Hot Topics in Polysaccharide Chemistry – Selected Examples

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Summary: The paper highlights recent developments in polysaccharide chemistry. Cellulose tert-butyl- and thexyldimethylsilyl ethers with degree of substitution up to 2 were accessible and comprehensively characterized by means of NMR spectroscopy. These derivatives enable the preparation of 3-*O*-functionalized cellulose ethers. Especially the allyl ether as protecting group at position 3 can be used for the synthesis of 2,6-di-*O*-methyl cellulose. Nucleophilic displacement reactions of cellulose *p*-toluenesulfonic acid esters with amines afforded deoxyamino celluloses that form stable monolayers on different substrates. Based on 6-deoxy-6-azido cellulose, dendrons with a focal alkyne moiety were bound via the copper(I) catalyzed Huisgen reaction. Moreover, dextran derivatives were synthesized that form stable nanoparticles useful, e.g., for the determination of the pH value in biological systems.

Keywords: cellulose; coatings; dendrimers; dextran; nanoparticles; polysaccharides; synthesis

Introduction

At present, the main argument to study polysaccharides is the fact that they are the most important renewable resource. Of course that is true. However, there are other good arguments to consider this fascinating class of biopolymers as raw materials for the future. Polysaccharides possess unique structures combined with reactive groups that allow the design of structures and hence of properties. From the author's point of view, chemical modification is the most important path to adapt the properties to the application in question and even to develop novel functional polymers and advanced materials based on biomass. The hydroxyl groups show the typical reactions of low-molecular alcohols, i.e., they can form ethers and esters. It is also possible to oxidize the OH groups to ketones, aldehydes, and carboxylic groups, with and without cleavage of C–C-bonds of the repeating units. Moreover, the OH-group can be modified with a leaving group enabling nucleophilic displacement reactions and hence formation of deoxypolysaccharide derivatives.[1–5] Such derivatives possess typical properties of macromolecules, e.g., solubility in various solvents, film forming- and viscosity regulating ability.

Chemical modification of polysaccharides is already carried out commercially for many decades.[6,7] For the structurally most uniform polysaccharide cellulose being a β-1-4 linked polyglucan, ethers and esters are prepared that find applications in various fields including cosmetics, food, constructing materials, paper and oil well drilling as well as in pharmaceutical applications and as filters, membranes and films as schematically shown in Figure 1. It is interesting to note that the commercial chemical modification is limited to some ethers including methyl-, ethyl-, hydroxyalkyl-, and carboxymethyl moieties and some esters including acetate, propionate, butyrate, phthalic acid half ester and to products with two or even

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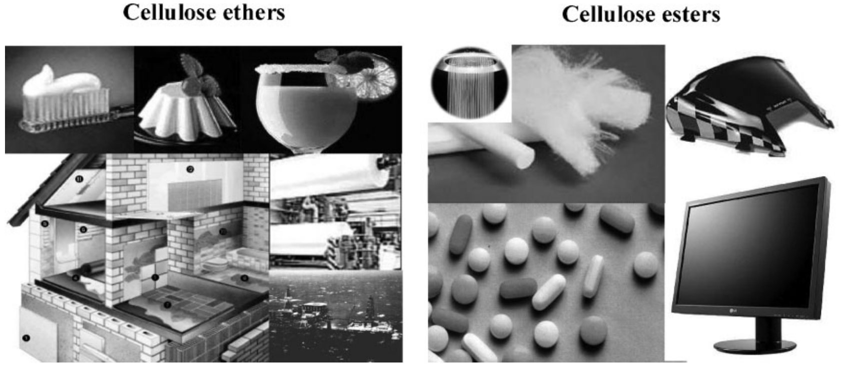


Figure 1.
Typical application fields of cellulose derivatives.[8]

three of the functional groups mentioned (Figure 2). With respect to the structure of the repeating unit, i.e., the presence of 3 hydroxyl functions of different reactivity, the resulting polysaccharide derivative is composed of up to 8 different repeating units, namely 6-mono-*O*-, 2-mono-*O*-, 3-mono-*O*-, 2,3-di-*O*-, 2,6-di-*O*-, 3,6-di-*O*-, 2,3,6-tri-*O*-, and non-functionalized repeating units. It is well known that these functional groups are distributed in a random- or statistic manner in the polysaccharide backbone. Consequently, the question appeared how the distribution of

