

Regioselective Synthesis of Cellulose Derivatives

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Abstract

Cellulose is the most abundant polysaccharide on earth and it is relatively a simple homopolymer ($\rightarrow 4\text{-}\beta\text{-D-Glcp-1}\rightarrow$) with three hydroxyl groups, differing only subtly in reactivity. The position of substitution has a powerful influence on physical properties of cellulose derivatives. To better understand the structure and property relationships of cellulose derivatives, it is critical to have all homopolymers related to important cellulose ethers and esters available. However, regiocontrol in cellulose chemistry is still a difficult, mostly unconquered frontier.

In this dissertation, the main objective is to develop novel synthetic methods to synthesize regioselectively substituted cellulose derivatives including cellulose ethers and esters, and apply advanced characterization tools to understand structure and its influence on properties, which will give us deep insights into the composition of more random commercial derivatives, maximizing the content of advantageous monosaccharides. Several strategies to regioselectively synthesize cellulose derivatives are discussed in detail. The obtained regioselective cellulose derivatives were fully characterized analytically. Structure-property relationships of these regioselectively substituted cellulose derivatives were also studied.

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Chapter 1 Dissertation Overview

Cellulose is the most abundant polysaccharide on earth and it is a relatively simple homopolymer ($\rightarrow 4\text{-}\beta\text{-D-Glcp-1}\rightarrow$). Cellulose can be transformed into other products via derivatization. Cellulose acetate, methyl cellulose, and carboxymethyl cellulose have all become the basis of many commercial products for industrial exploitation and investment.

From some instances, we have learned that position of substitution has a powerful influence on properties of cellulose derivatives. However, the regioselective synthesis of cellulose derivatives can be challenging. For example, cellulose acetate which only has one substituent type could have eight isomeric monosaccharide components; if there are two types of substituent, such as cellulose acetate propionate, up to 27 possible monosaccharides can be present.

To better understand the structure-property relationships of cellulose derivatives, it is necessary to have all isomers available. Also, the regioselective cellulose derivatives which could be used as biobased materials with excellent properties including low toxicity and high biocompatibility are critical for drug delivery, especially non-oral drug delivery, since the FDA frowns upon using polymers that haven't been well characterized inside the body.

The research in this dissertation will be focusing on synthesis of regioselectively substituted cellulose derivatives. Detailed spectroscopic analysis of these derivatives will be described as well. The physical properties of these derivatives will be tested so as to relate properties to nanostructure.

Chapter 2 will give a comprehensive literature review on regioselective esterification and etherification of cellulose. Chapter 3 will present formation of cellulose esters with bulky acyl

groups including pivalate, adamantate, and 2,4,6-trimethylbenzoate by acylation of cellulose with the corresponding acid chlorides. The structure of cellulose esters obtained will be studied by means of NMR techniques. The effects on substitution of using different esterifying reagents and solvents will be compared. In Chapter 4, we will report the general synthetic methods, based on computational studies of models of potential synthetic intermediates, for the successful regioselective synthesis of cellulose-2,6-di-*O*-esters and cellulose-2,6-di-*O*-(ester A)-3-*O*-(ester B) derivatives. We will also describe the first analytical and structure-property studies of these regioselectively substituted cellulose esters. In Chapter 5, subsequent reactions will be carried out on remaining hydroxyl groups of 3-*O*-benzyl and 3-*O*-allyl cellulose towards bulky ether protective groups in order to achieve the regioselectivity at primary hydroxyl groups. Several promising intermediates with high potential for the synthesis of regioselectively substituted cellulose esters and ethers will be discussed. In Chapter 6, unexpected deacylation of cellulose esters by tetrabutylammonium fluoride will be described. More surprisingly, this deacylation shows substantial selectivity for removal of the acyl groups from the esters of the secondary alcohols at C-2 and C-3, affording cellulose-6-*O*-esters with high regioselectivity. Chapter 7 will cover synthesis of cellulose levulinate in DMAc/LiCl using different activating levulinic acid derivatives. The role of levulinate as a protective group will also be explored. Chapter 8 will summarize the research results in this dissertation and talk about the future work.

Chapter 2 Literature Review on Synthesis of Regioselectively

Substituted Cellulose Derivatives

(Adapted from: Fox, S.C.; Li, B.; Xu, D.; Edgar, K.J. *Biomacromolecules*, 2011, 12, 1956-1972.)

2.1 Cellulose and its derivatives

Plants, algae, and some bacteria can produce tons of organic matter each year from the fixation of carbon dioxide through photosynthesis. Half of this biomass makes up the biopolymer cellulose, which, as a result, may be the most abundant molecule on earth.¹ As the principal structural element, this carbohydrate macromolecule makes up the cell wall of green plants, algae, and the oomycetes.² Some specific bacteria also secrete it to form biofilms.³ At the same time, cellulose is a major component of wood as well as cotton and other textile fibers such as linen, hemp, and jute.⁴ Cellulose has always played a vital role in human life, and its applications could be considered a landmark in the understanding of human evolution.

Cellulose is not a new substance, and its history can be traced back to ancient times. Dyeing cellulosic fibers, burning wood, producing charcoal, and producing cellulose substrates for writing and printing were all practiced by humans thousands of years ago.¹ Cellulose nitrate was first made by Schönbein in 1848.⁵ An organo-soluble cellulose acetate was synthesized by Schützenberger in 1865.⁶ Celluloid (nitrocellulose) was manufactured by the Hyatt Manufacturing Company.⁷ The structure of cellulose was then determined by Hermann Staudinger in 1920.⁸

Generally speaking, cellulose has many applications, such as in stabilizers, dispersing agents, emulsifiers, thickeners, and gelling agents,⁹ and water-soluble adhesives and binders.¹⁰

Cardboard and paper which are made from cellulose have already been used for hundreds of years.¹¹ Due to the inertness of cellulose, they find applications as fillers in drugs and as stabilizers in foods.¹² Cellulose can also be transformed into other products via derivatization. For example, cellophane, which is a thin film used for food packaging, is made from cellulose xanthate. Rayon,¹³ also called art silk, is an important regenerated cellulose fiber that has been used for textiles since the last century and it is produced by the “viscose process”.^{14, 15} Cellulose acetate, methyl cellulose, and carboxymethyl cellulose have all become the basis of many commercial products for industrial exploitation and investment.¹

Recently, because of growing environmental problems caused by burning fossil fuel and the consequent increase in demand for recycling processes, cellulose, which is an abundant biodegradable, non-toxic and renewable natural polymer, is a good candidate for replacement of other materials. Cellulosic ethanol is a relatively new biofuel source and it has the potential to replace fossil fuels.¹⁶ Recycled paper can be converted to cellulose insulation. This environmentally friendly material is often used for building insulation to isolate sound or heat from the surrounding environment.¹⁷

2.2 Cellulose chemistry

2.2.1 Cellulose structure

Cellulose is a linear homopolymer comprised of D-glucose units, also called anhydroglucose units (AGU). The units are linked together by acetal bonds. Compared with the linkage of $\alpha(1\rightarrow4)$ -glycosidic bonds in starch and glycogen, the linkage for cellulose is

$\beta(1\rightarrow4)$.¹⁸ Based on its structure (Figure 2.1), cellulose is a syndiotactic polymer and the molecular structure adopts an extended and rather stiff rod-like conformation.

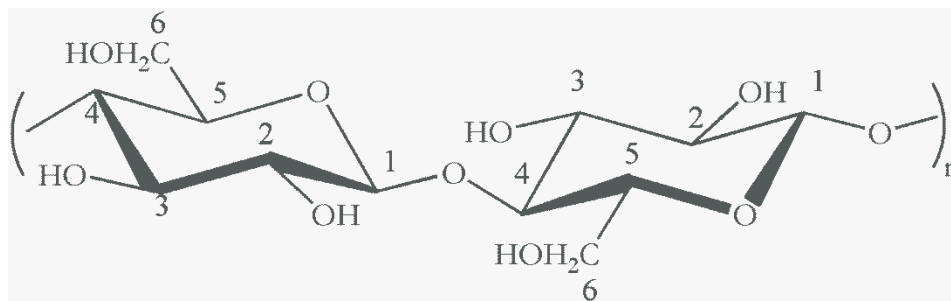


Figure 2.1 *Cellulose chemical structure*

There are three hydroxyl groups at the C-2, C-3, and C-6 positions. The C-2 and C-3 positions have secondary hydroxyl groups, while the C-6 position has a primary hydroxyl group, and they can undergo specific primary and secondary alcohol reactions. The AGU in cellulose has a 4C_1 chair conformation with the free hydroxyl groups in equatorial positions, which can be identified by NMR measurements.¹⁸ The three hydroxyl groups in cellulose can form both inter- and intra-molecular hydrogen bonds. The major intra-molecular hydrogen bonds occur at $O_3-H\cdots O_5'$ and $O_2-H\cdots O_6'$, and the major inter-molecular hydrogen bonds are at $O_6-H\cdots O_3'$.¹⁹ The packing of the cellulose molecules in the inter- and intra-molecular hydrogen bonded systems is very dense, and this results in cellulose forming semi-crystalline morphologies.¹⁹ Due to these hydrogen bonds, the cellulose chain can exhibit high stiffness and tensile strength. The hydrogen bonds are also the reason for the stabilization of the “two-fold screw axis” and

“two-fold helical” structure. At the same time, those hydrogen bondings are responsible for the difficulties in dissolving cellulose in normal organic solvents,²⁰ discussed in detail later.

2.2.2 Cellulose classification

The natural crystalline form of cellulose is metastable cellulose I.²¹ Cellulose I contains two co-existing phases, cellulose I_α and cellulose I_β that have different properties dependent on the cellulose source. I_α is triclinic and found more in algae and bacteria while I_β is monoclinic and abundant in higher plants.²² Cellulose I can transit into a more stable structure, that is cellulose II, via regeneration and mercerization.²³ Cellulose III is formed either from cellulose I or II when treated with liquid ammonia or amines such as ethylene diamine.²⁴ Cellulose IV, which is generally considered to be a disordered form of cellulose I, is obtained upon the treatment of regenerated cellulose fibers at high temperature in glycerol.²⁵

2.2.3 Cellulose reactivity

Chemical reactions of cellulose depend strongly on the accessibility of the hydroxyl groups in the AGU, and they can be affected by the inner surface of the pore and void system, supramolecular order and fibrillar structure. Accessibility of a cellulose sample is dependent on the reactions involved.²⁶ Cellulose molecules are in ordered lattices in the crystalline domain and interact through multiple hydrogen bonds.¹⁹ To react cellulose, the lattice structure must have enough space, through swelling, to enable the reactants to pass through the crystals and contact the cellulose molecule. Such reaction examples are in forming cellulose nitrate, cellulose acetate and cellulose xanthate.²⁷ Cellulose can be swollen in several ways, such as with strong acids, bases or concentrated salt solutions.^{28, 29} The three hydroxyl groups have different reactivities.

The acidity of those hydroxyl groups decreases in the order OH-2>OH-3>OH-6. When OH-2 is ionized or substituted, the acidity in position 3 levels off, while OH-6 becomes the most acidic. For etherification reactions, OH-2 is often the most reactive because it is the most acidic. For esterification reactions, OH-6 is the first to react, since steric hindrance is considered as the most important factor for such reactions, particularly for bulky reacting species.³⁰

2.2.4 Cellulose degradation

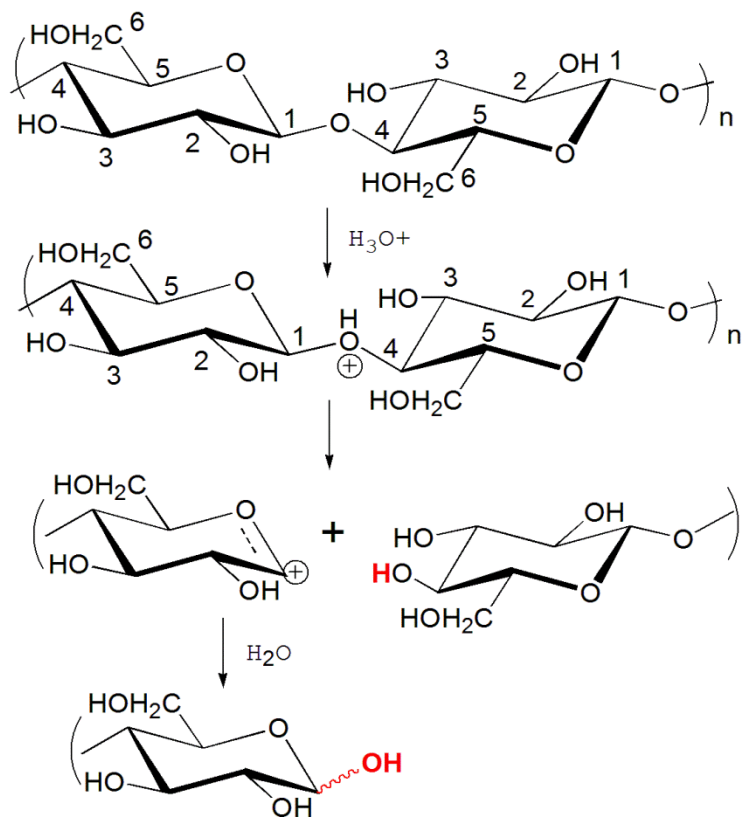
Degradation of cellulose draws people's interest because cellulose can be returned to the natural carbon cycle via biodegradation and this should be emphasized since it allows for safe disposability after use. Cellulose is non-toxic to living organisms. Humans and other mammals can excrete it without chemical change. Due to these properties, cellulose is essentially connected with many applications such as food, paper, the oil industry, drug delivery and so on.²⁶ The process of degradation involves different forms of energy, i.e. chemical, mechanical, thermal, enzymatic and radiative energy, and different reaction routes.²⁶

Also because degradation almost always occurs during cellulose derivatization and can impact product properties, this must be taken into consideration when performing cellulose reactions.

2.2.5 Hydrolytic degradation

Hydrolysis is the most important pathway of cellulose degradation (see Scheme 2.2). This process involves breakage of glycosidic bonds between AGUs, and this can be catalyzed either by an acid or enzyme. The major mechanism is the bridging oxygen is protonated and a carbocation is formed at C-1 position, which is then attacked by water.^{31, 32} Generally speaking,

hydrolytic degradation can be considered as addition of water to the cellulose, which is the reversal of polycondensation to form cellulose.³³

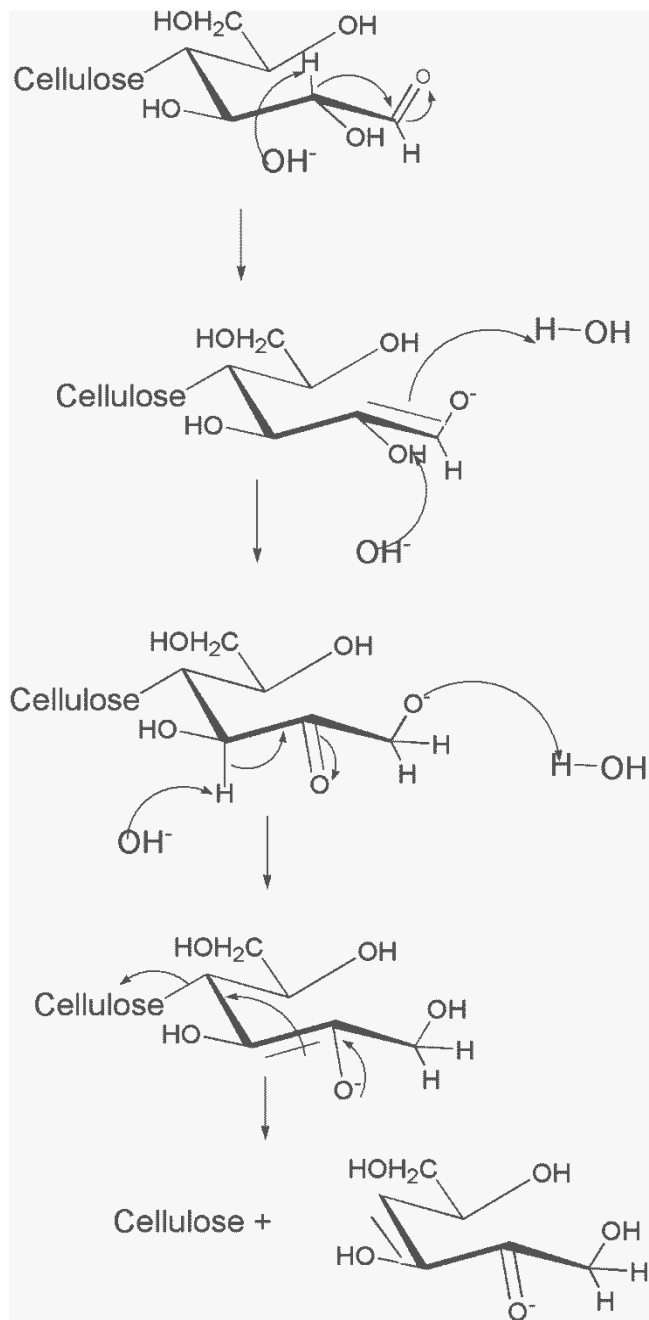


Scheme 2.1 *Hydrolytic degradation of cellulose*

2.2.6 Alkaline degradation

At room temperature and in the absence of oxygen, cellulose is very stable to aqueous alkali even with a high concentration. However, if air is present, dramatic chain degradation occurs. At or above 100°C even without oxygen, excessive chain degradation can take place. At

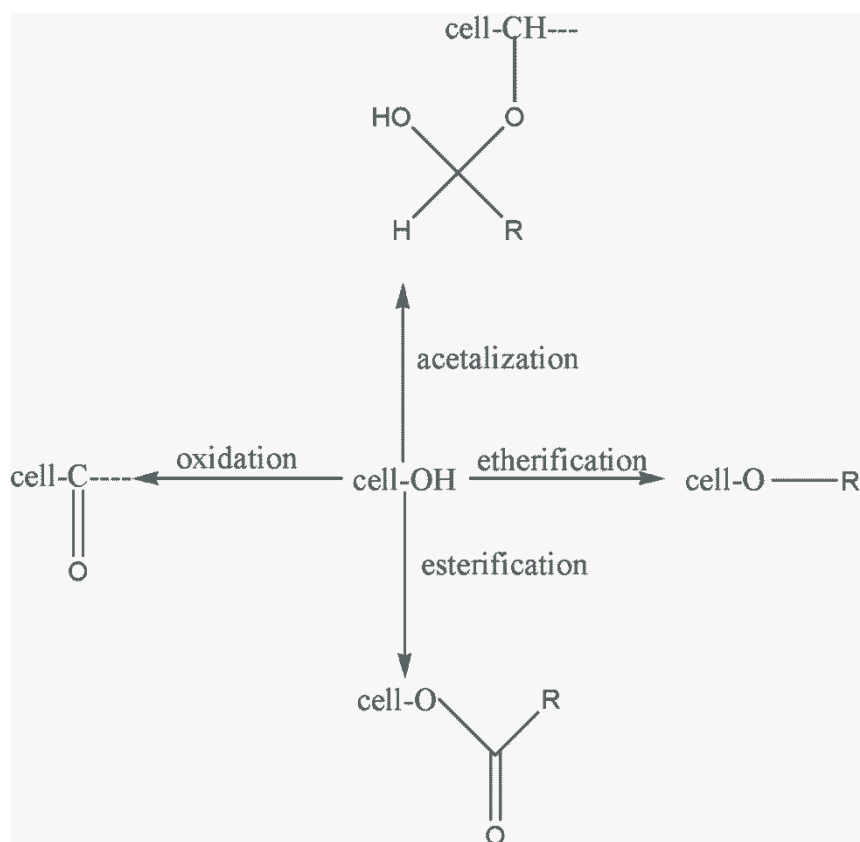
higher concentrations of base, this process leads to significant low molecular weight fractions, most of which contain carboxylic acids. Also near 100 °C, a stepwise peeling of monomer units will occur, which results in decreased molecular weight.³³ (see Scheme 2.2)



Scheme 2.2 *Alkaline degradation of cellulose*

In summary, cellulose degradation via different forms has significant effects on chemical processing of cellulose. Chain degradation should be avoided as much as possible, especially for cellulose esters and ethers. This can be achieved by decreasing the O₂ content, controlling the pH and in other ways, but sometimes more control over the degradation process is required. For example, to lower the viscosity of the solution when processing cellulose and its derivatives, a controlled reduction of degree of polymerization (DP) is applied. Another example is the product ‘charcoal’ which is obtained by controlled pyrolysis of lignocelluloses.³³

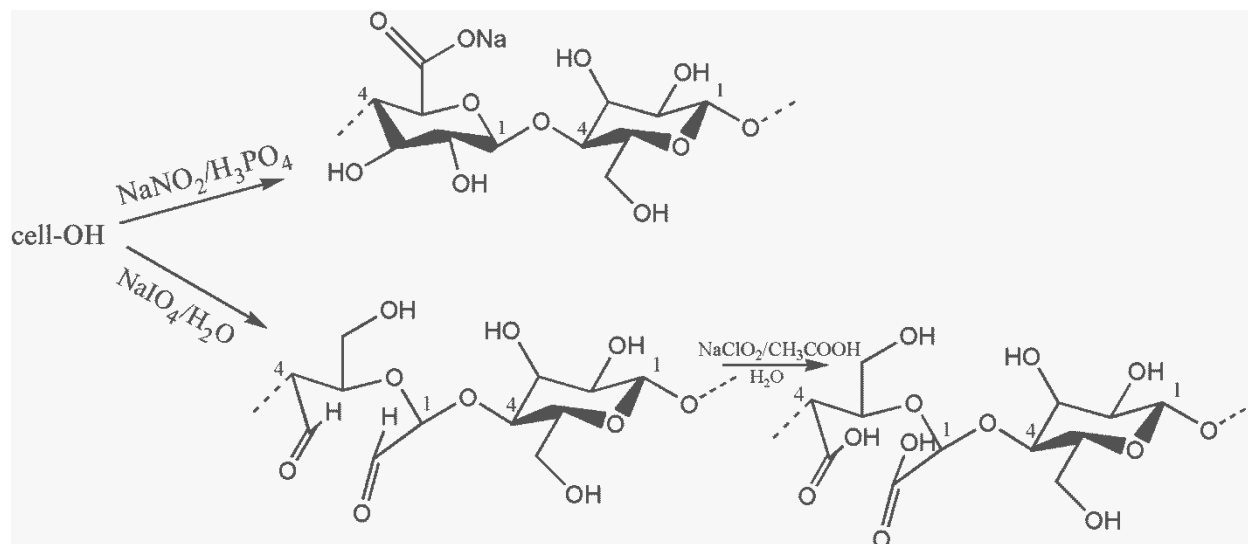
2.3 Cellulose reactions



Scheme 2.3 *Cellulose reactions*

Due to the special structure of cellulose, cellulose reactions have different features. Firstly, the free hydroxyl groups present in each AGU of cellulose are excellent target sites for a chemical transformation, however they have different reactivities. Secondly, the acetal linkage connecting two AGUs is sensitive to hydrolysis such that degradation of cellulose often occurs during derivatization reactions, especially in acidic systems.³⁴ All of the three hydroxyl groups can undergo the classical reactions of an alcoholic hydroxyl group, including etherification, esterification, acetalization and oxidation reactions.³⁴

Esterification can be realized with the polymer reacting with acid anhydrides. Acid chlorides can be utilized as an important alternative. Cellulose ethers can be synthesized by methods including Williamson ether synthesis and Michael addition.³⁵ Oxidation can occur at a hydroxyl group of cellulose (see Scheme 2.4). The OH-6 can form either an aldehyde or a carboxyl group, while OH-2 or OH-3 can normally only form keto groups. An exception can occur under conditions that cause bond scission, for example, periodate or permanganate oxidation.^{36, 37} In such a case, the cellulose backbone will break up into acyclic polymer, and OH-2 and OH-3 can convert to dialdehyde or diacid via oxidation or to dialcohol via reduction.



Scheme 2.4 *Cellulose oxidation*

Almost all of these reactions are determined by donor and acceptor properties, that is, the oxygens on cellulose act as electron donors and the reagents act as electron acceptors. Most commercial products are partially substituted cellulose derivatives with many free hydroxyl groups. The extent of the reaction can be characterized by defining DS, the degree of substitution, which indicates the average number of hydroxyl groups substituted per AGU.³⁵

2.4 Dissolution of cellulose

As mentioned, due to the supra-molecular structure, cellulose is almost insoluble in all common organic solvents. However, it is necessary to find ways to dissolve cellulose for fiber spinning and other related processes. Also, homogeneous reactions of cellulose have many advantages including better control of degree of substitution and functionalization pattern which will facilitate development of new cellulose derivatives with excellent end-use properties.

Comprehensive description of all cellulose solvents is beyond the scope of this section, but several solvents commonly used to dissolve cellulose will be mentioned.

2.4.1 DMAc/LiCl

The use of *N,N'*-dimethylacetamide (DMAc) and LiCl together to dissolve cellulose was first reported by McCormick in 1979.³⁸ It has been so far proved the most versatile and dependable way of dissolving cellulose and performing cellulose reactions in solution. The procedure for dissolving cellulose in DMAc/LiCl is highly specific and a clear and viscous solution could be obtained. Cellulose can be dissolved at a concentration of 5-10% while a higher concentration would make the solution too viscous to handle.⁸ One drawback for this method is that moderate degradation is often involved due to the heat activation between 120 °C and 160 °C with some yellow color showing up during dissolution process. The degradation results from the formation of highly reactive *N,N*-dimethylketeniminium ions from DMAc when LiCl is in present at temperatures above 80 °C.³⁹ Although heat activation has disadvantages, it is very effective to remove traces of water in the mixture by distilling off some of the solvent while it is at elevated temperature. This is quite important for performing water sensitive reactions of cellulose.

An alternative activation method is solvent exchange at room temperature.⁴⁰ Cellulose first swells in water, then it is filtered out, followed by the addition of DMAc. An intermediate solvent such as methanol is usually used before exchanging with DMAc. This solvent exchange method does not cause any degradation of the cellulose. However, it is hard to remove all the moisture from the cellulose solution.

