Chloride (TosCl) in DMA/LiCl Applying Triethylamine as Base (2 mol/mol TosCl) for 24 h at 8°C

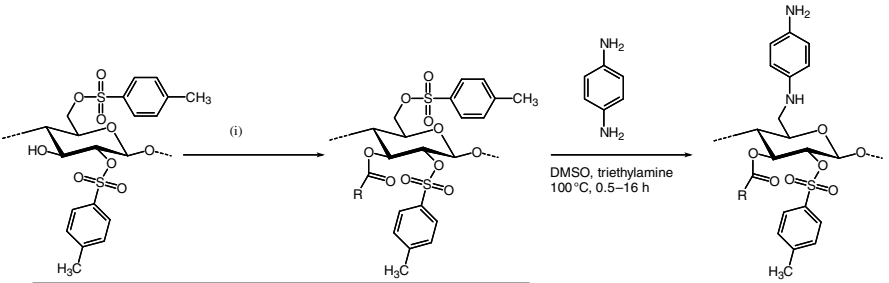
Cellulose	Degree of Polymerization	Molar Ratio TosCl/AGU[a]	Cellulose Tosylate		
			DS[b]	S (%)	Cl (%)
Microcrystalline	280	1.8	1.36	11.69	0.47
Spruce sulfite pulp	650	1.8	1.34	11.68	0.44
Cotton linters	850	0.6	0.38	5.51	0.35
		1.2	0.89	9.50	0.50
		2.1	1.74	12.90	0.40
		3.0	2.04	13.74	0.50
Beech sulfite pulp	1020	1.8	1.52	12.25	0.43

Adapted from Rahn et al. (1996).
[a] AGU anhydroglucose unit.
[b] Degree of substitution, calculated on the basis of sulfur content.

retention values of up to 11,000% (Heinze, 1998). A number of aminodeoxy celluloses are accessible. The nucleophilic displacement reaction with various amines results in water-soluble 6-deoxy-6-trialkylammonium cellulose (Koschella and Heinze, 2001). The initial chirality of the cellulose has no significant influence on its reactivity with

TABLE 1.3 Examples of Products Yielded by Nucleophilic Displacement Reactions of Cellulose Tosylate

Reagent	Product	References
$Na_2S_2O_3$	6-Deoxy-6-*S*-thiosulfato cellulose	Klemm (1998)
$NaSCH_3$ (subsequent carboxymethylation)	6-Deoxy-6-thiomethyl-2,3-di-carboxymethyl cellulose	Wenz et al. (2005)
$NaSO_3$	Sodium deoxysulfate-*co*-tosylate cellulose	Arai and Aoki (1994); Arai and Yoda (1998)
Iminodiacetic acid	6-Deoxy-6-iminodiacetic acid cellulose sodium salt	Heinze (1998)
Triethylamine	6-Deoxy-6-triethylammonium cellulose	Koschella and Heinze (2001)
N,N-Dimethyl-1,3-diaminopropane	6-Deoxy-6-(*N,N*-dimethyl-3-aminopropyl)ammonium cellulose	Koschella and Heinze (2001)
2,4,6-Tris(*N,N*-dimethylaminomethyl) phenol	6-Deoxy-6-(2,6-di(*N,N*-dimethylaminomethyl)phenol-4-methyl-*N,N*-dimethylamino cellulose	Koschella and Heinze (2001)
R(+)-, *S*(−)-, and racemic 1-phenylethylamine	6-Deoxy-6-(1-phenylethyl) amino cellulose	Heinze et al. (2001)
Aminomethane	6-Deoxy-6-methylamino cellulose	Knaus et al. (2003)



R	Reaction conditions (i)				
	Reagent	Solvent	Base (catalyst)	Temperature [°C]	Time (h)
CH_3	$(H3CCO)_2O$	DMF	Pyridine ($NaOOCCH_3$)	20	48
		DMF	Pyridine (DMAP)	60	16
		Pyridine	–	70	1

FIGURE 1.3 Reaction path for the synthesis of 6-deoxy-6-amino cellulose ester derivatives by subsequent acylation and nucleophilic displacement with phenylenediamine of tosyl cellulose. Adapted from Tiller et al. (2000).

the two enantiomeric amines by the S_N reaction of cellulose tosylate with *R*(+)-, *S*(−)- and racemic 1-phenylethylamine (Heinze et al., 2001). Methylamino celluloses are suitable as hydrophilic polymer matrices for immobilization of ligands for extracorporeal blood purification, for example, quaternary ammonium groups (Knaus et al., 2003). Conversion of cellulose tosylate with diamines or oligoamines yields polymers of the type P-CH_2-NH-(X)-NH_2 (P = cellulose, (X) = alkylene, aryl, aralkylene, or oligoamine) at position 6 and solubilizing groups at positions 2 and 3, which form transparent films that may be applied for the immobilization of enzymes like glucose oxidase (GOD), peroxidase, and lactate oxidase (Figure 1.3). The products are useful as biosensors (Tiller et al., 1999, 2000; Berlin et al., 2000, 2003; Becher et al., 2004).

Water-soluble and film-forming amino cellulose tosylates from alkylenediamines can be used as enzyme support matrices with Cu^{2+} chelating properties (Jung and Berlin, 2005). The synthesis of 6-deoxy-6-amino cellulose via azido derivative is described in detail (Figure 1.4). The reaction conditions for a complete functionalization at position 6 are optimized, as well as various subsequent reactions of the product are studied (e.g., *N*-carboxymethylation, *N*-sulfonation) (Liu and Baumann, 2002; Heinze et al., 2006b).

1.3.2.1 Huisgen Reaction: "Click Chemistry" with Cellulose Recently, Sharpless introduced click chemistry, that is, a modular approach that uses only the most practical and reliable transformation, which are experimentally simple, needing no protection from oxygen, requiring only stoichiometric amounts of starting materials, and generating no by-products (Kolb et al., 2001). The 1,3-dipolar cycloaddition of an azide moiety and a triple bond (Huisgen reaction) is the most popular click reaction to date (Rostovtsev et al., 2002; Lewis et al., 2002). Sharpless describes the

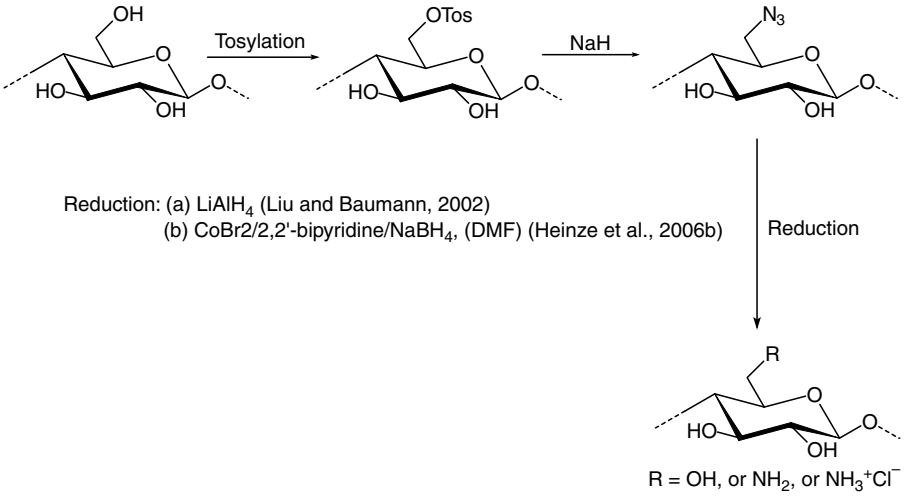


FIGURE 1.4 Scheme of the synthesis of 6-deoxy-6-amino cellulose via cellulose tosylate and reduction of 6-deoxy-6-azido cellulose.

Huisgen reaction as "the cream of the crop" of click chemistry. The path of tosylation, S_N with sodium azide and subsequent copper-catalyzed Huisgen reaction, has significantly broaden the structural diversity of polysaccharide derivatives because the method yields products that are not accessible via etherification and esterification, the most commonly applied reactions (Liebert et al., 2006). The preparation of 6-deoxy-6-azido cellulose and subsequent copper-catalyzed Huisgen reaction of 1,4-disubstituted 1,2,3-triazols formed as linker lead to novel cellulose derivatives with methylcarboxylate, 2-aniline, and 3-thiophene moieties (Figure 1.5). No side reactions occur, the synthesis leads to pure and well-soluble derivatives with conversion efficiency of the azido moiety of 75–98% depending on the reaction temperature and the molar ratio (Table 1.4).

As can be concluded from the ^{13}C NMR spectra exemplified for the spectrum of 6-deoxy-6-methylcarboxytriazolo celluloses (DS 0.81) acquired in DMSO, no structure impurities are present (Figure 1.6). The signals at 48.5 ppm represent the methyl ester, and at 160.6 ppm the signals of the carbonyl group appear. The C-atoms of the triazole moieties give signals at 138.6 and 129.9 ppm, and peaks in the range of 51.6–110 ppm are related to the carbons of the repeating unit. A weak signal at about 60 ppm reveals the existence of remaining OH groups at position 6.

The 1,3-dipolar cycloaddition reaction of 6-azido-6-deoxycellulose with acetylene-dicarboxylic acid dimethyl ester and subsequent saponification with aqueous NaOH yield bifunctional cellulose-based polyelectrolytes (Figure 1.7) (Koschella et al., 2010).

Up to 62% of the azide moieties are converted. Starting with a 6-azido-6-deoxy cellulose with a DS of 0.84, the reaction is completed within 4 h using 2 mol of acetylenecarboxylic acid dimethyl ester per mole modified AGU to get 6-deoxy-6-(1-triazolo-4,5-disodiumcarboxylate) cellulose with a DS up to 0.52. The products form water-insoluble complexes with multivalent metal ions and organic

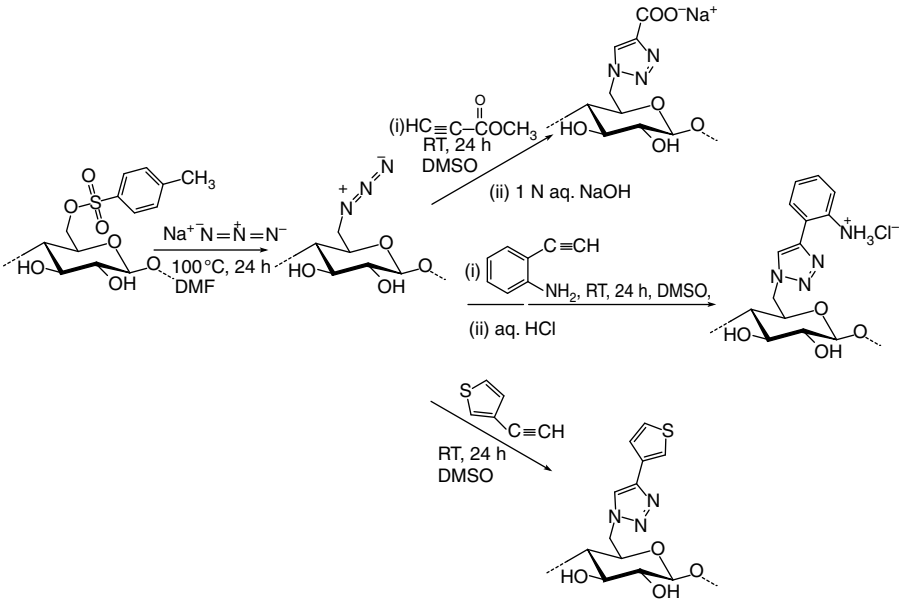


FIGURE 1.5 Reaction path for the preparation of 6-deoxy-6-azido cellulose and subsequent copper-catalyzed Huisgen reaction of 1,4-disubstituted 1,2,3-triazols used as linker for the modification of cellulose with methylcarboxylate, 2-aniline, and 3-thiophene moieties.

polycations that may possess different shapes; metal salts like calcium(II) chloride or aluminum(III) chloride yield a bagel-like shape. The polyelectrolyte complex with poly(diallyldimethylammonium) chloride is very smooth and unstable "tubes" are formed (Figure 1.8).

A promising approach for the synthesis of unconventional cellulose products is the introduction of dendrons in the cellulose backbone, which are easily accessible through the convergent synthesis of dendrimers (Vögtle et al., 2007). Apart from

TABLE 1.4 Conditions of the Copper-Catalyzed Huisgen Reaction of 6-Deoxy-6-Azido Cellulose (Azido Cellulose) and Degree of Substitution (DS) of the Products

Azido Cellulose	Reagent			Product	
DS	Type	Molar Ratio[a]	Temperature (°C)	DS	Conversion efficiency (%)
0.88	Methyl propiolate	1	25	0.86	98
0.88	2-Ethynylaniline	1	25	0.67	76
0.99	2-Ethynylaniline	3	25	0.80	81
0.99	3-Ethynylthiophene	3	25	0.91	92
0.99	3-Ethynylthiophene	3	70	0.93	94

Adapted from Liebert et al. (2006).

[a] Mole reagent per mole repeating unit of 6-deoxy-6-azido cellulose, reaction time 24 h.

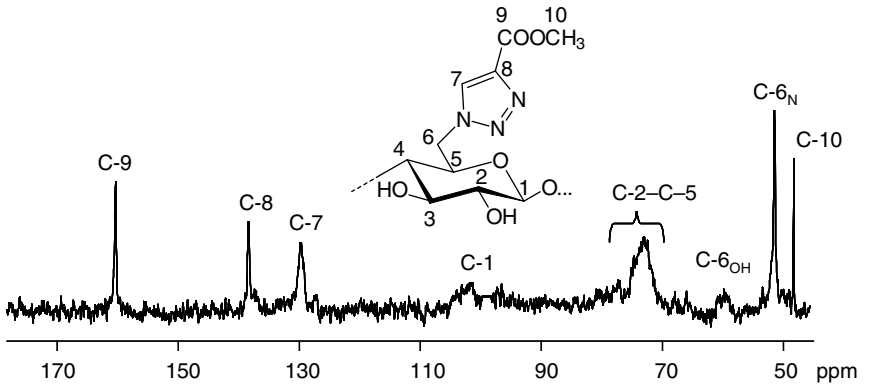


FIGURE 1.6 ^{13}C NMR spectrum of methylcarboxytriazolo celluloses (DS 0.81) in DMSO-d_6. Reproduced with permission from Wiley–VCH, Liebert et al. (2006).

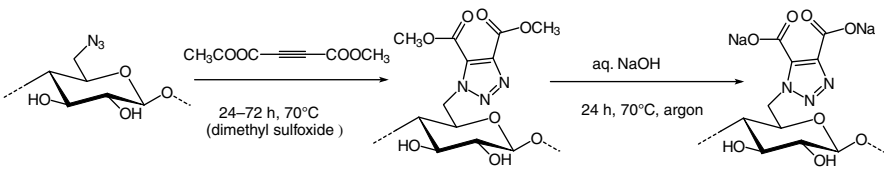


FIGURE 1.7 1,3-Dipolar cycloaddition of 6-azido-6-deoxycellulose with acetylenecarboxylic acid dimethyl ester.