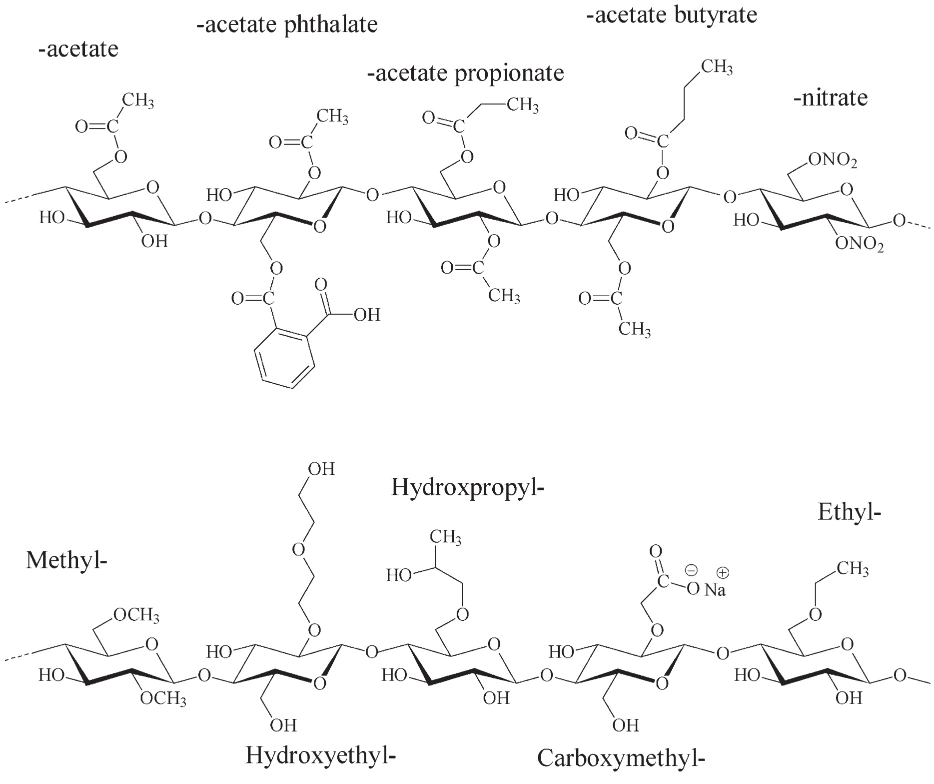


Figure 2.
Schematic presentation of cellulose esters (top) and ethers (bottom) commercially produced.

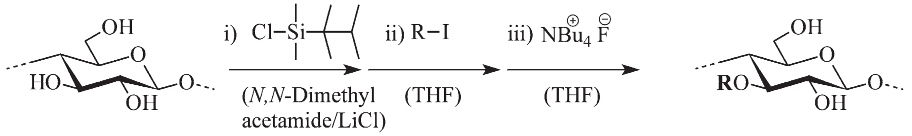
the functional groups can be controlled. In particular, products with a regioselective functionalization are an indispensable prerequisite to evaluate "real" structure property relationships.

Regioselectivity

In polysaccharide chemistry, regioselectivity means a pre-set functionalization of one or two selected hydroxyl groups within the repeating unit. Moreover, regioselectivity is also considered as a structural feature of substituent distribution within and between the polymer chains that is hard to realize by polymer analogous reactions. One example is the so-called structure-selective functionalization, which leads to blocks of lower and higher functionalization along the polymer chain.[9,10] The functionalization occurs preferred in the amorphous regions due to a stepwise activation of the polymer with aqueous sodium hydroxide of comparable low concentration. Moreover, the synthesis-concept of induced phase separation can be applied for the synthesis of block-wise functionalized cellulose derivatives.[11–13] It includes the addition of solid NaOH particles to a solution of cellulose dissolved in *N,N*-dimethyl acetamide (DMA)/LiCl. Later this concept was successfully applied to solutions of cellulose derivatives bearing hydrolytically unstable substituents. As a consequence, a partial hydrolysis and hence activation of the hydroxyl groups occurs in regions of the polymer chain that are in close contact with NaOH.

Regioselectively functionalized polysaccharide derivatives are accessible via protecting group techniques. For cellulose, procedures were established to protect the hydroxyl groups at position 6 as well as at positions 2 and 6 with bulky silyl compounds applying defined conditions.[14,15] The protection of positions 2 and 6 is especially important due to the fact that the lowest reactive hydroxyl group at position 3 can be modified regioselectively. Various commercially important ether functions (methyl-[16], ethyl-[17], and methoxyethyl moieties[18] were attached at position 3 yielding cellulose derivatives with interesting properties (Figure 3). 3-Mono-*O*-methyl cellulose is insoluble in water and organic solvents. The methyl ether influences the formation of intra- and intermolecular hydrogen bonds, as revealed by FTIR-spectroscopy.[19] Further 3-*O*-ethers dissolve in water and organic media depending on their alkyl chain length. For instance, the temperature of the important thermoreversible flocculation can be adjusted by the functionalization pattern. e.g., ethyl cellulose with statistic functionalization flocculates at 35 °C while the 3-*O*-ethyl cellulose becomes insoluble at 65 °C (Figure 4).[17] The thermoreversible flocculation effect could not be observed for 3-mono-*O*-methoxyethyl cellulose.

The well-established synthesis of 2,6-di-*O*-thexyldimethylsilyl (TDMS) cellulose could be further elaborated. Thus, it was demonstrated that also high-molecular cotton linters (degree of polymerization 1433) could be converted to a TDMS



Tetrahydrofuran (THF)
Butyl (Bu)

For instance: R CH_3 Macromol. Biosci. 2001, 1:49
C_2H_5 Polym. Bull. 2006, 57:33
$CH_2CH_2OCH_3$ Carbohydr. Res. 2008

Figure 3.
Synthesis path for the preparation of regioselectively 3-O-functionalized cellulose derivatives.

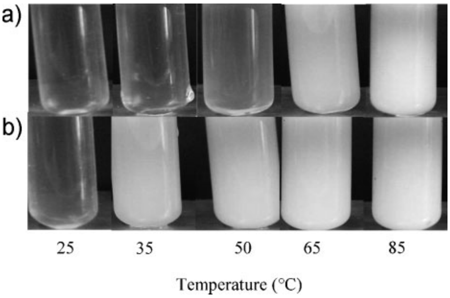


Figure 4.
Aqueous solutions of 3-mono-*O*-ethyl cellulose (a) and ethyl cellulose with random functionalization pattern (b) at different temperatures.

cellulose with the target degree of substitution (DS) of 2.[20] A crucial step was the mercerization that enabled the formation of optically clear solutions of cellulose in DMA/LiCl. Moreover, it was found that already a molar ratio anhydroglucose unit (AGU):TDMS-Cl of 1:3 is sufficient to achieve desired DS after 24 h at 100 °C.