The mechanism of dissolving cellulose in DMAc/LiCl is still under discussion, but it is accepted that Li cation can interact with the O atoms of OH groups so that the hydrogen bonding is disrupted, leading to the cellulose dissolution. In addition to that, the dipolar aprotic solvent DMAc could further stabilize the Li cation by coordination.⁴¹

2.4.2 DMSO/TBAF

DMSO/TBAF is a relatively new cellulose solvent that is perhaps the most efficient solvent yet discovered for cellulose dissolution.⁴² It can dissolve cellulose (with a DP up to 650) faster and under milder conditions than any other cellulose solvent, leading to a clear cellulose solution within 15 mins at room temperature. Cellulose ether synthesis works pretty well in this solvent system⁴³, however the synthesis of cellulose esters leads to a lower DS in comparison with other non-derivatizing solvents.⁴⁴ Authors have speculated that this is due to the fact that TBAF is obtained as a trihydrate and these waters of hydration limit product DS by consuming acylating reagent. Furthermore, the waters of hydration cannot be removed by normal solvent drying techniques, because anhydrous TBAF is thermally unstable and it could lead to a β -elimination reaction of TBA cation upon removal of water, degrading the TBAF salt.⁴⁵

2.4.3 Ionic liquids (ILs)

Early in this decade, the Rogers group found that ionic liquids (ILs) can dissolve cellulose.⁴⁶ Since then, more and more attention has been paid to this new solvent family and many cellulose modifications have been performed in ILs. ILs are typically salts of organic amines which have low melting point (below 100 °C) and extremely low volatility. Among all

ILs, imidazolium ILs have been of the greatest interest ones for cellulose due to their high effectiveness for dissolving cellulose. 1-Butyl-3-methylimidazolium chloride (Bmim^+Cl^-) can dissolve cellulose with a DP up to 1000 by simply heating and stirring a slurry of cellulose, with a concentration as high as 25%.⁴⁶ Other commonly used ILs are 1-ethyl-3-methylimidazolium chloride (Emim^+Cl^-), 1-allyl-2,3-dimethylimidazolium bromide ($\text{Admim}^+\text{Br}^-$), 1-butyl-2,3-dimethylimidazolium chloride ($\text{Bdmim}^+\text{Cl}^-$) and they can dissolve cellulose at 12%, 12%, and 9% concentrations respectively (Figure 2.6).⁴⁷ ILs are highly hygroscopic and typically contain hundreds to thousands of ppm water even after drying at 60 °C under vacuum for 2 days.⁴⁸ This could become an issue for acylation of cellulose since water can react preferentially with the acylating agent, resulting in a lower DS value compared with reaction in DMAc/LiCl.⁴⁴

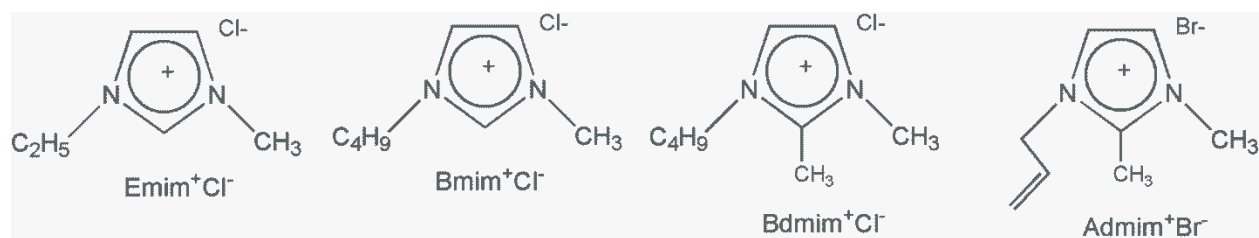


Figure 2.2 *Ionic liquids*

2.5 Regioselective derivatization of cellulose

The term regioselectivity on cellulose refers to an exclusively or significantly preferential reaction at one or two of the three hydroxyl groups of each AGU, in other words, the selectivity of substitution position among the three reactive sites within each AGU.⁴⁹ For example, cellulose acetate (CA) which only has one substituent type could have eight isomeric monosaccharide components (see Figure 2.3); if there are two types of substituent, such as cellulose acetate

propionate, up to 27 possible monosaccharides can be present. The degree of substitution has an effect on the properties of cellulose derivatives; but the distribution of functional groups also plays an important role. It has been shown solubility, optical property, crystallinity, and thermal property can all be affected by regioselectivity.⁵⁰ For example, the partially regioselective synthesis of cellulose acetate propionate (CAP) affords improved optical properties vs. standard, presumably randomly substituted CAP; optical properties are quite important for the use of cellulose ester films in flat screen display applications.⁵¹ Other investigators have shown that regioselectively substituted cellulose acetates have unique characteristics in comparison to presumably randomly substituted commercial materials, with respect to chain conformation, solubility and associative properties and structures in solution.⁵²

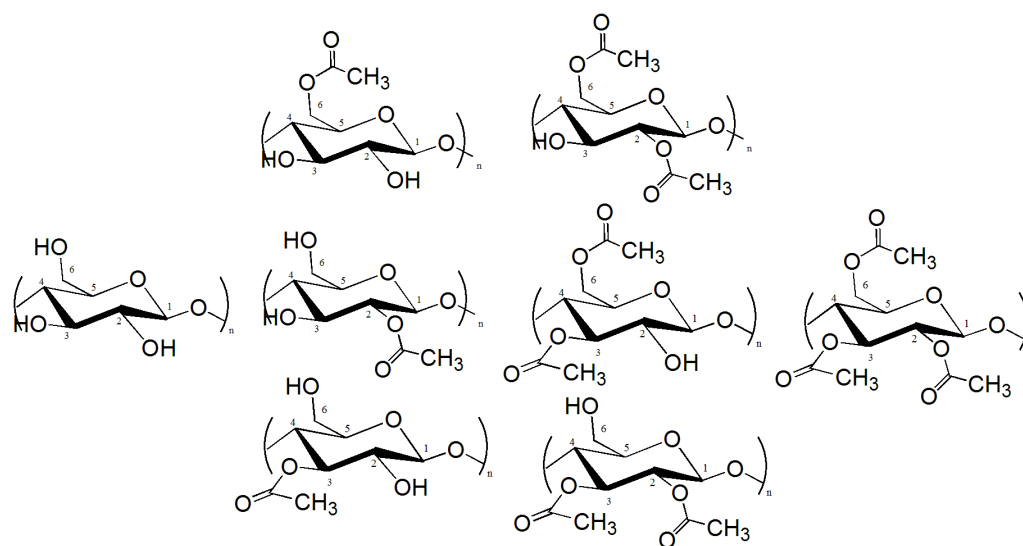


Figure 2.3 *Cellulose acetate isomers*

The hypothesis of our work is that to better understand the structure-property relationships of cellulose derivatives, it is critical to have cellulose derivatives with a defined substitution pattern available. Also, regioselective cellulose derivatives have many potential

applications including multilayered assemblies, liquid crystalline polymers, selective membranes, sensor matrices, recognition devices and bioactive materials.⁴⁹

Up to now, regioselective synthesis of cellulose derivatives is still a challenge. This could be due to the low reactivity of hydroxyl groups and small reactivity differences between the three hydroxyl groups. The low reactivity results from steric hinderance and high propensity for intra- and intermolecular hydrogen bonding, which can be disrupted by dissolving and reacting cellulose in solvents. The reactivity differences are from the lower steric hinderance of the primary hydroxyl group and higher acidity of the hydroxyl group at C-2, but both differences are subtle.

The advent of cellulose solvents has facilitated the regioselective synthesis of cellulose derivatives because the hydrogen bonds could be disrupted as a result of cellulose dissolution, increasing the reactivity of hydroxyl groups and permitting milder reaction conditions, leading to higher selectivity.

The main literature strategy for regioselective synthesis of cellulose derivatives is to apply bulky protective groups, which can be introduced selectively to one or two of the three reacting sites depending on reaction conditions. The protected substrate is stable under some circumstances for the following derivatization of the remaining hydroxyl groups; after that, the protective groups are removed under conditions which do not disturb other substituents. Another method is the direct regioselective oxidation, halogenation, or tosylation at C-6, leaving free hydroxyl groups at C-2 and C-3 for further reactions; in the case of halogenation or tosylation, the substituent at C-6 acts as a good leaving group for subsequent substituent reactions. The third literature method is *de novo* synthesis of regioselective cellulose derivatives. All the three methods will be discussed in detail.

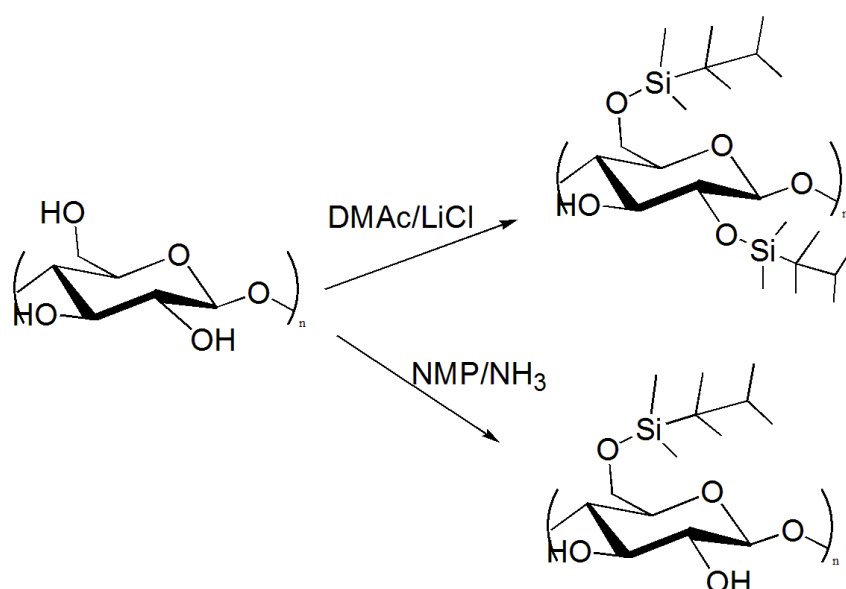
2.5.1 Bulky protective groups

The difficulty for the reaction of cellulose lies in regioselective transformations among multiple OH functional groups. Thus, there is the need to find efficient protecting groups which could be used and removed under different conditions. Compared to the other two OH groups, the hydroxyl group at the C-6 position is more reactive because of steric effects. Thus, to carry out a reaction on the other two hydroxyl groups, the C-6 hydroxyl should first be protected, then it can be deprotected once the targeted product is formed. Protection can be realized by both etherification and esterification. The reactions are usually conducted in homogeneous systems, for example DMAc/LiCl.³⁵

2.5.2 Regioselective silylation

Hexyldimethylsilyl (TDMS) is a very efficient protective group with a high regioselectivity for primary hydroxyl or both primary hydroxyl and secondary hydroxyl at C-2 depending on the dispersity of cellulose in reaction mixture. If cellulose is dissolved, TDMS-Cl can react with cellulose both at C-6 and C-2 hydroxyl groups; under heterogeneous conditions, only the primary hydroxyl group is silylated, without any reaction happening at C-2. The first heterogeneous reaction was performed in DMF saturated with ammonia at -15 °C and a DS of 0.99 was obtained.⁵³ Alternatively, silylation in NMP with saturated ammonia at -25 °C has been reported to produce up to 96% O-6 silyl.⁵⁴ A homogeneous system in DMAc/LiCl with pyridine added was also investigated for synthesis of TDMS cellulose, and the DS can be up to 1.90.⁵⁵ Imidazole was then applied as a base instead of pyridine, affording the remarkable result of a DS

of 2.0 with perfect regioselectivity at both C-6 and C-2.⁵⁶ The reason for the magnitude of O-2 selectivity is not clear yet. The substitution pattern of TDMS cellulose ether was analyzed by HPLC after permethylation followed by hydrolyzing the cellulose backbone with acid. TDMS can be removed by tetrabutylammonium fluoride, so subsequent reactions at C-3 position with appropriate alkyl halide in the presence of a strong base, followed by the removal of TDMS at C-6 and C-2 by TBAF could produce a series of regioselective cellulose derivatives.



Scheme 2.5 *Regioselective silylation*

Kadla et al.⁵⁷ successfully synthesized 3-*O*-hydroxyethyl cellulose via 2,6-di-*O*-hexyldimethylsilyl cellulose. These products can be used to produce microporous honeycomb structured films.

Klemm et al. synthesized the novel compounds 3-*O*-allyl and 3-*O*-methyl cellulose after etherifying the remaining O-3 hydroxyl group of 2,6-di-*O*-hexyldimethylsilyl cellulose followed by desilylation.⁵⁶ The double bond of the allyl group from 3-*O*-allyl-2,6-di-TDMS was converted

to 3-hydroxypropyl group by hydroboration with (9-borabicyclo[3.3.1]nonane) and subsequent alkaline oxidation with hydrogen peroxide. After deprotection of the hexyldimethylsilyl group with TBAF, 3-mono-*O*-3'-hydroxypropyl cellulose was formed.⁵⁸ 3-Mono-*O*-hydroxyethyl cellulose was synthesized similarly by reacting 2,6-TDMS cellulose with 2-(2-bromoethoxy)tetrahydropyran.⁵⁹ Both of 3-mono-*O*-3'-hydroxypropyl and 3-mono-*O*-hydroxyethyl cellulose were water soluble.

3-*O*-Ethyl cellulose⁶⁰ and 3-*O*-propyl cellulose⁶¹ were synthesized by reacting 2,6-di-*O*-TDMS cellulose with ethyl iodide and 1-iodopropane respectively, followed by deprotection with TBAF. Both 3-*O*-ethyl cellulose and 3-*O*-propyl cellulose are water soluble, however, the regioselective products have a different gelation temperature from conventional water soluble ethyl cellulose or propyl cellulose which are more randomly substituted.

Another water soluble cellulose ether, 3-*O*-(2-methoxyethyl)cellulose, was synthesized by Heinze et al.⁶² TDMS cellulose was allowed to react with 1-bromo-2-methoxyethane, followed by deprotection of the TDMS groups to give 3-*O*-(2-methoxyethyl)cellulose. Klemm et al.⁶³ reported the synthesis of 3-*O*-alkyl ethers (including *n*-pentyl, isopentyl, and dodecyl) by reaction of the 2,6-bis-TDMS intermediate with the corresponding alkyl bromide.

3-*O*-Propargyl cellulose⁶⁴ was synthesized by Heinze et al. using the same methodology. The triple bond of the propargyl group can react with azido-propyl-polyamidoamine (PAMAM) dendrons to produce 3-*O*-94-ethyl-1-*N*-propyl-PAMAM-[1,2,3-triazole]) cellulose with dendritic structures.

Kamitakahara et al.⁶⁵ synthesized 2,6-di-*O*-methyl cellulose from natural cellulose. 3-*O*-Allyl-2,6-di-*O*-TDMS cellulose was first synthesized and then it was transformed to

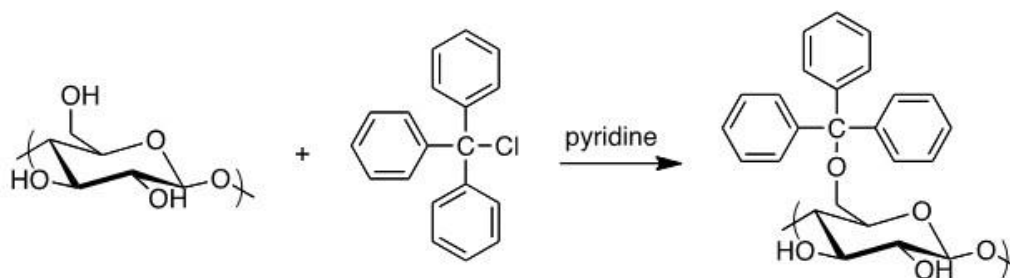
3-mono-*O*-acetyl-2,6-di-*O*-methylcellulose after several steps. The acetyl group was finally hydrolyzed with sodium methoxide to give 2,6-di-*O*-methyl cellulose.

Another interesting silyl protective group is the tert-butyldimethylsilyl group.⁶⁶ A DS of 2 can be realized by reacting cellulose with tert-butyldimethylchlorosilane in DMAC/LiCl. Imidazole was used as base. The regioselectivity is the same as with hexyldimethylchlorosilane except for the presence of a small amount of 3,6-di-*O*- and 6-mono-*O*-silyl structures. In addition, if the reaction was carried out at high temperature, 2,3,6-tri-*O*-silyl groups were found.

2.5.3 Regioselective tritylation

Triphenylmethyl (trityl) is another widely used protective group. Cellulose can react with triphenylchloromethane (trityl chloride) in the presence of an organic base. Tritylation is usually performed in DMAc/LiCl⁶⁷, but it was also carried out in ILs including Bmim⁺Cl⁻ and Amim⁺Cl⁻.^{68, 69} The DS of trityl can vary from 0.93 to 1.07, depending on reaction conditions, such as reaction time, temperature and molar ratio.⁷⁰ It was found that almost 90% of primary OH could be tritylated, and the selectivity for such a reaction was at C-6 rather than at C-2 and C-3, although there was a small portion of tritylation at C-2 and C-3.³⁷ Trityl groups substituted with methoxy are another useful ether protective group utilized in cellulose functionalization. The reaction rates with the methoxy substituents have been reported to be 10 times faster than with unsubstituted trityl.³⁹ A degree of substitution of 0.96 at C-6 for tritylation only requires four hours at 70 °C. Even with longer reaction time, higher temperature or excess reagent, substitution at the C-2 and C-3 positions was less than 11%. The rate acceleration results from the stabilization of the intermediate triarylmethyl cation by the electron donating effect of methoxy group. Both the trityl and methoxy-trityl can be removed by acid hydrolysis. The only

difference is that it takes only 5.5h to remove methoxy-trityl group while it requires 100h for trityl group.³⁹ This opens a gateway to producing regioselective cellulose derivatives.



Scheme 2.6 *Regioselective tritylation*

2,3-Di-*O*-methyl and 2,3-di-*O*-ethyl cellulose were first synthesized by use of a trityl protective group.⁷⁰ It was then found that even with small differences in DS and distribution of the methyl group can strongly affect phase separation behavior of methyl cellulose in aqueous solution.⁷¹ 6-*O*-Alkyl cellulose ethers were also synthesized using trityl group. After triylation, allylation of 6-*O*-trityl cellulose was applied with allyl chloride and sodium hydroxide in DMSO. The allyl group is stable against both acid catalyzed detritylation and alkaline etherification conditions. Allyl was then isomerized to 1-propenyl by potassium *t*-butoxide, then the vinyl ether was easily removed by acid hydrolysis.⁷² The regioselectively substituted methyl cellulose was studied with respect to inter- and intramolecular hydrogen bonding.⁷³ The investigators showed that intermolecular hydrogen bonding disappeared for 6-*O*-methyl cellulose while it predominated in 2,3-di-*O*-methyl cellulose, leading to a significant difference in solubility; 6-*O*-methyl cellulose is soluble in many organic solvents, whereas 2,3-di-*O*-methyl cellulose is only soluble in polar aprotic solvents.

Hydroxyethyl and hydroxypropyl cellulose were synthesized in isopropanol and water via trityl cellulose; a molar substitution (MS) of 2.0 was achieved with the addition of ionic and nonionic surfactants.⁷⁴ 2,3-Di-*O*-hydroxyethyl cellulose and 2,3-di-*O*-2'-hydroxypropyl cellulose were water-soluble after detritylation even at low MS (0.3 and 0.8 respectively). Randomly substituted hydroxypropyl celluloses must reach MS of 4.0 in order to be water soluble.

2,3-Di-*O*-carboxymethyl cellulose was synthesized by reaction of 6-*O*-trityl cellulose with sodium monochloroacetate, and subsequent detritylation with HCl in methanol. DS (CH_2COOH) as high as 1.91 was obtained.⁷⁵

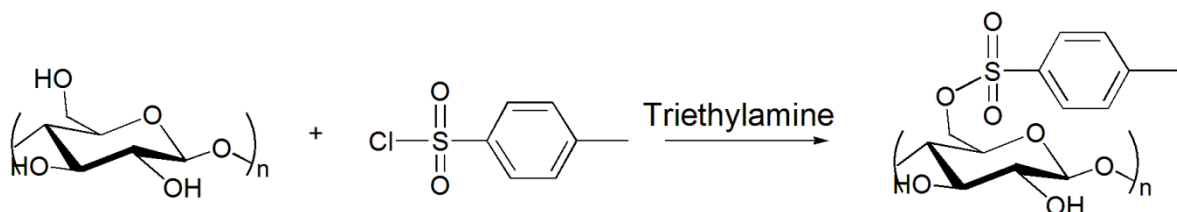
The free hydroxyl groups of trityl cellulose at C-2 and C-3 could be further esterified with a carboxylic anhydride. The regenerated primary hydroxyl after detritylation with acid can react with a different carboxylic anhydride, resulting in a 2,3-A-6-B type of regioselectively substituted cellulose triesters. 6-*O*-Acetyl-2,3-di-*O*-propionyl cellulose and 6-*O*-propionyl-2,3-di-*O*-acetyl cellulose were synthesized and they were used as model compounds to help assign NMR peaks of cellulose esters.⁷⁶ Single Lamellar crystals of some regioselectively substituted cellulose heteroesters including 6-*O*-acetyl-2,3-di-*O*-propionyl cellulose, 6-*O*-propionyl-2,3-di-*O*-acetyl cellulose, 6-*O*-acetyl-2,3-di-*O*-butyl cellulose and 6-*O*-butyl-2,3-di-*O*-acetyl cellulose were synthesized via trityl cellulose, then crystallized from a mixture of dibenzyl ether and *n*-tetradecane.⁷⁷ The structure and properties of these regioselectively substituted cellulose esters were studied and it was found that the substituent position has an important influence on cellulose chain conformation and association in solution.⁷⁸ 6-*O*-Acetyl-2,3-di-*O*-benzoyl cellulose and 6-*O*-benzoyl-2,3-di-*O*-acetyl cellulose were studied as stationary phases for chiral separations, which were affected significantly by the position of cellulose ester substitution.⁷⁹

The liquid crystalline properties of regioselectively substituted cellulose derivatives synthesized via the trityl cellulose intermediate were investigated. 6-*O*-Trityl-2,3-di-*O*-ethyl cellulose, 6-*O*-trityl-2,3-di-*O*-benzyl cellulose and 6-*O*- α -(1-naphthylmethyl)-2,3-di-*O*-pentyl cellulose can form chiral nematic phases in organic solvents and their optical properties vary with structure and DS value.^{80, 81} Chiroptical properties of Langmuir-Blodgett films of 6-*O*- and 2,3-di-*O*-octadecyl cellulose were studied by AFM and XRD.⁸² The substituent position of carbazole group (C-6 vs. C2/3) can affect the electronic properties of cellulose derivatives and this is quite important for potential application as organic light emitting diodes.⁸³ 2,3-Di-*O*-cinnamoyl cellulose, 6-*O*-acetate-2,3-di-*O*-cinnamoyl cellulose and 6-*O*-cinnamoyl-2,3-di-*O*-acetyl cellulose were synthesized and the cinnamate group was introduced as a photosensitive and electroconductive group.⁸⁴

2.5.4 Tosylation

Cellulose can react with *p*-toluenesulfonyl (tosyl) chloride in DMAc/LiCl to form cellulose tosyl esters with DS ranging from 0.4 to 2.3 by changing the molar ratio of tosyl chloride to AGU. More interestingly, tosylation could be highly selective at C-6 (see Figure 2.10).⁸⁵ Triethylamine is usually used as a base instead of pyridine, resulting in a higher DS of tosyl group.⁸⁶ Recently, tosylation was also carried out in [Amim]Cl.⁸⁷ Tosyl cellulose synthesized in [Amim]Cl with a DS of 0.84 was derivatized exclusively at C-6; with increasing DS, there was also some substitution at C-2. The solubility of cellulose tosylate is dependent on DS value. For example, a derivative of DS 0.9 is soluble in polar aprotic solvents; when the DS increased to 1.4, the product became soluble in acetone, THF and dioxane; if the DS is above 1.8, the product can be dissolved in chloroform and dichloromethane.⁸⁸ The advantage of the tosyl

group is that it serves not only as a protective group at C-6, but is also a good leaving group. By the direct replacement of tosyl group by an attacking nucleophile, a number of 6-deoxy-cellulose derivatives can be synthesized.



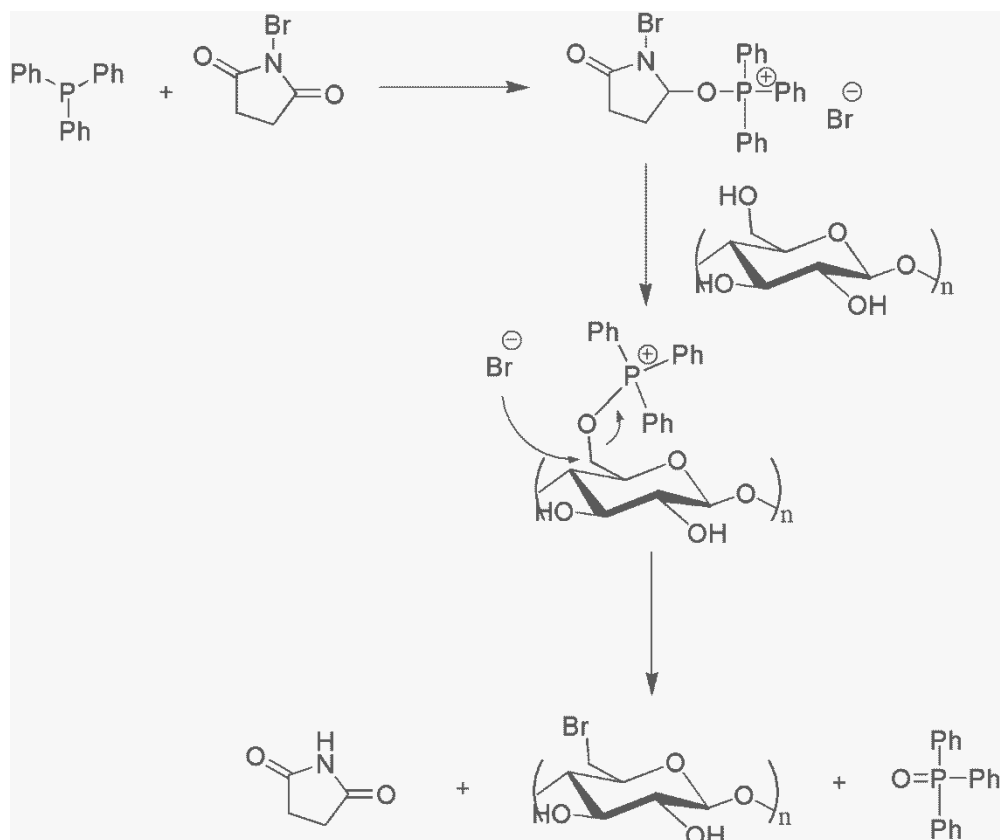
Scheme 2.7 Cellulose tosylation

The remaining hydroxyl groups could be further modified by aliphatic, aromatic and unsaturated acid anhydrides and isocyanates to form corresponding tosyl cellulose derivatives with different properties.⁸⁹

2.5.5 Halogenation

Cellulose dissolved in DMAc/LiBr can react with triphenylphosphine and N-bromosuccinimide to form 6-deoxy-6-bromo-cellulose.⁹⁰ Compared with tosylation, bromination is highly regioselective with a DS up to 0.98 and there is no reaction at secondary hydroxyl groups within AGU.⁹¹ The role of bromide at C-6 is the same as tosyl group, that is, it can act both as a protective group and a good leaving group for subsequent reactions; Unfortunately, 6-deoxy-6-bromo-cellulose is not soluble in common organic solvents except in DMAc/LiBr. By changing LiBr and N-bromosuccinimide to LiCl and N-chlorosuccinimide, chlorination can also be effected, however, regioselectivity is poor and a DS of 1.86 can be reached.⁹² The mechanism lies in that the bulky triphenylphosphonium intermediate tends to form

at C-6 due to steric hindrance and the following bromination is a S_N2 reaction, favoring the configuration inversion at C-6.



Scheme 2.8 *Proposed mechanism for cellulose bromination*

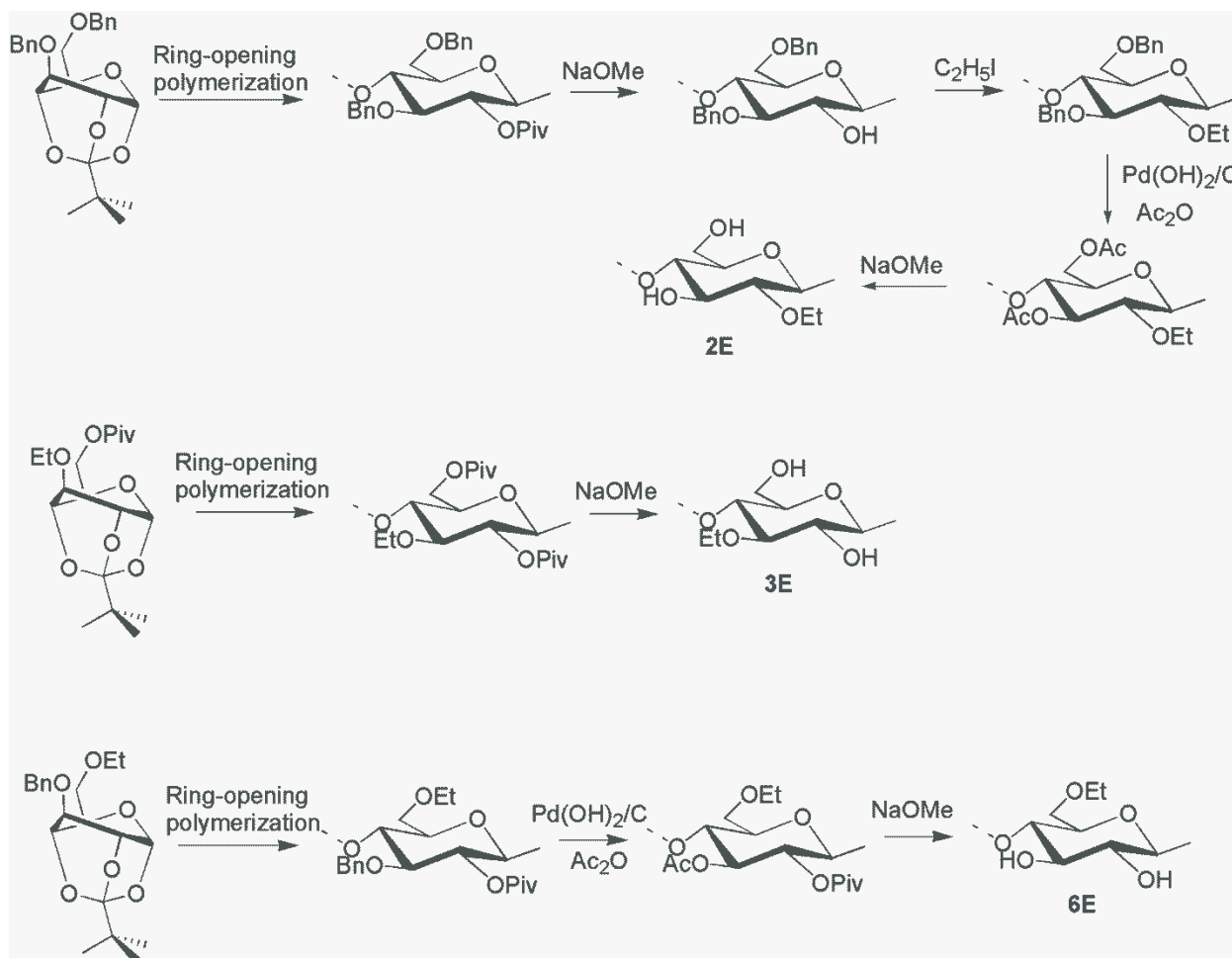
Subsequent nucleophilic replacement reactions were carried out on 6-deoxy-6-bromo-cellulose both heterogeneously and homogeneously.^{93,94} Several regioselectively substituted products were synthesized and their properties were also investigated.^{95, 96}

2.5.6 De novo synthesis of cellulose derivatives

Cellulose was first synthesized in vitro by Kobayashi et al. by polymerizing β -D-cellobiosyl fluoride using cellulase enzyme catalyst; a DP of 22 was achieved.⁹⁷ Subsequently, Nakatsubo and co-workers first chemically synthesized cellulose by cationic ring-opening polymerization of 3,6-di-O-benzyl- α -D-glucopyranose-1,2,4-orthopivalate with a DP as high as 55.⁹⁸ By using these *de novo* synthesis pathways, other regioselective cellulose derivatives can be synthesized. The advantage of *de novo* methods is that the structure of regioselective cellulose derivatives is completely controlled. However, *de novo* synthesis involves much more labor and the product usually has a lower DP than those made from high molecular weight cellulose.