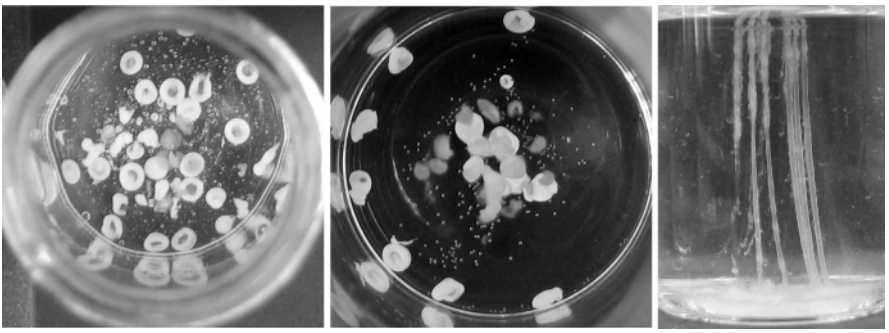


FIGURE 1.8 Ionotropic gels of 6-deoxy-6(1-triazolo-4,5-disodiumcarboxylate) cellulose (DS 0.51) with aqueous calcium chloride (5 w/v), aqueous aluminum(III) chloride (5% w/v), and poly(diallyldimethylammonium) chloride (1% w/v). Reproduced with permission from Elsevier, Koschella et al. (2010).

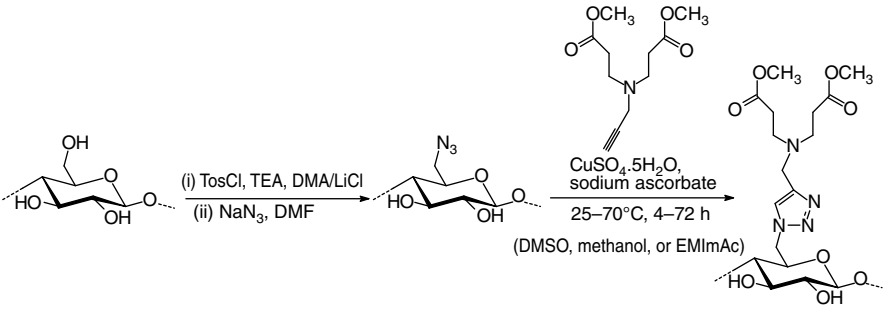


FIGURE 1.9 Reaction path for the conversion of cellulose with propargyl-PAMAM dendron of first generation via tosylation, nucleophilic displacement by azide, and conversion with the dendron.

the first described amino triester-based dendrons (Behera's amine) with an isocyanate moiety (Hassan et al., 2004, 2005), carboxylic acid-containing dendrons (Heinze et al., 2007; Pohl et al. 2008a) are explored, which are allowed to react with cellulose or cellulose derivatives like ethyl cellulose (Khan et al., 2007), hydroxypropyl cellulose (Oestmark et al., 2007), or carboxymethyl cellulose (CMC) (Zhang and Daly, 2005, 2006; Zhang et al., 2006a). Regioselective introduction of dendrons in cellulose is achieved by the reaction of 6-deoxy-6-azido cellulose with propargyl-polyamidoamine (PAMAM) dendron homogeneously in DMSO or heterogeneously in methanol in the presence of $CuSO_4 \cdot 5H_2O$/sodium ascorbate (Figure 1.9, Table 1.5)

TABLE 1.5 Degree of Substitution (DS) of Dendritic PAMAM-Triazolo Cellulose Derivatives of First (1), Second (2), and Third (3) Generations Synthesized Homogeneously in Dimethylsulfoxide (DMSO) or 1-Ethyl-3-Methylimidazolium Acetate (EMImAc) as well as Heterogeneously in Methanol by Reacting 6-Deoxy-6-Azido Cellulose (DS 0.75) with Propargyl Polyamidoamine Dendrons of First, Second, and Third Generations via Copper-Catalyzed ($CuSO_2 \cdot 5H_2O$/Sodium Ascorbate) Huisgen Reaction

Conditions				Product	
Molar Ratio	Solvent	Temperature (°C)	Time (h)	Generation	DS
1:1	DMSO	25	48	First	0.68
1:3	DMSO	25	24	First	0.65
1:3	DMSO	60	24	First	0.69
1:3	DMSO	25	24	Second	0.56
1:3	DMSO	25	72	Third	0.31
1:1	EMImAc	25	24	First	0.52
1:2	EMImAc	25	24	First	0.55
1:3	EMImAc	25	24	Second	0.48
1:1	EMImAc	25	72	Third	0.28
1:1	Methanol	25	72	First	0.63
1:3	Methanol	25	24	First	0.63

(Pohl et al., 2008b). Even ionic liquids (ILs) like 1-ethyl-3-methylimidazolium acetate (EMImAc) could successfully be applied as reaction medium due to the solubility of 6-deoxy-6-azido cellulose (Figure 1.9, Table 1.5) (Heinze et al., 2008a; Schöbitz et al., 2009).

Under homogeneous conditions, 6-deoxy-6-azido cellulose reacts with propargyl-PAMAM dendrons of first to third generation. The structure characterization of the dendritic PAMAM-triazolo celluloses succeeded by FTIR and NMR spectroscopy, including two-dimensional techniques. The HSQC-DEPT NMR spectrum of second-generation PAMAM-triazolo celluloses (DS 0.59) allows the complete assignment of the signals of the protons of the substituent in ^{1}H NMR spectra (Figure 1.10).

In Figure 1.11, a comparison of ^{13}C NMR spectra of first-, second-, and third-generation PAMAM-triazolo celluloses synthesized in EMImAc demonstrate the possibility to assign the signals of the dendrons and the AGU. However, the intensity of the peaks of the carbon atoms of the repeating unit decreases due to the large number of branches and corresponding carbon atoms.

Water-soluble deoxy-azido cellulose derivatives could be obtained by heterogeneous carboxymethylation applying 2-propanol/aqueous NaOH as medium. Starting from the cellulose derivatives with different DS values of the azide moiety (0.58–1.01), various DS values of the carboxymethyl functions (1.01–1.35) could be realized (Pohl, 2009a). The carboxymethyl deoxy-azido cellulose provides a convenient starting material for the selective dendronization of cellulose via Huisgen reaction yielding water-soluble carboxymethyl 6-deoxy-(1-*N*-(1,2,3-triazolo)-4-PAMAM) cellulose derivatives of first (DS 0.51) (Figure 1.12), second (DS 0.44), and third generation (DS 0.39).

The conformation and the flexibility of the dissolved polymer are estimated qualitatively using conformation zoning and quantitatively using the combined global method. Sedimentation conformation zoning shows a semiflexible coil conformation and the global method yields persistence length in the range of 2.8–4.0 nm with no evidence of any change in flexibility after dendronization (Table 1.6).

6-Deoxy-(1-*N*-(1,2,3-triazolo)-4-PAMAM) cellulose of the 2.5th generation (DS 0.25) is a promising starting polymer for biofunctional surfaces (Pohl et al., 2009b), either by embedding the dendronized cellulose in cellulose acetate (DS 2.5) matrix or by modifying the deoxy-azido cellulose film heterogeneously with the dendron (Figure 1.13). The heterogeneously functionalized cellulose solid support provides the higher amount of amino groups (determined by acid orange 7). The enzyme immobilization on the dendronized cellulose films after activation with glutardialdehyde is demonstrated using glucose oxidase (GOD) as a model enzyme. The specific enzyme activity of immobilized GOD (28.73 mU/cm^2) and the coupling efficiency (2.2%) are rather small compared to the blend of dendronized cellulose and cellulose acetate (135.16 mU/cm^2, 27.2%). Nevertheless, the heterogeneous approach of dendronization with propargyl-polyamidoamine dendron of 2.5th generation affords an interesting possibility for biofunctionalized surfaces and thus protein attachment.

Chemoselective synthesis of dendronized cellulose may be realized with regioselectively functionalized propargyl cellulose at position 6 (Pohl and Heinze, 2008)

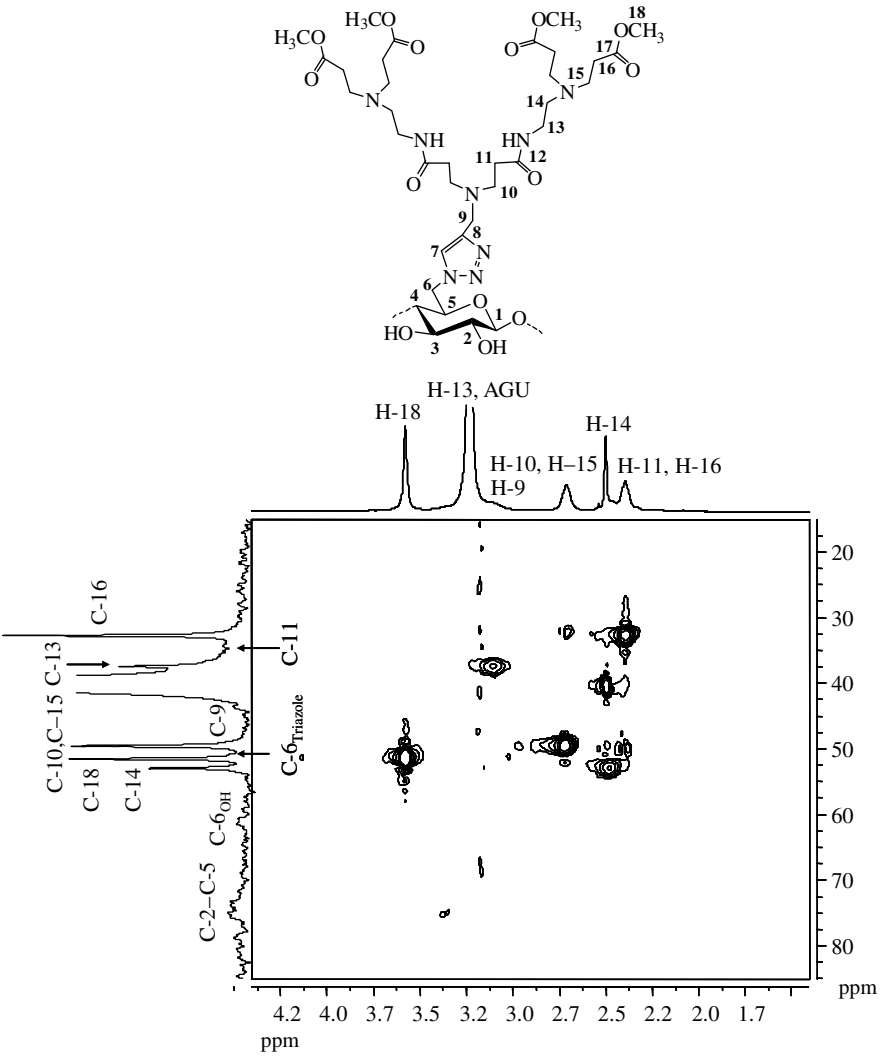


FIGURE 1.10 HSQC-DEPT NMR spectrum of second-generation PAMAM-triazolo celluloses (DS 0.59). Adapted from Pohl et al. (2008b).

or at position 3 (Fenn et al., 2009) (see Section 1.5.3). By nucleophilic displacement reaction of 6-*O*-tosyl cellulose (DS 0.58) with propargyl amine, 6-deoxy-6-amino-propargyl cellulose is formed that provides an excellent starting material for the dendronization of cellulose via the copper-catalyzed Huisgen reaction yielding 6-deoxy-6-amino-(4-methyl-(1,2,3-triazolo)-1-propyl-polyamido amine) cellulose derivatives of first (DS 0.33) and second (DS 0.25) generation (Figure 1.14).

3-Mono-*O*-propargyl cellulose could be synthesized by treatment of 2,6-di-*O*-thexyldimethylsilyl (TDS) cellulose with propargyl bromide in the presence of

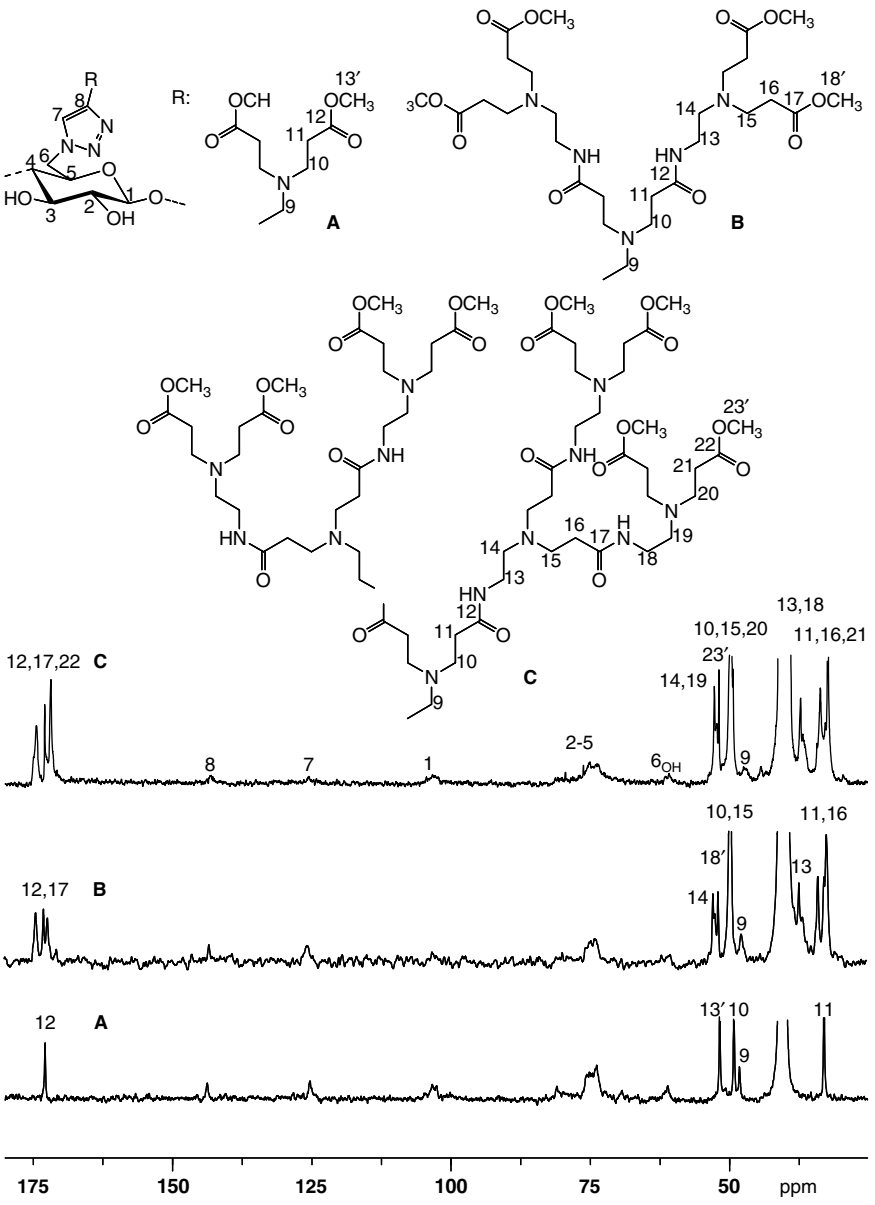


FIGURE 1.11 ^{13}C NMR spectra of **A** first (DS 0.60), **B** second (DS 0.48), and **C** third (DS 0.28) generation PAMAM-triazolo celluloses in DMSO-d_6 at 60°C.). Reproduced with permission from John Wiley & Sons, Inc., Heinze et al. (2008a).

sodium hydride and the subsequent complete removal of the silicon-containing group of the 3-mono-*O*-propargyl-2,6-di-*O*-thexyldimethylsilyl cellulose with tetrabutylammonium fluoride trihydrate (see Section 5.3). Copper-catalyzed Huisgen reaction with azido-propyl-polyamidoamine dendron of first and second generation leads to

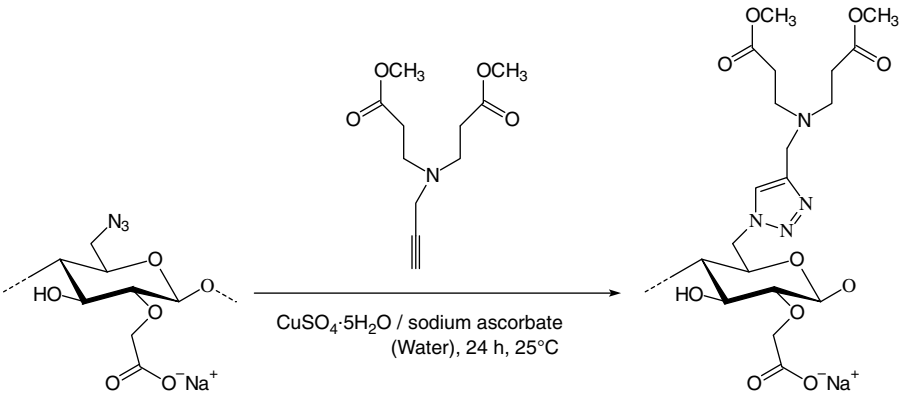


FIGURE 1.12 Homogeneous conversion of carboxymethyl 6-deoxy-6-azidocellulose (DS_{Azide} 0.81, DS_{CM} 1.25) with first generation of propargyl-polyamidoamine dendron via the copper-catalyzed Huisgen reaction.

regioselectively functionalized 3-*O*-(4-methyl-1-*N*-propyl-polyamidoamine-(1,2,3-triazole)) cellulose (Figure 1.15) (Fenn et al., 2009).