Other bulky silyl ethers, e.g., tert-butyl (TBDMS) ethers were also described as protecting groups.[21] It could be demonstrated that the conversion of cellulose in DMA/LiCl solution yields a TBDMS ether with DS 0.97 selectively silylated at position 6.[22] Further exploration of this synthesis path proofed that TBDMS-Cl is also able to react with the OH groups at position 2 and 6. Thus, conversion of cellulose with 4 mol TBDMS-Cl in the presence of excess imidazole yields 2,6-di-*O*-TBDMS cellulose with DS 2 after 24 h at room temperature.[23] Structure analysis by means of NMR spectroscopy after methylation, desilylation, and acetylation revealed the selective introduction of the silyl ethers. A negligible amount of substructures was determined (Figure 5). The cross-peaks corresponding to 6-mono-*O*-acetyl-2,3-di-*O*-methyl-, 3,6-di-O-acetyl-2-mono-*O*-methyl cellulose, and 2,3,6-tri-*O*-acetyl repeating units were detected in the spectra although at rather low intensity.

The allyl ether of cellulose was also utilized as protecting group. Thus, methylation of 3-mono-*O*-allyl cellulose followed by cleavage of the allyl ether afforded 2,6-di-*O*-methyl cellulose, which represents a structural feature of the commercially produced methyl cellulose.[24] This new cellulose derivative was found to be highly crystalline and insoluble in organic solvents and water. Moreover, the hydroboration and subsequent oxidation of 3-mono-*O*-allyl cellulose yield 3-mono-*O*-(3'-hydroxypropyl) cellulose, which is reported in another contribution to this issue of *Macromolecular Symposia*.

Another important area of research in the field of polysaccharides is the preparation of novel derivatives and/or applying unconventional synthesis paths.

Nucleophilic Displacement Reactions with Cellulose

The introduction of leaving groups allows nucleophilic displacement (S_N) reactions with cellulose. An efficient method to produce polysaccharides bearing leaving groups is the conversion of the biopolymer to cellulose *p*-toluenesulfonic acid ester (tosylate).[25] Subsequent S_N reactions yielded various deoxycellulose derivatives, e.g., with halides, the corresponding deoxyhalogeno celluloses could be obtained.[1,2] The conversion of cellulose tosylate with ammonia yields cross-linked and hence insoluble deoxyaminocelluloses.[3-5] Much more feasible is the introduction of the deoxyamino group via deoxyazido cellulose followed by reduction of the azide moiety applying different reducing agents.[5,26,27]

Water soluble deoxyamino cellulose derivatives were obtained by S_N reactions with tertiary amines.[28] Further studies with di- or oligoamines were carried out to yield soluble aminocelluloses bearing primary amino groups at the end of the spacer moiety. The S_N reaction occurs in a regioselective manner, i.e., only the primary tosylate is substituted. It is important to adjust the reaction conditions to prevent cross-linking. Subsequent functionalization of positions 2 and 3 may be used to obtain products that are soluble in water or organic solvent (Figure 6).