By a method analogous to the polymerization of β -D-cellobiosyl fluoride, 6-O-methyl cellulose was synthesized via 6-O-methyl- β -cellobiosyl fluoride with a DP only 14.⁹⁹ Starting from glucose orthopivalate ester monomers, 2-O-methyl cellulose, 3-O-methyl cellulose, 6-O-methyl cellulose, 2,3-di-O-methyl cellulose, 2,6-di-O-methyl cellulose, and 3,6-di-O-methyl cellulose were synthesized by Karakawa et al. and the DP varied from 22.3 to 41.5.¹⁰⁰ Kamitakahara et al.¹⁰¹ prepared 2,6-di-O-methyl-3-O-acetyl-cellulose via the ring-opening polymerization of 3-O-benzyl-6-O-pivaloyl- α -D-glucopyranose-1,2,4-orthopivalate and a DP of about 43.9 was reported. Regioselectively substituted cellulose ethers with methyl or ethyl as substituents can be synthesized via ring-opening polymerization of 3-O-benzyl-6-O-ethyl/methyl- α -D-glucopyranose-1,2,4-orthopivalate.¹⁰² The products can help to elucidate structure-property relationships. For example, the involvement of a small amount (more than 10%) of ethyl group at C-6 can make 6-O-methyl cellulose soluble in water.¹⁰² Through ring-opening polymerization of glucopyranose orthopivalate derivatives, 2-O-ethyl-cellulose, 3-O-ethyl-cellulose, and

6-O-ethyl-cellulose were all synthesized.¹⁰³ The 2-O-ethyl-cellulose and 3-O-ethyl-cellulose have DP values of only 11 and 49 respectively, while three 6-O-ethyl-cellulose samples were prepared with DP values of 13, 60, and 36. Regioselectively substituted carboxymethyl cellulose including 2-O-carboxymethyl-cellulose, 3-O-carboxymethyl-cellulose, and 6-O-carboxymethyl were synthesized by Nishio et al.¹⁰⁴



Scheme 2.9 *De novo synthesis of regioselectively substituted ethyl cellulose*

2.6 Conclusions

The effect of regiocontrol on cellulose chemistry is still a difficult, mostly unconquered frontier. The advent of cellulose solvents and some synthetic strategies including protective groups, C-6 activation and *de novo* synthesis permits use of milder conditions and more selective reagents. Having all homopolymers related to important cellulose ethers and esters available will allow us to understand the nanostructural dependence of key properties including optical properties, solubility, thermal properties, and colligative properties. It will help us to identify their independent spectral characteristics, and will give us deep insights into the composition of more random commercial derivatives, maximizing the content of advantageous monosaccharides. In all, the regioselective synthesis of cellulose derivatives will contribute to understanding of the relationship between large scale industrial processing and end-use properties based on substitution pattern.

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Chapter 3: Studies on Regioselective Acylation of Cellulose with Bulky Acyl Chlorides

(Adapted from: Xu, D.; Li, B.; Tate, C.; Edgar, K.J. *Cellulose*, 2011, 718, 405-419.)

3.1 Abstract

The regioselective esterification of cellulose by reaction with bulky acyl halides including pivaloyl chloride, adamantoyl chloride and 2,4,6-trimethylbenzoyl chloride was studied. Functionalization conditions to achieve a given degree of substitution (DS) and the resulting pivalate substitution pattern were described in detail. One- and two-dimensional NMR spectroscopy techniques were used to confirm the structure of the esters obtained. We compared the effects on substitution of using different esterifying reagents and solvent systems including DMAc/LiCl, DMSO/TBAF, and ionic liquids (ILs).

3.2 Keywords

regioselective acylation, cellulose pivalate, cellulose adamantate, cellulose 2,4,6-trimethylbenzoate, mesitoyl cellulose, NMR spectroscopy, distribution pattern, regioselective substitution

3.3 Introduction

The regioselective synthesis of polysaccharides is crucial to in-depth understanding of their structure-property relationships. It is remarkable that so little is known even today about how to

accomplish regioselective substitution of these abundant, renewable, and useful natural polymers. Cellulose is the most abundant polysaccharide, its structure is relatively simple (a homopolymer, ($\rightarrow 4\text{-}\beta\text{-D-Glcp-1}\rightarrow$)) and its derivatives are the most commercially important of any polysaccharide. Yet our knowledge of how to make derivatives regioselectively is not adequate to illuminate structure-property relationships even of the simplest derivatives of this most fundamental polysaccharide. From the isolated instances where some progress has been made¹⁻³, we have learned that position of substitution has a powerful influence on properties⁴. For example, the partially regioselective synthesis of cellulose acetate propionates (CAPs) affords improved optical properties vs. standard, presumably randomly substituted CAPs; these properties are quite important for the use of cellulose ester films in flat screen display applications.⁵ Other investigators have shown that regioselectively substituted cellulose acetates have unique characteristics in comparison to presumably randomly substituted commercial materials, with respect to chain conformation, solubility and associative properties and structures in solution.⁶

The difficulty in synthesis of regioselectively substituted polysaccharide derivatives, and in particular cellulose derivatives, is the low reactivity of the hydroxyl groups, requiring relatively harsh derivatization conditions, combined with small reactivity differences between (in the case of cellulose) the 6, 3, and 2-OH groups. The low reactivity is caused by a combination of steric hindrance and the high propensity for intra- and intermolecular hydrogen bonding of cellulose. One can reduce the influence of hydrogen bonding and enhance reactivity by dissolving cellulose and reacting it in solution. This permits the exploitation of the reactivity differences between the hydroxyl groups, for example the lower steric hindrance of the primary OH at C-6, and the greater acidity of the OH group at C-2. Still, the reactivity differences are

sufficiently subtle that the use of sterically demanding protecting groups is generally required in order for substantial selectivity to be achieved.^{7, 8} In the limited literature on regioselective modification of cellulose, bulky ether protecting groups have been most popular. The reaction of a bulky etherification reagent can be quite selective for the C-6 OH, if the bulk is sufficient, using steric hindrance as the selectivity mechanism. For example, *tert*-butyldimethylsilyl (TBDMS) is a useful protective group for cellulose. In homogeneous solution (DMAc/LiCl), both the 6 and 2 positions within the cellulose anhydroglucose unit (AGU) can react with *tert*-butyldimethylchlorosilane, forming the 2,6-di-*O*-TBDMS cellulose ether. On the other hand, in heterogeneous reaction media (NMP/NH₃) at -15 °C, silylation is nearly entirely selective for the 6-OH.^{9, 10} Triphenylmethyl (trityl) has also been shown to be a selective cellulose 6-OH protecting group. Cellulose reacts with trityl selectively at the 6-position to form cellulose 6-mono-*O*-trityl ether in DMSO/N₂O₄, DMAc/LiCl, or DMSO/SO₂/DEA.¹¹ Trityl substituted with 4-methoxy in one of the three phenyl rings is an interesting cellulose selective protecting group¹², because 4-monomethoxytrityl chloride reacts ten times faster with cellulose than does unsubstituted trityl chloride, and the methoxytrityl reacts with high regioselectivity at the 6-OH in DMAc/LiCl within 4 h at 70 °C (DS 1.0).

While bulky ether protecting groups have shown promise for the synthesis of certain regioselectively substituted cellulose derivatives, like all protective groups their utility is limited by their stability. Trityl and trialkylsilyl groups tend to be stable to anionic conditions of the sort used for synthesis of cellulose ethers. On the other hand, they tend not to be stable under aqueous acidic conditions, such as those often encountered during the synthesis and isolation of polysaccharide esters. It would greatly expand the tools available to the polysaccharide synthetic chemist if protective groups with greater acid stability were available and could be used to

regioselectively modify polysaccharides, and especially cellulose. Acyl groups tend to be more stable to acid than to base, and can tolerate mildly acidic conditions. Of course, in the important case where polysaccharide esters are the final desired products, the ability to esterify regioselectively could in some cases obviate the need for protective groups. While a number of publications have addressed the regioselectivity of cellulose acylation in relation to narrow sets of conditions or reagents, no systematic study of the regioselectivity of reaction of cellulose with bulky acylating reagents has been published, to our knowledge.

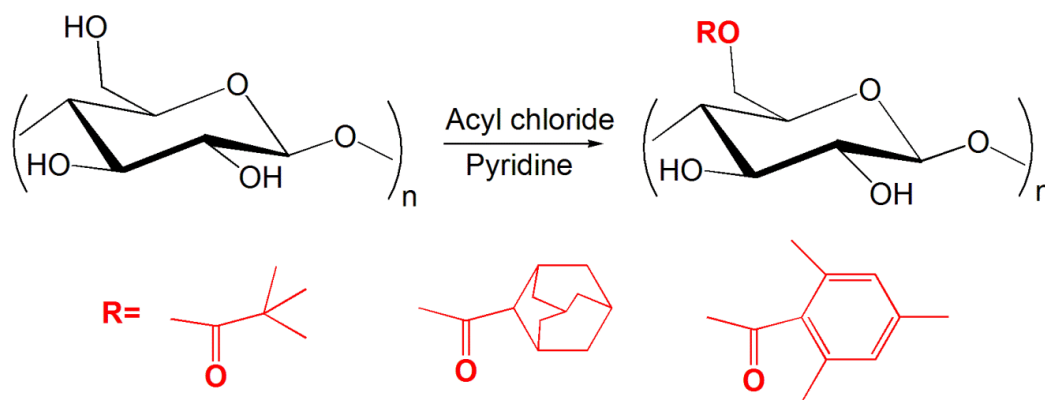
Comprehensive description of attempts at regioselective synthesis of cellulose esters is beyond the scope of this article (see 2001 review by Heinze and Liebert¹³), but we will mention a few relevant attempts. Two approaches to regioselective acylation have been selective hydrolysis of cellulose esters, and acylation of partially, selectively protected cellulose. A recent attempt at regioselective hydrolysis began with acetylation of cellulose in DMAc/LiCl solution (pyridine/Ac₂O) that was partly selective. The partially acetylated cellulose was then reacted in DMSO with 80 wt% aqueous hydrazine monohydrate at 30 °C; this mild hydrazinolysis gave partial regioselectivity, affording CA with DS 0.6 at O-6 exclusively.^{11, 14}

Use of ether protective groups to permit synthesis of cellulose esters regioselectively has progressed further. By acylation of the previously mentioned 6-, 2,6- hexyldimethylsilyl and 6-trityl protected celluloses, cellulose 2,3-diacetate, cellulose 2,3-di-acetate-6-propionate, cellulose 6-acetate-2,3-dipropionate¹⁵, 2,3-dimethylcellulose-6-acetate, 3-methylcellulose-2,3-diacetate, and 3-allylcellulose-2,6-diacetate^{9, 16} were all prepared (after deprotection and other functionalization steps).

Another approach that has had partial success is selective acylation with a labile acyl group, such as formyl¹⁷ or trifluoroacetyl¹⁸. Following acylation at the other OH groups with a

more stable ester group such as acetyl or propionyl, the labile acyl group is then then hydrolytically removed. The strong acids (formic, trifluoroacetic) can cause substantial cellulose degradation, but these methods can afford significant partial regioselectivity, especially in comparison with conventional heterogeneous methods.

Hence we chose to carry out a study designed to test the practical limits of using bulky acylating reagents, in particular acid chlorides, to achieve regioselective modification of cellulose in solution at the less hindered primary hydroxyl group (O-6), using steric hindrance as the mechanism of selectivity. We wished to establish functionalization conditions for given degrees of substitution (DS), and the substitution pattern of the resulting acyl moieties. We felt that such systematic studies would be of significant value to the literature of regioselective cellulose modification. We chose to compare the effects on DS and selectivity of several practical bulky acylating reagents, used in each of three important, modern cellulose solvent systems: DMAc/LiCl, DMSO/TBAF, and the ionic liquid 1-allyl-3-methylimidazolium chloride ([Amim]Cl).



Scheme 3.1 *The regioselective synthesis of cellulose esters*

3.4 Experimental

3.4.1 Materials

Cellulose (Avicel PH-101, DP = 260) was dried under vacuum before use. Pivaloyl chloride, 2,4,6-trimethylbenzoyl chloride, and tetrabutylammonium fluoride trihydrate were purchased from Acros Organics and used without further purification. The adamantoyl chloride was acquired from Aldrich and used as received. N,N-Dimethyl acetamide (DMAc), dimethyl sulfoxide (DMSO), and pyridine were obtained from Fisher and dried over molecular sieve (Type 4 Å, 8-12 mesh beads). [Amim]Cl was synthesized according to a literature method^{19, 20}.

3.4.2 Measurements

FTIR spectra were recorded with a MIDAC M2004 FT-IR spectrophotometer. The ¹H and ¹³C NMR spectra were acquired on a Varian INOVA 400 (400 MHz) spectrometer at room temperature. HMBC spectrum was acquired on a 600 NMR Bruker Avance II spectrometer (600 MHz) at 50 °C. Size exclusion chromatography (SEC) was run in NMP/LiBr on a Waters Alliance model 2690 chromatograph equipped with a Waters 1515 isocratic HPLC pump. Monodispersed polystyrene standards were utilized to construct a universal molecular weight calibration curve. A Viscotek 270 viscosity detector and a Waters 2414 differential refractive index detector were used for the determination of molecular weight.

3.4.3 Dissolution of cellulose in DMAc/LiCl

For a typical procedure²¹, 1 g cellulose (6.173 mmol) was suspended in 37.5 mL DMAc, and the mixture was heated to 150 °C over 26 min. LiCl was added and the mixture was heated to 170 °C over 8 min. Distillate (10 mL) was collected at 170 °C. The reaction mixture was finally cooled down to room temperature and stirred overnight.

3.4.4 Dissolution of cellulose in DMSO/TBAF

For a typical procedure²², 1 g cellulose (6.173 mmol) was dissolved in 66 mL DMSO containing 6.6 g TBAF at room temperature. Within 15 min, a clear solution was formed.

3.4.5 Dissolution of cellulose in [Amim]Cl

For a typical procedure^{20, 23}, 10 g dried [Amim]Cl and 1 g cellulose (6.173 mmol) were placed in a 50 mL flask with a magnetic bar. The mixture was then stirred at 60 °C for 12 h to guarantee a complete dissolution of cellulose and a clear solution was finally obtained.

3.4.6 Esterification of cellulose with pivaloyl chloride in DMAc/LiCl

Cellulose (10 g, 6.173 mmol) was dissolved in DMAc/LiCl by the standard procedure. Pyridine (3 mL, 6 mol/mol AGU) and pivaloyl chloride (0.76 mL, 6.173 mmol, 1 mol/mol AGU) were then added to the solution dropwise. The mixture was allowed to react at 70 °C for 24 h under N₂. The homogeneous mixture was then cooled and added slowly to 200 mL water. The crude product was collected by filtration, then was redissolved in 10 mL ethanol. This solution

was added slowly with rapid stirring to 500 mL water. After filtration and washing with excess water several times, the sample was dried under vacuum at 40°C to yield product **3**.

Yield: 0.93g

Degree of substitution (DS): 0.56 (determined by ^1H NMR spectroscopy after peracetylation).

FT-IR (cm^{-1}): 3492 $\nu(\text{OH})$, 2972, 2961, 2910, 2876 $\nu(\text{C-H})$, 1480, 1459, 1397, 1366 $\nu(\text{C}(\text{CH}_3)_3)$, 1281 $\nu(\text{C-O-C}_{\text{Ester}})$, 1727 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 1.23, 1.10 (CH_3 -pivalate), 1.97 (CH_3 -acetate), 3.51-5.05 (AGU).

^{13}C NMR (in CDCl_3): δ (ppm) = 169.15-170.13 (CO), 100.57 (C^1), 99.28 (C^1), 71.75-73.04 (C^2 , C^3 , C^5), 75.91 (C^4), 62.00 (C^6), 30.67, 29.61 (C-pivalate), 20.43-20.78 (CH_3 -pivalate and acetate).

3.4.7 Esterification of cellulose with pivaloyl chloride in DMSO/TBAF

Cellulose (1.00 g, 6.173 mmol) was dissolved in DMSO/TBAF by the standard procedure. Pyridine (3 mL, 6 mol/mol AGU) and pivaloyl chloride (2.28 mL, 18.519 mmol, 3 mol/mol AGU) were then added dropwise to the solution. The mixture was allowed to react at room temperature for 72 h under N_2 . The homogeneous mixture was then added slowly to 200 mL water. The crude product was collected by filtration, then was redissolved in 10 mL ethanol. This solution was added slowly with rapid stirring to 500 mL water. After filtration and washing with excess water several times, the sample was dried under vacuum at 40 °C to yield product **19**.

Yield: 0.88 g.

DS 0.92 (determined by ^1H NMR spectroscopy after peracetylation).

FT-IR (cm^{-1}): 3492 $\nu(\text{OH})$, 2972, 2961, 2910, 2876 $\nu(\text{C-H})$, 1480, 1459, 1397, 1366 $\nu(\text{C}(\text{CH}_3)_3)$, 1281 $\nu(\text{C-O-C}_{\text{Ester}})$, 1727 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 1.23, 1.10 (CH_3 -pivalate), 1.97 (CH_3 -acetate), 3.51-5.05 (AGU).

3.4.8 Esterification of cellulose with pivaloyl chloride in [Amim]Cl

Cellulose (1.00 g, 6.173 mmol) was dissolved in [Amim]Cl by the standard procedure. Pyridine (3 mL, 6 mol/mol AGU) and pivaloyl chloride (2.28 mL, 18.519 mmol, 3 mol/mol AGU) were then added dropwise to the solution. The mixture was allowed to react at room temperature for 72 h under N_2 . The homogeneous mixture was then added slowly to 200 mL water. The crude product was collected by filtration, then was redissolved in 10 mL ethanol. This solution was added slowly with rapid stirring to 500 mL water. After filtration and washing with excess water several times, the sample was dried under vacuum at 40 $^\circ\text{C}$ to yield product **20**.

Yield: 0.83g

DS 1.39 (determined by ^1H NMR spectroscopy after peracetylation).

FT-IR (cm^{-1}): 3492 $\nu(\text{OH})$, 2972, 2961, 2910, 2876 $\nu(\text{C-H})$, 1480, 1459, 1397, 1366 $\nu(\text{C}(\text{CH}_3)_3)$, 1281 $\nu(\text{C-O-C}_{\text{Ester}})$, 1727 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 1.23, 1.10 (CH_3 -pivalate), 1.97 (CH_3 -acetate), 3.51-5.05 (AGU).

3.4.9 Esterification of cellulose with adamantoyl chloride in DMAc/LiCl

Cellulose (1.00 g, 6.173 mmol) was dissolved in DMAc/LiCl. Pyridine (3 mL, 6 mol/mol AGU) and adamantoyl chloride (1.227 g, 6.173 mmol, 1 mol/mol AGU) were then added to the solution. The mixture was allowed to react at room temperature for 72 h under N_2 . The homogeneous mixture was added slowly to 200 mL water, then the precipitate was collected by

filtration, washed with ethanol (3 x 250 mL), and dried under vacuum at 40°C to yield product **24**.

Yield: 1.35 g

Degree of substitution (DS): 0.46 (determined by ^1H NMR spectroscopy after perpropionylation).

FT-IR (cm^{-1}): 3347 $\nu(\text{OH})$, 2905, 2850, 1452, 1409, 1343, 1323, 1233, 1181 $\nu(\text{adamantate})$, 1281 $\nu(\text{C-O-C}_{\text{Ester}})$, 1690 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 1.70-2.35 (H-adamantane), 2.05 (CH_2 -propionate), 1.05, 1.17 (CH_3 -propionate), 3.49-5.07 (AGU).

^{13}C NMR (in CDCl_3): δ (ppm) = 172.46-173.70 (CO), 100.54 (C^1), 71.54-73.02 (C^2 , C^3 , C^5), 75.75 (C^4), 62.00 (C^{6s}), 61.58 (C^6), 52.10, 36.67 (C- adamantane), 27.12-27.34 (CH_2 -propionate), 8.91-9.05 (CH_3 -propionate).

3.4.10 Esterification of cellulose with 2,4,6-trimethylbenzoyl chloride in DMAc/LiCl

Cellulose (1.00 g, 6.173 mmol) was dissolved in DMAc/LiCl. Pyridine (3 mL, 6 mol/mol AGU) and 2,4,6-trimethylbenzoyl chloride (2.06 mL, 12.346 mmol, 2 mol/mol AGU) were then added to the solution dropwise. The mixture was allowed to react at room temperature for 72h under N_2 . The homogeneous mixture was added slowly to 200 mL water with rapid stirring, then the precipitate was collected by filtration, washed with ethanol (3 x 250 mL), and dried under vacuum at 40°C to yield product **30**.

Yield: 2.11g

Degree of substitution (DS): 0.28 (determined by ^1H NMR spectroscopy after peracetylation).

FT-IR (cm^{-1}): 3460 $\nu(\text{OH})$, 2885 $\nu(\text{C-H})$, 1610, 1427, 1377 $\nu(\text{C-C}_{\text{Aromatic}})$, 1261 $\nu(\text{C-O-C}_{\text{Ester}})$, 1719 $\nu(\text{CO}_{\text{Ester}})$, 855, 776 $\nu(\text{C-H}_{\text{Aromatic}})$.

^1H NMR (in CDCl_3): δ (ppm) =6.80, 6.88 (H-aromatic), 1.86-2.29 (H-trimethyl), 1.97 (CH_3 -acetate), 3.51-5.07 (AGU).

^{13}C NMR (in CDCl_3): δ (ppm) =169.17, 172.35-173.63 (CO), 100.08 (C^1), 71.75-73.34 (C^2 , C^3 , C^5), 75.91 (C^4), 62.29 (C^6), 128.40-130.29, 135.35, 139.74 ($\text{C}_{\text{Aromatic}}$), 19.93-21.14 (Ar-CH_3), 27.19 (CH_2 -propionate), 9.11(CH_3 -propionate).

3.4.11 Peracetylation

Polymer **1** (0.3 g) was dissolved in a mixture of pyridine (5 mL), 4-(dimethylamino)pyridine (20 mg), and acetic anhydride (1.1 mL, 10mol/mol AGU). After stirring for 24h at 80°C, the product was precipitated into water (100 mL), washed several times with water, and dried under vacuum at 40 °C.

3.4.12 Perpropionylation²⁴

Polymer (**2** or **3**, 0.3g) was dissolved in a mixture of pyridine (5 mL), 4-(dimethylamino)pyridine (20 mg), and propionic anhydride (1.2 mL, 10mol/mol AGU). After stirring for 24 h at 80 °C, the product was precipitated from water (100 mL), washed several times with water, and dried under vacuum at 40 °C.

3.5 Results and discussion

3.5.1 General methods

In order to investigate the regioselectivity limits of direct cellulose esterification, we reacted cellulose in solution with several esterifying reagents whose bulk would test those limits; pivaloyl chloride²⁵, adamantoyl chloride^{24, 26} and 2,4,6-trimethylbenzoyl chloride²⁷. All have been used previously for selective acylations. The pivaloyl group has been investigated as a protecting group for alcohols, including carbohydrates.^{25, 28, 29} It is relatively stable against acidic conditions but can be removed in the presence of base. As expected, these previous studies show that pivaloylation is more favored with primary than with secondary alcohols. The adamantoyl moiety as a protective group is sensitive towards base and it also shows some antimicrobial, antibacterial and antitumor activity.²⁶ The Heinze group has successfully synthesized adamantoyl cellulose by reacting cellulose with adamantoyl chloride or adamantane carboxylic acid with TosCl or 1,1'-carbonyldiimidazole (CDI) activation in DMAc/LiCl solution,²⁶ or by reaction with adamantane carboxylic acid in the presence of CDA in DMSO/TBAF²⁴. The adamantate ester products vary in DS depending on stoichiometry and reaction conditions, with a maximum DS of 2.1 attained by Heinze and co-workers. We include adamantate in this study as a relevant comparative example. 2,4,6-Trimethylbenzoyl chloride (mesitoyl chloride) has been used to protect hydroxyl groups during multi-step syntheses either in the presence of pyridine or silver cyanide to form mesitoyl esters^{30, 31}. The mesitoyl group is exceptionally stable even to basic alcoholysis or hydrolysis, and can be used as a protective group in the regioselective synthesis of 6-deoxy-6-fluorolactosides.³²

3.5.2 Cellulose pivalates

Table 3.1 shows the results of cellulose pivaloylation in the three solvent systems examined; first we will discuss results with the well-known and highly useful DMAc/LiCl solvent system^{33, 34}. Cellulose reacted smoothly with pivaloyl chloride (PivCl) in DMAc/LiCl to afford cellulose pivalate, a representative ¹H NMR spectrum of which (after peracetylation) is shown in Figure 3.2. Cellulose pivalate structure is confirmed by its IR spectrum, in particular the pivalate ester carbonyl absorption at 1727 cm⁻¹. The DS value of the pivaloyl unit was determined by the ratio of the integrals of the cellulose backbone protons (integrated from 3.51-5.05 ppm) and the pivaloyl methyl resonances (δ (ppm) =1.10-1.23). The DS value ranged from 0.34 to 2.72 depending on the reaction conditions, including reaction time, temperature, and molar equivalents of pivaloyl chloride per AGU. At a ratio of 1 equiv PivCl per AGU, a low DS of 0.34 was attained with a reaction time of 6 h at 70 °C. If the ratio was increased to 4 mol PivCl per AGU (24 h at 70 °C), the highest DS (2.72) achieved in these studies was reached. Reaction proceeded at room temperature but was much slower; at 1 equiv PivCl per AGU, the reaction time was 3X longer to reach the same DS as at 70 °C. Several series of reactions examined the influence of reaction time at constant equiv PivCl/AGU (Table 3.1; Figure 3.3). Naturally, as PivCl/AGU increased from 1 to 4, product DS increased. For the purposes of evaluating C-6 selectivity it was critical for us to identify conditions for making a product with DS close to 1, and we found that this can be achieved either by treating cellulose with 1.5 equiv/AGU for 6h or with 1.3 or 1.4 equiv/AGU for 24 h. In other words, reaction is rather slow and controllable with PivCl at 70 °C in DMAc/LiCl.

Table 3.1 *Conditions and results of the homogeneous reaction of cellulose with pivaloyl chloride.*

Molar Ratio^a	Time (h)	Temperature (°C)	Solvent	Sample	DS^b_{piv}
1:1.0	6	70	DMAc/LiCl	1	0.34
1:1.0	12	70	DMAc/LiCl	2	0.41
1:1.0	24	70	DMAc/LiCl	3	0.56
1:1.0	72	20	DMAc/LiCl	4	0.57
1:1.3	6	70	DMAc/LiCl	5	0.65
1:1.3	12	70	DMAc/LiCl	6	0.83
1:1.3	24	70	DMAc/LiCl	7	0.91
1:1.4	6	70	DMAc/LiCl	8	0.77
1:1.4	12	70	DMAc/LiCl	9	0.81
1:1.4	24	70	DMAc/LiCl	10	0.93
1:1.5	6	70	DMAc/LiCl	11	1.03
1:1.5	12	70	DMAc/LiCl	12	1.13
1:1.5	24	70	DMAc/LiCl	13	1.38
1:2.0	6	70	DMAc/LiCl	14	1.41
1:2.0	12	70	DMAc/LiCl	15	1.55
1:2.0	24	70	DMAc/LiCl	16	1.68
1:2.0	72	20	DMAc/LiCl	17	1.52
1:3.0	72	20	DMAc/LiCl	18	1.82
1:3.0	72	20	DMSO/TBAF	19	0.92
1:3.0	72	20	[Amim]Cl	20	1.39
1:4.0	6	70	DMAc/LiCl	21	2.25
1:4.0	12	70	DMAc/LiCl	22	2.57
1:4.0	24	70	DMAc/LiCl	23	2.72

^aMol pivaloyl chloride per mol anhydroglucose unit. ^bDegree of substitution of pivaloyl moieties determined after peracetylation by ¹H NMR spectroscopy.