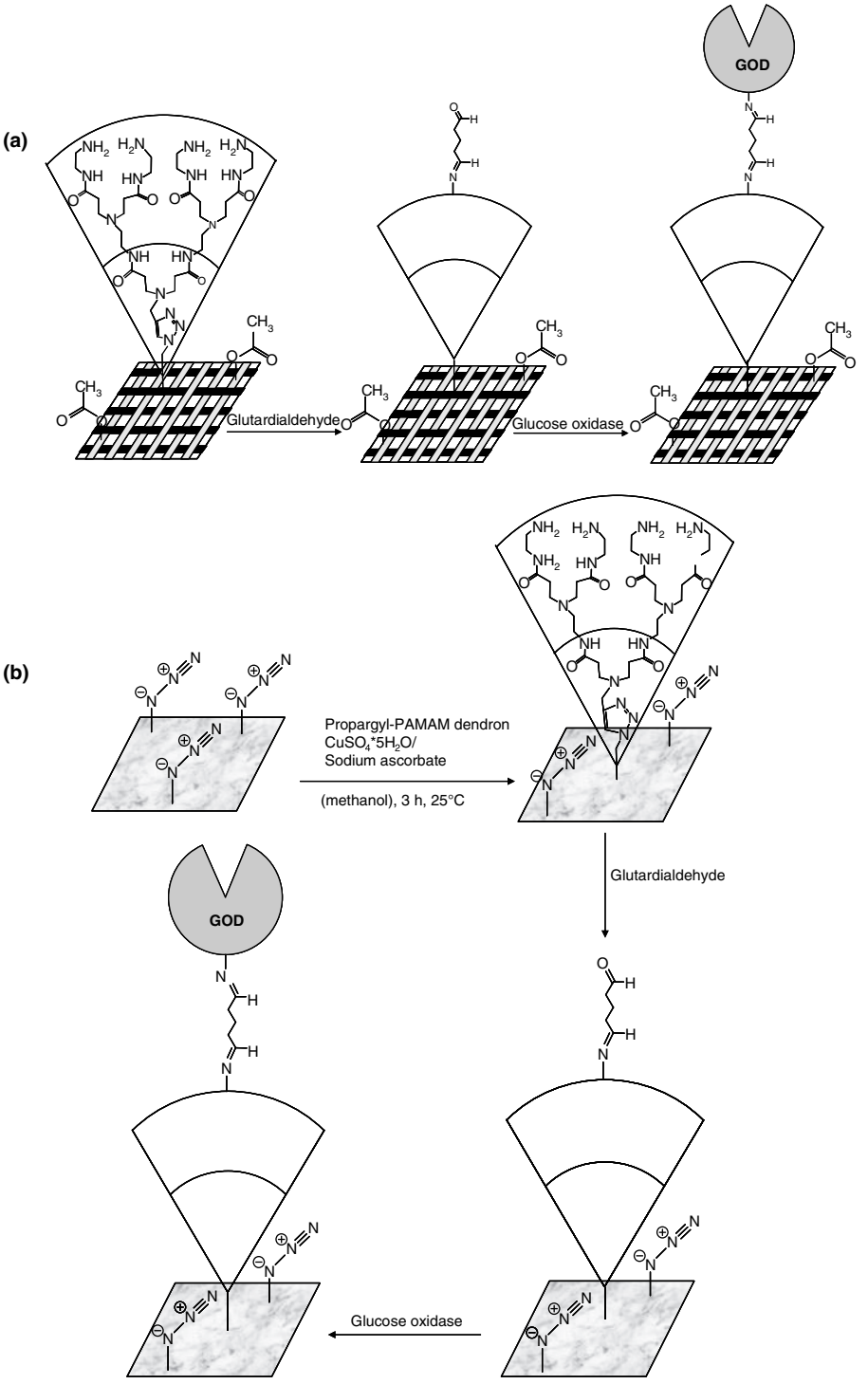
1.4 SULFATION OF CELLULOSE

Polysaccharide sulfuric acid half-esters are often referred to as polysaccharide sulfates (PSS), constituting a complex class of compounds occurring in living organisms. They possess a variety of biological functions, for example, inhibition of blood coagulation, or may be present as component of connective tissues (Fransson, 1985). These polysaccharides are usually composed of different sugars, including

TABLE 1.6 Conformational Parameters for Carboxymethyl Deoxy-Azido Cellulose and Dendronized Carboxymethyl 6-Deoxy-(1-*N*-(1,2,3-Triazolo)-4-PAMAM) Celluloses

Sample	DS_{Azide}	DS_{CM}	DS_{Dend}/ Generation	f/f_0	L_P (nm)	M_L (g/(mol nm))	Conformation Zone
CM-deoxy-azido cellulose	0.81	1.25	–	3.6	3.0	310	C
CM-6-(1,2,3-TA) (PAMAM)C	0.30	1.25	0.51/First	2.9	2.8	470	C
CM-6-(1,2,3-TA) (PAMAM)C	0.37	1.25	0.44/Second	4.3	3.7	450	C
CM-6-(1,2,3-TA) (PAMAM)C	0.42	1.25	0.39/Third	5.0	4.0	420	C

Zone C = semiflexible conformation.
CM: carboxymethyl; CM-6-(1,2,3-TA)(PAMAM)C: carboxymethyl 6-deoxy-(1-*N*-(1,2,3-triazolo)-4-PAMAM) cellulose.
Adapted from Pohl et al. (2009a).


(a)
GOD
Glutardialdehyde
Glucose oxidase
(b)
Propargyl-PAMAM dendron
CuSO4*5H2O/
Sodium ascorbate
(methanol), 3 h, 25°C
Glutardialdehyde
GOD
Glucose oxidase

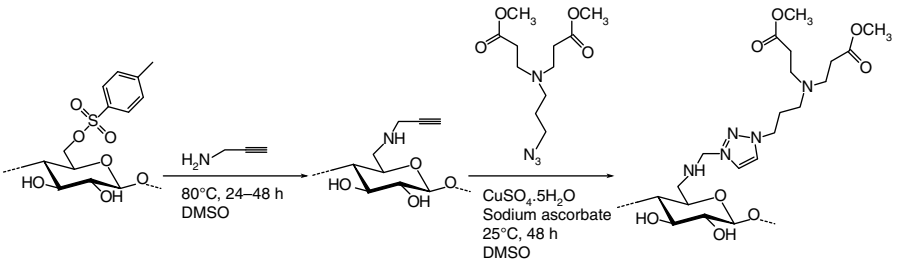


FIGURE 1.14 Reaction path for the synthesis of 6-deoxy-6-amino-(4-methyl-(1,2,3-triazolo)-1-propyl-polyamido amine) cellulose derivatives of first generation (DS 0.33) via 6-deoxy-6-aminopropargyl cellulose. Adapted from Pohl and Heinze (2008).

aminodeoxy and carboxy groups containing derivatives, for example, β-D-glucuronic acid, α-L-iduronic acid, and *N*-acetyl-β-D-galactosamine (Nakano et al., 2002). Heparan sulfate, chondroitin-6-sulfate, and dermatan sulfate are among the most important naturally occurring PSS (Figure 1.16).

Promising biological properties are not only observed for naturally occurring PSS but also for semisynthetic ones that can be received by introduction of sulfate groups into the polymer backbone of polysaccharides such as cellulose, dextran, pullulan, or chitosan. They have a number of advantages over their natural occurring counterparts. The isolation of the naturally occurring PSS often requires high cost due to intensive enrichment, extraction, and purification procedures, while homopolysaccharides suitable for sulfation are often easily available by biotechnological processes (dextran, pullulan) or even by industrial scale production (cellulose, xylan, and chitosan). On one hand, natural PSS constitute of very complex structures making it difficult to elucidate structure–property correlations, while on the other hand, ease of chemical modification of polysaccharides in combination with modern structure characterization methods offers a broad structural diversity of semisynthetic PSS with well-defined chemical structures. These products can mimic the structure and biological activity of naturally occurring PSS and are intensively studied regarding their applications in various fields especially in biotechnology and medicine.

Many procedures for the preparation of cellulose sulfates (CS) have been developed (Figure 1.17). The properties of CS, like water solubility, superstructure formation, and biological activity, strongly depend on the DS, on the molecular weight, and on the distribution of substituents within the repeating unit and along the polymer chain, which are ascertained by the course of reaction. The influence of the pattern of substitution on the properties is especially distinct at very low DS values.

FIGURE 1.13 Scheme preparation of biofunctional surfaces. (a) Blend of 6-deoxy-6-(1,2,3-triazolo)-4-polyamidoamine cellulose (DS 0.25) and cellulose acetate (DS 2.50). (b) Heterogeneous functionalization of deoxy-azido cellulose film with propargyl-polyamidoamine dendron of 2.5th generation via copper-catalyzed Huisgen reaction and for both subsequent surface activation with glutardialdehyde for covalent immobilization of glucose oxidase. Adapted from Pohl et al. (2009b).

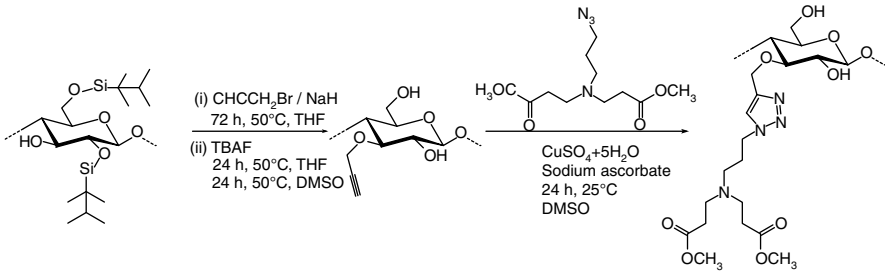


FIGURE 1.15 Reaction scheme for the synthesis of 3-*O*-(4-methyl-1-*N*-propyl-polyamidoamine-(1,2,3-triazole)) cellulose of first generation via 3-*O*-propargyl cellulose. Adapted from Fenn et al. (2009).

Complete heterogeneous sulfation of cellulose is carried out with mixtures of H_2SO_4 and propanol (Yao, 2000; Lukanoff and Dautzenberg, 1994). The course of the reaction is largely committed by the equilibrium formation of propylsulfuric acid. Cooling to about $-10^{\circ}C$ is necessary in order to limit acid-catalyzed chain cleavage. The CSs yielded are not uniformly substituted and contain large amounts of water-insoluble parts without previous activation of the cellulose. An increase of the DS due to increasing reaction time, temperature, and amounts of H_2SO_4 is in general not only combined with a decrease of insoluble parts but also with considerable polymer degradation and hence lower solution viscosities of the aqueous solutions of the products (Figure 1.18) (Lukanoff and Dautzenberg, 1994).

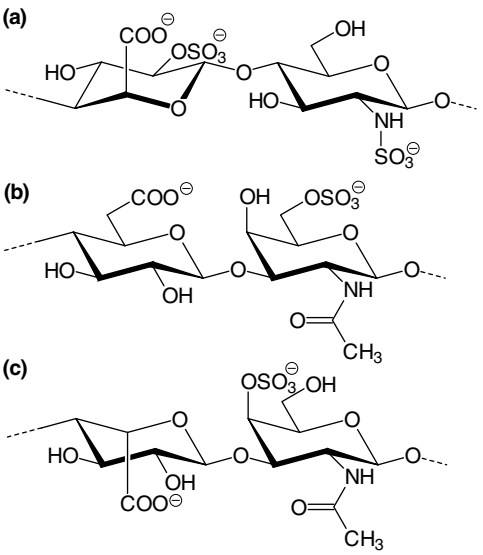


FIGURE 1.16 Typical repeating units of heparan sulfate (a), chondroitin-6-sulfate (b), and dermatan sulfate (c).

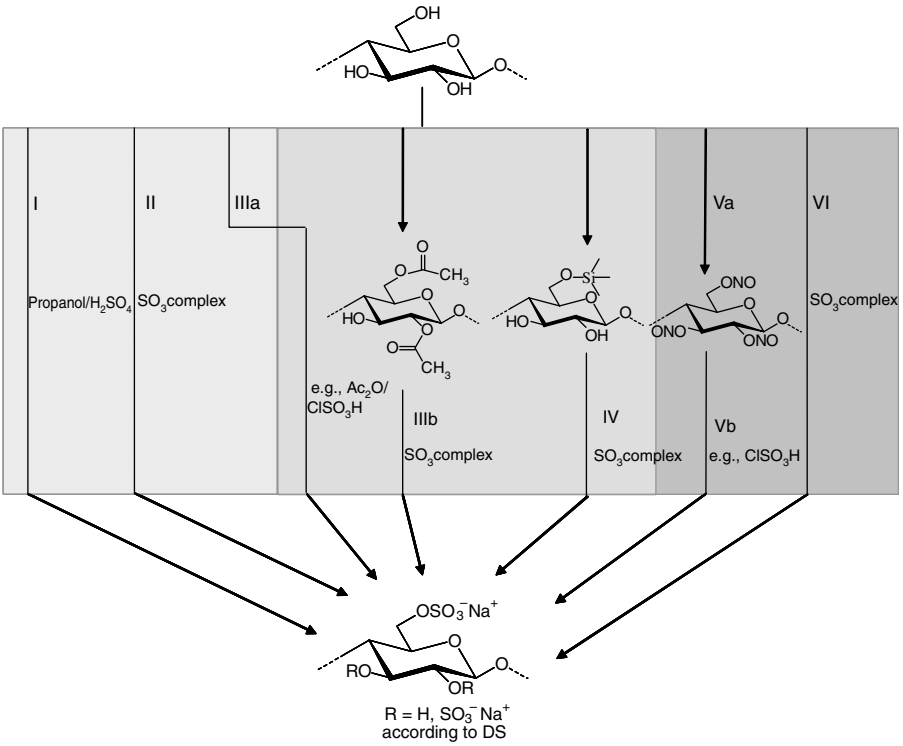


FIGURE 1.17 Overview of different approaches for the preparation of cellulose sulfate under heterogeneous (light gray), quasi-homogeneous (medium gray), and homogeneous (dark gray) conditions. I: heterogeneous sulfation with propanol/H_2SO_4; II: sulfation in DMF or pyridine under heterogeneous starting conditions; IIIa: parallel acetylation and sulfation of cellulose; IIIb: sulfation of cellulose acetate; IV: sulfation of trimethylsilyl cellulose; Va: dissolution of cellulose in N_2O_4/DMF; Vb: sulfation of cellulose trinitrite in N_2O_4/DMF solution; and VI: direct sulfation in ionic liquids.