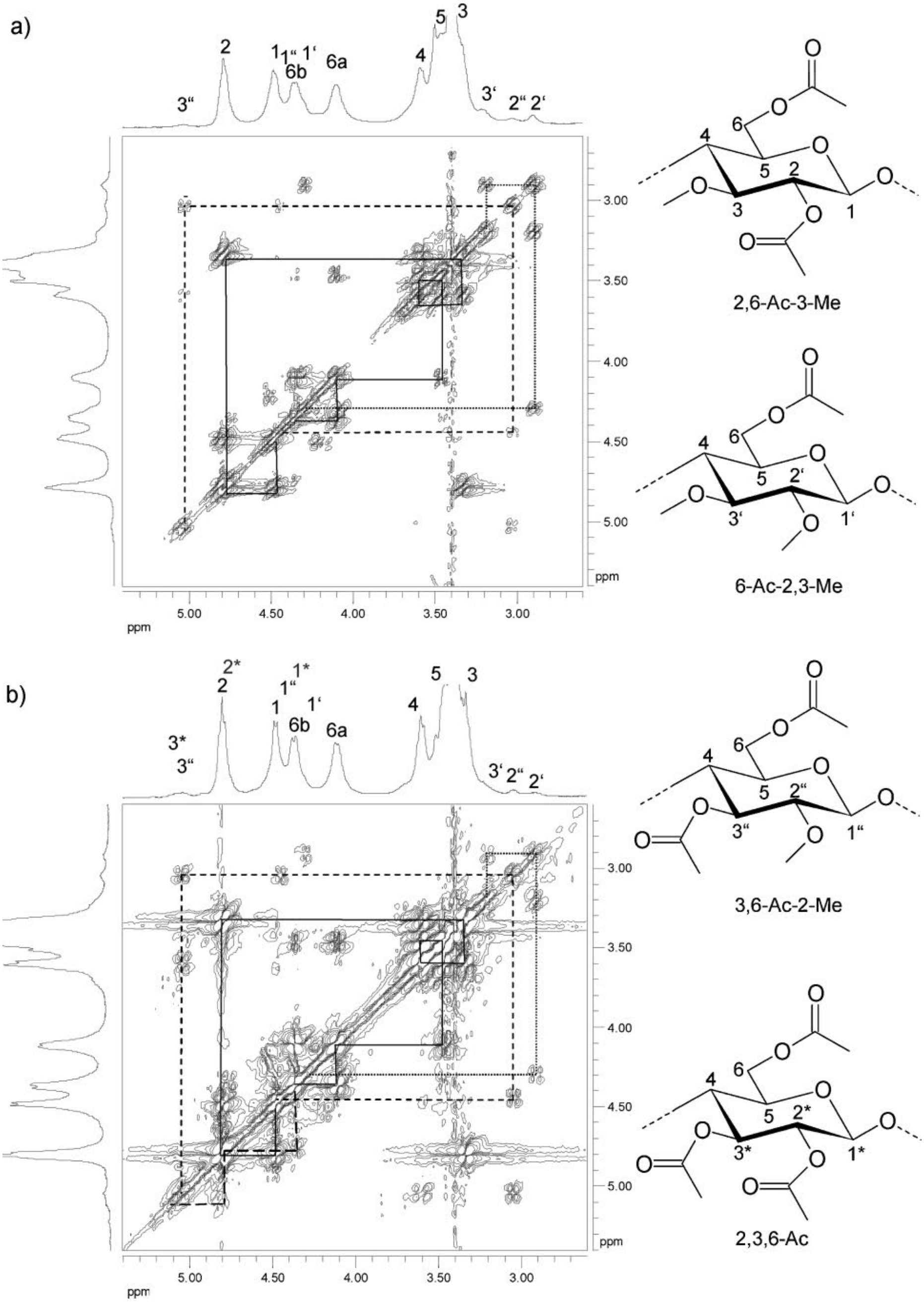


Figure 5.

^{1}H,^{1}H COSY NMR spectra of acetyl methyl celluloses synthesized from tert-butyldimethylsilyl cellulose with degree of substitution of 1.98 (a) and 2.11 (a). Assigned cross-peaks: 2,6-di-*O*-acetyl-3-mono-*O*-methyl (————, 2,6-Ac-3-Me), 6-mono-*O*-acetyl-2,3-di-*O*-methyl (---------, 6-Ac-2,3-Me), 3,6-di-*O*-acetyl-2-mono-*O*-methyl — — —, 3,6-Ac-2-Me), 2,3,6-tri-*O*-acetyl (—— ——, 2,3,6-Ac), positions marked with *.

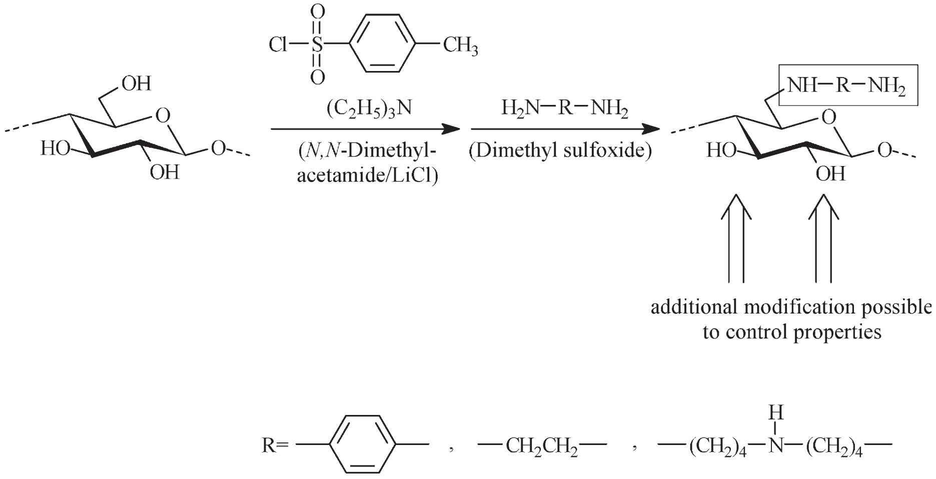


Figure 6.
Reaction scheme for nucleophilic displacement reactions at position 6 of the anhydroglucose unit via cellulose *p*-toluenesulfonic acid esters.

An amazing property of such aminocelluloses is their ability to form very stable monolayers on various substrates. The remaining amine groups can be used to create materials with different biofunctions for instance by covalent binding of an enzyme (Figure 7).[29] As schematically shown in Figure 8, the formation of the monolayer is simple. The substrate is treated with a diluted solution of the amino cellulose (about 0.5%, w/w) followed by intensive washing and drying.

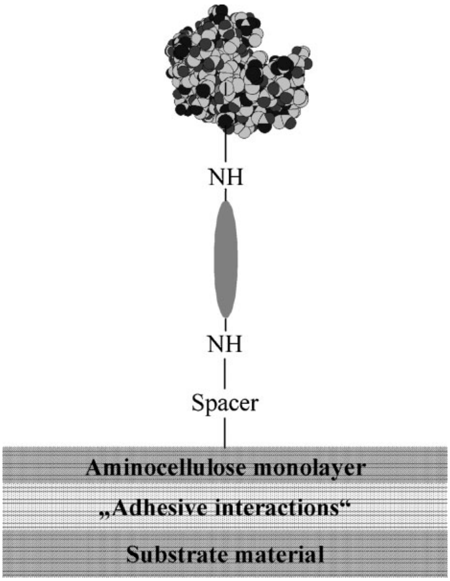


Figure 7.
Schematic representation of a surface bearing chemically bonded biomolecules.

The monolayer formation could be proofed by different techniques including atomic force microscopy, contact angle measurements and ellipsometry. The surface roughness of a gold nanocrystal is in the range of 0.2 nm (Figure 9a) as revealed by atomic force microscopy (AFM). The substrate treated sample possesses a slightly increased roughness of about 1 nm (Figure 9b). It should be mentioned that nanolayer can be formed on various substrates including synthetic polymers, fibres, metals and many others.

The azide moiety is also a 1,3-dipol and hence undergoes 1,3-dipolar cycloaddition reactions with alkyne moieties, which yield substituted triazoles. The copper(I) catalyzed conversion of azides with alkynes is called "Huisgen reaction", which combines very mild reaction conditions and high yields. It is also known as "click reaction". It could be demonstrated that also deoxyazido cellulose can be used as reactant in such click reactions.[30–32] Due to the ease of handling, the click reaction with other alkyne moieties was studied.