On the critical question of regioselectivity (Table 3.2), ^1H NMR showed pivaloyl methyl resonances around 1.10-1.23 ppm, where the peak at 1.23 ppm is much stronger than that at 1.10 ppm, indicating that reaction occurs both at *O*-6 and *O*-2 but with preference for less-hindered *O*-6 by analogy of assignment of acetate peaks³⁵. The distribution of the pivaloyl group was evaluated by ^1H and ^{13}C NMR on peracetylated samples. The partial DS was calculated based on the ratio of the integrals of the cellulose backbone protons and pivaloyl methyl resonance at *O*-6 (1.23 ppm), *O*-2 (1.10 ppm) and *O*-3 (0.95 ppm). For the sample 11 with DS equal to 1.03, the partial DS at *O*-6 is 0.74 while that at *O*-2 is 0.29, and the DS at *O*-3 is approximately zero because no peak was observed for *O*-3. For the sample 13 with DS = 1.38, the partial DS figures at *O*-6, *O*-2 and *O*-3 are 0.86, 0.45 and 0.07 respectively. For sample 11 with DS 1.03, the only C-6 ^{13}C NMR resonance (Figure 3.4) occurred at δ (ppm) = 62.00, shifted downfield by 1.9 ppm compared to unfunctionalized cellulose, which confirms pivaloyl substitution at *O*-6. There are two peaks showing up for C-1 in CDCl_3 , one at δ (ppm) = 100.57 and the other at δ (ppm) = 99.28, which is due to the influence of a pivaloyl substituent at the adjacent C-2; this confirms some *O*-2 substitution for the DS 1.03 sample. Two- dimensional NMR was used to further confirm the distribution of pivaloyl moiety within the AGU. The 2D-heteronuclear multiple-bond connectivity (HMBC)¹⁵ spectrum of cellulose pivalate after peracetylation (sample 18, DS=1.82) under most NMR experimental conditions showed no clear correlation peak between H-6 and the pivaloyl carbonyl carbon. Apparently for this derivative, the three bond correlation is rather weak. One HMBC spectrum did however show correlation peaks between the pivaloyl carbonyl carbon signal at about δ =178 ppm and both the H-6 proton signals as well as the pivaloyl methyl group. The positions of acetyl groups also were clearly assigned.¹⁵ The acetyl carbonyl carbon peaks at about 170 ppm were correlated in HMBC (see

Figure 3.5) with AGU protons at the sites of acetylation at H-2 and H-3 respectively. In addition, the correlation peaks between acetyl methyl protons and carbonyl carbons were evident. There was no correlation signal for H-6 and the acetyl carbonyl carbons, which indirectly confirmed that O-6 is the favored site for pivaloylation. Overall the evidence is conclusive that the pivaloyl group preferentially reacts in DMAc/LiCl solution with the cellulose primary hydroxyl groups as expected, but that reaction also occurs at the secondary hydroxyl groups; **regioselectivity is never complete.**

Table 3.2 *Partial degree of substitution values of cellulose esters*

Sample	Solvent	Temperature (°C)	Total DS	DS _{O-6}	DS _{O-2/3}
11	DMAc/LiCl	70	1.03	0.74	0.29
13	DMAc/LiCl	70	1.38	0.86	0.52
17	DMAc/LiCl	70	1.52	0.93	0.59
18	DMAc/LiCl	20	1.82	1.00	0.82
19	DMSO/TBAF	20	0.92	0.35	0.57
20	[Amim]Cl	20	1.39	0.83	0.56
24	DMAc/LiCl	20	0.46	0.32	0.14
25	DMAc/LiCl	20	1.25	1.00	0.25
26	DMAc/LiCl	20	1.74	1.00	0.74
28	[Amim]Cl	20	0.89	0.69	0.20
30	DMAc/LiCl	20	0.46	0.40	0.06
33	[Amim]Cl	20	1.21	0.83	0.38

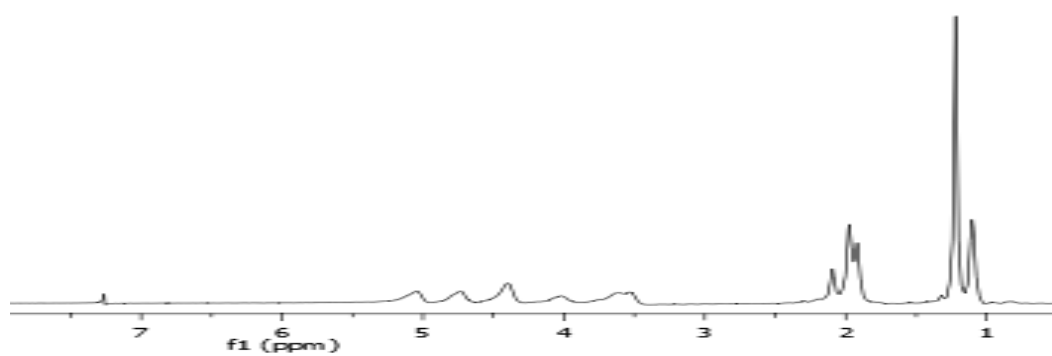


Figure 3.1 ^1H NMR spectrum of cellulose pivalate ($\text{DS}=1.03$) after peracetylation

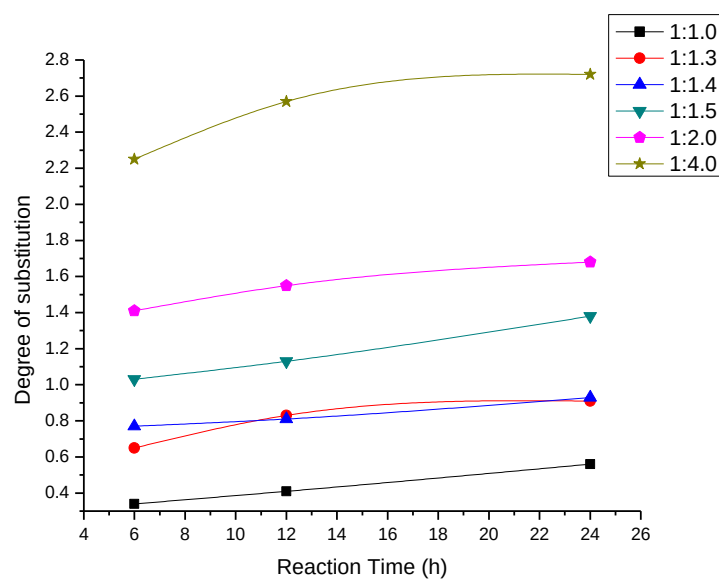


Figure 3.2 Cellulose pivalate DS vs. reaction time for different equiv/AGU pivaloyl chloride ($70\text{ }^{\circ}\text{C}$, DMAc/LiCl)

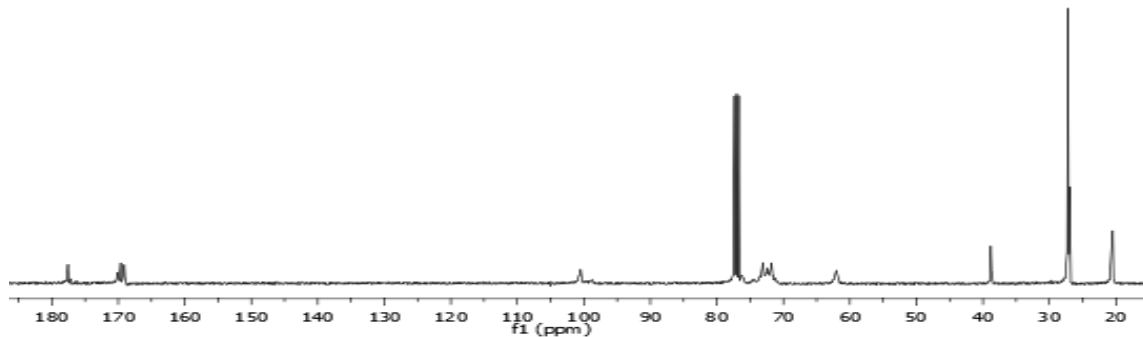


Figure 3.3 ^{13}C NMR spectrum of cellulose pivalate ($\text{DS} = 1.03$) after peracetylation

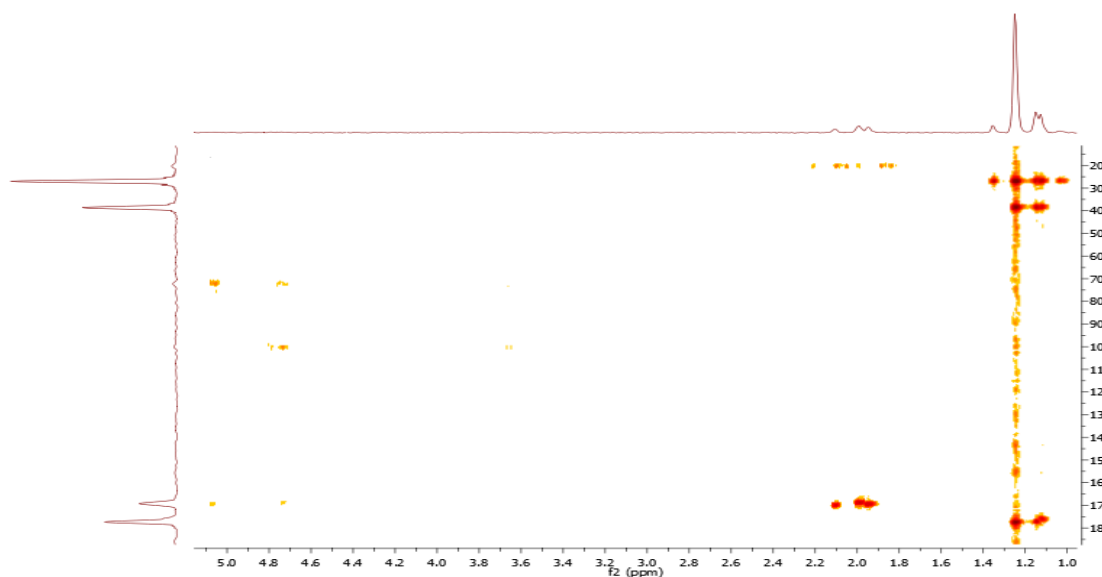


Figure 3.4 HMBC spectrum of cellulose pivalate ($\text{DS} = 1.82$) after peracetylation

We investigated pivaloylation of cellulose in DMSO/TBAF as well (Table 3.1). DMSO/TBAF is a relatively new cellulose solvent that is perhaps the most efficient yet discovered for cellulose dissolution, dissolving even high molecular weight cellulose within roughly 15 min even at room temperature. It suffers however from the drawback that TBAF is a trihydrate, and that the waters of hydration can't be removed by normal solvent drying techniques without significant degradation of the TBA cation. Reaction of cellulose with 3

equiv/AGU PivCl in DMSO/TBAF for 3 days at room temperature afforded cellulose pivalate with DS = 0.92 (sample 19, Table 3.1), or much lower than with the same amount of reagent in DMAc/LiCl (sample 18, Table 3.1). Initially, we thought with the steric bulk of the pivaloyl group, water is a far more effective nucleophile than cellulose and reaction with water of hydration and adventitious water predominates. However, from a very recent result by our group (see **Chapter 6**), we now know that TBAF can deacylate cellulose pivalate and this could be the real reason for the lower DS value in DMSO/TBAF. This problem precluded synthesis of high DS cellulose pivalates in DMSO/TBAF, and made it impractical even to synthesize the DS 1.0 samples needed to evaluate positional selectivity. However, for the DS = 0.92 sample, the partial DS at O-6 is only 0.35 while DS at O-2/3 is 0.57, which means that we did not observe the expected selectivity for the less hindered primary hydroxyl in DMSO/TBAF. This result is in accordance with previous papers^{22, 24} about acetylation in DMSO/TBAF. The fact that the reaction mixture gelled and became heterogeneous after adding pivaloyl chloride may have been a contributor to this surprising result.³⁶

In 2002, the Rogers group showed that ILs can be used to dissolve cellulose²³, and ever since there has been substantial interest in using this new cellulose solvent family for cellulose modifications³⁷⁻³⁹. 1-Allyl-3-methylimidazolium chloride [Amim]Cl is a widely used solvent and has been shown to be one of the more suitable ionic liquid reaction media for homogenous acylation for cellulose²⁰, therefore we chose it for these studies. Reaction of cellulose with 3 equiv/AGU PivCl in AMIMCl at room temperature for 3 days afforded a DS(Piv) of 1.39, which is much higher than that achieved with equal PivCl molar equivalents in DMSO/TBAF, but lower than in DMAc/LiCl. It should be noted that the lower viscosity of the cellulose solution in ILs such as [Amim]Cl makes it practical to run reactions at lower temperatures including room

temperature; at room temperature a solution of cellulose in DMAc/LiCl of equivalent concentration is extremely viscous. ILs are quite hygroscopic and typically contain hundreds to thousands of ppm water even after drying at 60°C under vacuum for 2 days.⁴⁰ For example, for 10 g of [Amim]Cl solution containing a hypothetical 5000 ppm water, there will be 2.78 mmol water present, in comparison with 6.17 mmol cellulose used in our 1 g scale reactions. Thus [Amim]Cl hygroscopicity can have a substantial impact on the DS achieved, particularly when more bulky and less reactive acyl halides such as these are employed. Purification of cellulose pivalate from [Amim]Cl is time-consuming, since complete removal of the IL requires several cycles of product dissolution and reprecipitation from water. We observed very similar regioselectivity from the reaction of PivCl with cellulose in [Amim]Cl ($DS_{O-6}=0.83$, $DS_{O2/3}=0.56$) to that observed in DMAc/LiCl, evaluated using the same NMR techniques.

3.5.3 Cellulose adamantate

Cellulose adamantate was synthesized by reaction of cellulose in DMAc/ LiCl with adamantoyl chloride (AdCl), and the remaining OH groups were perpropionylated for the purpose of facilitating NMR analysis. The DS (Table 3.3) ranged from 0.46 to 1.74 dependent on the equiv AdCl/AGU used. The peaks from ¹H NMR spectra were assigned and the DS and partial DS were calculated in accordance with the previous studies of Heinze and coworkers.²⁴ The adamantate proton resonances overlap the methylene protons of the propionate. In comparison with Heinze's results²⁶, we obtained (Table 3.3) higher DS values which could be explained by the 3X longer reaction time (from 24 h to 72 h) at room temperature. Increasing the molar equiv/AGU of AdCl leads to increasing DS values, consistent with their findings. Little or no adamantate substitution was observed when the reaction was performed in DMSO/TBAF

even with 3 equiv AdCl/AGU. However, the Heinze group²⁴ successfully synthesized cellulose adamantate in this solvent system by using N,N'-carbonyldiimidazole (CDI) and adamantane 1-carboxylic acid. They observed regioselectivity similar to that we observed with cellulose pivaloylation carried out in DMSO/TBAF, that is unexpectedly high selectivity for O-2. The lower reactivity of the adamantoyl chloride, combined with the competing waters of hydration and adventitious water, prevent substantial reaction with cellulose in DMSO/TBAF. The reaction in [Amim]Cl gave a relatively low DS value of 0.89. The distribution of the adamantoyl group resulting from reactions in DMAc/LiCl was previously investigated by the Heinze group²⁶. Adamantoyl substitution preference was for O-6 but regioselectivity was incomplete, in contrast to small molecule organic chemistry. Our results showed the same pattern. For instance, sample **24** (DS=0.46) shows a partial DS at O-6 of 0.32 while combined DS at O-2 and O-3 is approximately 0.14 (resolution incomplete between O-2/3 resonances). Both samples **25** and **26** show complete substitution at O-6, and a partial DS at O-2 and O-3 of 0.28 and 0.74 respectively. Sample **28** (synthesized in [Amim]Cl) had similar functionalization pattern with partial DS of 0.69 at O-6 and 0.20 at O-2/3.

Table 3.3 *Conditions and results of the homogeneous reaction of cellulose with adamantoyl chloride*

Molar Ratio^a	Time (h)	Temperature (°C)	Solvent	Sample	DS^b_{ada}
1:1.0	72	20	DMAc/LiCl	24	0.46
1:2.0	72	20	DMAc/LiCl	25	1.25
1:3.0	72	20	DMAc/LiCl	26	1.74
1:3.0	72	20	DMSO/TBAF	27	0

1:3.0	72	20	[Amim]Cl	28	0.89
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^aMol adamantoyl chloride per mol anhydroglucose unit. ^bDegree of substitution of adamantoyl moieties determined after perpropionylation by ¹H NMR spectroscopy.

3.5.4 Cellulose 2,4,6-trimethylbenzoate (cellulose mesitylate)

The results of cellulose reaction with mesitoyl chloride (MesCl) in DMAc/LiCl are displayed in Table 3.4. Cellulose mesitylate products could be readily identified by infrared and NMR spectroscopies. The FT-IR spectra of the products contained absorption peaks at 855 and 776 cm⁻¹, which is the fingerprint area for the substituted benzene ring⁴¹, and also a carbonyl absorption at 1719 cm⁻¹ for the ester moiety. In addition to identification of characteristic NMR resonances, the ¹H NMR spectrum allowed calculation of the total DS of 2,4,6-trimethylbenzoate from the ratio of the aromatic protons to the backbone protons of the AGU after perpropionylation. 2,4,6-Trimethylbenzoyl chloride seemed to be less reactive than the other two bulky acid chlorides examined, affording maximum DS of only 0.63 (sample 31, Table 3.4) even with 3 equiv MesCl/AGU. This may be a result of both steric hindrance and the electron donating effect of the three methyl substituents on the phenyl ring. In the ¹H NMR spectra of the peracetates (Figure 3.6), the benzylic methyl singlets overlap with the acetate CH₃ group resonances. Partial DS was calculated to investigate the distribution of ester moieties. For a sample with DS of 0.46 (sample 30), partial DS at O-6 is 0.40 while the total at O-2 and O-3 is only 0.06. ¹³C NMR (Figure 3.7) showed the aromatic ring carbons from 128.40 ppm to 139.74 ppm and the benzylic methyls at 19.93-21.14 ppm. Resonances from 71.75 ppm to 75.91 ppm belong to C-2, C-3, C-4 and C-5. The peak for C-6 showed a downfield shift of about 3 ppm

compared with pure cellulose in DMSO-d₆, as a result of the electron-withdrawing mesitoyl group attached to O-6. There is only one signal for C-1 at 100.08 ppm without any other peaks in the same region. The failure to observe a separate C-1 resonance from the C-2 substituted species may be due to low intensity, owing to the low DS at C-2 (DS_{O-2/3} = 0.06). There are multiple acetyl carbonyl resonances at 172.35-173.63. These peaks were assigned by analogy to O-acetyl groups of propionylated cellulose acetate⁴² and HMBC technique (Figure 3.8). The propionyl carbonyl carbon peaks at about 170 ppm correlated with AGU protons at H-6, H-2 and H-3 respectively (DS_{propionyl} = 2.54). The correlation peaks between propionyl methyl and methylene protons and carbonyl carbons showed up clearly. The peaks belonging to aromatic carbons around 130 ppm correlated with trimethyl groups at 2.25 ppm and aromatic protons at 6.88 ppm based on two-bond couplings. Overall it is clear that 2,4,6-trimethylbenzoyl chloride reacts with cellulose at both primary and secondary hydroxyl groups; there is partial but incomplete selectivity for C-6.

Table 3.4 *Conditions and results of the homogeneous reaction of cellulose with 2,4,6-trimethylbenzoyl chloride*

Molar Ratio^a	Time (h)	Temperature (°C)	Solvent	Sample	DS^b_{mes}
1:1.0	72	20	DMAc/LiCl	29	0.28
1:2.0	72	20	DMAc/LiCl	30	0.46
1:3.0	72	20	DMAc/LiCl	31	0.63
1:3.0	72	20	DMSO/TBAF	32	0
1:3.0	72	20	[Amim]Cl	33	1.21

^aMol 2,4,6-trimethylbenzoyl chloride per mol anhydroglucose unit. ^bDegree of substitution of 2,4,6-trimethylbenzoyl moieties determined after perpropionylation by ¹H NMR spectroscopy.

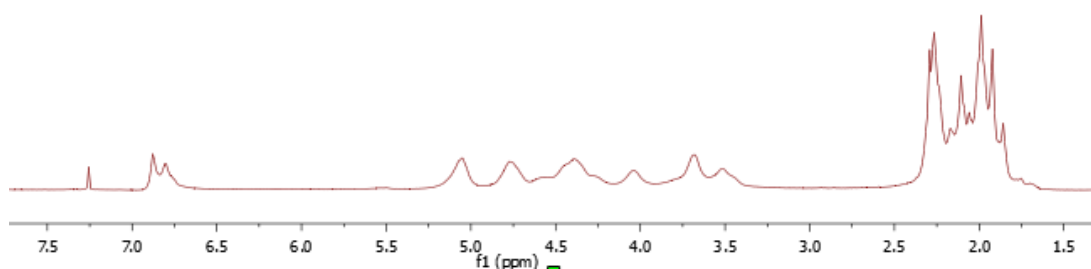


Figure 3.5 ^1H NMR spectrum of cellulose 2,4,6-trimethylbenzoate ($DS=0.46$) after peracetylation

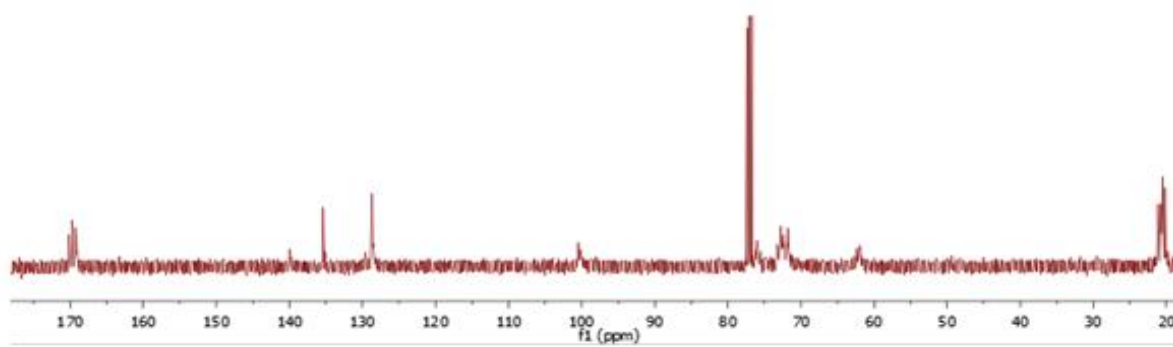


Figure 3.6 ^{13}C NMR spectrum of cellulose 2,4,6-trimethylbenzoate ($DS=0.46$) after peracetylation

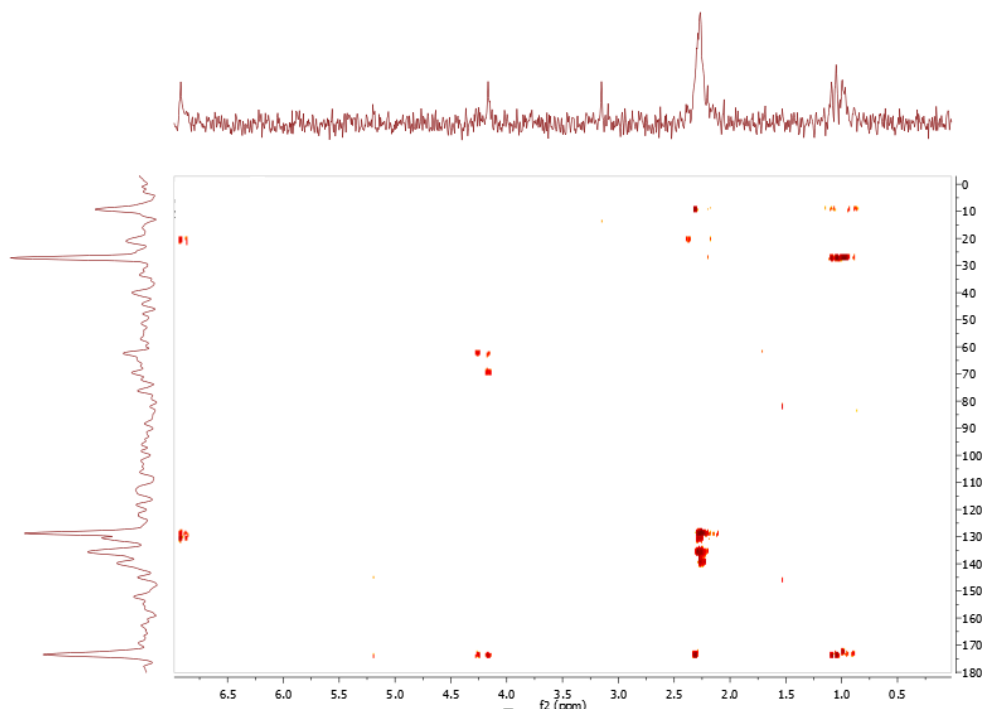


Figure 3.7 HMBC spectrum of cellulose 2,4,6-trimethylbenzoate (DS=0.46) after perpropionylation

Attempts to react cellulose with mesityl chloride in DMSO/TBAF did not afford products with detectable mesityl substitution. Interestingly, we obtained cellulose mesitylates by reaction in the [Amim]Cl IL with DS almost twice as high as that obtained in DMAc/LiCl under equivalent reaction conditions (compare entries 3 and 5 of Table 3.3). Regioselectivity is similar to that seen in DMAc/LiCl, as indicated in the results in Table 3.5. The cellulose mesitylate (sample **33**, DS=1.21) has partial degrees of substitution of 0.83 at *O*-6 and 0.38 at *O*-2/3.

Overall, we find that DMAc/LiCl and [Amim]Cl are more useful than DMSO/TBAF for these cellulose esterifications with bulky acyl chlorides, which may be largely attributable to the different water contents of these three solvents (Fig. 3.9). For example with pivaloyl cellulose, highest DS values were obtained in DMAc/LiCl and somewhat lower DS in [Amim]Cl, but much lower DS values were obtained with DMSO/TBAF as reaction solvent. The same trend

was observed for adamantoyl chloride reactions, with the extreme result of no reaction occurring in DMSO/TBAF. With 2,4,6-trimethylbenzoyl cellulose, it was surprising that DS was higher in [Amim]Cl than under equivalent conditions in DMAc/LiCl, but again we saw no reaction in DMSO/TBAF. To compare solvent effects, we find DMAc/LiCl and ILs are more versatile than DMSO/TBAF for cellulose esterifications which could be explained by the different water content in these three solvents. For pivaloyl cellulose, the highest DS value was obtained in DMAc/LiCl and a lower DS value in ILs. But there is a sharp decreasing of DS value when the reaction was carried out in DMSO/TBAF. The same trend was observed for adamantoyl cellulose except no reaction happened in DMSO/TBAF. With 2,4,6-trimethylbenzoyl cellulose, it was surprising that DS value was higher in [Amim]Cl than under equivalent conditions in DMAc/LiCl, but again we saw no reaction in DMSO/TBAF.

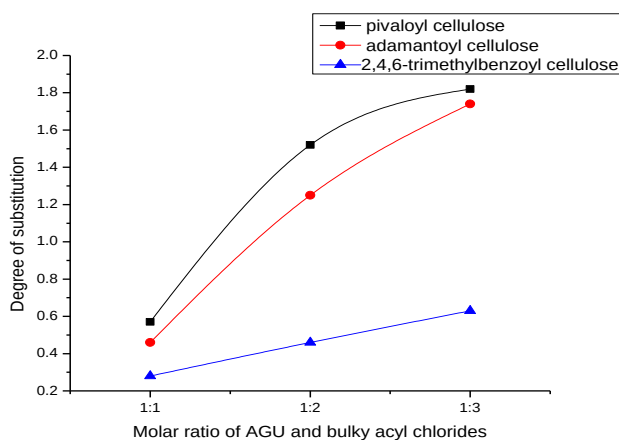


Figure 3.8 *Relative efficiencies of cellulose acylation using the three bulky acid chlorides (all DMAc/LiCl, 20 °C)*

Table 3.5 summarizes the solubilities of the prepared cellulose esters. It is convenient to combine the results from the different reaction solvents, since we observed little dependence of solubility on preparation solvent; only type of substituent and DS mattered within this sample set.

All cellulose pivalate samples are soluble in ethanol and polar aprotic solvents including DMSO, DMF, pyridine and NMP. For cellulose pivalates with DS above 1.5, the polymer is soluble in THF, but still not soluble in CHCl₃ and acetone. Low DS (<0.46) cellulose adamantates were only soluble in DMSO. At and above DS 1.25 we saw THF solubility, while only our DS 1.74 product was soluble in CHCl₃, DMF and NMP, but not in acetone and ethanol. Cellulose mesitylate of DS 0.28 had no apparent solvent solubility, but at and above DS 0.46, the product was soluble in polar aprotic solvents including DMSO, DMF, pyridine and NMP. Cellulose mesitylates of this study never achieved solubility in more moderate polarity solvents such as THF, CHCl₃, acetone and ethanol, even at our highest DS of 1.21 (though we would predict that more heroic efforts could achieve a higher DS, more soluble cellulose mesitylate).