Sulfation of cellulose suspended in DMF with a SO_3 complex starts under heterogeneous conditions and leads to the dissolution of the CS formed at a certain DS. This method is suitable for the preparation of CS with high DS > 1.5 only. Lower substituted derivatives are sulfated in the swollen amorphous parts of the cellulose, while the crystalline parts remain unfunctionalized. Thus, water insolubility and nonuniform sulfation among the cellulose chains, that is, different amounts of water-soluble parts (high DS) and water-insoluble parts (low DS) are formed (Schweiger, 1972).

Sulfation of cellulose derivatives, in particular cellulose acetate, cellulose nitrite, and trimethylsilyl cellulose (TMSC), and subsequent cleavage of the initial functional group are a valuable quasi-homogeneous route for the CS preparation. The major drawbacks are the requirement of large amounts of chemicals and the additional effort necessary for both the reaction and purification processes.

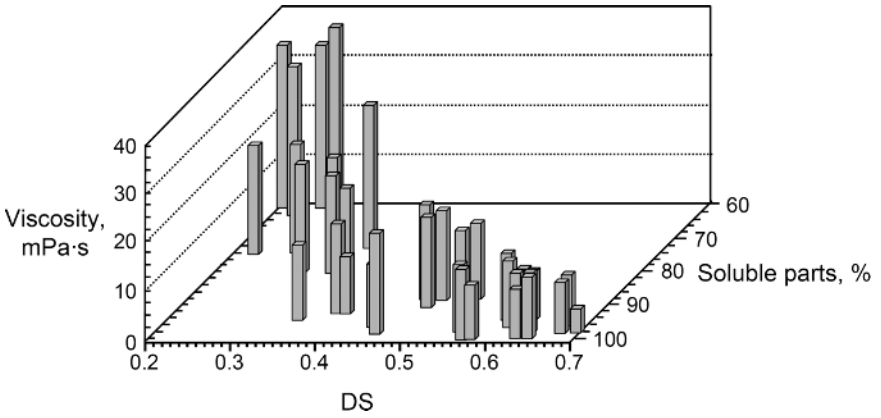


FIGURE 1.18 Correlation of DS value, viscosity, and amount of water-soluble part of cellulose sulfates obtained by heterogeneous sulfation of cellulose using propanol/H_2SO_4 mixtures. Adapted from Lukanoff and Dautzenberg (1994), and with permission from Nova Science Publishers, Heinze et al. (2010a).

In this context, N_2O_4/DMF was intensively studied as derivatizing cellulose solvent for the preparation of CS, although it is very hazardous. The intermediately formed cellulose nitrite is attacked by various reagents (SO_3, $ClSO_3H$, SO_2Cl_2, and H_2NSO_3H), resulting in CSs via transesterification with DS values ranging from 0.3 to 1.6 after cleavage of the residual nitrite moieties during the workup procedure under protic conditions (Schweiger, 1974; Wagenknecht et al., 1993). The regioselectivity of the transesterification reaction can be controlled by reaction conditions used (Table 1.7). The polymer degradation is rather low-yielding products that form high-viscous solutions. Besides their promising properties, the application of CS prepared in N_2O_4/DMF, especially for biomedical application, is limited due to the high toxicity of the solvent and the by-products formed (nitrosamines).

TABLE 1.7 Regioselectivity of Sulfation of Cellulose Nitrite with Different Reagents (2 mol/mol AGU) Depending on the Reaction Conditions

Reaction Conditions			Cellulose Sulfate			
			Partial DS			
Reagent	Time (h)	Temperature (°C)	2	3	6	Total DS
$NOSO_4H$	4	20	0.04	0	0.31	0.35
NH_2SO_3H	3	20	0.10	0	0.30	0.40
SO_2Cl_2	2	20	0.30	0	0.70	1.00
SO_3	3	20	0.26	0	0.66	0.92
SO_3	1.5	−20	0.45	0	0.10	0.55

DS values were determined by means of NMR spectroscopy.
Adapted from Wagenknecht et al. (1993).

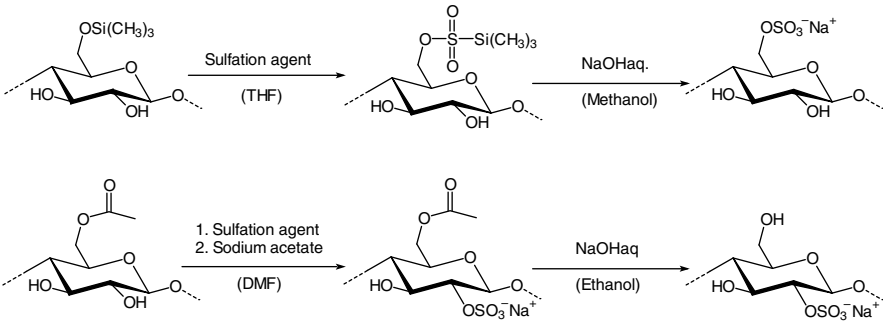


FIGURE 1.19 Synthesis of cellulose sulfate via trimethylsilyl cellulose (upper scheme) and starting from cellulose acetate (lower scheme).

In order to avoid the toxic N_2O_4/DMF solvent, TMS cellulose was used, which is soluble in various organic solvents, for example, DMF and tetrahydrofuran (THF), that readily reacts with SO_3–pyridine or SO_3–DMF complex (Wagenknecht et al., 1992). The synthesis of TMS cellulose is quite easy and can be achieved by homogeneous reaction of cellulose in DMA/LiCl and ionic liquids with hexamethyldisilazane or heterogeneously in DMF/NH_3 with trimethylchlorosilane (DS $<$ 1.5) (Köhler et al., 2008; Mormann and Demeter, 1999; Heinze, 1998).

Similar to the sulfation of cellulose nitrite, the TMS group acts as leaving group. The first step consists of an insertion of SO_3 into the Si–O bond of the silyl ether (Figure 1.19). The instable intermediate formed is usually not isolated. Subsequent workup with aqueous NaOH results in a cleavage of the TMS group under formation of CS (Richter and Klemm, 2003).

It is described that due to the course of reaction, the $DS_{Sulfate}$ is limited by the DS_{TMS} of the starting TMS cellulose and can be adjusted in the range of 0.2–2.5. Typical reaction conditions and DS values are summarized in Table 1.8. The sulfation reaction is fast and takes about 3 h with negligible depolymerization. Thus, products of high molar mass are accessible if TMS cellulose of high DP was applied as starting material. For instance, the specific viscosity of a CS with DS 0.60 is 4900 (1% in H_2O) (Wagenknecht et al., 1992).

The sulfation could be carried out in a one-pot reaction, that is, without isolation and redissolution of the TMS cellulose (Wagenknecht et al., 1992). After silylation of cellulose in DMF/NH_3, the excess of NH_3 is removed under vacuum followed by separation of the NH_4Cl formed. The sulfating agent, for example, SO_3 or $ClSO_3H$, dissolved in DMF is added and the CS is formed.

Carboxylic acid esters of cellulose, in particular commercially available cellulose acetate with DS 2.5 as well as cellulose formiate both dissolved in DMF, are useful intermediates for the preparation of CS (Philipp et al., 1990). In case of cellulose formiate, the $DS_{Sulfate}$ can be higher than the amount of remaining OH groups partly because of the displacement of formiate moieties by sulfate groups. In contrast, no transesterification appears during sulfation of cellulose acetate. The acetyl groups act as protecting group and the sulfation with SO_3–pyridine, SO_3–DMF complex, or

TABLE 1.8 Sulfation of Cellulose via TMS Cellulose

Reaction Conditions				Product
TMS Cellulose		Sulfating Agent		
DS_{TMS}	Solvent	Type	mol/mol AGU	$DS_{Sulfate}$
1.55	DMF	SO_3	1.0	0.70
1.55	DMF	SO_3	2.0	1.30
1.55	DMF	SO_3	6.0	1.55
1.55	DMF	$ClSO_3H$	1.0	0.60
1.55	DMF	$ClSO_3H$	2.0	1.00
1.55	DMF	$ClSO_3H$	3.0	1.55
2.40	THF	SO_3	1.0	0.71
2.40	THF	SO_3	1.7	0.90
2.40	THF	SO_3	3.3	1.84
2.40	THF	SO_3	9.0	2.40

Adapted from Wagenknecht et al. (1992).

acetylsulfuric acid proceeds exclusively at the remaining hydroxyl functions (Figure 1.19). The cellulose acetosulfate formed is neutralized with sodium acetate and subsequently treated with NaOH in ethanol to cleave the acetate moieties in an inert atmosphere within 16 h at room temperature (RT).

Regioselective deacetylation of cellulose acetate at position 2 is achieved by treating the starting polymer (DS 2.5) with amines of low basicity, such as hexamethylene diamine, together with certain amounts of water at 80°C (Wagenknecht, 1996). Thus, CS with preferred sulfation at position 2 could be isolated (Table 1.9).

Acetosulfation, that is, competitive esterification of cellulose suspended in DMF, DMA, or *N*-methylpyrrolidone (NMP) with a mixture of acetic anhydride

TABLE 1.9 Partial DS Values of Cellulose Sulfate obtained by Conversion Position 2 and 3 of partly in 1 Deacetylated Cellulose Acetate with NH_2SO_3H in DMF (80°C, 2 h)

Cellulose Acetate, DS					Cellulose Sulfate, DS			
Overall	Position 2	Position 3	Position 6	mol/mol AGU	Overall	Position 2	Position 3	Position 6
2.65[a]	0.80	0.85	1.0	1	0.26	0.17	0.08	0.0
1.86[a]	0.45	0.45	0.90	2	0.92	0.55	0.20	0.17
1.48[a]	0.20	0.20	0.85	3	1.15	0.74	0.13	0.28
2.40[b]	0.85	0.80	0.75	1	0.52	0.17	0.15	0.20

Adapted from Wagenknecht (1996).

[a] Regioselectively deacetylated cellulose acetate.

[b] Statistical cellulose acetate.

and SO_3 or $ClSO_3H$, is another route toward CS with distinct sulfation at position 6 (Hettrich et al., 2008; Zhang et al., 2009, 2010a, 2010b). The synthesis involves the formation of a mixed cellulose acetosulfate combined with dissolution of the polysaccharide derivative in the dipolar aprotic solvent. Acetylating agent up to 6–11 mol and sulfating agent up to 3 mol are needed to yield CS with $DS_{sulfate}$ up to about 2. As a result of this quasi-homogeneous reaction, water solubility of CS is achieved at rather low $DS > 0.3$. In addition, high solution viscosities can be observed when celluloses with high DP such as cotton linters are used.

Homogeneous sulfation of dissolved cellulose can also overcome the problem of irregular substituent distribution. Although widely used for the esterification of cellulose with carboxylic acids, DMA/LiCl is not the solvent of choice for sulfation, because insoluble products of low DS are obtained due to gel formation by addition of the sulfating agent (Klemm et al., 1998a). Several other cellulose solvents including *N*-methylmorpholine-*N*-oxide (NMNO) have also been investigated for the homogeneous sulfation of cellulose, but showed coagulation of the reaction medium yielding badly soluble CS (Wagenknecht et al., 1985).

Promising solvents for the sulfation of cellulose are ionic liquids. This group of salt-like compounds with melting points below 100°C turned out to be excellent media for shaping and functionalization of cellulose (Swatloski et al., 2002; El Seoud et al., 2007). Cellulose dissolved in 1-butyl-3-methylimidazolium chloride (BMIMCl)/cosolvent mixtures can be easily transformed into CS by using SO_3–pyridine and SO_3–DMF complex or $ClSO_3H$ (Gericke et al., 2009a). Highly substituted CSs are described for sulfation in BMIMCl at 30°C (Wang et al., 2009), but it has to be noted that cellulose/IL solutions slowly turned solid upon cooling to room temperature depending on cellulose and moisture content. Furthermore, they have rather high solution viscosities, which make it very difficult to ensure sufficient miscibility and to guarantee even accessibility of the sulfating agent to the cellulose backbone. Consequently, the synthesis of CS with a uniform distribution of sulfate groups along the polymer chains demanded a dipolar aprotic cosolvent that drastically reduces the solution viscosity (Gericke et al., 2009a). The reactivity of the sulfating agent is not influenced by the cosolvent. At a molar ratio of 2 mol SO_3–DMF complex per mole AGU, the sulfation of microcrystalline cellulose in BMIMCl and BMIMCl/DMF mixtures yields CS with comparable DS values of about 0.9. While the CS synthesized without cosolvent shows water insolubility, the other one readily dissolves in water (Gericke et al., 2009a). On one hand, the increase of temperature results in a considerable decrease of the viscosity of cellulose/IL solutions, which improves solution miscibility (Gericke et al., 2009b), while on the other hand, high temperatures favor the acid-catalyzed chain degradation leading to rather low solution viscosities of aqueous solutions of the resulting CSs of about 2 mPa·s (1%).

The homogeneous sulfation in IL allows tuning of CS properties by simply adjusting the amount of sulfating agent and choosing different types of cellulose (Table 1.10). The reaction proceeds with almost no polymer degradation if conducted at room temperature (Gericke et al., 2009a). This makes the procedure very valuable for the preparation of water-soluble CS over a wide DS range. Especially CS with low DS could be prepared efficiently in IL/cosolvent mixture that is of interest for the bioencapsulation (see pp. 25).

TABLE 1.10 DS Values and Water Solubility of Cellulose Sulfates Obtained by Sulfation of Spruce Sulfite Pulp Dissolved in BMIMCl/DMF at Different Conditions

Reaction conditions				Product	
Sulfating Agent					
Type	mol/mol AGU	Time (h)	Temperature (°C)	DS	Water solubility
SO_3–Py[a]	0.7	2	25	0.14	No
SO_3–Py	0.8	2	25	0.25	Yes
SO_3–Py	0.9	2	25	0.48	Yes
SO_3–Py	1.1	2	25	0.58	Yes
SO_3–Py	1.3	1	80[b]	0.52	Yes
SO_3–Py	1.4	2	25	0.81	Yes
SO_3–DMF	1.0	2	25	0.34	Yes
SO_3–DMF	1.5	2	25	0.78	Yes
$ClSO_3H$	1.0	3	25	0.49	Yes

Adapted from Gericke et al. (2009a).
[a] SO_3–pyridine complex.
[b] Without cosolvent.

Sulfation of cellulose in BMIMCl/DMF yields a preferred 6-sulfated product. A typical ^{13}C NMR spectrum of CSs with DS 0.48 prepared in BMIMCl/DMF and the assignment of the peaks are shown in Figure 1.20. The signal at 67.3 ppm corresponds to sulfation at position 6. Peaks in the region of 82 ppm that would correspond to sulfated position 2 or 3 are missing in the spectrum and no splitting of the C-1 signal can be observed, which would indicate sulfation at position 2.