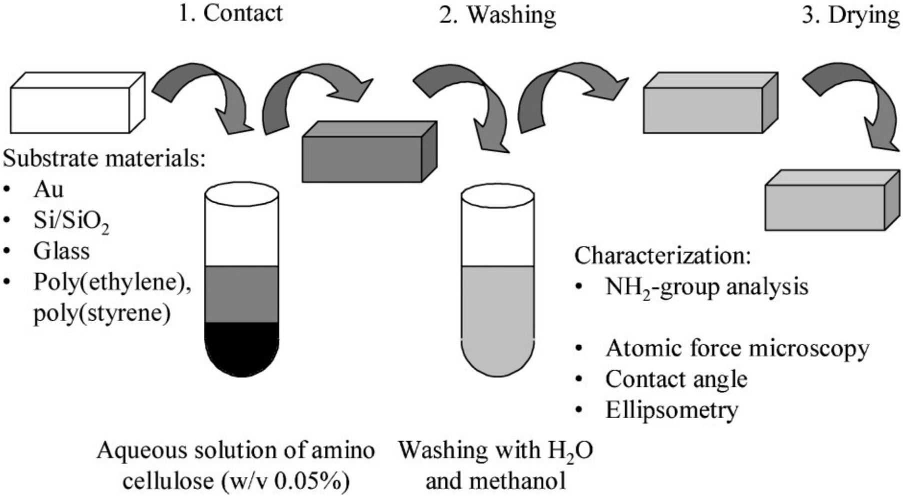


Figure 8.
Surface modification of different substrates with monolayers from cellulose derivatives.

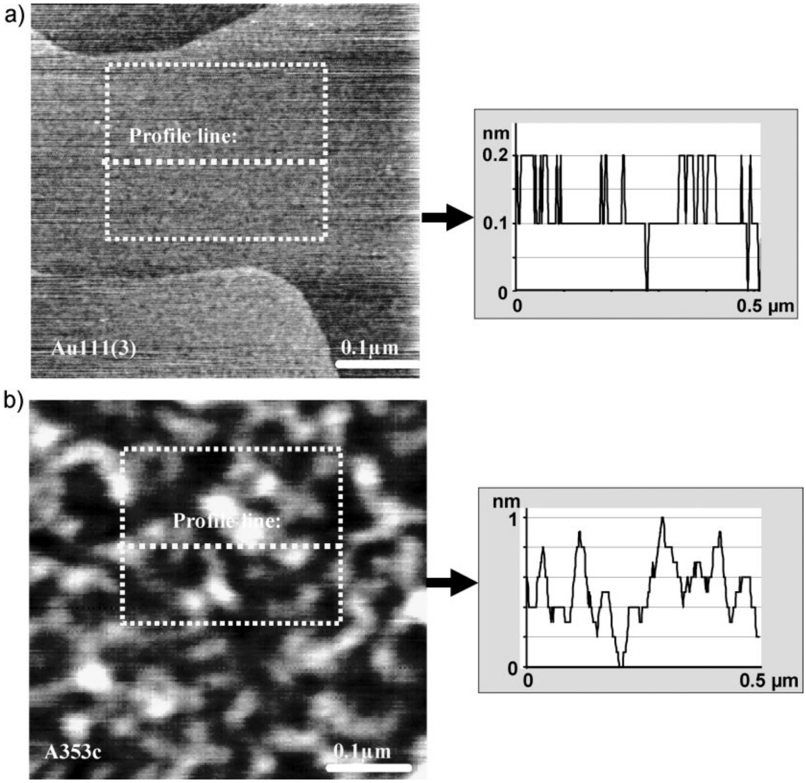


Figure 9.
Atomic force microscopic images of an unmodified Au/111/substrate surface (a) and 6-deoxy-6-ethylenediamino cellulose modified Au/111 substrate surface (b), adapted from A. Jung, B. Wolters, P. Berlin (Bio)functional surface structural design of substrate materials based on self-assembled monolayers from aminocellulose derivatives and amino(organo)polysiloxanes. Thin Solid Films 515 (2007) 6867–6877.