Table 3.5 *Solubility of cellulose esters with different degrees of substitution*

Sample	Ester	DS	THF	CHCl ₃	DMSO	DMF	Acetone	Pyridine	EtOH	NMP
Type										
4	Piv	0.57	- ^a	-	+ ^b	+	-	+	+	+
17	Piv	1.52	+	-	+	+	-	+	+	+
18	Piv	1.82	+	-	+	+	-	+	+	+
19	Piv	0.92	-	-	+	+	-	+	+	+
20	Piv	1.39	+	-	+	+	-	+	+	+
24	Ada	0.46	-	-	+	-	-	-	-	-
25	Ada	1.25	+	-	+	-	-	-	-	-
26	Ada	1.74	+	+	+	+	-	+	-	+
28	Ada	0.89	+	-	+	-	-	-	-	-
29	Mes	0.28	-	-	-	-	-	-	-	-

30	Mes	0.46	-	-	+	+	-	+	-	+
31	Mes	0.63	-	-	+	+	-	+	-	+
33	Mes	1.21	-	-	+	+	-	+	-	+

^a- insoluble; ^b+ soluble; Piv = Pivaloyl; Ada = Adamantoyl; Mes = Mesityl; THF = tetrahydrofuran; DMSO = dimethylsulfoxide; DMF = dimethylformamide; NMP = N-methylpyrrolidinone.

It is always important to consider the impact of polymer molecular weight on properties, and in the case of slow acylation reactions with bulky acyl halides, it is not unreasonable to be concerned about the possibility of severe polysaccharide chain degradation. Analysis of selected bulky cellulose esters by GPC in NMP/LiBr showed that DPs for cellulose pivalates and adamantates are 112 and 146 respectively, which indicates only moderate chain scission during functionalization, since the original DP of our microcrystalline cellulose (Avicel) starting material was 280. However, more extensive scission occurs during cellulose condensation with the less-reactive 2,4,6-trimethylbenzoyl chloride, affording a DP by GPC of 54.

3.6 Conclusions

Cellulose esters with bulky acyl groups including pivalate, adamantate, and 2,4,6-trimethylbenzoate were successfully prepared by reaction of cellulose with the corresponding acid chlorides. DMAc/LiCl was a uniformly suitable and useful solvent system for these reactions, whereas the water content of [Amim]Cl reduced the efficiency of reaction. TBAF can deacylate cellulose esters and this could be the reason why a lower DS value was obtained from DMSO/TBAF. The esterification was in most cases selective for the primary

hydroxyl groups as expected, but even with these bulky acyl groups, acylation at the secondary alcohols O-2 and O-3 was still observed. ***No conditions for truly regiospecific acylation were identified.*** We believe that regioselective substitution strategies that rely only on acylation with bulky activated carboxylic acid derivatives are unlikely to be successful for any practical ester type (perhaps a very large dendritic acyl moiety, for example, would afford more selectivity). Bulky ether groups are more selective for O-6 substitution because the bulky substituent is one atom closer to the cellulose backbone, and because of the smaller bond angle in the sp^3 -hybridized ether bond vs. the sp^2 -hybridized ester bond; clearly the intervening carbonyl in cellulose ester substituents makes a big difference. These studies also show the advantages of the venerable DMAc/LiCl solvent system in comparison with the newer DMSO/TBAF and [Amim]Cl ionic liquid cellulose solvent systems (which admittedly have their own advantages in terms of ease of dissolution and viscosity, respectively). The ability to prepare a truly dry DMAc/LiCl/cellulose reaction mixture, and the difficulty of doing so with ionic liquid based systems, causes differences in efficiency of acylation when less-hindered acyls are used (e.g., acetyl or propionyl). That is to say, more equiv/AGU must be used because of the loss of some reagent to reaction with water. The novel cellulose pivalates and mesitylates of this study have interesting properties and will be further studied in our laboratory. Deacylation of cellulose esters by TBAF will be fully investigated in **Chapter 6**.

3.7 Acknowledgements

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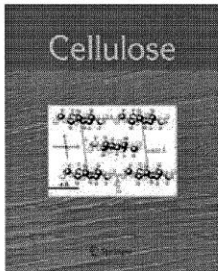
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Chapter 4: Regioselective Synthesis of Cellulose Ester

Homopolymers

(Adapted from: Xu, D.; Voiges, K.; Elder, T.; Mischnick, P.; Edgar, K. J., *Biomacromolecules*, 2012, 13(7), 2195-2201.)

4.1 Abstract

Regioselective synthesis of cellulose esters is extremely difficult, due to the small reactivity differences between cellulose hydroxyl groups, small differences in steric demand between acyl moieties of interest, and the difficulty of attaching and detaching many protecting groups in the presence of cellulose ester moieties without removing the ester groups. Yet the synthesis of homopolymers of particular regioselectively substituted anhydroglucose esters is of critical importance, in order to allow us to determine the analytical characteristics of such homopolymers, their structure property relationships, and to obtain guidance that may ultimately enable identification and synthesis of cellulose derivatives with superior properties for various applications. We report here a new, general synthesis of both cellulose-2,6-*O*-diesters and cellulose-2,6-*A-O-3-B-O*-triesters with a high degree of regioselectivity, employing 3-*O*-allylcellulose as a key protected precursor. 3-*O*-Allylcellulose was identified as a protected intermediate with high potential for the synthesis of these derivatives with the aid of molecular modeling of corresponding glucose analogs. We report also the first analytical and structure property studies of these regioselectively substituted cellulose esters.

4.2 Keywords

regioselective, acylation, 3-*O*-benzyl cellulose, 3-*O*-allyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, NMR spectroscopy, distribution pattern

4.3 Introduction

Despite the rich literature and widespread utility of the esters of renewable cellulose with carboxylic acids¹, their regioselective synthesis is still a great challenge. Because of the extensive hydrogen and hydrophobic bonding, crystallinity, and resulting poor solubility of cellulose, it has been necessary to use forcing conditions (strong catalysts like H₂SO₄ or HClO₄, high temperatures, and/or long reaction times) to achieve high levels of substitution. Only with the discovery in recent decades of powerful solvent systems that can dissolve cellulose, especially LiCl/N,N-dimethylacetamide (DMAc)^{2, 3}, tetrabutylammonium fluoride (TBAF)/dimethylsulfoxide (DMSO)^{4, 5}, and several ionic liquid solvents⁶, has it been possible to use mild reaction conditions and more selective reagents, enabling the development of a few successful strategies for regioselective etherification and esterification of cellulose⁷. In particular, selective substitution at the primary OH in position 6 has become possible, using sterically bulky etherification reagents like triphenylmethyl (trityl) chloride⁸, and *tert*-butyldimethylsilyl chloride (TBDMS Cl)⁹. Once the 6-OH has been protected as the ether, the secondary hydroxyl groups can be acylated and then the 6-*O*-protective ether group (trityl or methoxytrityl) can be deprotected using mild aqueous acid, to afford cellulose-2,3-*O*-diesters¹⁰. In a complementary strategy, reaction of the 6-*O*-ether with a second, orthogonal protecting group (e.g., allyl) at the secondary alcohols, followed by deprotection at *O*-6, substitution at *O*-6, and then deprotection at *O*-2 and

O-3 has been used to prepare regioselectively substituted cellulose-6-O-ethers¹¹. It is illustrative of the difficulties involved in regiospecific cellulose ester synthesis (in this case, presumably the issue of selective protecting group removal in the presence of the ester) that there appear to be no reports of using this strategy to prepare cellulose-6-O-esters.

From these few examples, we know that position of substitution has a powerful influence on key properties of cellulose esters including solubility^{12, 13}, crystallinity¹⁴, optical retardation¹⁵, and thermal properties¹⁶. Very recently, Xu and Edgar reported that direct synthesis of cellulose esters with a high proportion of ester substituents at O-6 is possible by reaction of high DS cellulose esters (e.g., cellulose triacetate, cellulose tripropionate, or cellulose acetate of DS 2.5) with tetrabutylammonium fluoride in DMSO or THF⁵. Fluoride-catalyzed deacylation occurs with remarkable facility and even more remarkable selectivity, with a high degree of deacylation at the more hindered secondary alcohol esters (2-O-acyl and 3-O-acyl), and little or no deacylation at the 6-O-acyl group under the proper reaction conditions. It would be extremely valuable to develop synthetic routes to the homopolymers corresponding, for example, to the 6 possible monosaccharides that comprise a cellulose ester with only one substituent type (2-, 3-, and 6-monoesters; 2,3-, 2,6-, and 3,6-diester; the two other possible monosaccharides (unsubstituted and fully substituted) are synthetically trivial). For example, one such key target homopolymer would be poly($\rightarrow$ 4- β -D-2,6-di-O-acetyl-glucopyranose-1 $\rightarrow$). By synthesizing these homopolymers, we can generate critical understanding of structure property relationships in cellulose (and indeed in polysaccharide) esters that is currently simply not accessible. Of equal importance, we can create homopolymer standards that will provide the analytical data set necessary to help interpret spectra of random and other cellulose ester copolymers generated by non-regioselective synthetic methods. We report here the first regioselective synthesis of

cellulose-2,6-*O*-diesters and of regioselectively substituted cellulose triesters with one ester type at O-2 and O-6, and a second type at O-3.

4.4 Experimental

4.4.1 Materials

Cellulose (Avicel PH-101, DP 280) was vacuum-dried before use. Hexyldimethylsilyl chloride, imidazole and TBAF•3H₂O were purchased from Acros Organics; NaH, allyl chloride, acetic anhydride, propionic anhydride and pyridine were purchased from Fisher; all reagents were used without further purification. Commercial cellulose esters were from Eastman Chemical Company.

4.4.2 Measurements

FTIR spectra were recorded with a Thermo Electron Nicolet 8700 FT-IR spectrophotometer. ¹H and ¹³C NMR spectra were acquired on a Varian INOVA 400 (400MHz) spectrometer at room temperature or 50°C. DS values were calculated from the integration ratios of acetyl or propionyl proton resonances to those of the backbone hydrogens. HMBC and COSY spectra were acquired on a 600 NMR Bruker Avance II spectrometer (600MHz) at 50°C. Differential scanning calorimetry (DSC) was conducted using a TA Instruments DSC Q2000. DSC data were obtained from 35°C to 200°C at heating/cooling rates of 20°C /min under nitrogen. Glass transition temperatures were determined as the midpoint of heat capacity change in the glass transition region during the second heating cycle. Molecular weights of the

synthesized polymers were determined using size exclusion chromatography (SEC) with refractive index (RI) and viscometer DP detectors vs. polystyrene standards. SEC measurements were performed at 30°C in CHCl₃ (compounds **9**, **11**, CTP, CA-398-30 and CAP-504-0.2) or NMP/LiBr (CA-435-75S and CA-320S), with a sample concentration 5.00 mg/mL at a flow rate of 1.00 mL/min on a Waters Alliance model 2690 chromatograph. The degree of substitution (DS) values were determined by means of ¹H NMR spectroscopy, according to the following equations respectively.

Peracetylated 3-*O*-benzyl cellulose:

$$DS_{\text{benzyl}} = 7I_{\text{phenyl}}/5I_{\text{Backbone}}$$

$$DS_{\text{Acetate}} = 7I_{\text{Acetate-CH}_3}/3I_{\text{Backbone}}$$

Peracylated 3-*O*-allyl cellulose:

$$DS_{\text{Acetate}} = 22I_{\text{Acetate-CH}_3}/(I_{\text{Backbone}} + 5I_{\text{Acetate-CH}_3})$$

$$DS_{\text{Propionate}} = 22I_{\text{Propionate-CH}_3}/(I_{\text{Backbone}} + 5I_{\text{Propionate-CH}_3})$$

$$DS_{\text{Allyl}} = 3 - DS_{\text{Acetate}} \text{ or } 3 - DS_{\text{Propionate}}$$

4.4.3 3-*O*-Benzyl-2,6-di-*O*-thexyldimethylsilyl cellulose

2,6-Di-*O*-thexyldimethylsilyl cellulose (10 g, 22.38 mmol) was suspended in 100 mL dry THF. To the solution, NaH (5.37 g, 228.8 mmol, 10 mol/mol modified AGU) was added. Then benzyl bromide (26.6 mL, 228.8 mmol, 10 mol/mol modified AGU) was added dropwise with vigorous stirring. The mixture was stirred at room temperature for 1 day and at 50 °C for another 3 days. The reaction was quenched by addition of isopropanol and poured into 500 mL

phosphate buffer solution (pH = 7.0). The precipitate was collected, washed with 500 mL ethanol and dried under vacuum at 40 °C.

Yield: 80% (based on 2,6-di-*O*-thexyldimethylsilyl cellulose).

Degree of substitution (DS): $DS_{\text{benzyl}} = 0.98$ (determined by ^1H NMR spectroscopy).

FT-IR (cm^{-1}): 2866, 2954 $\nu(\text{C-H})$, 1361, 1463 $\nu(\text{C-C}_{\text{Aromatic}})$, 1251 $\nu(\text{C-Si})$, 828, 776 $\nu(\text{C-H}_{\text{Aromatic}})$.

^1H NMR (in CDCl_3): δ (ppm) = 0.11-1.61 (thexyldimethylsilyl group), 4.97 ($\text{CH}_2\text{-C}_6\text{H}_5$), 7.27, 7.41 (H-aromatic), 3.28-4.73 (AGU).

4.4.4 3-*O*-Benzyl cellulose

3-*O*-Benzyl-2,6-di-*O*-thexyldimethylsilyl cellulose (20 g, 44.8 mmol) was dissolved in 100 mL DMSO and treated with TBAF (56.6 g, 179.4 mmol, 4 mol/mol modified AGU). The mixture was stirred at 50 °C for 3 days. The mixture was poured into 1000 mL water, then the product was collected by filtration, washed thoroughly with water, and dried under vacuum at 40 °C. The crude product (5.0 g) was suspended in 100 mL DMAc and 10 g LiCl. TBAF (10 g) was then added. The temperature was raised to 50 °C and the solution was kept at this temperature for another 3 days under stirring. The mixture was added dropwise into 500 mL ethanol. The product was isolated by filtration, then the precipitate was washed with ethanol and dried under vacuum at 40 °C.

Yield: 40% (based on 3-*O*-benzyl-2,6-di-*O*-thexyldimethylsilyl-cellulose).

Degree of substitution (DS): $DS_{\text{benzyl}} = 0.98$ (determined by ^1H NMR spectroscopy).

FT-IR (cm^{-1}): 3458 $\nu(\text{OH})$, 2863, 2958 $\nu(\text{C-H})$, 1371, 1450 $\nu(\text{C-C}_{\text{Aromatic}})$, 820, 741 $\nu(\text{C-H}_{\text{Aromatic}})$.

^1H NMR (in DMSO- d_6): δ (ppm) = 5.51 ($\text{CH}_2\text{-C}_6\text{H}_5$), 7.21-7.43 (H-aromatic), 3.17-4.86 (AGU).

4.4.5 Attempted debenzylation of peracetylated 3-*O*-benzyl cellulose

3-*O*-Benzyl cellulose (0.2 g, 0.79 mmol) was dissolved in 5 mL pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL acetic anhydride. After stirring for 24h at 80°C, the product was precipitated from 100 mL water, then washed several times with water. The crude product was collected by filtration, then was redissolved in 5 mL CHCl_3 . This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C to yield peracetylated 3-*O*-benzyl cellulose. To a solution of 50 mg peracetylated 3-*O*-benzyl cellulose in 5 mL THF/acetic acid (1:1, v/v), 200 mg palladium hydroxide over carbon was added. The reaction mixture was kept under a hydrogen pressure of 450 kPa at 50 °C. After 1 day, the solution was filtered through Celite and concentrated to dryness. The solid product was washed with excess water and dried under vacuum at 40 °C.

Yield: 80% (based on 3-*O*-benzyl-2,6-di-*O*-acetyl-cellulose).

FT-IR (cm^{-1}): 3460 $\nu(\text{OH})$, 2868, 2954 $\nu(\text{C-H})$, 1375, 1453 $\nu(\text{C-C}_{\text{Aromatic}})$, 824, 776 $\nu(\text{CH}_{\text{Aromatic}})$.

Degree of substitution (DS): $\text{DS}_{\text{acetate}} = 1.98$, $\text{DS}_{\text{benzyl}} = 0.46$ (determined by ^1H NMR spectroscopy).

^1H NMR (in CDCl_3): δ (ppm) = 7.22-7.42 (H-aromatic), 5.36, 5.53 ($\text{CH}_2\text{-C}_6\text{H}_5$), 3.01-4.87 (AGU), 1.87, 1.77 ($\text{CH}_3\text{-acetate}$).

4.4.6 3-*O*-Allyl-2,6-di-*O*-acyl-cellulose

3-*O*-Allyl cellulose (**5**, 200 mg, 0.99 mmol) was dissolved in 5 mL pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL acetic or propionic anhydride. After stirring for 24h at 80°C, the product was precipitated into 100 mL water, collected by filtration and washed several times with water. The crude product was redissolved in 5 mL CHCl₃. This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C to yield product **6** (2,6-di-*O*-acetate) or **7** (2,6-di-*O*-propionate).

Characterization data for 3-O-allyl-2,6-di-O-acetyl-cellulose:

FT-IR (cm⁻¹): 3088 ν(=C-H), 2884 ν(C-H), 1635 ν(C=C), 1220 ν(C-O-C_{Ester}), 1739 ν(CO_{Ester}).

DS: DS_{acetate} = 1.97, DS_{allyl} = 1.03 (determined by ¹H NMR spectroscopy).

¹H NMR (in CDCl₃): δ (ppm) 2.03 (CH₃-acetate), 5.04-5.73 (H-allyl), 3.38-4.78 (AGU).

Characterization data for 3-O-allyl-2,6-di-O-propionyl-cellulose:

FT-IR (cm⁻¹): 3089 ν(=C-H), 2888 ν(C-H), 1636 ν(C=C), 1271 ν(C-O-C_{Ester}), 1736 ν(CO_{Ester}).

DS: DS_{propionate} = 1.96, DS_{allyl} = 1.04 (determined by ¹H NMR spectroscopy).

¹H NMR (in CDCl₃): δ (ppm) 2.31 (CH₂-propionate), 1.11 (CH₃-propionate), 5.01-5.68 (H-allyl), 3.34-4.79 (AGU).

4.4.7 2,6-Di-*O*-acyl-cellulose

3-*O*-Allyl-2,6-di-*O*-acyl-cellulose (**6** or **7**, 120 mg) was dissolved in 8 mL chloroform and 5 mL methanol and to this solution was added 10 mg PdCl₂. After stirring at room temperature

for 24h, the mixture was filtered through Celite and evaporated to afford the 2,6-di-*O*-acyl-cellulose product **8** (2,6-di-*O*-acetyl-cellulose) or **10** (2,6-di-*O*-propionyl-cellulose).

Characterization data for 2,6-di-O-acetyl-cellulose:

DS: DS_{acetate} = 1.97 (determined by ¹H NMR spectroscopy).

FT-IR (cm⁻¹): 3405 ν(OH), 2885 ν(C-H), 1271 ν(C-O-C_{Ester}), 1730 ν(CO_{Ester}).

¹H NMR (in pyridine-*d*₅ with 1 drop trifluoroacetic acid (TFA) added to shift water peak out of region of interest): δ (ppm) 5.66 (H-3), 5.43 (H-2), 5.31 (H-1), 5.05 (H-6), 4.81 (H-6'), 4.51 (H-4), 4.17 (H-5), 2.22, 2.09 (CH₃-acetate).

Characterization data for 2,6-di-O-propionyl-cellulose:

DS: DS_{propionate} = 1.96 (determined by ¹H NMR spectroscopy).

FT-IR (cm⁻¹): 3453 ν(OH), 2958 ν(C-H), 1275 ν(C-O-C_{Ester}), 1726 ν(CO_{Ester}).

¹H NMR (in pyridine-*d*₅ with 1 drop TFA added): δ (ppm) 5.60 (H-3), 5.32 (H-2), 5.00 (H-1), 4.71 (H-6), 4.39 (H-6'), 4.05 (H-4), 3.91 (H-5), 2.44 (CH₂-propionate), 1.15 (CH₃- propionate).

4.4.8 2,6-Di-*O*-acyl-3-*O*-acyl'-cellulose

2,6-Di-*O*-acyl-cellulose (100 mg) was dissolved in 5 mL pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL acetic (**11**) or propionic (**9**) anhydride. After stirring for 24h at 80 °C, the product was precipitated into 100 mL water, collected by filtration, then washed several times with water. The crude product was redissolved in 5 mL CHCl₃. This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing

with excess ethanol several times, the sample was dried under vacuum at 40°C to yield triester products **11** or **9**.

Characterization data for 2,6-di-O-acetyl-3-O-propionyl-cellulose, 9:

FT-IR (cm⁻¹): 2945 ν (C-H), 1275 ν (C-O-C_{Ester}), 1756 ν (CO_{Ester}).

¹H NMR (in CDCl₃): δ (ppm) =5.03 (H-3), 4.71 (H-2), 4.38 (H-1), 4.31 (H-6), 3.99 (H-6'), 3.64 (H-4), 3.47 (H-5), 2.15 (CH₂-propionate), 1.00 (CH₃- propionate), 2.04, 1.91 (CH₃-acetate).

¹³C NMR (in CDCl₃): δ (ppm) =168.95, 170.15, 173.10 (C=O), 100.31 (C-1), 72.11 (C-2), 75.95 (C-4), 72.27 (C-3), 75.75 (C-5), 62.19 (C-6), 20.61, 20.41 (CH₃ - acetate), 27.09 (CH₂ - propionate), 8.90 (CH₃ - propionate).

Characterization data for 3-O-acetyl-2,6-di-O-propionyl-cellulose, 11:

FT-IR (cm⁻¹): 2940 ν (C-H), 1275 ν (C-O-C_{Ester}), 1750 ν (CO_{Ester}).

¹H NMR (in CDCl₃): δ (ppm) =5.05 (H-3), 4.80 (H-2), 4.38 (H-1), 4.38 (H-6), 4.04 (H-6'), 3.69 (H-4), 3.49 (H-5), 2.37, 2.24 (CH₂ -propionate), 1.16, 1.06 (CH₃ - propionate), 1.90 (CH₃ -acetate).

¹³C NMR (in CDCl₃): δ (ppm) =169.38, 172.67, 173.58 (C=O), 100.36 (C-1), 71.77 (C-2), 76.08 (C-4), 72.64 (C-3), 73.31 (C-5), 62.12 (C-6), 20.36 (CH₃ - acetate), 27.31, 27.26 (CH₂-propionate), 8.95, 8.80 (CH₃- propionate).

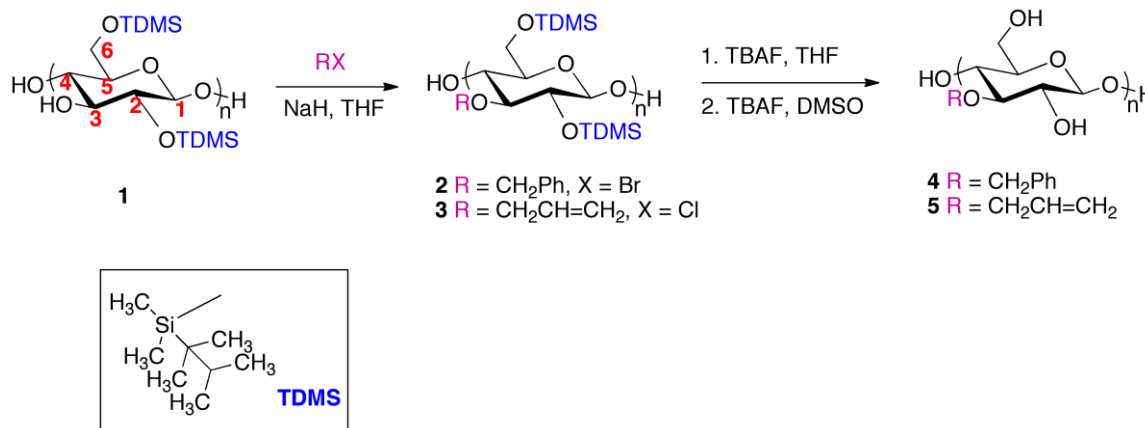
4.4.9 Computational details

Density functional calculations were performed with geometry optimization at the M05-2X/6-611+G(d,p) level with an integration grid of 70590 as implemented in

Gaussian09.Revision B.01^[TE1]. Frequency calculations were performed to verify the identification of an energetic minimum.

4.5 Results and Discussion

Initially we intended to synthesize the cellulose-2,6-O-esters by starting with 3-O-benzylcellulose, available by benzylation and subsequent desilylation of Klemm's bis(2,6-O-TDMS)cellulose¹⁷ (Scheme 4.1).



Scheme 4.1 *Synthesis of 3-protected cellulose ethers*

Preparation of 3-*O*-benzylcellulose went smoothly, and subsequent acylation with acetic anhydride afforded the desired 3-*O*-benzylcellulose-2,6-di-*O*-acetate (or, in the case of propionic anhydride, the 2,6-di-*O*-propionate); 80°C, 24h, 54 equiv acetic anhydride in pyridine/4-dimethylaminopyridine. Debenzylation was carried out by means of catalytic hydrogenation. However, hydrogenation of 3-*O*-benzylcellulose-2,6-di-*O*-acetate proved surprisingly difficult. Hydrogenation using Pd/C at atmospheric H₂ pressure and ambient

temperature in THF and acetic acid (1:1 volume ratio) for one day gave unexpected results. ^1H NMR analysis of the product showed almost no debenzylation (DS (benzyl) = 0.98). Hydrogenation using the stronger catalyst $\text{Pd}(\text{OH})_2/\text{C}$ at room temperature and atmospheric pressure of H_2 (24 h) still gave incomplete debenzylation (DS (benzyl) 0.56). Harsh conditions were then applied. Using $\text{Pd}(\text{OH})_2/\text{C}$ at 80 °C under 450 kPa H_2 for 36h afforded a black powder with no solubility in common organic solvents, indicating profound degradation of the cellulose chain (at the same pressure and 50 °C, only partial debenzylation again was observed; DS (benzyl) 0.46). The unexpectedly poor reactivity of 3-*O*-benzylcellulose was further revealed when we attempted to react it with silyl chlorides. Since Klemm and co-workers have shown that unsubstituted cellulose reacts with one equivalent of TDMS chloride to afford greater than 95% selective O-6 etherification, we had reasoned that the added bulky benzyl ether substituent at O-3 of **4** should virtually eliminate any O-2 substitution, leading to orthogonally protected 3-*O*-benzyl-6-*O*-silylcellulose ethers with very high regioselectivity. These protected cellulose ethers could be gateway intermediates to a variety of cellulose ether and ester homopolymers of regiospecifically substituted glucosyl units. In the event, we found that 3-*O*-benzylcellulose was quite resistant to silylation under standard or even forcing conditions. For example, reaction with 4 equiv TDMSCl at 100 °C (24 h, DMAc solvent, imidazole catalyst) gave a product with DS (TDMS) only 0.04! Similar results were obtained even when using the less bulky trimethylsilyl chloride.

At a loss to explain the poor reactivity of 3-*O*-benzylcellulose and its 2,6-di-*O*-acetate derivative, we carried out computational studies using density functional calculations on appropriate model compounds; in particular methyl 4-*O*-methyl- β -glucopyranoside (**M1**), and analogues of **4** (methyl 3-*O*-allyl-4-*O*-methyl- β -glucopyranoside, **M2**) and **5**

(methyl 3-*O*-benzyl-4-*O*-methyl- β -glucopyranoside, **M3**). Plots of the highest occupied molecular orbital clearly indicate the presence of substantial orbital density at the C-6 position for methyl 4-*O*-methyl- β -glucopyranoside and the 3-*O*-allylcellulose model **5** (Figures 4.1 and 4.2), which is completely absent from the 3-*O*-benzylcellulose model **4** (Figure 4.3)¹⁸.