Disadvantages of IL are their costs and the high viscosities. These drawbacks are compensated by the ease of recycling due to their negligible vapor pressure. Reusability of IL for sulfation has already been reported for BMIMCl leading to

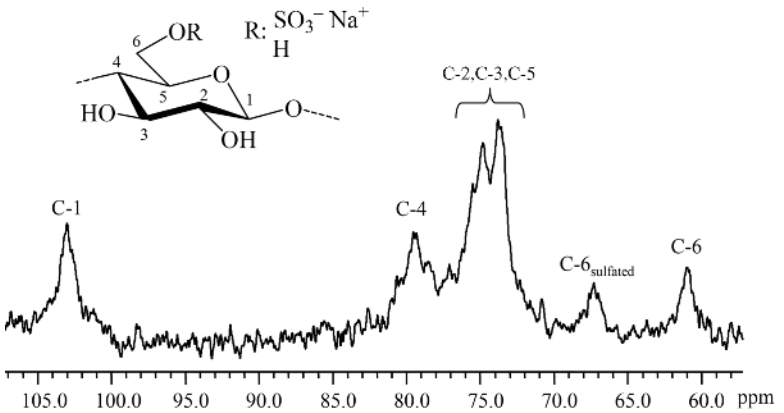


FIGURE 1.20 ^{13}C NMR spectrum (in D_2O) of cellulose sulfates (DS = 0.48) obtained by sulfation in BMIMCl/DMF with SO_3–DMF. Reproduced with permission from Wiley–VCH, Gericke et al. (2009a).

similar DS values compared to fresh IL (Gericke et al., 2009a). Furthermore, the use of cosolvents and the development of low viscous task-specific IL, bearing additional functional groups, can lead to further improvement of the homogeneous sulfation of cellulose. It should be noted that IL can act as "noninnocent" solvents that participate in the reaction. For instance, sulfation of cellulose in the room-temperature IL 1-ethyl-3-methylimidazolium acetate yields cellulose acetate instead of CS (Liebert et al., 2009). Similar side reactions were previously observed for acylation, tritylation, and tosylation of cellulose in EMIMAc (Köhler et al., 2007).

Thus, acetosulfation and homogeneous sulfation in IL are suitable pathways for the preparation of well-soluble, high-molecular weight CS under lab-scale conditions. Commercial application of acetosulfation, however, is limited due to the large amounts of acetylating agent necessary and the inefficient workup.

Besides the bioactivity, sulfates of polysaccharides were investigated toward their ability to form polyelectrolyte complexes (PEC) with various synthetic (Li and Yao, 2009; Renken and Hunkeler, 2007a, 2007b; Zhang et al., 2005, 2006b) and natural polycations (Xie et al., 2009). The process is based on the sequential deposition of interactive polymers from their solutions by electrostatic, van der Waals, and hydrogen bonding, as well as charge transfer interactions (Decher, 1996). These interactions can be applied to create layer-by-layer (LbL) assemblies of functional material surfaces with defined biodegradability or bioactivity (Heinze et al., 2006c).

Microencapsulation of biological material within PEC capsules based on CS has been studied for numerous applications, especially in biotechnology and medicine (Dautzenberg et al., 1999). CSs for bioencapsulation are preferably synthesized via homogeneous sulfation in IL because water-soluble products with high solution viscosities and rather low DS values of 0.3–0.7 are required (Gericke et al., 2009a). CSs of higher DS lead to complexes of low stability (Dautzenberg et al., 1993). Capsular PECs can be achieved with diameters in millimeter till 100 μm scale by dropping a polyanion solution into a polycation precipitation bath, such as poly (diallyldimethylammonium chloride) (polyDADMAC) (Figure 1.21).

Immobilization of enzymes allows simple recovery and improves their mechanical stability drastically during agitation, which makes this technique very attractive for large-scale biotechnological processes where high durability is required (Hanefeld et al., 2009). After encapsulation within PEC capsules, the velocity of substrate conversion is determined by diffusion through the PEC membrane leading to a decrease of relative enzyme activity. For GOD-containing capsules, they retain 14% of their initial activity after encapsulation within CS-polyDADMAC (Gericke et al., 2009a). Higher capsule stability without further loss of GOD activity is maintained using a more complex four-component system composed of CS, sodium alginate (SA), $CaCl_2$, and the cation poly(methylene-*co*-guanidine) (PMCG) (Vikartovská et al., 2007). The capsule preparation includes the formation of calcium alginate gel and subsequently polyanion–polycation complexation. Relative activity of GOD-CS-SA-PMCG capsules is 13%. Another elegant two-component approach for enhancing PEC properties applies water-insoluble CS with very low DS values of about 0.15, dissolved in ionic liquid, for the formation of CS–polyDADMAC capsules with increased mechanical stability (Figure 1.22a) (Gericke et al., 2009c). The increase of mechanical

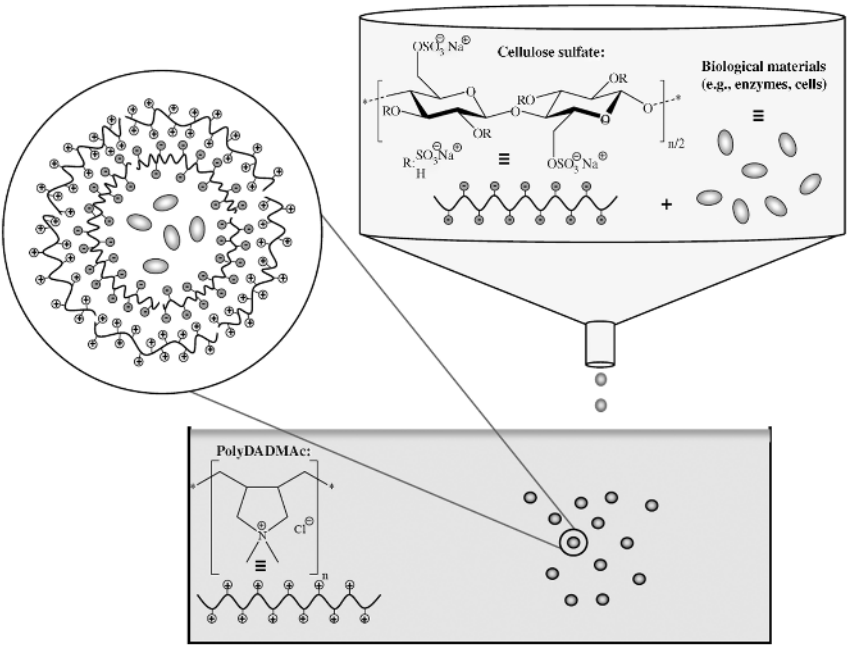


FIGURE 1.21 Scheme of the microencapsulation of biological material in polyelectrolyte complex capsules based on cellulose sulfate and poly(diallyldimethylammonium chloride) (polyDADMAC). Reproduced with permission from Wiley–VCH, Gericke et al. (2009a).

stability can be attributed to reestablished hydrogen bonds of the low substituted CS in addition to the electrostatic interaction of polyanion–polycation (Figure 1.22b). Despite the fairly harsh conditions, enzyme entrapment is also realized with IL-based CS/polyDADMAC capsules. The membrane properties, determining matter transfer between the inner core of the PEC capsule and the outer medium, are comparable to common capsules from water-soluble CS, because the same relative activity of 14% of the initial activity is found. Thus, sulfation, *in situ* PEC formation, and encapsulation in a one-pot procedure may be established. After completed reaction, GOD is suspended in the reaction mixture and GOD–PEC capsules are prepared by dropping the mixture directly into aqueous polyDADMAC, omitting time- and energy-consuming isolation and purification steps.

The high biocompatibility and lack of cytotoxicity of CS-polyDADMAC capsules make them ideal candidates for the encapsulation of cells (Pelegrin et al., 1998; Wang et al., 1997). PEC layer is inert to metabolic breakdown, can survive for several months *in vivo*, and prevents recognition and attack of the protected cells by the immune system (Pelegrin et al., 1998). Thus, xenotransplantation of encapsulated cells may become a powerful therapeutic tool for the treatment of various diseases, including cancer and diabetes. Encapsulation of insulin producing porcine islet cells demonstrates that the CS-polyDADMAC PEC membrane is permeable for vital nutrients as well as oxygen, allowing glucose-dependent cell growth

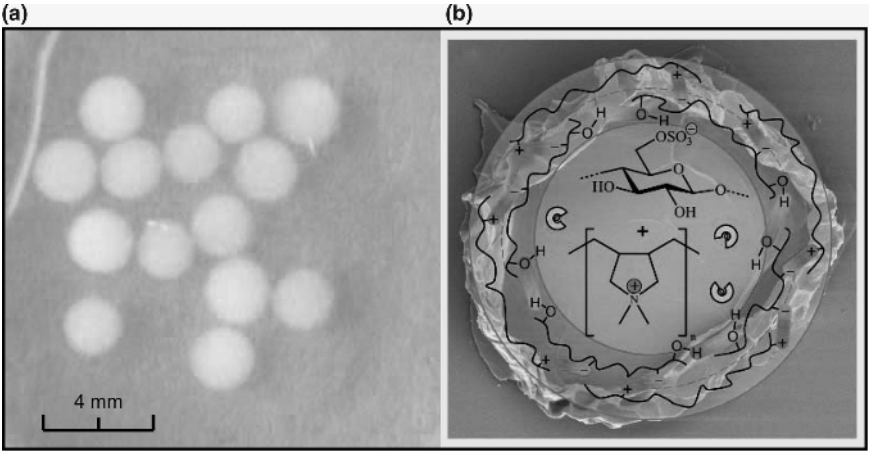


FIGURE 1.22 (a) Polyelectrolyte capsules prepared from water-insoluble cellulose sulfate (CS). (b) Scheme of the *in situ* polyelectrolyte complex formation and enzyme encapsulation using water-insoluble CS and ionic liquids. Reproduced with permission from Nova Science Publishers, Heinze et al. (2010a).

(Schaffelner et al., 2005). Moreover, PEC immobilization is used to protect cells during cryopreservation (Stiegler et al., 2006).

PEC capsules with trigger-controlled release have been studied applying cellulose-producing cells (Fluri et al., 2008). Transgenic mammalian cells, which exhibit doxycycline (DOX)-controlled (1 → 4)-β-glucanase expression, are encapsulated within CS-based PEC capsules. The removal of the inducer molecule DOX suppressing cellulase accumulation enabled time-dependent capsule rupture and discharge of therapeutic proteins (Figure 1.23).

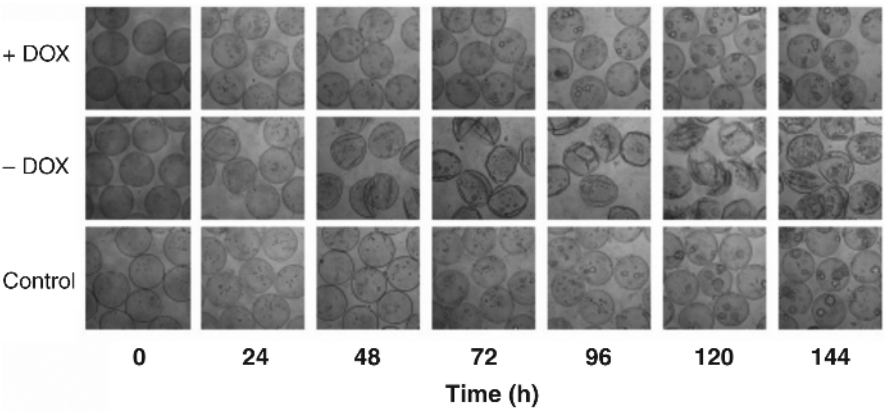


FIGURE 1.23 Encapsulated (1 → 4)-β-glucanase secreting mammalian cells cultivated in the presence (+DOX) and absence (−DOX) of doxycycline. Control cell line produces no cellulose. Reproduced with permission from Nova Science Publishers, Heinze et al. (2010a).

1.5 REGIOSELECTIVELY FUNCTIONALIZED CELLULOSE ETHER

Etherification is a very important branch of commercial cellulose functionalization. Cellulose ethers are prepared in technical scale by reaction of alkali cellulose with alkylating reagents, for example, epoxides, alkyl-, and carboxymethyl halides (Brandt, 1986; Klemm et al., 1998b). In heterogeneous synthesis, the accessibility of the hydroxyl groups is determined by hydrogen bond-breaking activation and by interaction with the reaction media (Klemm et al., 1998b, 2005). The reaction of cellulose with reagents of low steric demand leads to a random distribution of ether functions within AGU and along the polymer chain provided a sufficient activation is carried out. It is well known that not only DS but also the pattern of substitution may influence the properties of cellulose ethers (Heinze, 2004). To gain detailed information about the influence of the structures on properties of cellulose derivatives, not only a comprehensive structure characterization but also cellulose ethers with a defined distribution of the functional groups (i.e., regioselective functionalization pattern) are indispensable for the establishment of the structure–property relationships. "Regioselectivity" in cellulose chemistry means an exclusive or significant preferential reaction at one or two of the three positions 2, 3, and 6 of AGU as well as along the polymer chain (Figure 1.24).

Up to now, the most important approach to control the functionalization within the repeating unit is the application of protecting groups (Figure 1.25). Other methods comprising, for example, selective cleavage of primary substituents by chemical or enzymatic treatment play a minor role (Deus et al., 1991; Wagenknecht, 1996; Altaner et al., 2003). Examples are the deacetylation of cellulose acetate under aqueous acidic or alkaline conditions or in the presence of amines (see Section 1.4). In addition, activating groups like the tosyl moiety may also be disposed for selective reactions (see Section 1.3.1).

The most widely used protecting group for the primary OH group is the triphenylmethyl (trityl) moiety (Figure 1.26). Heterogeneous introduction of the trityl groups starts with an activated polymer obtained either by deacetylation of cellulose acetate (Harkness and Gray, 1990; Kondo and Gray, 1991) or by mercerization of cellulose (Kern et al., 2000) followed by a conversion in anhydrous pyridine. More efficient tritylation of cellulose yielding polymers with DS values of 1.0 takes place in DMA/LiCl (preferred solvent) and DMSO/SO_2/diethylamine (Kasuya and Sawatari, 2000; Hagiwara et al., 1981). Methoxy-substituted triphenylmethyl compounds are more effective protecting groups for the primary hydroxyl group of cellulose (Camacho et al., 1996). The conversion of cellulose dissolved in DMA/LiCl with 4-monomethoxytriphenylmethyl chloride is 10 times faster than the reaction with unsubstituted trityl chloride. Complete functionalization of the primary hydroxyl groups occurs within 4 h and 70°C. Even after long reaction times, excess of the reagent, and elevated temperatures, alkylation at the positions 2 and 3 is less than 11%, which is in the same range as for the unsubstituted trityl function. Moreover, the detritylation proceeds 20 times faster (Heinze, 2004).