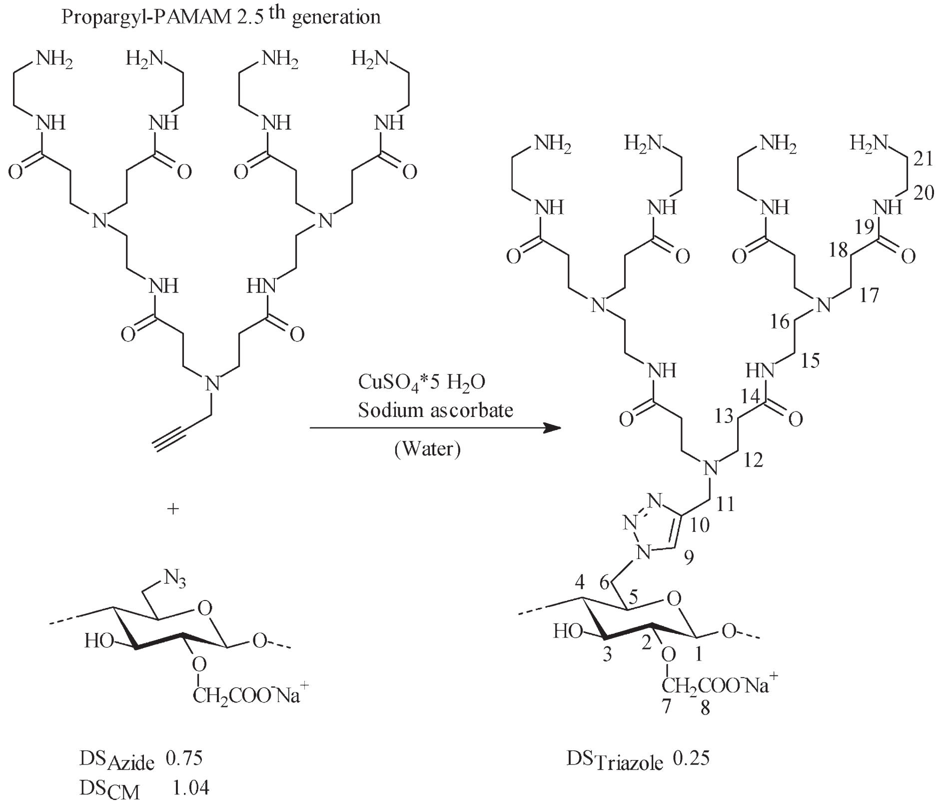


Figure 10.

Conversion of 6-deoxy-6-azidocarboxymethyl cellulose (degree of substitution of deoxyazido groups, DS_{Azide}, 0.75, DS of carboxymethyl groups, DS_{CM}, 1.04) with a propargyl polyamidoamine (PAMAM) dendron of the 2.5th generation in water.

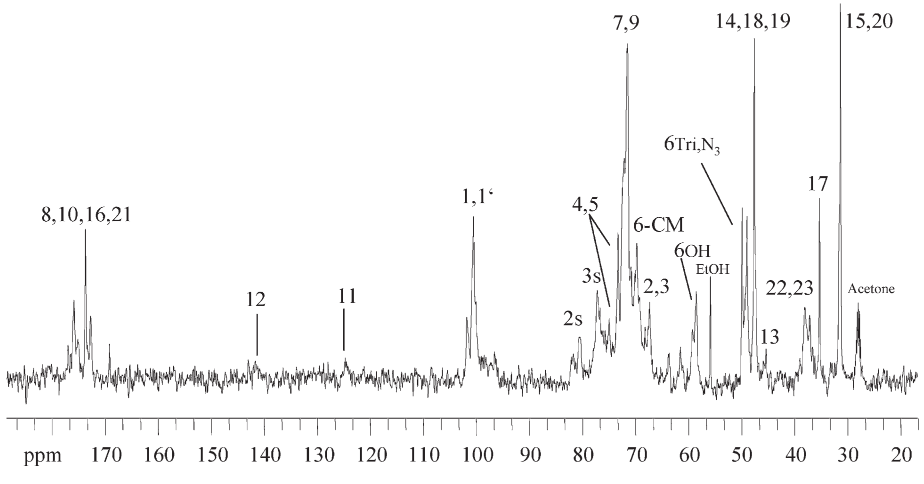


Figure 11.

^{13}C NMR spectrum 6-deoxy-6-amino-(4-methyl-[1,2,3-triazole]-1-propyl-polyamido amine) carboxymethyl cellulose (degree of substitution of triazolo groups, $DS_{triazole}$, 0.25, DS of carboxymethyl groups, DS_{CM}, 1.04). The structure is shown in Figure 10.

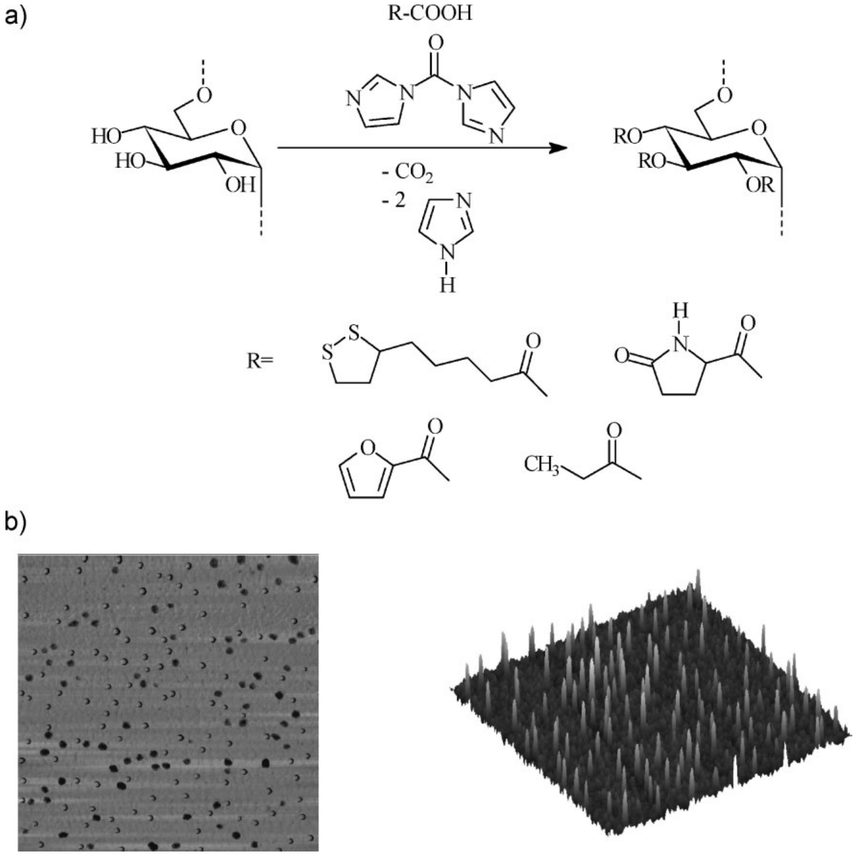


Figure 12.