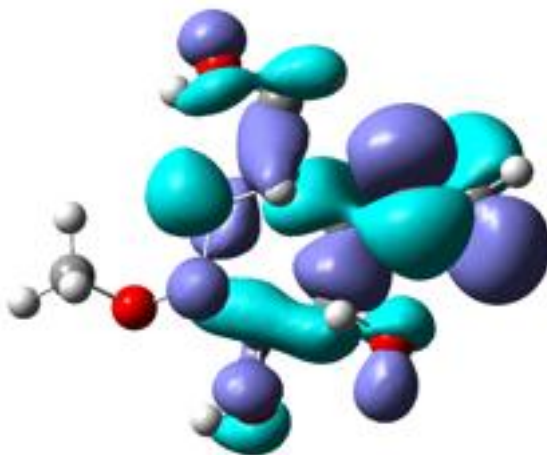


Figure 4.1 HOMO plot of methyl 4-*O*-methyl- β -D-glucopyranoside, M1

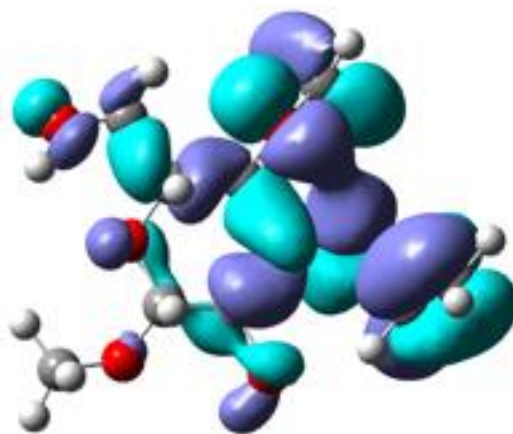


Figure 4.2 HOMO plot of methyl 3-*O*-allyl-4-*O*-methyl- β -D-glucopyranoside, M2

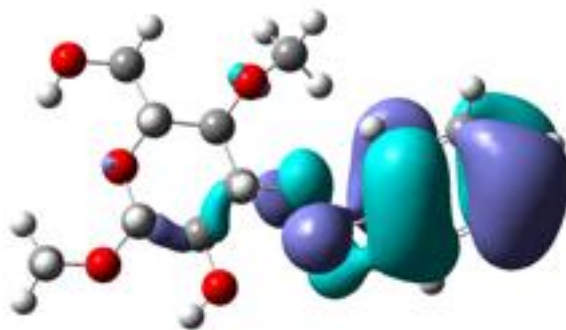
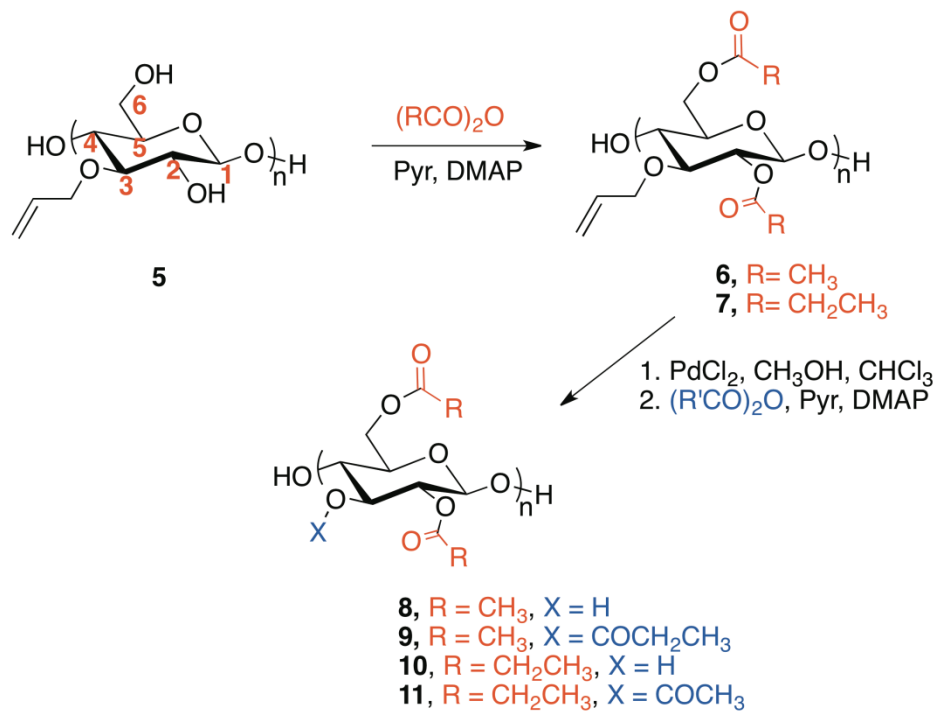


Figure 4.3 HOMO plot of methyl 3-O-benzyl-4-O-methyl- β -D-glucopyranoside M3

These computational results clearly predicted higher nucleophilicity for the hydroxyl groups of 3-O-allylcellulose than those of 3-O-benzylcellulose. In addition, previous investigators had shown¹⁹ that hydrogenolysis of benzyl groups is retarded by electron withdrawing substituents in the benzene ring, and enhanced by electron-donating substituents. They attributed this effect to the partial positive charge on the benzylic carbon during the rate-determining step of hydrogenolysis. If low electron density at the benzylic carbon (perhaps in combination with steric issues created by the bulk of the cellulose chain and the heterogeneous nature of Pd-catalyzed hydrogenolysis²⁰) were the cause of the low reactivity observed, perhaps homogeneously-catalyzed removal of the allyl group would be more facile.

We tested these predictions by synthesizing 3-O-allylcellulose by the methods of Heinze et al.⁹ (Scheme 4.1), then reacting the protected intermediate with carboxylic anhydrides (Scheme 4.2). Complete desilylation of **3** required sequential treatments with TBAF in THF and then in DMSO, but was successful after this two-step process. Subsequent acylation was smooth and complete, affording for example 3-O-allylcellulose-2,6-di-O-acetate **6** and the corresponding 2,6-di-O-propionate **7** that were completely and regioselectively substituted as indicated by proton NMR spectroscopy. *The key deallylation step proceeded readily under mild conditions* (room temperature, 24h, PdCl₂ in CHCl₃/MeOH) to afford cellulose-2,6-O-diacetate **8** and

cellulose-2,6-di-*O*-propionate **10**. By ^1H NMR the DS in each case was 2.0, confirming the chemoselectivity of the Pd-catalyzed deallylation (due at least in part to the mild conditions that in this case were effective in allyl removal; we have observed in related systems that $\text{PdCl}_2/\text{MeOH}/\text{CHCl}_3$ treatment can result in partial deacylation of other cellulose esters).



Scheme 4.2 *Synthesis of cellulose-2,6-*O*-diesters*

This methodology was very useful, as shown above, for the regioselective synthesis of cellulose-2,6-di-*O*-esters, for example cellulose-2,6-di-*O*-acetate and cellulose-2,6-di-*O*-propionate, both of which are homopolymers of monosaccharides that are components of important commercial cellulose esters including cellulose diacetate and cellulose acetate propionate. It was also straightforward to convert these cellulose-2,6-di-*O*-esters into cellulose triester homopolymers in which one type of acyl group was attached to O-2 and O-6,

and a second type of acyl group was attached to O-3. Acylation of cellulose-2,6-di-*O*-acetate with propionic anhydride (pyridine, DMAP, 80°C, 24 h) cleanly afforded the desired cellulose-2,6-di-*O*-acetate-3-*O*-propionate **9**. Similarly, treatment of cellulose-2,6-di-*O*-propionate with acetic anhydride cleanly afforded cellulose-2,6-di-*O*-propionate-3-*O*-acetate **11**. No ester group migration was evident from the NMR spectra of these derivatives (e.g., Figure 4.4, ¹³C spectrum of cellulose-2,6-di-*O*-acetate-3-*O*-propionate (**9**)).

Analysis of the bulk position of substitution was accomplished by NMR spectroscopy, with heteronuclear multibond correlation spectroscopy (HMBC) being particularly useful²¹. The fully substituted esters had good organic solubility, permitting NMR analysis in CDCl₃ solution. The ¹H and ¹³C NMR spectra were fully assigned by the methods of Heinze²², Azuma²³ and co-workers.

The HMBC spectrum (Figure 4.5) showed a correlation between the acetyl carbonyl carbon signal at 168.95 ppm and the H-2 proton signal at 4.71 ppm, confirming esterification at O-2. The propionyl carbonyl carbon (173.10 ppm) at position 3 was correlated with the H-3 proton signal (5.03 ppm), confirming propionylation at O-3. Correlation peaks between the C-6 acetyl carbonyl and the C-6 anhydroglucose (AGU) protons were not observed; our experience is that these C-6 correlation peaks are always weaker and often not observed. In contrast to the triesters, the 2,6-*O*-diesters had generally poor organic solubility, with pyridine-*d*-5 being the only convenient NMR solvent. The diester and triester products are summarized in Table 4.1, along with brief descriptions of their physical characteristics. We include for comparison the commercial cellulose esters that are closest in composition to these regioselectively substituted cellulose esters. While quantitative measurement of the monosaccharide composition of cellulose

esters has been quite difficult to date, the best data available (from careful analysis of the ^1H and ^{13}C NMR spectra of cellulose acetate^{24, 25}, which is one of the simplest possible cases, containing only one ester type) indicate that commercial cellulose esters are indeed statistical mixtures of all possible monosaccharides. It is interesting therefore to note the different and generally inferior solubility of the regioselectively substituted diesters. Thermal properties¹⁶ are also strongly impacted by regiochemistry; for example, the T_g of cellulose-2,6-di-*O*-propionate is much lower (146°C) than that of commercial CAP-504-0.1 (T_g 161°C), which has a similar DS and a presumably random substituent pattern.

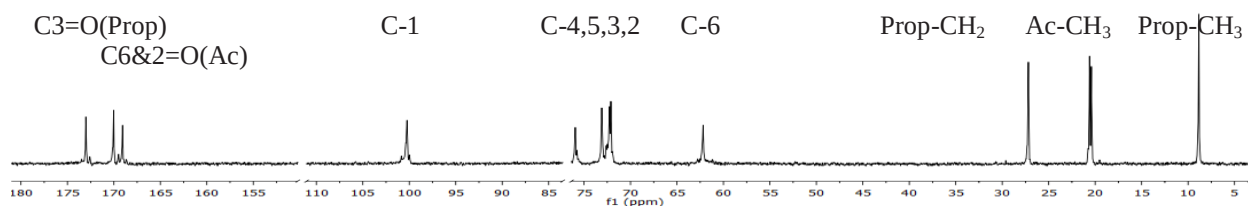


Figure 4.4 ^{13}C NMR spectrum of cellulose-2,6-di-*O*-acetate-3-*O*-propionate

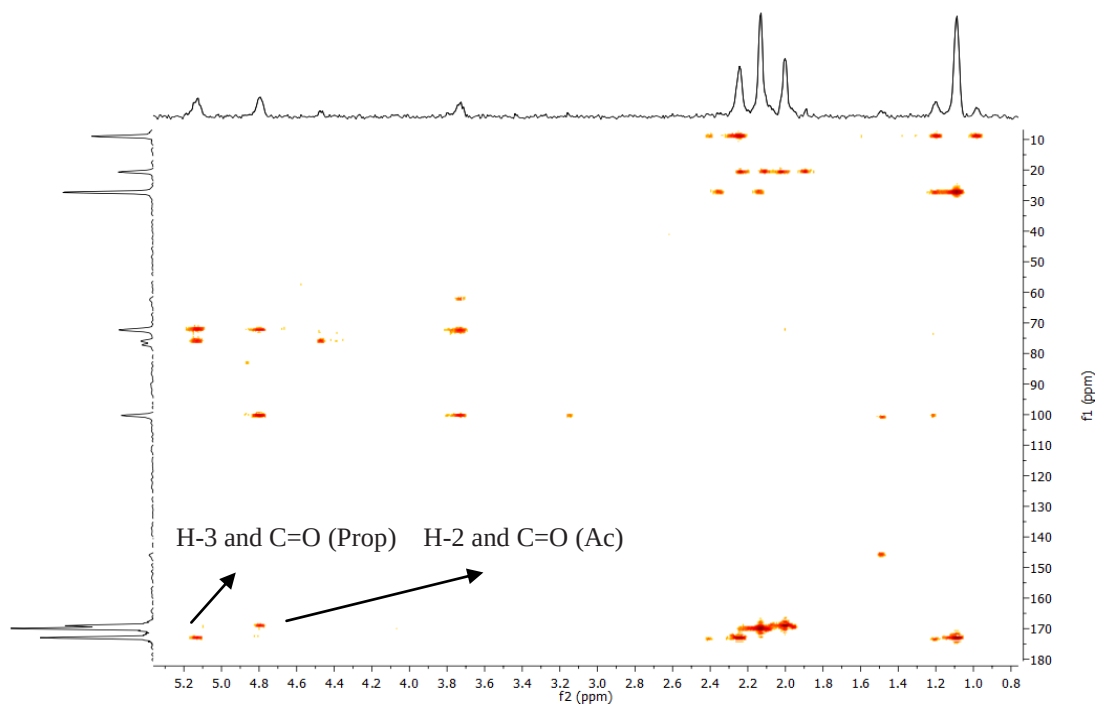


Figure 4.5 *HMBC NMR spectrum of cellulose-2,6-di-O-acetate-3-O-propionate*

Table 4.1 *Cellulose ester homopolymer properties compared with those of random copolymers of similar DP*

Cellulose ester ^[a]	DS ^[b]	DP ^[c]	T _g (°C) ^[c]	Solubility ^[c]
2,6-Pr-3-Ac	Ac 1.0, Pr 2.0	193	139	THF, CHCl ₃ , DMSO, Pyr
CTP	Pr 3.0	180	165	THF, CHCl ₃ , DMSO, Pyr
2,6-Ac-3-Pr	Ac 2.0, Pr 1.0	151	137	THF, CHCl ₃ , DMSO, Pyr
CA-435-75S ^[f]	Ac 2.9	426	186	DMSO
CTA	Ac 3.0	n/a	185	DMSO (swollen)

2,6-Ac	Ac 2.0	n/a	143	Pyr
CA-320S ^[f]	Ac 1.8	159	184	DMSO, Pyr
CA-398-30 ^[f]	Ac 2.4	189	185	THF, CHCl ₃ , DMSO, Pyr
2,6-Pr	Pr 2.0	n/a	146	Pyr
CAP-504-0.1 ^[f]	Ac 0.1, Pr 2.1	53	161	THF, CHCl ₃ , DMSO, Pyr

[a] Ac = acetyl, Pr = propionyl, CTA = cellulose triacetate (CTA was made by peracylation of cellulose with acetyl chloride in DMAc/LiCl), CTP = cellulose tripropionate (CTP was made by peracylation of cellulose with propionic anhydride in DMAc/LiCl) [b] By ¹H NMR [c] By SEC in CHCl₃ or NMP/LiBr; 2,6-Ac and 2,6-Pr not soluble so not measured [d] DSC second heating scan [e] Tested in tetrahydrofuran (THF), CHCl₃, dimethylsulfoxide (DMSO), pyridine (Pyr), ethanol. Insoluble in each solvent except those listed in table. [f] Commercial esters (Eastman Chemical Co.)

It was also important to quantify the degree of regioselectivity of these transformations. Unfortunately there are no general, quantitative methods for determining the monosaccharide composition (e.g., X% β -D-2-O-acetyl-6-O-propionyl-Glc-*p*) of cellulose esters, as there are for cellulose ethers²⁶. While cellulose ether linkages are stable during hydrolysis of the polysaccharide to monosaccharides, ester linkages are cleaved and also do not survive the alkaline conditions of permethylation. Mild methylation procedures have been investigated, but are not generally applicable^{27,28}. Acyl groups can in principle be preserved under conditions of reductive depolymerization²⁹ but the method is prone to incompleteness and side reactions. Since

cellulose ethers are key intermediates in our syntheses, it was possible and useful to determine their monosaccharide compositions, after permethylation of free hydroxyl groups, to provide upper limits on the regioselectivity of our synthetic methods. The latest cellulose ether intermediate in the synthesis is 3-*O*-allylcellulose (**5**). Therefore, we analyzed this ether quantitatively with respect to monosaccharide composition. Permethylation (CH₃I, DMSO, NaH, room temperature for 24 h, then 50 °C, 72 h) followed by deallylation (PdCl₂, CHCl₃, CH₃OH, room temperature, 24 h) afforded the substrate for analysis. Analysis by hydrolysis to monosaccharides, reduction to alditols, acetylation and chromatography showed that the permethylated product was composed of 84-85%³⁰ 2,6-di-*O*-methyl-substituted glucose, containing small amounts of other methylated AGUs including 6-*O*-methyl (5%), 3,6-di-*O*-methyl (3.5%), 2-*O*-methyl- (3%), and 2,3,6-tri-*O*-methyl- (2%) glucose ethers. The 6- and 2-monomethyl ethers could have arisen from slightly incomplete desilylation, and the 3,6-dimethyl ether could have arisen from slightly incomplete allylation. However, the 2,3,6-tri-*O*-methylcellulose by-product is a clear indication of incomplete allylation, partial deallylation during TBAF-catalyzed desilylation, or both. We tend to favor the TBAF mechanism (isomerisation to the vinyl ether which is hydrolyzed off during workup), since we know that TBAF is a strong base and capable of such catalysis⁵. Thus, the actual regioselectivity at intermediate **5** is at least 85%.

4.6 Conclusions

In summary, we have developed general synthetic methods, based on computational studies of models of potential synthetic intermediates, for the successful regioselective synthesis of cellulose-2,6-di-*O*-esters and cellulose-2,6-di-*O*-(ester A)-3-*O*-(ester B) derivatives. The

methods should be broadly applicable to other cellulose ester types. These syntheses of cellulose ester homopolymers are an important step towards broader and deeper understanding of cellulose ester structure-property relationships, the relationships of analytical characteristics to substitution regiochemistry, and towards learning how to more finely control the properties of these important sustainable-based derivatives.

4.7 Acknowledgements

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Chapter 5: Studies on Subsequent Reactions of 3-*O*-Benzyl and 3-*O*-Allyl Cellulose with Bulky Ether Protective Groups

5.1 Abstract

The free hydroxyl groups of 3-*O*-benzyl and 3-*O*-allyl cellulose were derivatized with bulky ether protective groups in order to synthesize versatile synthons for the preparation of regioselectively substituted cellulose ethers and esters. 3-*O*-Benzyl cellulose showed surprisingly low reactivity for nucleophilic reactions, while 3-*O*-allyl cellulose will readily undergo such reactions. We compared the relationship between substitution and reagent type. Several important protected intermediates were successfully synthesized via 3-*O*-allyl cellulose with high potential for the synthesis of regioselectively substituted cellulose esters and ethers.

5.2 Keywords

regioselective, 3-*O*-benzyl cellulose, 3-*O*-allyl cellulose, silylation, tritylation, NMR spectroscopy, degree of substitution, protective group

5.3 Introduction

Cellulose is a highly abundant polysaccharide on earth and with a simple homopolymer structure ($\rightarrow 4\text{-}\beta\text{-D-Glcp-1}\rightarrow$) with three hydroxyl groups of subtle reactivity differences. Scientists have learned that position of substitution has a powerful influence on physical

properties including solubility^{1,2}, optical properties³, thermal properties⁴, and crystallinity^{5,6}. For cellulose derivatives with one substituent type like cellulose acetate (CA), there are 8 possible monosaccharides present in the polymer. If there are two substituent types present, such as in cellulose acetate propionate (CAP) or cellulose acetate butyrate (CAB), there can be up to 27 distinct monosaccharides.⁷

Regioselective synthesis of cellulose derivatives can be challenging. Up to now, the main strategy for regioselective synthesis of cellulose derivatives is to apply bulky protective groups, which can be introduced selectively to one or two of the three reacting sites depending on reaction conditions. The protected substrate is stable under some circumstances for the derivatization of the remaining hydroxyl groups; after that, the protective groups are removed under conditions in which other cellulose substituents are unaffected. The primary hydroxyl group at the C-6 position is most accessible because of steric demand. For example, if the reaction medium is heterogeneous (cellulose/NMP/NH₃, -15 °C), silylation of cellulose with hexyldimethylsilyl (TDMS) occurs nearly exclusively at O-6 with a DS of 0.99. Under homogeneous reaction conditions in DMAc/LiCl, cellulose can react with TDMS-Cl at both C-6 and C-2, reaching DS 2.0 in the presence of imidazole catalyst with no detectable O-3 substituent.⁸ The triphenylmethyl (trityl) protective group can be selectively introduced at C-6 to form 6-mono-O-trityl cellulose.⁹ Trityl substituted with a p-methoxy moiety is a more efficient protective group. The reaction rate with cellulose for 4-monomethoxytrityl chloride is ten times faster than unsubstituted trityl and the conversion at O-6 can be realized in DMAc/LiCl within 4h at 70 °C with a DS value of 0.96.⁹ Regioselectivity of tritylation is high but imperfect, with less than 11% of tritylation at the C-2 and C-3 positions.

By means of the 2,6-bis-(hexyldimethylsilyl)cellulose, pure 3-alkylcellulose ethers can be readily synthesized.⁷ In order to increase substitution selectivity of bulky groups at the cellulose C-6 position, we thought the presence of another protective group at C-3 may make substitution of the neighboring C-2 more difficult, affording very high selectivity for O-6 substitution. If this hypothesis is correct, we should have access to orthogonally protected cellulose in which all three hydroxyl groups are differentiated with respect to reactivity. These intermediates are very important since they can lead to synthesis of a broad range of regioselectively substituted cellulose esters and ethers.

We report herein the attempted substitution of 3-O-benzyl cellulose with other bulky ether protective groups. Molecular modeling was applied to explain the lower reactivity of 3-O-benzyl cellulose compared with unfunctionalized cellulose, and predict the effect of allyl substituent at O-3 on the nucleophilicity of the remaining C-6 and C-2 hydroxyl groups. We establish functionalization conditions for given degree of substitution and substitution pattern of the 3-O-allyl cellulose derivatives reacting with bulky ether protective groups. We discuss the potential application of several important protected intermediates for regioselective synthesis of cellulose derivatives.

5.4 Experimental

5.4.1 Materials

Cellulose (Avicel PH-101, DP=280) was dried under vacuum before use. Other reagents were purchased from Fisher and used without further purification.

5.4.2 Measurements

FTIR spectra were recorded with a Thermo Electron Nicolet 8700 FT-IR spectrophotometer by using KBr pellets. ^1H and ^{13}C NMR spectra were acquired on a Varian INOVA 400 (400 MHz) spectrometer at room temperature or 50 °C. DS values were calculated from the integration ratios of acetyl or propionyl proton resonances to those of the backbone hydrogens. HMBC and COSY spectra were acquired on a 500 NMR Bruker Avance II spectrometer (500 MHz) at 50 °C.

5.4.3 3-*O*-Benzyl-2,6-di-*O*-thexyldimethylsilyl cellulose

2,6-Di-*O*-thexyldimethylsilyl cellulose was synthesized according to Koschella et al.¹⁰ 2,6-Di-*O*-thexyldimethylsilyl cellulose (10 g, 22.38 mmol) was suspended in 100 mL dry THF. To the solution, NaH (5.37 g, 228.8 mmol, 10 mol/mol modified AGU) was added. Then benzyl bromide (26.6 mL, 228.8 mmol, 10 mol/mol modified AGU) was added dropwise with vigorous stirring. The mixture was stirred at room temperature for 1 day and at 50 °C for another 3 days. The reaction was quenched by addition of isopropanol and poured into 500 mL phosphate buffer solution (pH = 7.0). The precipitate was collected, washed with 500 mL ethanol and dried under vacuum at 40 °C.

Degree of substitution (DS): $\text{DS}_{\text{benzyl}}$ 0.98 (determined by ^1H NMR spectroscopy).

FT-IR (cm^{-1}): 2866, 2954 $\nu(\text{C-H})$, 1361, 1463 $\nu(\text{C-C}_{\text{Aromatic}})$, 1251 $\nu(\text{C-Si})$, 828, 776 $\nu(\text{C-H}_{\text{Aromatic}})$.

^1H NMR (in CDCl_3): δ (ppm) = 0.11-1.61 (TMS group), 4.97 (benzyl methylene), 7.27, 7.41 (H-aromatic), 3.28-4.73 (AGU).

5.4.4 3-*O*-Benzyl cellulose

3-*O*-Benzyl-2,6-di-*O*-hexyldimethylsilyl cellulose (20 g, 44.8 mmol) was dissolved in 100 mL DMSO and treated with TBAF (56.6 g, 179.4 mmol, 4 mol/mol modified AGU). The mixture was stirred at 50 °C for 3 days. The mixture was poured into 1000 mL water, then the product was collected by filtration, washed thoroughly with water, and dried under vacuum at 40 °C. The crude product (5.0 g) was suspended in 100 mL DMAc and 10 g LiCl. TBAF (10 g) was then added. The temperature was raised to 50 °C and the solution was kept at this temperature for another 3 days under stirring. The mixture was added dropwise into 500 mL ethanol. The product was isolated by filtration, then the precipitate was washed with ethanol and dried under vacuum at 40 °C.

Degree of substitution (DS): $\text{DS}_{\text{benzyl}} = 0.98$ (determined by ^1H NMR spectroscopy after perpropionylation).

FT-IR (cm^{-1}): 3458 $\nu(\text{OH})$, 2863, 2958 $\nu(\text{C-H})$, 1371, 1450 $\nu(\text{C-C}_{\text{Aromatic}})$, 824, 741 $\nu(\text{C-H}_{\text{Aromatic}})$.

^1H NMR (in DMSO-d_6): δ (ppm) = 7.21-7.43 (H-aromatic), 5.51 ($\text{CH}_2\text{-C}_6\text{H}_5$), 3.17-4.86 (AGU).

5.4.5 Dissolution of 3-*O*-benzyl cellulose in DMAc/LiCl

3-*O*-Benzyl cellulose (0.2 g, 0.79 mmol) was suspended in 6 mL DMAc followed by the addition of 0.3 g LiCl (5% w/v). The mixture was heated to 70 °C. Within 1 h, a solution was formed.

5.4.6 Attempted silylation of 3-*O*-benzyl cellulose with hexyldimethylsilyl chloride (TDMS-Cl)

In a typical reaction, a solution of 0.2 g 3-*O*-benzyl cellulose in DMAc/LiCl was treated with 0.26 g imidazole (4.8 mol/mol AGU) and 0.62 ml TDMS-Cl (4 mol/mol AGU) (see Table 5.1). The mixture was stirred for 1 d at 100 °C, precipitated in 100 mL water/ethanol, washed with ethanol and dried. Peracetylation was then applied on product in order to improve its organic solubility.

DS: DS_{TDMS} 0.04, DS_{Acetate} 1.96, DS_{Benzyl} 1.00 (determined by ¹H NMR spectroscopy after peracetylation)

FT-IR (cm⁻¹): 2868, 2954 ν(C-H), 1742 ν(C=O), 1367 ν(C-C_{Aromatic}), 824, 739 ν(C-H_{Aromatic}).

¹H NMR (in CDCl₃): δ (ppm) = 4.85, 5.05 (CH₂-C₆H₅), 7.22-7.26 (H-aromatic), 3.28-4.87 (AGU), 1.76, 1.88 (acetate), 0.11-1.22 (TDMS group).

5.4.7 Attempted silylation of 3-*O*-benzyl cellulose with trimethylsilyl chloride (TMS-Cl)

In a typical reaction, a solution of 0.2 g 3-*O*-benzyl cellulose in DMAc/LiCl was treated with 0.1 g NaH (10 mol/mol AGU) and 0.18 g TMS-Cl (4 mol/mol AGU) (see Table 5.2). The mixture was stirred for 1 d at 50 °C, precipitated in 100 mL water/ethanol, washed with ethanol and dried.

DS: DS_{TMS} 0 (determined by ¹H NMR spectroscopy)

FT-IR (cm⁻¹): 3505 ν(OH), 2868, 2954 ν(C-H), 1367 ν(C-C_{Aromatic}), 824, 739 ν(C-H_{Aromatic}).

^1H NMR (in DMSO- d_6): δ (ppm) = 7.29-7.46 (H-aromatic), 4.84, 5.54 ($\text{CH}_2\text{-C}_6\text{H}_5$), 3.18-4.87 (AGU).

5.4.8 3-O-Allyl cellulose

3-O-Allyl cellulose was synthesized according to Koschella et al.¹⁰ 2,6-Di-O-thexyldimethylsilyl cellulose (10 g, 22.38 mmol) was suspended in 100 mL dry THF. To the solution, NaH (5.37 g, 228.8 mmol, 10 mol/mol modified AGU) was added. Then allyl chloride (18.3 mL, 228.8 mmol, 10 mol/mol modified AGU) was added dropwise with vigorous stirring. The mixture was stirred at room temperature for 1 day and at 50 °C for another 3 days. The reaction was quenched by addition of isopropanol and poured into 500 mL phosphate buffer solution (pH = 7.0). The precipitate was collected, washed with 500 mL ethanol and dried under vacuum at 40 °C. The product (8 g, 16 mmol) was treated with 20.7 g TBAF (4 mol/mol modified AGU) in THF at 50 °C for 1 day. The mixture was poured into 500 mL ethanol, then the product was collected by filtration, washed thoroughly with ethanol, and dried under vacuum at 40 °C. The crude product (1.86 g) was suspended in 30 mL DMSO and treated with 4.0 g TBAF at 50 °C for 1 day. 3-O-Allyl cellulose was isolated by precipitation from ethanol and the product was washed with excess ethanol.

5.4.9 Dissolution of 3-O-allyl cellulose in DMAc/LiCl

3-O-Allyl cellulose (0.2 g, 0.99 mmol) was suspended in 6 mL DMAc. LiCl (0.3 g, 5% w/v) was added and the mixture was heated to 70 °C. Within 1 h, a solution was formed.

5.4.10 Silylation of 3-*O*-allyl cellulose with hexyldimethylsilyl chloride (TDMS-Cl)

In a typical reaction, a solution of 0.2 g 3-*O*-allyl cellulose in DMAc/LiCl was treated with 0.32 g imidazole (4.8 mol/mol AGU) and 0.6 ml TDMS-Cl (3mol/mol AGU) (see Table 5.3). The mixture was stirred for 1d at room temperature, precipitated in 100 mL water/ethanol, washed with ethanol and dried.

DS_{TDMS} 0.78 (determined by ¹H NMR spectroscopy)

FT-IR (cm⁻¹): 3500 ν(OH), 3088 ν(=C-H), 2870, 2955 ν(C-H), 1251, 834, 779 ν(C-Si).

¹H NMR (in CDCl₃): δ (ppm) = 5.10, 5.23, 5.90 (allyl group), 3.25-4.58 (AGU), 0.11-1.22 (TDMS group).