Trialkyl- (with at least one bulky alkyl moiety) and triarylsilyl groups are known to protect the primary groups of cellulose. Pawlowski describes the synthesis of

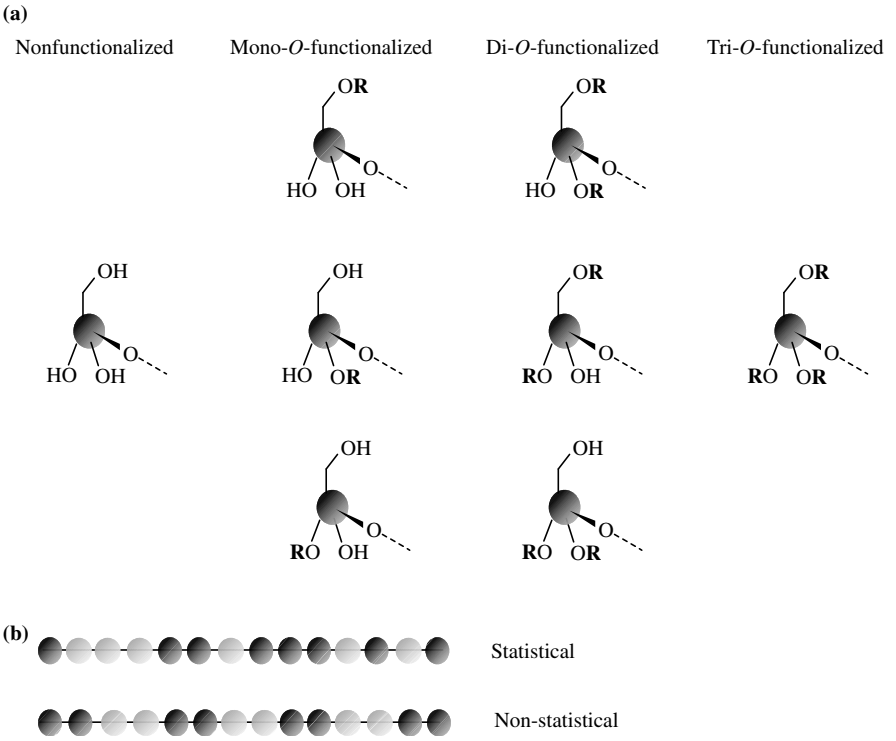


FIGURE 1.24 Distribution of the functional groups by regiocontrolled synthesis of cellulose derivatives (a) within the anhydroglucose units and (b) along the polymer chain. With permission from Elsevier, Heinze and Petzold (2008).

tert-butyldimethylsilyl cellulose with a DS of 0.68 in DMA/LiCl with functionalization at position 6 (Pawlowski et al., 1988). Among this type of derivatives, 6-*O*-thexyldimethylsilyl cellulose is most suitable (Figure 1.26) (Koschella and Klemm, 1997; Petzold et al., 2003). The synthesis starts with a heterogeneous phase reaction in ammonia-saturated polar aprotic liquids at −15°C by conversion of the cellulose with TDS chloride leading to a specific state of dispersion after evaporation of the ammonia at about 40°C, which does not permit any further reaction of the secondary hydroxyl groups, even with a large reagent excess, increased temperature, or long reaction time (Petzold et al., 2003). The degree of

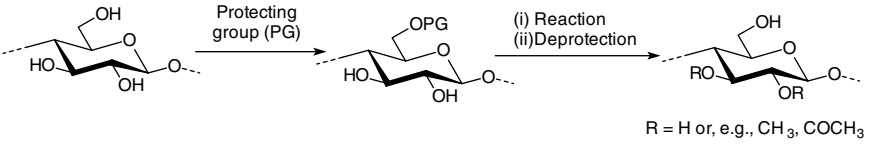


FIGURE 1.25 Scheme of protecting group technique as the main tool for regioselective functionalization of cellulose exemplified for the 2,3-di-*O*-cellulose derivatives.

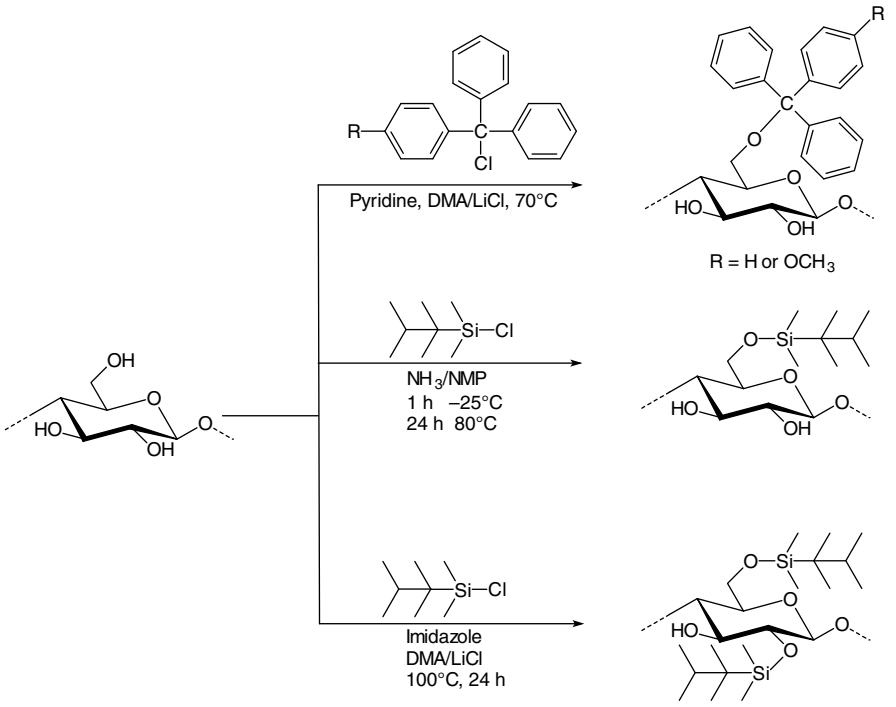


FIGURE 1.26 Protecting group techniques: tritylation with trityl chloride or derivatives in *N*,*N*-dimethyl acetamide (DMA)/LiCl, silylation with thexyldimethylchlorosilane in *N*-methyl-2-pyrrolidone (NMP)/ammonia for the regioselective blocking of the primary OH group, and silylation in DMA/LiCl to protect the 6 and 2 positions simultaneously.

TDS groups introduced by homogeneous silylation in DMA/LiCl to a total DS value of 0.99 is determined to be 85% at position 6 only (GC/MS analysis). However, the homogeneous reaction in DMA/LiCl may yield 2,6-di-*O*-TDS cellulose (Koschella and Klemm, 1997; Heinze, 2004; Fenn et al., 2007).

The structural uniformity and regioselectivity of the silylated cellulose products are characterized by means of one- and two-dimensional NMR techniques after subsequent acetylation of the remaining hydroxyl groups (Figure 1.27) (Hagiwara et al., 1981; Petzold et al., 2003) or after permethylation of the residual OH groups and chain degradation by means of HPLC and GC-MS (Mischnik et al., 1995; Camacho et al., 1996; Koschella and Klemm, 1997; Kern et al., 2000).

Recently, *tert*-butyldimethylsilyl cellulose with a degree of substitution of up to 2 could be obtained by homogeneous conversion of the biopolymer with *tert*-butyldimethylchlorosilane in DMA/LiCl in the presence of imidazole. The cellulose derivatives are characterized in detail by means of two-dimensional NMR spectroscopic techniques, including subsequent derivatization of the original polymer by consecutive methylation–desilylation–acetylation (Figure 1.28). The very well-resolved NMR

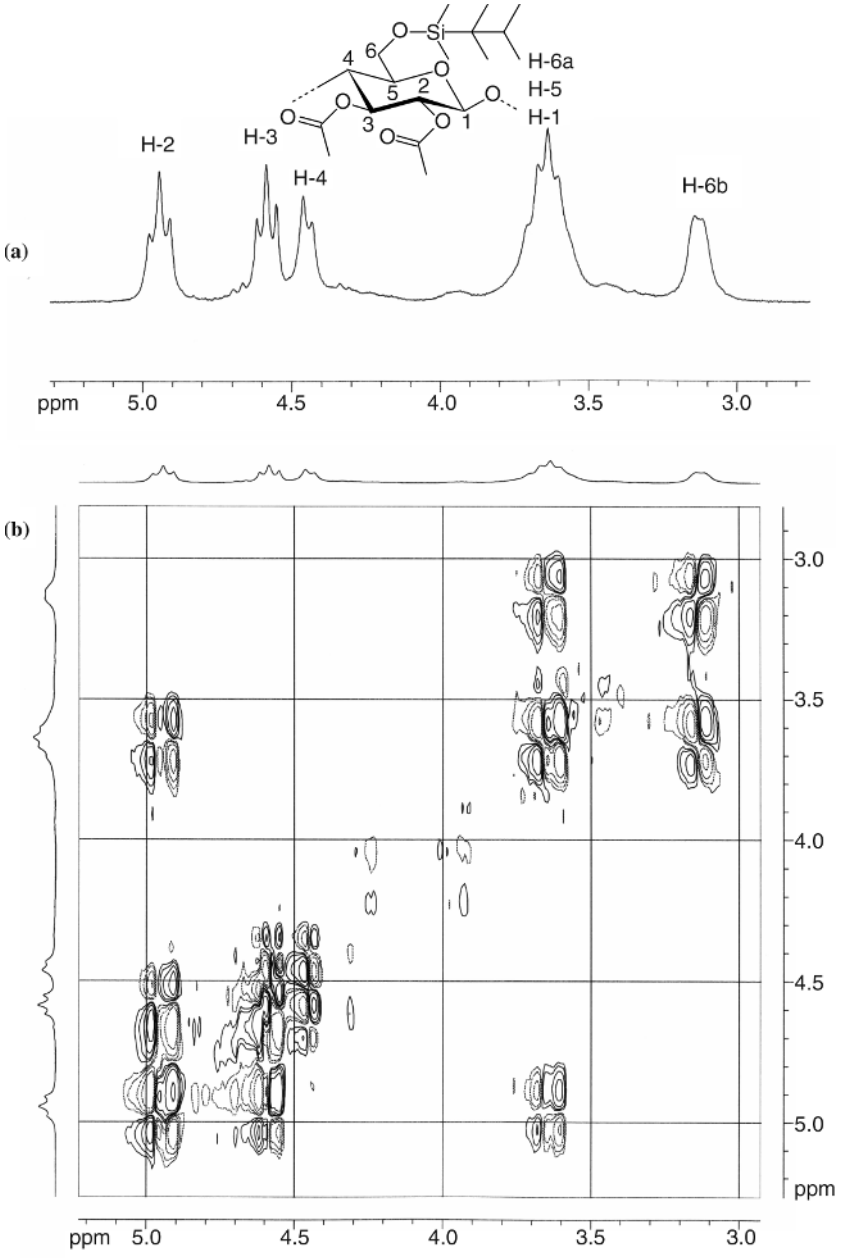


FIGURE 1.27 ^{1}H NMR spectrum (a) and $^{1}H/^{1}H$-correlated NMR spectrum (b) of peracetylated 6-*O*-thexyldimethylsilyl celluloses in $CDCl_3$: assigned cross-peaks of the anhydroglucose unit (2,3-*O*-Ac-6-*O*-TDS) (Ac = acetyl). Reproduced with permission from Wiley–VCH, Petzold et al. (2003).

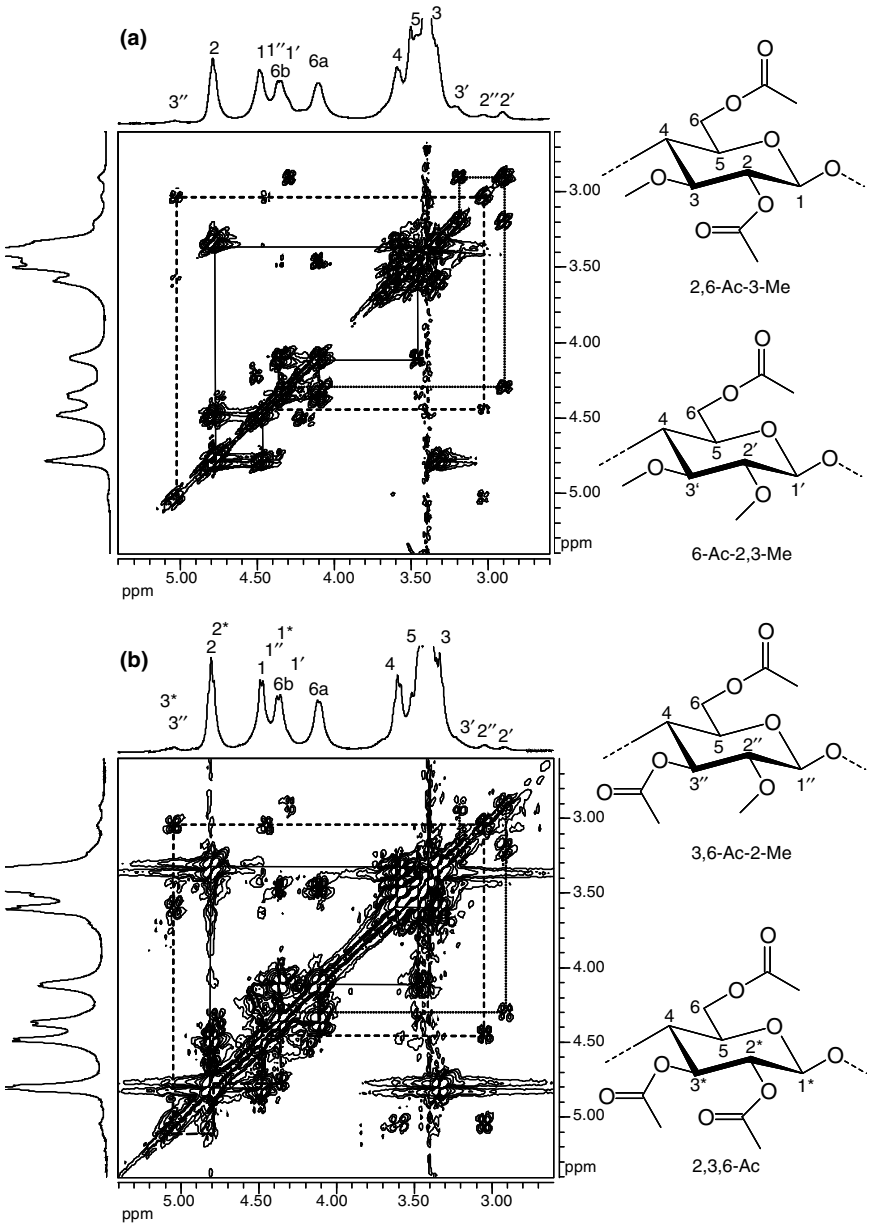


FIGURE 1.28 $^{1}H,^{1}H$ COSY NMR spectra of two acetyl methyl celluloses in $CDCl_3$. Silylation conditions for (a) DS_{Si} 1.98: molar ratio 1:3.5:4.2 (cellulose:TBS chloride:imidazole), 24 h, 20°C; (b) DS_{Si} 2.11: molar ratio 1:4.0:4.8 (cellulose:TBS chloride:imidazole), 24 h, 100 °C; assigned cross-peaks: — cross-peaks of the unit 2,6-di-*O*-acetyl-3-mono-*O*-methyl (2,6-Ac-3-Me); ···· cross-peaks of the unit 6-mono-*O*-acetyl-2,3-di-*O*-methyl (6-Ac-2,3-Me), positions marked with′, (dashed lines) cross-peaks of the unit 3,6-di-*O*-acetyl-2-mono-*O*-methyl (3,6-Ac-2-Me), positions marked with″, — — cross-peaks of the unit 2,3,6-tri-*O*-acetyl (2,3,6-Ac), positions marked with *. Adapted from Heinze et al. (2008b).

spectra indicate that depending on the reaction temperature, 2,6-di-*O*-*tert*-butyldimethylsilyl moieties are the main repeating units. 3,6-Di-*O*- and 6-mono-*O*-functionalized repeating units are identified in very small amounts if the reaction is carried out at room temperature. In addition, 2,3,6-tri-*O*-silylated functions appear if reaction is carried out at temperature of 100°C (Heinze et al., 2008b).

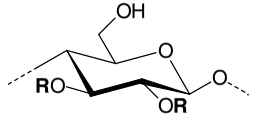
1.5.1 2,3-Di-*O*-Ethers of Cellulose

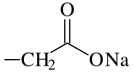
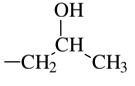
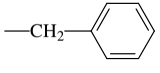
The 6-mono-*O*-trityl cellulose or the more efficient 6-*O*-mono-*O*-(4-mono-methoxy) trityl derivative and the 6-mono-*O*-TDS cellulose are used to synthesize regioselectively functionalized cellulose ethers at positions 2 and 3 after the exclusive cleavage of the protecting groups (Table 1.11). The deprotection is carried out most efficiently with HCl in a suitable solvent (e.g., THF) in case of trityl derivatives. Tetrabutylammonium fluoride in THF is most successful for the cleavage of the silyl groups in TDS-protected derivatives.