Conversion of dextran with carboxylic acids *in situ* activated with *N,N'*-carbonyldiimidazole (a) and atomic force microscopic image of dextran lipoic acid ester absorbed on a gold slide (b, degree of substitution 0.44, size 3 μm^2).

Consequently, dendrons bearing a focal alkyne moiety were used as reactant. Typical examples are propargyl polyamidoamines (PAMAM). These dendrons of up to the 3rd generation were reacted with 6-desoxy-6-azido cellulose with DS_N of 0.75 in order to ensure the presence of CH_2N_3 groups only. $CuSO_4$ pentahydrate and sodium ascorbate were used to generate Cu(I) as catalyst (Figure 10). Furthermore, water solubility was achieved by introduction of carboxymethyl functions (DS_{CM} 1.04). Thus, the 1,3-dipolar cycloaddition reaction of this cellulose derivative can be carried out in water and leads to water-soluble products with interesting solution properties. Although the structure of the molecule is very complex, it could be described based on ^{13}C NMR spectra acquired in water (Figure 11).[33] The signals of the modified AGU appear in the range from 48 to 102 ppm. Four peaks can be assigned for position 6. Namely, a peak at approximately 60 ppm indicates CH_2OH groups due to the incomplete functionalization of position 6. Two peaks in the range of 50 ppm are attributed to the CH_2N_3 and CH_2-triazolo moieties, which is in agreement with the DS values of both functional groups. Moreover, a signal at 70 ppm is due to the carboxymethylated primary OH group. The peaks of the dendron could also be assigned as shown in Figure 11. Not only dendrons as useful functions on polysaccharides but also the type of linkage via a nitrogen heterocycle was not known up to now.

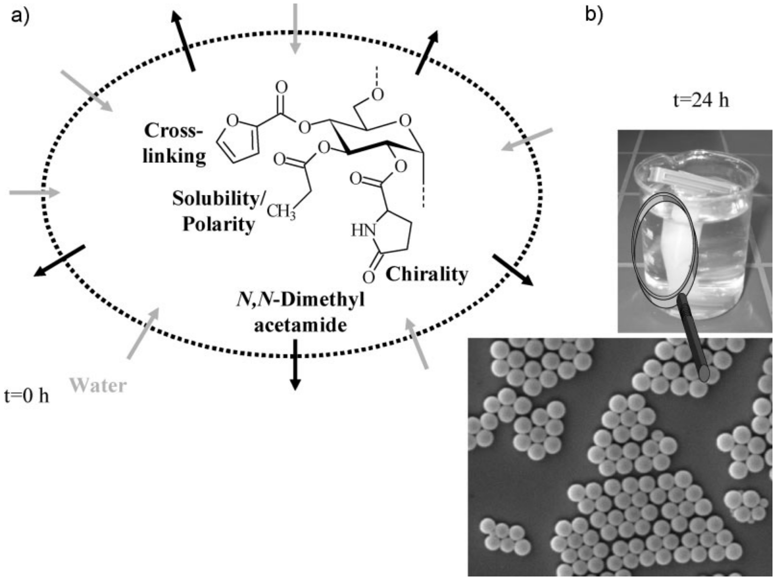


Figure 13.
Preparation of nanoparticles from dextran esters by means of dialysis of the solution in *N,N*-dimethyl acetamide against water (a). Photograph of the dialysis tube after 24 h and SEM image of the nanoparticle suspension (b).

Advanced Materials Based on Dextran

Another polysaccharide of interest is dextran. Compared to cellulose, the glucose units are linked together by α-1-6 linkages. Dextran possesses a rather flexible main chain forming comparably weak hydrogen bond systems that results in solubility of the polymer in organic solvents. A novel and efficient esterification path was developed by using a homogeneous conversion with *in situ* activated carboxylic acids of nearly all types that exist. This rather mild esterification method consists in the formation of reactive carboxylic acid derivatives by conversion with, e.g., *N,N*′-carbonyldiimidazole. A carboxylic acid imidazolide is formed under evolution of carbon dioxide. Subsequent reaction with polysaccharides affords the corresponding ester and imidazole. For instance sulphur containing acids were attached leading to polymers that self assemble on gold surfaces (Figure 12). As a consequence, biocompatible surfaces are formed. This is clearly proved by AFM.[34–36]

Another interesting approach to design nanostructures studied is based on dextran ester containing pyroglutamic- and furan carboxylic acid ester function that are biobased acids. The organic solution of the dextran ester is dialyzed applying a semipermeable membrane until the clear solution became turbid. A closer look on the turbid systems by scanning electron microscopy (after freeze drying and sputtering with gold) indicates that nanospheres of a diameter down to 60 nm with a narrow size distribution are formed (Figure 13). The size and the size distribution can be controlled by the structure of the polysaccharide ester and by various experimental conditions.[37–40]

There are many application fields for polysaccharide based nanoparticles and nanospheres. Due to the biocompatibility, interesting applications include controlled release formulations and interactions with cells regarding cell targeting. One of our studies concerned the development of sensors to evaluate the pH values into a cell. This could be realized by nanospheres obtained in the described way containing