5.4.11 Silylation of 3-*O*-allyl cellulose with *t*-butyldimethylsilyl chloride (TBDMS-Cl)

In a typical reaction, a solution of 0.2 g 3-*O*-allyl cellulose in DMAc/LiCl was treated with 0.32 g imidazole (4.8 mol/mol AGU) and 0.45 g TBDMS-Cl (3 mol/mol AGU) (see Table 5.4). The mixture was stirred for 1d at room temperature, precipitated in 100 mL water/ethanol, washed with ethanol and dried.

DS_{TBDMS} 1.24 (determined by ¹H NMR spectroscopy)

FT-IR (cm⁻¹): 3505 ν(OH), 3088 ν(=C-H), 2870, 2955 ν(C-H), 1250, 835 ν(C-Si).

¹H NMR (in CDCl₃): δ (ppm) = 5.10, 5.23, 5.90 (allyl), 3.25-4.58 (AGU), 0.87, 0.06 (TDMS group).

5.4.12 Silylation of 3-*O*-allyl cellulose with *t*-butyldiphenylsilyl chloride (TBDPS-Cl)

In a typical reaction, a solution of 0.2 g 3-*O*-allyl cellulose in DMAc/LiCl was treated with 0.32 g imidazole (4.8 mol/mol AGU) and 0.77 ml TBDMS-Cl (3 mol/mol AGU) (see Table 5.4). The mixture was stirred for 1d at room temperature, precipitated in at 50 °C for 100 mL water/ethanol, washed with ethanol and dried.

DS_{TBDPS} 0.88

FT-IR (cm⁻¹): 3500 ν (OH), 3088 ν (=C-H), 2870, 2955 ν (C-H), 1366 ν (C-C_{Aromatic}), 1255 ν (C-Si), 820, 735 ν (C-H_{Aromatic}).

¹H NMR (in CDCl₃): δ (ppm) = 7.72, 7.36 (H-aromatic), 5.10, 5.23, 5.90 (allyl), 3.30-4.60 (AGU), 1.06 (TBDPS group).

5.4.13 Silylation of 3-*O*-allyl cellulose with trimethylsilyl chloride (TMS-Cl)

In a typical reaction, a solution of 0.2 g 3-*O*-allyl cellulose in DMAc/LiCl was treated with 0.32 g imidazole (4.8 mol/mol AGU) and 0.38 ml TMS-Cl (3 mol/mol AGU) (see Table 5.4). The mixture was stirred for 1 d at room temperature, precipitated in 100 mL water/ethanol, washed with ethanol and dried.

DS_{TMS} 1.63

FT-IR (cm⁻¹): 3501 ν (OH), 3085 ν (=C-H), 2870, 2955 ν (C-H), 1250, 830, 778 ν (C-Si).

¹H NMR (in CDCl₃-d₁): δ (ppm) = 5.10, 5.23, 5.90 (Allyl), 3.27-4.37 (AGU), 0.09 (TMS group).

5.4.14 Tritylation of 3-*O*-allyl cellulose with 4-methoxytrityl-Cl

In a typical reaction, a solution of 0.2 g 3-*O*-allyl cellulose in DMAc/LiCl was treated with 0.62 mL pyridine (4.5 mol/mol AGU) and 1.23 g 4-methoxytrityl-Cl (4 mol/mol AGU) (see Table 5.5). The mixture was stirred for 4 h at 70 °C, precipitated in 100 mL methanol, washed with methanol and dried.

DS_{Trityl} 1.05

FT-IR (cm⁻¹): 3450 ν (OH), 3055 ν (CH_{aromatic}), 3080 ν (=C-H), 2955 ν (C-H), 1645, 1490 ν (C-C_{aromatic}).

¹H NMR (in CDCl₃): δ (ppm) = 6.75-7.75 (H-aromatic), 5.01, 5.23, 5.90 (allyl), 3.05-4.51 (AGU), 3.75 (methoxy group).

5.4.15 3,6-Di-*O*-acetyl-2-*O*-methyl cellulose

Tritylated 3-*O*-allyl cellulose (DS_{trityl} = 1.05, 4.74 g) was dissolved in 60 mL THF. 2.4 g NaH (10 mol/mol AGU) and 6.23 mL methyl iodide (10 mol/mol AGU) were added and the reaction mixture was stirred at room temperature for 1 day and at 50 °C for another 3 days. The reaction was quenched by addition of isopropanol and poured into 200 mL water. The precipitate was collected, washed with 500 mL ethanol and dried under vacuum at 40 °C. The product (4.88 g) was redissolved in 50 mL dichloromethane, followed by the addition of acetyl chloride (5.7 mL, 8 mol/mol AGU). The solution was stirred at room temperature for 1 day and precipitated into 200 mL methanol. The precipitate was collected, washed with 500 mL methanol and dried. 6-*O*-Acetyl-2-*O*-methyl-3-*O*-allyl cellulose (120 mg) was dissolved in 8 mL chloroform and 5 mL methanol and to this solution was added 10 mg PdCl₂. After stirring at room temperature for

24 h, the mixture was filtered through Celite and evaporated to dryness. Peracetylation was then applied to afford the final product.

FT-IR (cm^{-1}): 2945 $\nu(\text{C-H})$, 1275 $\nu(\text{C-O-C}_{\text{Ester}})$, 1756 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 5.03 (H-3), 3.01 (H-2), 4.27 (H-1), 4.48 (H-6), 4.17 (H-6'), 3.61 (H-4), 3.54 (H-5), 3.41 (C2-OCH_3), 2.08, 1.96 (CH_3 -acetate).

^{13}C NMR (in CDCl_3): δ (ppm) = 169.67 (C=O), 102.73 (C-1), 100.36 (C-1'), 81.59 (C-2), 76.21 (C-4), 73.55 (C-3), 72.91 (C-5), 62.35 (C-6), 60.59 (methyl carbon), 20.56 (CH_3 - acetate).

5.4.16 Peracetylation

Polymer (0.3 g) was dissolved in a mixture of pyridine (5 mL), 4-(dimethylamino)pyridine (20 mg), and acetic anhydride (1.1 mL, 10 mol/mol AGU). After stirring for 24 h at 80 °C, the product was precipitated into water (100 mL), washed several times with water. The crude product was redissolved in 5 mL CHCl_3 . This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C.

5.5 Results and discussion

5.5.1 Silylation of 3-*O*-benzyl cellulose

Considering the previous results in reaction of cellulose with TDMS-Cl to form 2,6-*O*-hexyldimethylsilyl cellulose,¹¹ we would like to investigate the effect of a 3-benzyl substituent on the regioselectivity of silylation of 3-*O*-benzyl cellulose. The results are displayed

in Table 5.1. Surprisingly, no reaction happened between 3-*O*-benzyl cellulose and TDMS-Cl in NMP. The solvent was then changed to DMAc/LiCl by following the same reaction condition of cellulose with TDMS-Cl. At a ratio of 2 equiv TDMS-Cl per AGU, a rather low DS of 0.01 was reached within a reaction time of 1d at room temperature. If the ratio was increased to 4 equiv TDMS-Cl per AGU and the temperature was increased to 100 °C, a DS of 0.04 was obtained, which is much lower compared to the same reaction on cellulose. Initially, we thought such a low DS could be due to the bulkiness of TDMS-Cl. A less bulky silyl reagent of TMS-Cl was then tried (see Table 5.2). However the conversion does not happen at all even with various reaction conditions, including reaction time, temperature, solvent and molar equivalents of TMS-Cl per AGU. A much stronger base of NaH instead of imidazole was applied and a dark colored solution was formed and no product was generated at 100°C, indicating a serious degradation of cellulose chain happened at such a high temperature. The reaction was repeated by decreasing temperature to 50 °C, affording no silylation at C-6 and C-2 (DS = 0.0). The reaction was also carried out in [Amim]Cl ionic liquid which is one of the most commonly used ionic liquids for homogenous functionalization for cellulose.¹² No reaction occurred in this solvent either. Concluding from these results, 3-*O*-benzyl cellulose seemed to be quite resistant to silylation. In order to explain the low reactivity of 3-*O*-benzyl cellulose, computational studies were applied. Plots of the highest occupied molecular orbital (HOMO) clearly indicate the absence of substantial electron density at the C-6 position for 3-*O*-benzylcellulose model,¹³ which may explain why silylation was retarded (Figure 5.1).

Table 5.1 *Subsequent reactions of 3-*O*-benzyl cellulose with TDMS-Cl*

Run	Molar Ratio	Time (h)	Temperature (°C)	Solvent	DS _{silyl}
1	1:2.0	24	Ambient	NMP	0
2	1:2.0	24	100	NMP	0
3	1:2.0	24	Ambient	DMAc/LiCl	0.01
4	1:4.0	24	100	DMAc/LiCl	0.04

Table 5.2 *Subsequent reactions of 3-O-benzyl cellulose with TMS-Cl*

Run	Molar Ratio	Time (h)	Temperature (°C)	Base	Solvent	DS _{silyl}
1	1:3.0	24	80	Imidazole	DMAc/LiCl	0
2	1:4.0	24	100	Imidazole	DMAc/LiCl	0
3	1:4.0	24	100	NaH	DMAc/LiCl	N/A
4	1:4.0	24	50	NaH	DMAc/LiCl	0
5	1:4.0	24	100	Imidazole	[Amim]Cl	0

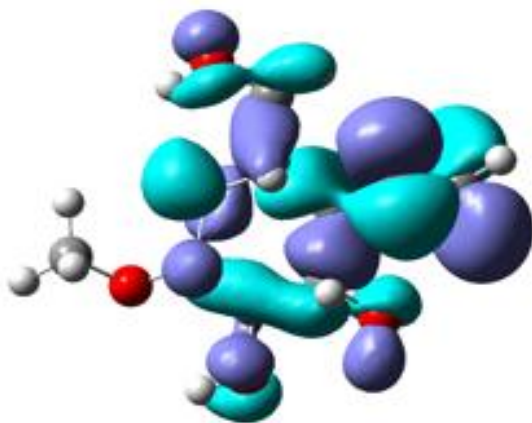


Figure 5.1 HOMO plot of *methyl 4-O-methyl-β-D-glucopyranoside, M1*

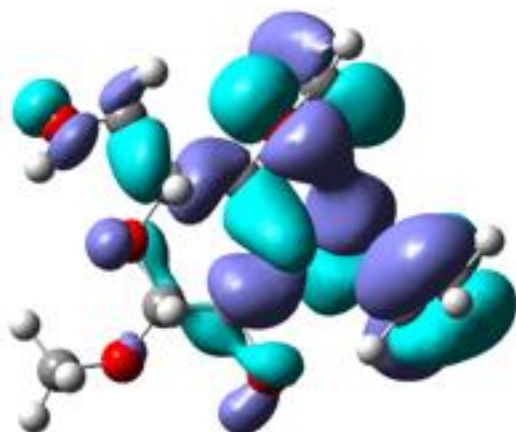


Figure 5.2 HOMO plot of *methyl 3-O-allyl-4-O-methyl-β-D-glucopyranoside, M2*

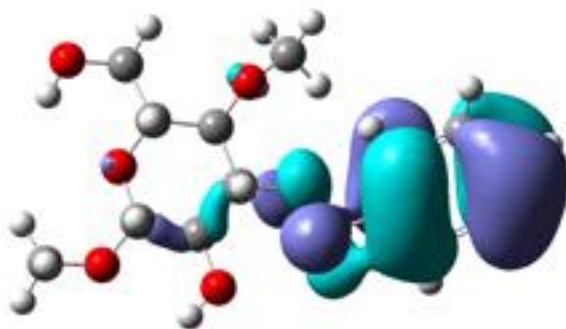


Figure 5.3 HOMO plot of *methyl 3-O-benzyl-4-O-methyl-β-D-glucopyranoside M3*

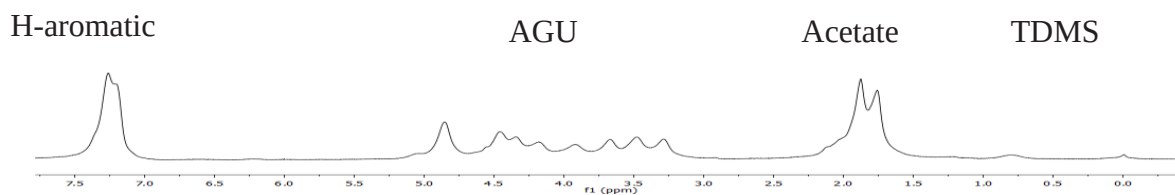


Figure 5.4 ^1H NMR (in CDCl_3) spectrum of 3-O-benzyl cellulose reaction product with TDMS-Cl after peracetylation

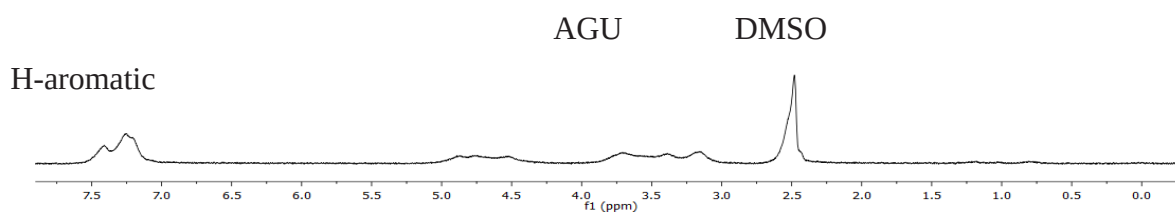


Figure 5.5 ^1H NMR (in $\text{DMSO}-d_6$ with a drop of TFA) spectrum of 3-O-benzyl cellulose reaction product with TMS-Cl

5.5.2 Silylation of 3-O-allyl cellulose

Since 3-O-benzyl cellulose failed to react with silylating reagent, we then chose to explore another protecting group, namely the allyl ether. 3-O-Allyl cellulose was first synthesized via

2,6-di-*O*-thexyldimethylsilyl cellulose.¹⁰ It is a rather interesting intermediate since it has two free hydroxyl groups at C-6 and C-2 which become reacting sites for subsequent reactions. Also the allyl group could be cleaved mildly by PdCl₂, leaving 3-OH for further functionalization.¹⁴ One example is 2,6-di-*O*-methyl cellulose which was synthesized from 3-*O*-allyl cellulose.¹⁵

We examined the predicted reactivity of 3-*O*-allyl cellulose by molecular modeling. Plots of the highest occupied molecular orbital clearly showed the presence of substantial electron density at the C-6 position for the 3-*O*-allyl cellulose model (Figure 5.2), which is completely absent from the 3-*O*-benzyl cellulose model (Figure 5.3). This enhanced electron density increased our confidence that 3-*O*-allyl cellulose would be a useful synthetic intermediate for our purposes.

3-*O*-Allyl cellulose was synthesized from 2,6-di-*O*-thexyldimethylsilyl cellulose according to Koschella et al.¹⁰ It was then allowed to react with hexyldimethylsilyl chloride in DMAc/LiCl in the presence of imidazole. The reaction of 3-*O*-allyl cellulose with TDMS-Cl leads to silylated products soluble in chloroform. The conditions and results of the silylation reactions are summarized in Table 5.3. The products were characterized by means of ¹H NMR spectroscopy (Figure 5.6). At a ratio of 3 mol TDMS-Cl per mol AGU, a DS of 0.78 was reached within a reaction time of 24 h at room temperature. The product was readily soluble in chloroform. With regard to the reaction efficiency, either increasing the reaction time from 24 h to 48 h or raising the reaction temperature to 100 °C gives a product with significantly higher DS value. Further extending the reaction time from 2 d to 3 d did not significantly increase silyl DS. An increase in the molar ratio of TDMS-Cl/AGU to 4 mol/mol yields a product with DS=1.10. For the sake of evaluating C-6 selectivity it was critical for us to identify conditions for making a

product with DS close to 1, and we found that this can be achieved by treating 3-*O*-allyl cellulose with 3.5 equiv/AGU for 1 d (DS=1.06).

Table 5.3 *Subsequent reactions of 3-*O*-allyl cellulose with TDMS-Cl in DMAc/LiCl*

Run	Molar Ratio (AGU/TDMS-Cl)	Time (h)	Temperature (°C)	DS _{silyl}
1	1:3.0	24	Ambient	0.78
2	1:3.0	24	100	1.32
3	1:3.0	48	Ambient	1.12
4	1:3.0	72	Ambient	1.16
5	1:4.0	24	Ambient	1.09

Other silylating reagents were used to compare the effects of increasing bulkiness on the regioselectivity of substitution of 3-*O*-allyl cellulose. TBDMS-Cl was used by Heinze to react with cellulose in DMAc/LiCl to form a 2,6-di-*O*-protected silyl cellulose.¹⁶ The regioselectivity for cellulose is the same as with hexyldimethylchlorosilane except for a small amount of 3,6-di-*O*- and 6-mono-*O*-silyl structures. In addition to that, if the reaction was carried out at high temperature, 2,3,6-tri-*O*-silylated products were found. TBDPS is another common protective group applied previously to synthesize TBDPS ethers.¹⁷ It is more stable to acids and under conditions of hydrogenolysis than other silyl and trityl ethers. It has not been explored on cellulose so far.

After silylation with those reagents at a constant ratio of 3 equiv/AGU, all of the 3-*O*-allyl cellulose silyl ethers were soluble in chloroform. The structures of the products were characterized by means of ¹H NMR spectra. TMS-Cl¹⁸ which is the least bulky reagent can react

with 3-*O*-allyl cellulose to afford a DS of 1.63 within 1 d at room temperature. TBDMS-Cl reacted with 3-*O*-allyl cellulose and the DS of TBDMS is equal to 1.24 after 1 d. Compared with Heinze's results, this DS value is low, since cellulose can react with TBDMS-Cl at the same molar ratio to afford a DS of 1.85 within just 2 h. The utility of TBDPS-Cl for the reaction with 3-*O*-allyl cellulose was explored and a DS of 0.88 is obtained, which is lower than TMS and TBDMS, but higher than TDMS. If with 3.5 equiv TBDPS-Cl, approximately 0.98 DS can be obtained, indicating the possibility of a very high selectivity at C-6.

Overall, the involvement of the allyl group at C-3 increased the selectivity of cellulose at C-6 when reacting with bulky protective groups as expected. We found that with increasing bulkiness of trialkylsilyl chloride, a lower DS of the silyl-protected 3-*O*-allyl cellulose was obtained. As a result, two promising regioselectively substituted intermediates with an approximate DS of 1.0 for the silyl group were synthesized from 3-*O*-allyl cellulose, by reaction with TDMS-Cl or TBDPS-Cl, respectively. After functionalization of these doubly protected intermediates at O-2, followed by the removal of silyl and allyl protective groups, 2-*O*-functionalized cellulose derivatives can be synthesized.

Table 5.4 *Subsequent reactions of 3-*O*-allyl cellulose with silyl protective groups in DMAc/LiCl*

Silyl-Cl	Molar ratio (AGU/Silyl-Cl)	Time (h)	Temperature (°C)	DS _{silyl}
TMS-Cl	1:3.0	24	Ambient	1.63
TBDMS-Cl	1:3.0	24	Ambient	1.24

TBDPS-Cl	1:3.0	24	Ambient	0.88
TBDPS-Cl	1:3.5	24	Ambient	0.98
TDMS-Cl	1:3.0	24	Ambient	0.78
TDMS-Cl	1:3.5	24	Ambient	1.06

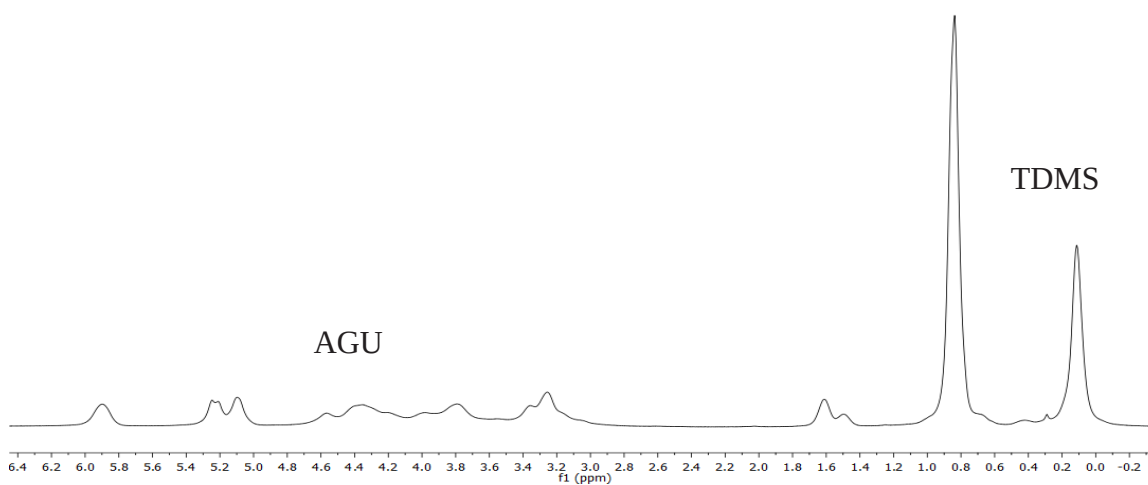


Figure 5.6 ^1H NMR (in CDCl_3) spectrum of 3-O-allyl cellulose reaction product with TDMS-Cl

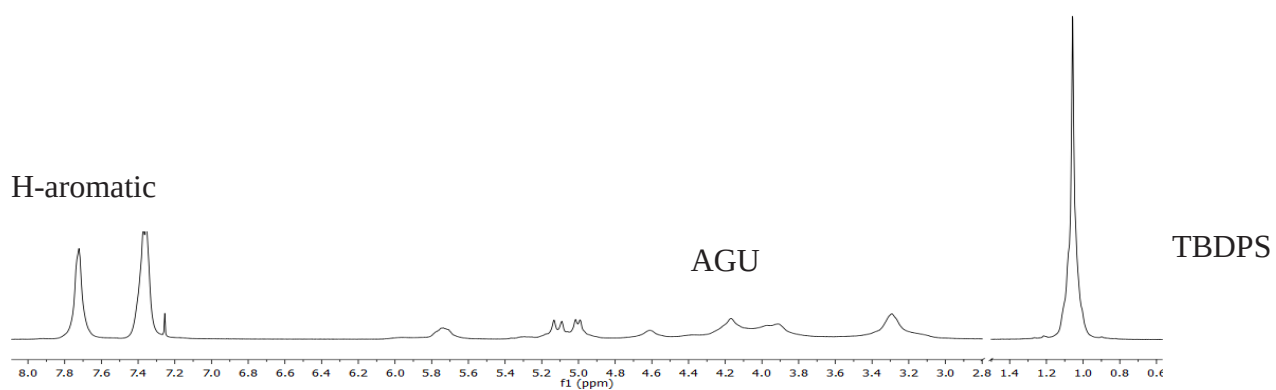


Figure 5.7 ^1H NMR (in CDCl_3) spectrum of 3-O-allyl cellulose reaction product with TBDPS-Cl

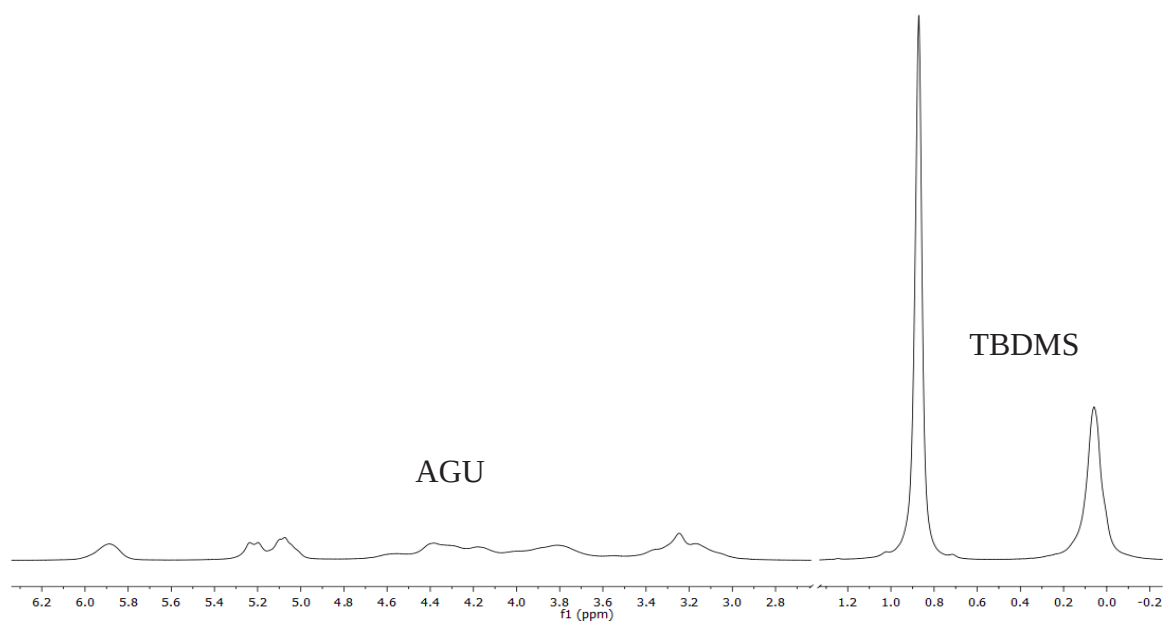


Figure 5.8 ^1H NMR (in CDCl_3) spectrum of 3-O-allyl cellulose reaction product with TBDMS-Cl

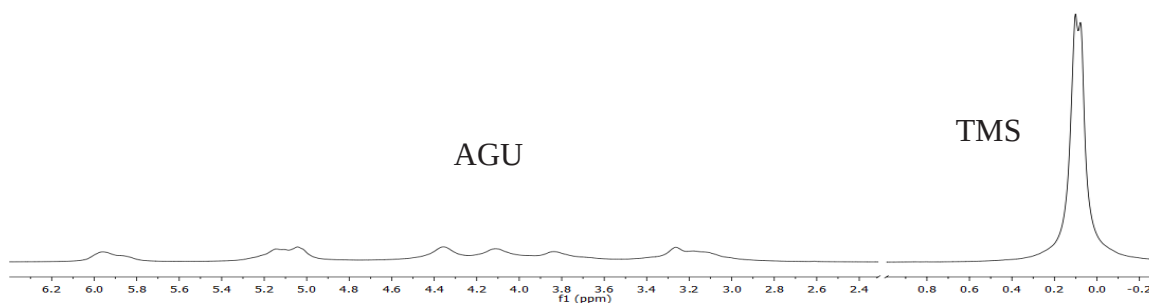


Figure 5.9 ^1H NMR (in CDCl_3) spectrum of 3-O-allyl cellulose reaction product with TMS-Cl

5.5.3 Tritylation of 3-O-allyl cellulose

The subsequent silylation of 3-O-allyl cellulose is promising and silyl protecting groups can be completely removed by treatment with tetrabutylammonium fluoride, opening up a relatively simple pathway to the regioselective synthesis of cellulose derivatives. However, our group has recently found that (Chapter 6) TBAF not only cleaves silyl groups but also esters.¹⁹ Therefore strategies requiring removal of silyl protecting groups by F^- in the presence of polysaccharide ester moieties are risky and probably impractical. Since the trityl group can be removed under mildly acidic conditions which may be compatible with ester functionality⁷, we investigated the tritylation of 3-O-allyl cellulose.

3-O-Allyl cellulose dissolved in DMAc/LiCl was treated with different molar ratios of 4-monomethoxytrityl chloride in the presence of pyridine (4.5 equiv per AGU) at 70 °C. Starting from the same reaction condition (3.0 equiv trityl-Cl per AGU and 4 h) of tritylation of cellulose⁹,

a DS of 0.60 was obtained, which is lower than for cellulose (DS = 1.0). As the molar ratio of trityl-Cl/AGU increased from 4 to 6, DS as high as 0.74 was reached, but full substitution at O-6 was not achieved. A series of reactions examined the influence of reaction time at constant 6 equiv trityl-Cl/AGU. The highest DS of 0.79 was achieved in these studies. In order to get a full trityl substitution at O-6, stronger bases including TEA and imidazole instead of pyridine were tried. At the comparable molar ratio of 1/4 (AGU/trityl-Cl), these stronger bases yielded higher DS values of 1.05 and 1.18 respectively within 4 hours. The product with a DS of 1.05 is very close to the target of 1.0 for regioselective synthesis of cellulose derivatives including both cellulose ethers and esters.

All the data indicate that the effect of allyl group on subsequent reactions of cellulose did exist and that increasing of the molar ratio, reaction time, using pyridine as the base did not afford complete conversion of position 6. A stronger base than pyridine is needed to yield a product with an approximate DS of one.