The alkylation of the 6-*O*-trityl cellulose is carried out in DMSO with solid NaOH as base and the corresponding alkyl halides at 70°C within several hours. Interestingly, a small amount of water in the mixture (about 1 mL per 60 mL DMSO) increases the conversion up to a nearly complete functionalization of the secondary hydroxyl groups (Kondo and Gray, 1991). Ionic 2,3-*O*-carboxymethyl cellulose is obtained with sodium monochloroacetate as etherifying reagent in the presence of solid NaOH in DMSO and detritylation with gaseous HCl in dichloromethane for 45 min at 0°C or alternatively with aqueous hydrochloric acid in an ethanol slurry (Heinze et al., 1994). 2,3-*O*-CMCs up to a DS of 1.91 were accessible while solubility in water appears at a DS of 0.3 (Liu et al., 1997). 2,3-Di-*O*-hydroxyethyl (HEC) and 2,3-di-*O*-hydroxypropyl celluloses (HPC) are synthesized by heterogeneous etherification of 6-*O*-(4-monomethoxytrityl) cellulose (MMTC) with alkylene oxide in a 2-propanol/10% NaOH–water mixture providing anionic and nonionic detergent is used in addition due to the very hydrophobic character of MMTC (Yue and Cowie, 2002; Schaller and Heinze, 2005). The polymers become water soluble, starting with a MS 0.25 (HEC) and 0.50 (HPC), while a conventional HPC is water soluble with MS > 4. 2,3-*O*-HEC samples without oxyethylene side chains are synthesized up to DS values of 0.87 and compared with 2,3-*O*-hydroxyethyl cellulose with side chains (MS 0.83) using 6-*O*-trityl cellulose, which is allowed to react on one hand with the protected etherifying agent 2-(2-bromoethoxy)tetrahydropyran and with 2-bromoethanol on the other (Petzold-Welcke et al., 2010b). One- and two-dimensional NMR spectroscopy is efficiently used for the characterization of the substitution pattern of the repeating units of the 2,3-*O*-hydroxyethyl celluloses after perpropionylation of the remaining OH groups. In addition, differences between the oxyethylene chain-containing HEC and the HEC without side chains are clearly evaluated by peak assignment of the carbon and proton signals of the substituents using the cross-peaks in the two-dimensional NMR spectra (Figure 1.29). The formation of oxyethylene side chains influences the properties of the HEC like the solubility of the products.

Cellulose ethers can exhibit the phenomenon of thermoreversible gelation that strongly depends on the functionalization pattern as demonstrated for selectively

TABLE 1.11 Examples of Regioselectively Functionalized 2,3-Di-*O*-Cellulose Ethers



R	DS	Protecting group	References
2,3-Di-*O*-methyl cellulose	—CH_3	Up to 1.77	Trt	Kondo and Gray (1991); Petzold-Welcke et al. (2010a)
		2.0	Trt	Kern et al. (2000); Kondo (1997)
		2.0	TDS	Koschella and Klemm (1997)
2,3-Di-*O*-ethyl cellulose	—CH_2–CH_2	Up to 1.93	Trt	Kondo and Gray (1991)
2,3-Di-*O*-CM cellulose		0.054–1.07	Trt MMTr	Liu et al. (1997)
		Up to 1.91		Heinze et al. (1994)
2,3-Di-*O*-hydroxyethyl cellulose		Up to MS 2.0	MMTrt	Schaller and Heinze (2005); Petzold-Welcke et al. (2010b)
2,3-Di-*O*-hydroxypropyl cellulose		Up to MS 2.0	MMTrt	(Schaller and Heinze, 2005)
2,3-Di-*O*-allyl cellulose	—$CH_2CH{=}CH_2$	2.0	Trt	Kondo (1993, 1994)
2,3-Di-*O*-benzyl cellulose		2.0	Trt	Kondo (1993, 1994)
2,3-Di-*O*-octadecyl cellulose	—$(CH_2)_{17}CH_3$	2.0	Trt	Kasai et al. (2005)

Trt: trityl, TDS: thexyldimethylsilyl, MMTrt: 4-monomethoxytrityl.

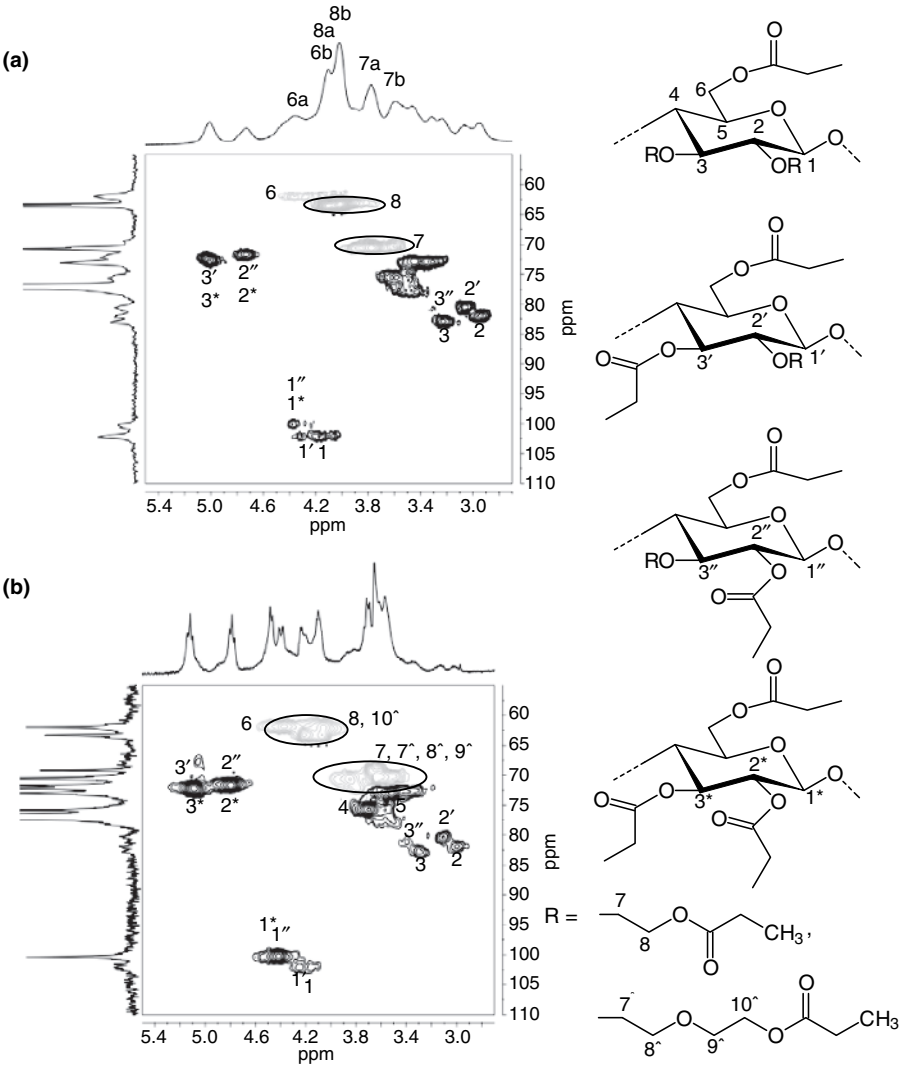


FIGURE 1.29 HSQC-DEPT spectra of (a) perpropionylated HEC (degree of substitution 0.87, synthesized with 2-(2-bromoethoxy)tetrahydropyran) and (b) perpropionylated HEC (molecular degree of substitution 0.83, synthesized with 2-bromoethanol) in CDCl3; negative signals scaled in gray. Reproduced with permission from Wiley–VCH, Petzold-Welcke et al. (2010b).

methylated cellulose (Hirrien et al., 1998). A series of 2,3-*O*-methyl celluloses (2,3-*O*-MC) are prepared starting from 6-*O*-trityl- and 6-*O*-monomethoxytrityl celluloses. Although there are differences in the total DS, it turned out that the thermal events are in strong correlation with the polymer composition (functionalization pattern) (Kern et al., 2000). In a polymer containing tri-*O*-methylated glucose units in combination with monomethylated ones, a distinct thermal

behavior is found, that is, the methyl cellulose shows thermoreversible gelation. In contrast, a MC mainly functionalized at position 2 and 3 shows no thermal gelation. It becomes obvious that the 2,3-di-*O*-methyl glucose units do not significantly affect intermolecular interactions that are necessary for the gelation. The methylation of the 6-*O*-TDS cellulose with methyl iodide and NaH in THF leads to a very structurally uniform 2,3-*O*-MC, which is insoluble in water but dissolves in NMP and methanol/chloroform in contrast to a MC prepared via 6-*O*-trityl cellulose (Koschella and Klemm, 1997).

1.5.2 6-Mono-*O*-Ethers of Cellulose

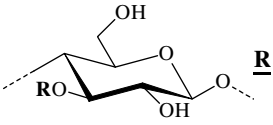
Up to now, the only path to 6-*O*-cellulose ethers is a time-consuming synthesis, which comprises two different protecting groups (Kondo, 1993). The procedure includes the conversion of 6-*O*-trityl cellulose with allyl chloride in the presence of NaOH, which results in a complete functionalization at positions 2 and 3, subsequent detritylation and isomerization of the allyl groups to 2,3-*O*-(1-propenyl) substituents with potassium *tert*-butoxide, and alkylation at position 6 followed by the cleavage of the 1-propenyl groups at positions 2 and 3 with HCl in methanol. The investigation of blends of 6-*O*-MC with poly(ethyleneoxide) (PEO) and poly(vinyl alcohol) (PVA) shows that hydrogen bond engaged at position 6 of cellulose should be more favorable than that at positions 2 and 3 (Kondo et al., 1994; Shin and Kondo, 1998). Gelation of the cellulose derivatives in THF solutions does not take place for 6-*O*-MC and 6-*O*-benzyl cellulose and the trisubstituted derivatives, whereas the 2,3-*O*-ethers form gels (Itagaki et al., 1997). While the gylcosidic bond between two adjacent substituted units of 6-*O*-MC can be cleaved with *Trichoderma viride* cellulase to give oligomers with a degree of polymerization of about 8, 2,3-*O*-MC is not degraded (Nojiri and Kondo, 1996). Long-chain 6-*O*-alkyl ethers of cellulose could be transferred to ultrathin films by Langmuir–Blottget technique (Kasai et al., 2005).

1.5.3 3-Mono-*O*-Ethers of Cellulose

The conversion of 2,6-di-*O*-TDS cellulose with an excess of alkyl halides in THF in the presence of NaH affords the fully etherified polymers that can be desilylated with fluoride ions yielding 3-mono-*O*-functionalized cellulose ethers (Table 1.12) (Koschella et al., 2001, 2006; Petzold et al., 2004; Heinze and Koschella, 2008; Fenn and Heinze, 2009; Fenn et al., 2009; Schumann et al., 2009; Heinze et al., 2010b).

3-Mono-*O*-methyl cellulose swells in polar media like DMSO indicating a strong network of hydrogen bonds. It becomes soluble by addition of LiCl that destroys the interactions. Increasing the length of the alkyl chains leads to 3-mono-*O*-alkyl celluloses soluble in water (C_2), in aprotic dipolar solvents (up to C_5 alkyl chains), or in nonpolar solvents like THF for C_5–C_{12} alkyl chains. Light scattering investigations of 3-*O*-*n*-pentyl-, 3-*O*-*iso*-pentyl-, and 3-*O*-dodecyl in THF disclose a different aggregation behavior. Although 3-*O*-dodecyl cellulose forms molecularly dispersed solutions (at concentration less than 2 mg/L), the C_5 ethers show aggregation numbers of 6.5 (*iso*-pentyl) and 83 (*n*-pentyl) (Petzold et al., 2004).

TABLE 1.12 Solubility of 3-*O*-Mono-Alkyl Celluloses

 R	Solubility				Reference
	Ethanol	DMSO	DMA	H_2O	
$-CH_3$	−	−	−	−	Koschella et al. (2001)
$-CH_2-CH_3$	−	+	+	+	Koschella et al. (2006)
$-CH_2-CH=CH_2$	−	+	+	−	Koschella et al. (2001)
$-CH_2-CH_2-OH$	−	+	+	+	Fenn and Heinze (2009)
$-CH_2-CH_2-O-CH_3$	−	+	+	+	Heinze and Koschella (2008)
$-CH_2-CH_2-CH_2-OH$	−	+	+	+	Schumann et al. (2009)
$-CH_2-CH_2-CH_3$	+	+	+	+[a]	Heinze et al. (2010b)
$-CH_2-C\equiv CH$	−	+	−	−	Fenn et al. (2009)
$-(CH_2)_4-CH_3$	+	+	+	−	Petzold et al. (2004)
$-(CH_2)_2-CH-(CH_3)_2$	+	+	+	−	Petzold et al. (2004)
$-(CH_2)_{11}-CH_3$	−	−	−	−	Petzold et al. (2004)
$-(CH_2-CH_2-O)_n-CH_3$; $n = 3, 7, 16$	−	−	−	−	Bar-Nir and Kadla (2009)

DMA: *N,N*-dimethyl acetamide; DMSO: dimethyl sulfoxide; soluble (+), insoluble (−).
[a] Soluble below 15°C, insoluble at room temperature.

Ethyl cellulose of different functionalization pattern possesses different temperatures for thermoreversible gelation. While ethyl cellulose with DS 0.7–1.7 already becomes water insoluble at about 30°C (Dönges, 1990), ethyl cellulose that is synthesized via induced phase separation (conversion of cellulose dissolved in DMA/LiCl with solid NaOH and ethyl iodide) possesses a distinct higher cloud point temperature of 56°C. A block-like distribution of substituents along the polymer chain is assumed as described for CMC and MC (Heinze, 1998; Liebert and Heinze, 1998). A similar value (63°C) is determined for the structurally uniform 3-mono-*O*-ethyl cellulose independent of DP (Sun et al., 2009). 3-Mono-*O*-methoxyethyl and 3-mono-*O*-hydroxyethyl cellulose show no thermoreversible gelation between 15°C and 95°C (Figure 1.30) (Sun et al., 2009; Fenn and Heinze, 2009).

Interestingly, 3-*O*-propyl cellulose shows water solubility below room temperature depending on the DS. 3-*O*-propyl cellulose with a DS of 1.02 has a cloud point at 15.2°C, whereas the sample with a DS of 0.71 possesses a slightly higher cloud point temperature of 23.5°C. Randomly distributed propyl celluloses with comparable DS values of 0.64 and 0.93 are insoluble in water (Heinze et al., 2010b).

One- and two-dimensional NMR spectroscopy demonstrates the uniform structure of the 3-*O*-alkyl ethers after peracetylation of the remaining OH groups, as shown in Figure 1.31, for 3-*O*-methoxyethyl-2,6-di-*O*-acetyl cellulose as a typical example (Heinze and Koschella, 2008).