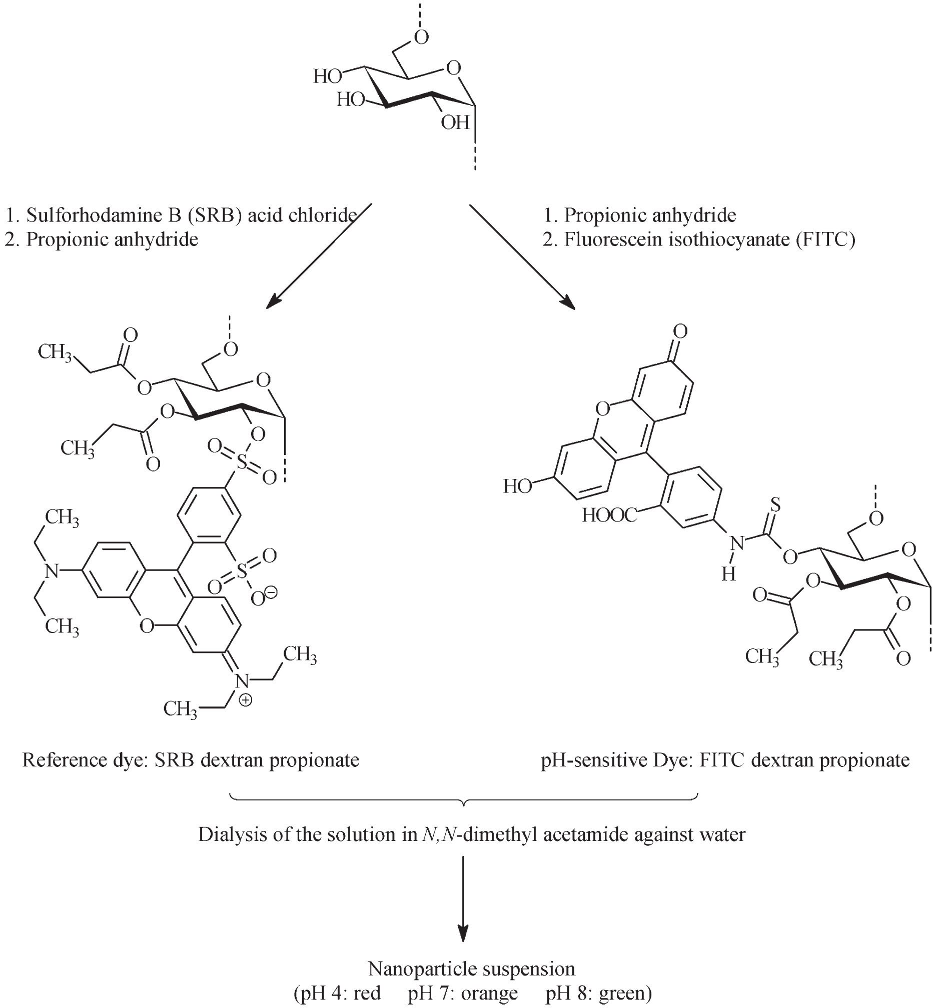


Figure 14.
Preparation of pH-sensitive nanoparticles by co-nanoprecipitation of dye-labelled dextran esters.

two fluorophors, one fluorophor (sulforhodamine B, SRB) that shows pH-independent fluorescence as reference and the other with a pH-dependent fluorescence (fluorescein isothiocyanate, FITC, Figure 14). It must be pointed out that it is not necessary to attach both dyes on one polysaccharide chain. Interestingly, it is sufficient to mix the solutions of both SRB- and FITC dextran derivatives prior to the dialysis procedure. Based on the calibration curve shown above the pH value can be measured. Confocal fluorescence microscopy indicates that the nanoparticles are incorporated into the cell, here human fibroblasts were studied (Figure 15).

Outlook

Tailoring the properties of polysaccharide derivatives is still a challenge in research of this important class of biopolymers. The results presented in this paper indicated that not only the regiochemistry of cellulose but also the preparation of new derivatives for highly sophisticated applications is of increasing importance. Various surfaces

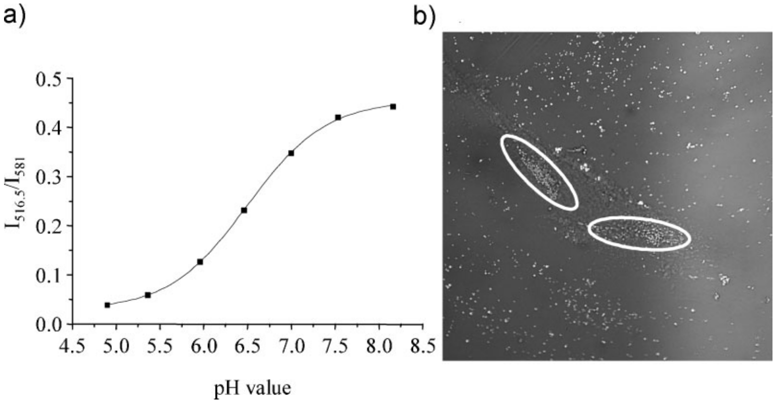


Figure 15.
Calibration curve (ratio of fluorescence intensities at 516.5 and 581 nm versus pH, a) and confocal fluorescence microscopic image of human fibroblast cells incubated with fluorescently labelled dextran nanoparticles (b). Red nanoparticles indicating pH ∼4 are marked.

can be coated with amino-modified polysaccharide derivatives bearing biomolecules as selective probes in, e.g., sensor applications. Their multifunctionality facilitates the modification with different moieties. Especially the *in situ* activation enables the esterification of polysaccharides with almost every carboxylic acid known. The DS can be controlled by the reaction conditions and further properties like solubility can be adjusted by derivatization of the remaining hydroxyl groups from partial to complete functionalization. Simple precipitation methods afford nanoparticle suspensions that were proved to be stable over a long period without aggregation. These nanoparticles could be incorporated in living cells in order to release pharmaceutical compounds or to measure the conditions inside the cell. New linkage-types like triazole moieties can be used to attach functional groups onto the polysaccharide backbone via the Cu(I) catalysed Huisgen reaction that can be conducted under mild conditions in a wide variety of solvents.

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