The synthesis of 3-mono-*O*-hydroxyethyl cellulose is realized by conversion of the 2,6-TDS cellulose with 2-(2-bromoethoxy)tetrahydropyran via a completely functionalized derivative. The complete removal of the protecting group first involves

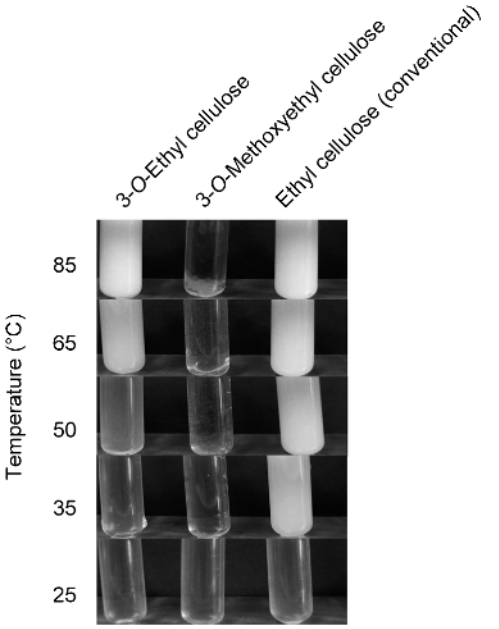


FIGURE 1.30 Photographs of cloud point of 3-*O*-ethyl cellulose and conventional ethyl cellulose compared with 3-*O*-methyoxyethyl cellulose. Note the slight banding for 3-*O*-ethyl cellulose and ethyl cellulose held at 85°C. Reproduced with permission from Wiley–VCH, Sun et al. (2009).

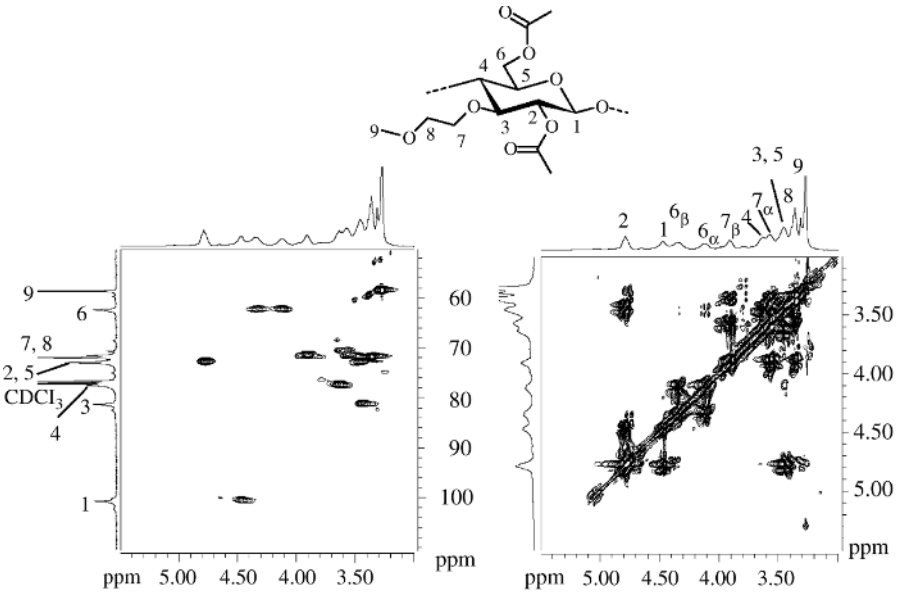


FIGURE 1.31 HMQC (left) and COSY (right) NMR spectra of peracetylated 3-*O*-methoxyethyl celluloses ($CDCl_3$). Reproduced with permission from Elsevier, Heinze and Koschella (2008).

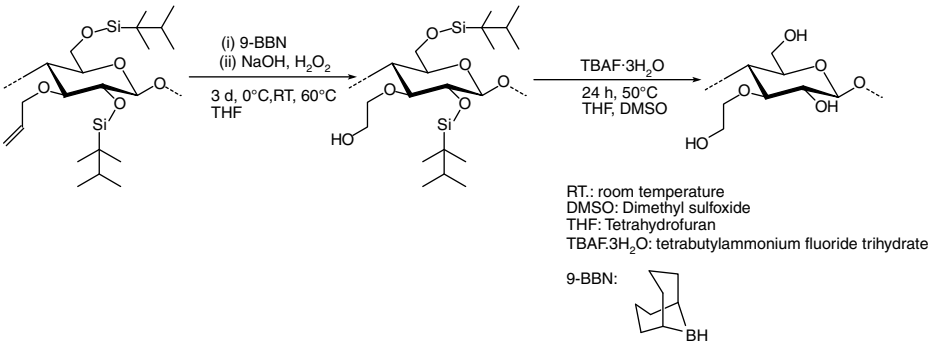


FIGURE 1.32 Reaction scheme for the preparation of 3-mono-*O*-(3′-hydoxypropyl) cellulose. Adapted from Schumann et al. (2009).

the split off of the TDS function with tetrabutylammonium fluoride trihydrate and subsequently of the tetrahydropyran moieties with hydrochloric acid (Fenn and Heinze, 2009).

The conversion of the double bond of 3-mono-*O*-allyl-2,6-di-*O*-TDS cellulose with 9-borabicycl(3.3.1)nonane and subsequent alkaline oxidation lead to the 3′-hydroxypropyl group. The treatment with tetrabutylammonium fluoride yields regioselectively functionalized 3-mono-*O*-(3′-hydroxypropyl) cellulose (Figure 1.32) (Schumann et al., 2009).

FTIR spectroscopy of 3-mono-*O*-methyl cellulose in combination with curve fitting and deconvolution shows that the resulting two main bands indicate the existence of another intramolecular hydrogen bond between OH-2 and OH-6 instead of intramolecular hydrogen bonds between OH-3 and OH-5 (Figure 1.33) (Kondo et al., 2008). The large deconvoluted band at 3340 cm^{-1} refers to strong interchain hydrogen bonds involving the hydroxyl groups at C-6. The crystallinity of 54% calculated from the WAXD also supports the dependency of the usually observed crystallization in cellulose of the hydroxyl groups at position 6 to engage in interchain hydrogen bonding.

1.5.4 2,6-Di-*O*-Ethers of Cellulose

The synthesis of 2,6-di-*O*-methyl cellulose involves the complete allylation of 2,6-di-thexyldimethylsilyl cellulose followed by the desilylation with tetrabutyl ammonium fluoride to get pure 3-mono-*O*-allyl cellulose. The product is methylated using methyl iodide in the presence of sodium hydride to get 3-mono-*O*-allyl-2,6-di-*O*-methyl cellulose (Figure 1.34) (Kamitakahara et al., 2008).

Deallylation proceeds with palladium(II) chloride to give 2,6-di-*O*-methyl cellulose, which is not isolated after the deprotection step. It is acetylated with acetic anhydride, *N,N*-dimethylaminopyridine, and pyridine leading to 3-mono-*O*-acetyl-2,6-di-*O*-methyl cellulose. ^{1}H and ^{13}C NMR spectra of 3-mono-*O*-acetyl-2,6-di-*O*-methyl celluloses indicate complete desilylation at positions 2 and 6 and acetylation

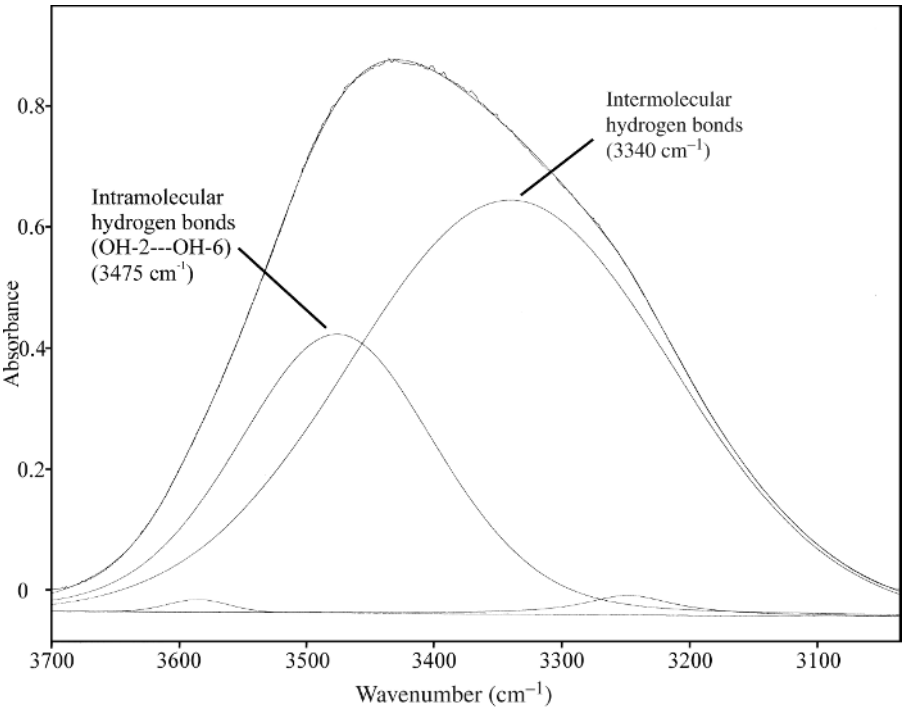


FIGURE 1.33 Curve fitting and peak assignments for the OH stretching region in 3-mono-*O*-methyl cellulose. Adapted from Kondo et al. (2008).

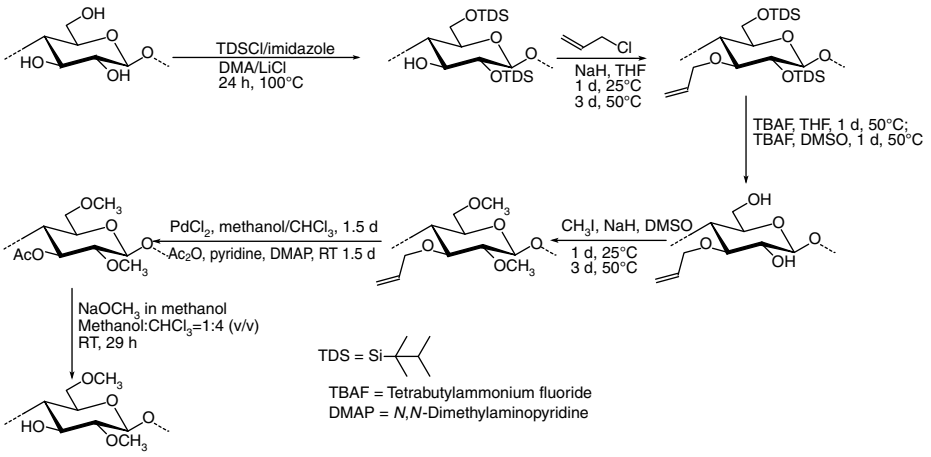


FIGURE 1.34 Synthesis path for 2,6-di-*O*-methyl cellulose. Adapted from Kamitakahara et al. (2008).

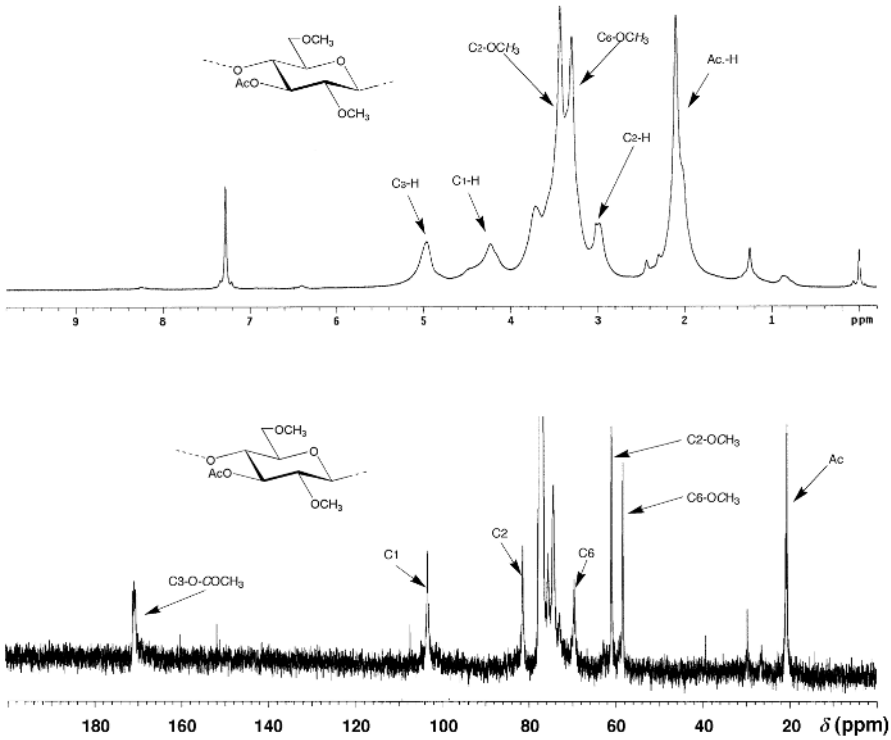


FIGURE 1.35 ^{1}H and ^{13}C NMR spectra of 3-mono-*O*-acetyl-2,6-di-*O*-methyl celluloses in $CDCl_3$. Adapted from Kamitakahara et al. (2008).

at position 3 by the low filed shift of the signal at 4.96 ppm (Figure 1.35). After deacetylation, 2,6-di-*O*-methyl cellulose is obtained, which is insoluble in all solvents tested.

1.6 SUMMARY

This chapter highlights unconventionally functionalized cellulose derivatives obtained by advanced synthesis paths like nucleophilic displacement (S_N) reactions, homogeneous sulfation in ionic liquids, and regioselective functionalization. A short overview about "classical" S_N reactions is also given. Moreover, the review is focused on novel cellulose products obtained by click chemistry (copper-catalyzed Huisgen reaction), starting from deoxyazido cellulose yielding derivatives with methylcarboxylate-, 2-aniline-, 3-thiophene moieties, for example, and new selectively dendronized cellulose-based materials. Structure characterization and selected applications are also briefly reviewed. Biofunctionalized surfaces based on dendronized cellulose are prepared. The well-defined cellulose sulfates synthesized in ionic liquids may mimic the structure and biological activity of naturally occurring polysaccharide sulfates and are applied for microencapsulation of

biological material in polyelectrolyte complex capsules. Regioselective derivatization of protected cellulosics leading to 3-*O*-, 2,3-*O*-, 6-*O*-, and 2,6-*O*-functionalized products is of recent interest because the products possess remarkable differences in properties compared to common cellulose derivatives and are hence important products for the establishment of "real" structure–property relationships. Moreover, these regioselectively functionalized cellulose derivatives are useful compounds to calibrate analytical techniques and for other research and application issues.

1.7 CONCLUSION AND FUTURE PERSPECTIVE

The examples discussed illustrate the enormous structural diversity and application potential of cellulose derivatives. Starting from cellulose sulfonates especially cellulose tosylate, SN reactions undoubtedly will lead to a variety of sophisticated products. Moreover, Huisgen reaction with cellulose is already successfully realized and new dendronized cellulose derivatives will appear. For instance, biofunctionalized surfaces based on dendronized cellulose are prepared either by embedding of dendritic 6-deoxy-6-(1,2,3-triazolo)-4-polyamidoamine cellulose (degree of substitution 0.25), obtained by homogeneous conversion of 6-deoxy-6-azido cellulose with propargyl-PAMAM dendron via the copper-catalyzed Huisgen reaction in a cellulose acetate (DS 2.50) matrix, or by the heterogeneous functionalization of deoxyazido cellulose film with the dendron. Cellulose sulfates with well-defined chemical structures can mimic the structure and biological activity of naturally occurring polysaccharide sulfates. Cellulose sulfates are applied for microencapsulation of biological material in polyelectrolyte complex capsules. Using ionic liquids as solvent, one-pot procedure for sulfation, *in situ* polyelectrolyte complex formation, and encapsulation are established. In the field of cellulose ethers, the regioselective introduction of the functional groups is still a synthetic challenge. These products will give new insights into the interaction of cellulose derivatives with each other, with other polymers and surfaces, and hence improve common applications and introduce cellulose-based materials in new application fields.

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