Table 5.5 *Subsequent reactions of 3-O-allyl cellulose with trityl-Cl in DMAc/LiCl*

Run	Molar ratio (AGU/Trityl-Cl)	Temperature (°C)	Base (1:4.5)	Rxn time (h)	DS
1	1:3	70	Pyridine	4	0.60
2	1:4	70	Pyridine	4	0.73
3	1:5	70	Pyridine	4	0.71
4	1:6	70	Pyridine	4	0.74
5	1:6	70	Pyridine	24	0.79
6	1:6	100	Pyridine	48	0.79

7	1:4	70	TEA	4	1.05
8	1:4	70	Imidazole	4	1.18

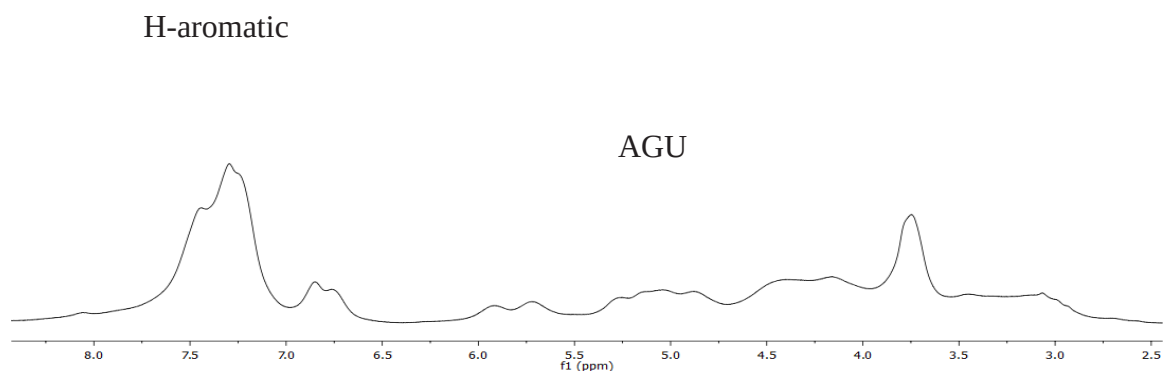
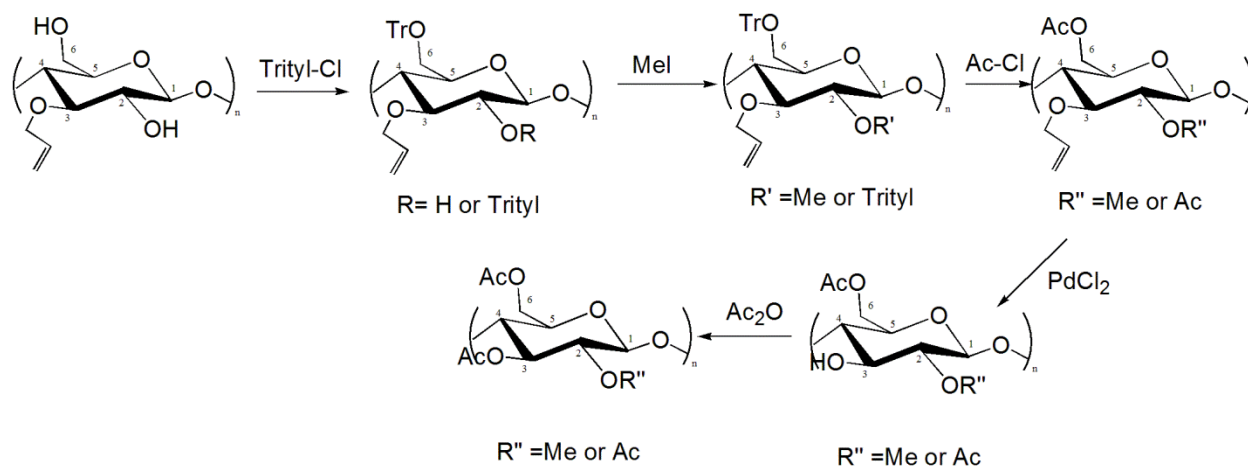


Figure 5.10 ¹H NMR (in CDCl₃) spectrum of 3-O-allyl cellulose reaction product with 4-methoxytrityl-Cl

5.5.4 Synthesis of 3,6-di-O-acetyl-2-O-methyl cellulose

It was important to quantify the degree of regioselectivity of these transformations. Cellulose methyl ethers are generally used for such analysis.²⁰ Therefore permethylation was applied on the tritylated 3-O-allyl cellulose with a DS of 1.05 for trityl group. Conversion of the trityl ether into acetate was performed with acetyl chloride, which is a simple one-pot procedure.²¹ Subsequent deallylation and peracetylation of free hydroxyl groups yield a product giving well resolved NMR spectra critical for the determination of substitution pattern (Scheme 5.1).

The peaks in NMR spectra were assigned not only based on two-dimensional (COSY and HMBC) NMR spectroscopy, but also on the signal assignments of regioselectively substituted cellulose derivatives (synthesized via *de novo* strategy) done by Kerakawa and co-workers.²²



Scheme 5.1 *Synthesis of 3,6-di-O-acetyl-2-O-methyl cellulose*

The COSY NMR spectrum (Figure 5.11) indicates 3,6-di-O-acetyl-2-O-methyl cellulose was successfully formed. All protons of this repeating unit can be identified by following cross-peaks. For example, the H-1 signal is at 4.27 ppm, H-2 at 3.01 ppm and H-3 at 5.03 ppm. However, there is a signal at 4.79 ppm, corresponding to H-2 of cellulose triacetate moiety. This is further confirmed by ¹³C NMR spectrum (Figure 5.12) since two C-1 signals showed up. The chemical shift at 102.73 ppm is from 3,6-di-O-acetyl-2-O-methyl repeating unit, and the one at 100.36 belongs to the cellulose triacetate substructure. The triacetate moiety is a result of partial tritylation at C-2 position rather than at C-6 position. The assignments of peaks were also verified by HMBC analysis. The HMBC spectrum (Figure 5.13) showed a correlation between the acetyl carbonyl carbon signal at 169.67 ppm and the H-3 proton signal at 5.03 ppm, confirming esterification at O-3. The carbon (81.59 ppm) at position 2 was correlated with the

methyl proton signal (3.41 ppm), confirming methylation at O-2. Correlation peaks between the C-6 acetyl carbonyl and the C-6 anhydroglucose (AGU) protons were not observed; our experience is that these C-6 correlation peaks are always weaker and often not observed. Additional correlation peaks showed up between the acetyl carbonyl carbon signal at 169.36 ppm and the H-2 proton signal at 4.79 ppm, indicating acetate substitution at O-2.

From the information above, the tritylation of 3-O-allyl cellulose with 4-monomethoxytrityl chloride in the presence of TEA in DMAc/LiCl showed the same regioselectivity as that of cellulose, that is, the trityl moiety is highly selective at C-6 except for a small amount at C-2. By subsequent methylation and acetylation, 3,6-di-O-acetyl-2-O-methyl cellulose was successfully synthesized, although a small amount of cellulose triacetate was produced. The quantitative determination of substructure will be finished by our collaborator Professor Mischnick in Germany.

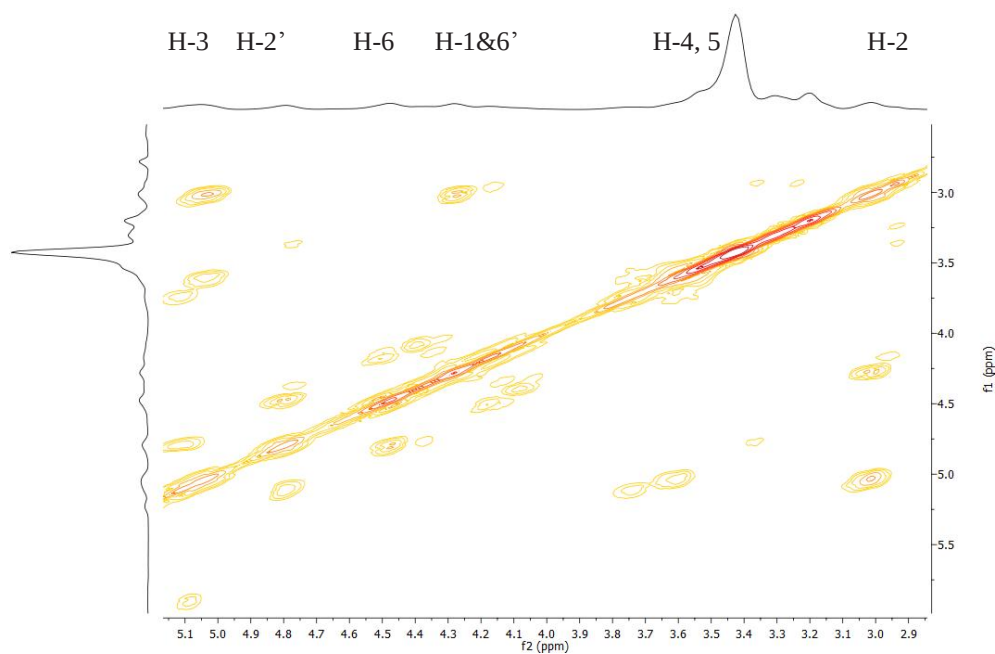


Figure 5.11 ^1H , ^1H COSY NMR (in CDCl_3) spectrum of 3,6-di-O-acetyl-2-O-methyl cellulose

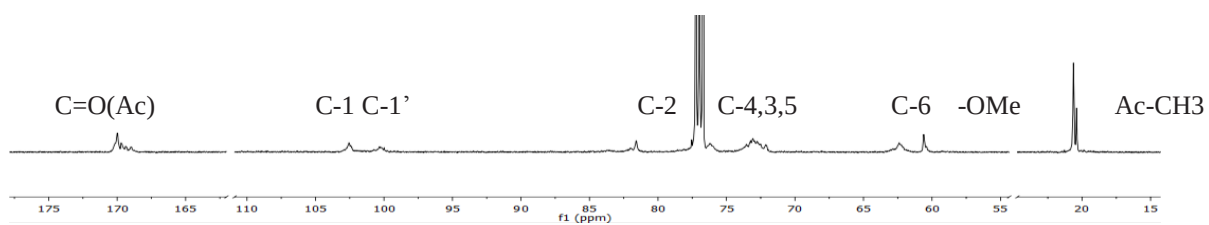


Figure 5.12 ^{13}C NMR (in CDCl_3) spectrum of 3,6-di-O-acetyl-2-O-methyl cellulose

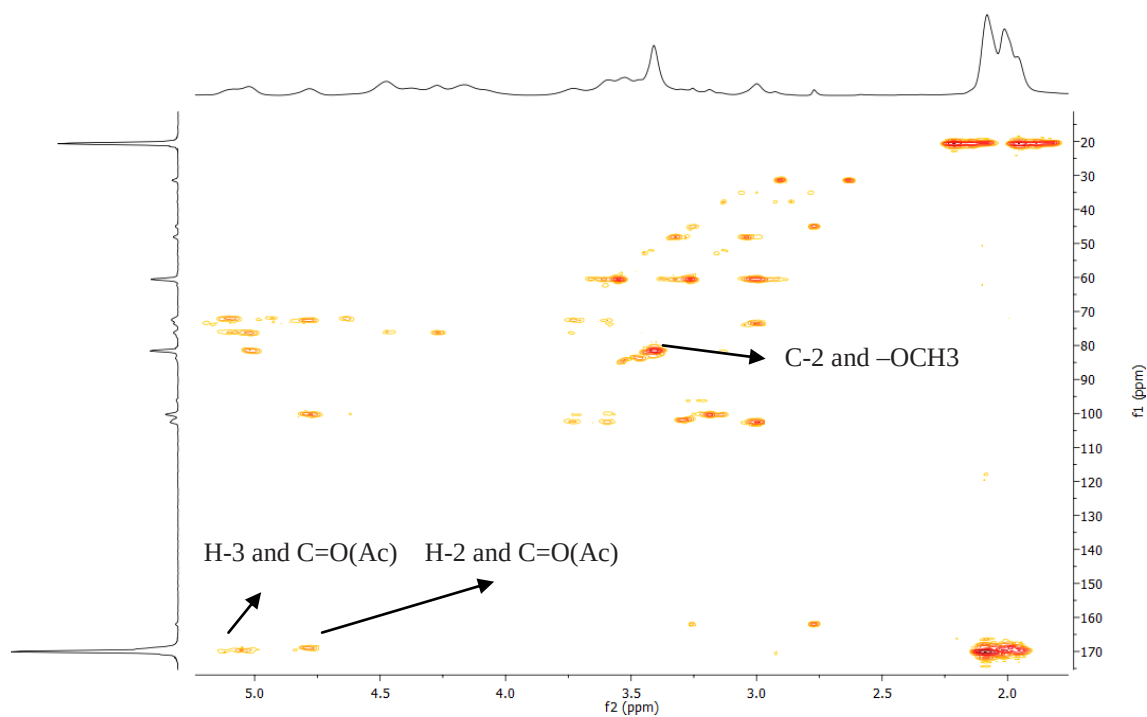


Figure 5.13 HMBC NMR (in CDCl_3) spectrum of 3,6-di-O-acetyl-2-O-methyl cellulose

5.6 Conclusions

The involvement of a protective group at C-3 changed the reactivity of cellulose derivatives vs. cellulose for subsequent reactions with bulky groups. 3-*O*-Benzyl cellulose has a surprisingly lower reactivity than cellulose towards silylation, which results from the absence of HOMO electron density at C-6 and C-2. Subsequent reactions of 3-*O*-allyl cellulose with bulky silyl and trityl protective groups were performed successfully. Some important intermediates with a DS around 1.0 were obtained, which open gateways to a variety of cellulose ether and ester homopolymers of regiospecifically substituted glucosyl units, among which, 3,6-di-*O*-acetyl-2-*O*-methyl cellulose was successfully synthesized via tritylated 3-*O*-allyl cellulose. Quantifying the degree of regioselectivity of these transformations will be our future work.

5.7 Acknowledgements

We thank the USDA for their financial support of this work through Grant No. 2011-67009-20090.

5.8 Abbreviations

Trityl triphenylmethyl

TDMS hexyldimethylsilyl

TMS trimethylsilyl

TBDPS *t*-butyldiphenylsilyl

TBDMS *t*-butyldimethylsilyl

TEA triethylamine

5.9 References

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Chapter 6: TBAF and Cellulose Esters: Unexpected Deacylation with Unexpected Regioselectivity

(Adapted from: Xu, D.; Edgar, K.J. *Biomacromolecules*, 2012, 13, 299-303.)

6.1 Abstract

Tetrabutylammonium fluoride has been found to catalyze the deacylation of cellulose esters. More surprisingly, the deacylation is highly regioselective. Even more remarkably, in contrast to the C-6 regioselectivity of other reactions of cellulose and its derivatives, this deacylation shows substantial selectivity for removal of the acyl groups from the esters of the secondary alcohols at C-2 and C-3, affording cellulose-6-*O*-esters with high regioselectivity by a simple one-step process employing no protective groups.

6.2 Keywords

cellulose ester, TBAF, deacylation, regioselectivity, polysaccharide, cellulose.

6.3 Introduction

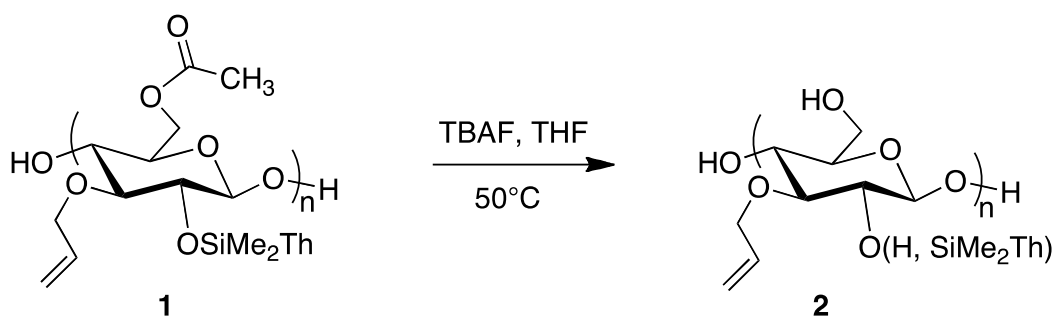
Regioselectivity in cellulose (and other polysaccharide) derivative synthesis is a difficult and important problem¹. The paucity of general solutions to this problem is a limiting factor in

the development of novel materials from renewable cellulose², which are an important part of a biorefinery-based economy³. Regioselectivity of substitution can have a strong impact on physical properties; solubility^{4,5}, optical properties⁶, thermal properties⁷, and crystallinity^{8,9} have all been shown to be strongly dependent on regioselectivity. The difficulty of regioselective substitution arises because of the low reactivity of cellulosic hydroxyls towards electrophiles, due to the restricted steric access, mobility, and wetting imposed by the linear, hydrophilic cellulose polymer structure. Often aggressive reaction conditions are required to drive reactions like esterification and etherification. The use of strong catalysts, high temperatures, and/or large molar excesses of reagents is not conducive to selectivity. The advent of solvents for cellulose has facilitated the first significantly regioselective syntheses of cellulose ethers and esters, by permitting the use of milder reaction conditions and reagents. Prior attempts to synthesize cellulose esters with high regioselectivity¹ have all involved the use of protective groups; these approaches add protection and deprotection steps to the synthesis, can significantly reduce overall yield, require high chemo- and regioselectivity in each of several steps, and can themselves reduce the reactivity of cellulose and impede succeeding reactions.

One of the few most interesting solvents for modification of cellulose has been dimethylsulfoxide (DMSO) containing tetrabutylammonium fluoride (TBAF)¹⁰. DMSO/TBAF dissolves cellulose faster and under milder conditions (room temperature, 15 min for degree of polymerization (DP) < 650) than any other cellulose solvent. Cellulose ether synthesis in DMSO/TBAF is effective¹¹, but several researchers have noted¹²⁻¹⁴ that the synthesis of cellulose esters in this solvent is of limited scope due to the low degree of substitution (DS) of the products obtained. This has been attributed by these authors (including ourselves) to the fact that TBAF as obtained is roughly a trihydrate; reaction of the waters of hydration (in preference to

cellulose) with the acylating reagent is cited as the probable cause of low DS ester products. What is more, the TBAF trihydrate is difficult to break by drying processes; attempts to do so result in β -elimination reactions of the TBA moiety, degrading the TBAF salt¹⁵.

In the course of our own work on synthesis of regioselectively substituted cellulose ethers and esters, we had occasion to prepare 3-allyl-2-thexyldimethylsilylcellulose-6-O-acetate **1** (Scheme 6.1).



Scheme 6.1 TBAF-catalyzed deacylation of 3-allyl-2-thexyldimethylsilylcellulose acetate

We attempted to deprotect silyl ether **1** with TBAF in THF¹⁶, but were surprised to observe complete cleavage of the acetate group (along with only partial cleavage of the silyl ether). Intrigued by this result, we wished to test its generality, choosing as substrate a commercial cellulose acetate (CA) of DS 2.42 (CA-398-30, Eastman Chemical Co.) because of its good solubility in THF, and report some unexpected results.

6.4 Experimental

6.4.1 Materials

Cellulose diacetate (CA-398-30, DS = 2.42, this data was originally from Eastman, but was also confirmed by ^1H NMR) was donated by Eastman Chemical Company. Cellulose triacetate and cellulose tripropionate were synthesized according to a literature method.^{17, 18} THF, DMSO and TBAF trihydrate were purchased either from Fisher or Sigma-Aldrich. All the chemicals were used without further purification.

6.4.2 Measurements

FTIR spectra were obtained from KBr pellets with a Thermo Electron Nicolet 8700 FT-IR spectrophotometer. The ^1H NMR, ^{13}C NMR, HMBC and COSY spectra were all acquired on a 600 NMR Bruker Avance II spectrometer (600 MHz) at 50 °C in CDCl_3 . The DS value of the acetyl unit was determined by the ratio of the integrals of the cellulose backbone protons and the acetyl resonances. The DS value of the propionyl unit was determined by the ratio of the integrals of the cellulose backbone protons and the propionyl methyl resonances.

$$\text{DS}_{\text{Acetate}} = 7I_{\text{Acetate}}/3I_{\text{Backbone}}$$

$$\text{DS}_{\text{Propionate}} = 7I_{\text{Propionate-CH}_3}/3I_{\text{Backbone}}$$

6.4.3 Hydrolysis of cellulose diacetate in THF

Cellulose diacetate (0.5 g, 1.9 mmol AGU) was dissolved in 20 mL THF. TBAF trihydrate (2.39 g, 4 mol/mol AGU) was then added to the solution. The mixture was allowed to react at 50 °C for 24 h and then precipitated in 150 mL water. The crude product was washed with water several time and dried under vacuum at 40 °C to yield product.

6.4.4 Perpropionylation of product

Polymer **1** (0.3 g) was dissolved in 5 ml pyridine, 20 mg 4-(dimethylamino)pyridine and 5 mL propionic anhydride. After stirring for 24 h at 80 °C, the product was precipitated from 100 mL water and washed several times with water. The crude product was collected by filtration and redissolved in 5 mL chloroform. This solution was added slowly with rapid stirring to 300 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C.

Table 6.1 ^1H and ^{13}C NMR Data for cellulose diacetate after 2 days hydrolysis in THF and perpropionylation

(Entry 7, Table 6.2)

Protons	AGU							Acetyl			Propionyl-CH ₂			Propionyl-CH ₃		
	1	2	3	4	5	6	6'	6	2	3	6	2	3	6	2	3
ppm	4.46	4.79	5.12	3.72	3.54	4.37	4.08	2.11	1.99	1.94	2.39	2.25	2.23	1.19	1.08	1.07

Carbons	AGU						Acetyl		Propionyl-Carbon		Propionyl-Carbonyl		
	1	2	3	4	5	6	CH3	Carbonyl	CH2	CH3	6	2	3
ppm	100.38	71.94	72.32	75.75	73.09	62.25	20.55	170.01	27.19	8.78	173.46	172.55	172.98

6.5 Results and discussion

Treatment of this DS 2.42 CA with TBAF in THF at 50°C (Scheme 6.2) provided a fascinating result. Substantial but not complete deacylation was observed, with the DS acetate reduced from 2.42 to 0.92 after 24 h. Upon careful examination of the product, in particular by ^1H and ^{13}C NMR of its perpropionylated derivative (to maximize solubility for NMR and to simplify the spectra, facilitating analysis)¹⁴, it became clear that not only had deacylation occurred with CA as well, but it had occurred in highly regioselective fashion. There was only one strong resonance for the acetyl methyl group in the proton NMR spectrum (Figure 6.1) at approximately 2.1 ppm, and likewise only one strong acetyl carbonyl in the ^{13}C NMR spectrum. The proton chemical shifts corresponded to those of cellulose-6-*O*-acetate, in accord with the work of Heinze¹⁹, and the spectra are consistent with the assignments of cellulose acetate monosaccharide resonances by Buchanan and co-workers^{20, 21}. As further confirmation, we carried out a heteronuclear multibond correlation NMR experiment (HMBC)²²; we have observed in the past that the cross peaks between ester carbonyls and the nearest ring hydrogens of the anhydroglucose (3-bond correlation) are not always strong enough to be observed, but when observed they are diagnostic of the position of substitution. In the case of the DS 0.88 CA product, the HMBC spectrum showed two clear correlation peaks between the two diastereotopic 6-H resonances at 4.37 and 4.08 ppm, and the acetate carbonyl ^{13}C resonance at 170 ppm (Figure 6.2).

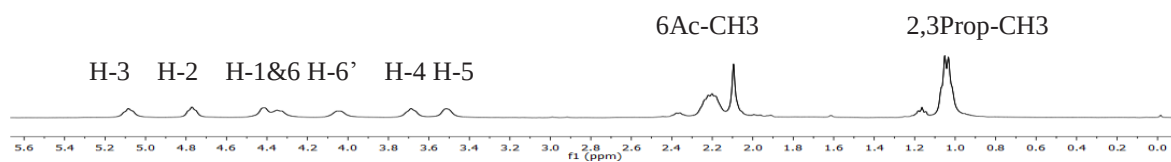
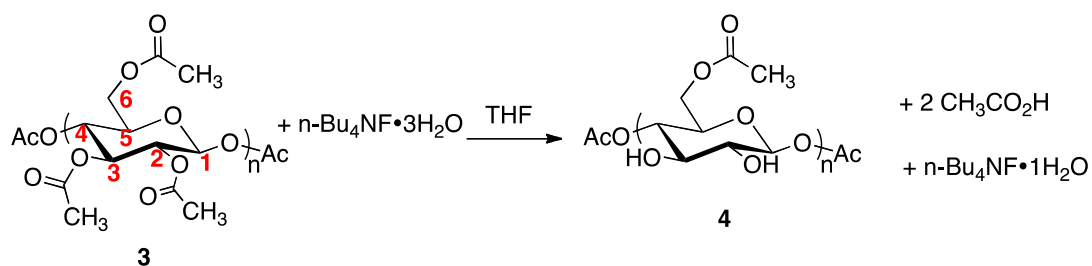


Figure 6.1 ^1H NMR spectrum of cellulose acetate **4** after perpropionylation (Entry 7, Table 6.2)



Scheme 6.2 Deacylation of CA by TBAF in THF

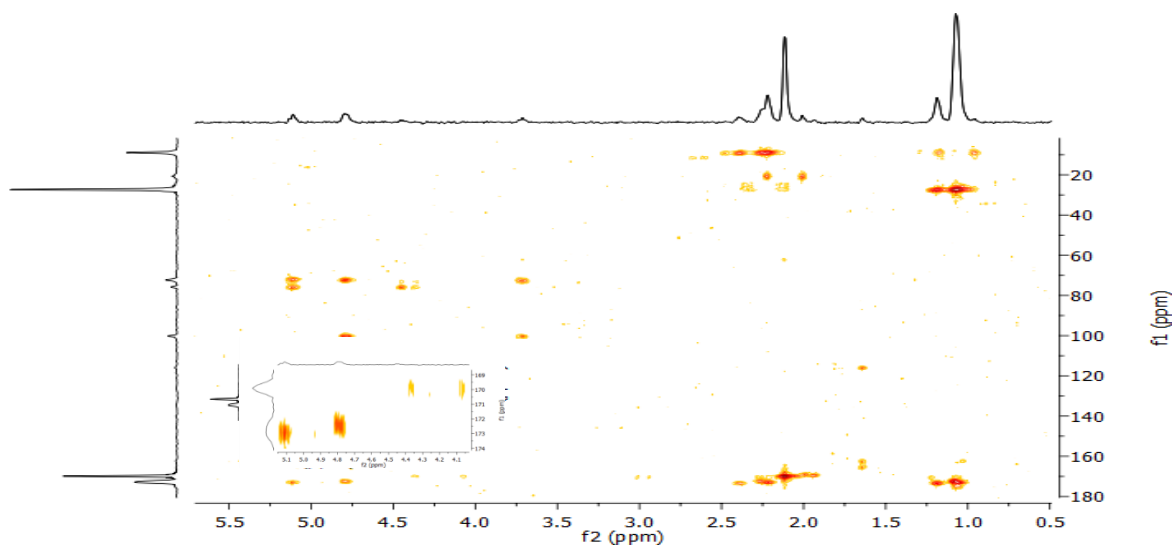


Figure 6.2 HMBC spectrum of CA (DS_6 0.79, $\text{DS}_{2,3}$ 0.09) (Entry 7, Table 1)

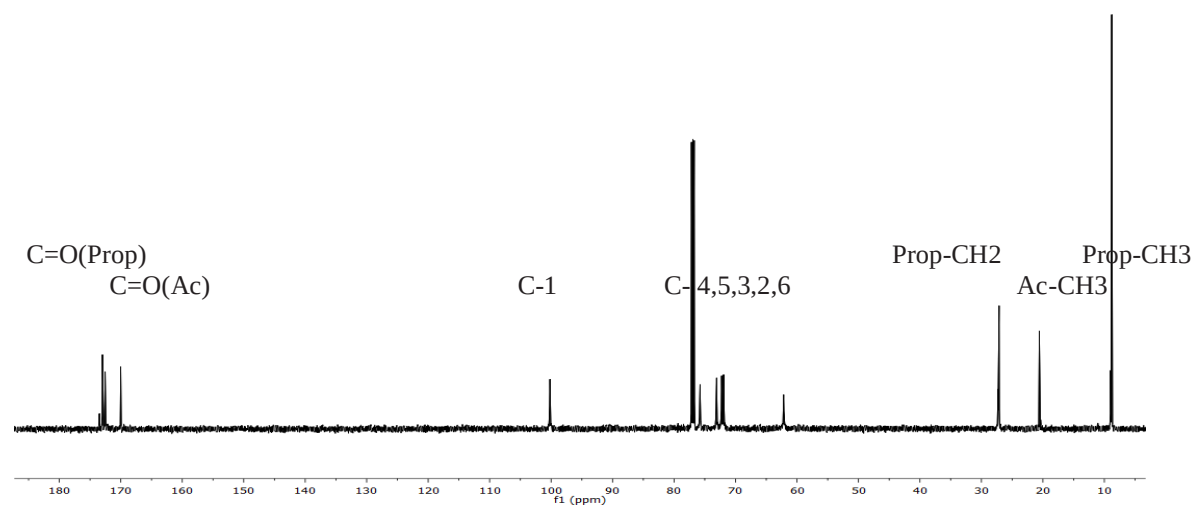


Figure 6.3 ^{13}C NMR spectrum of cellulose diacetate after 2 days TBAF deacylation in THF, followed by perpropionylation (Entry 7, Table 6.2)

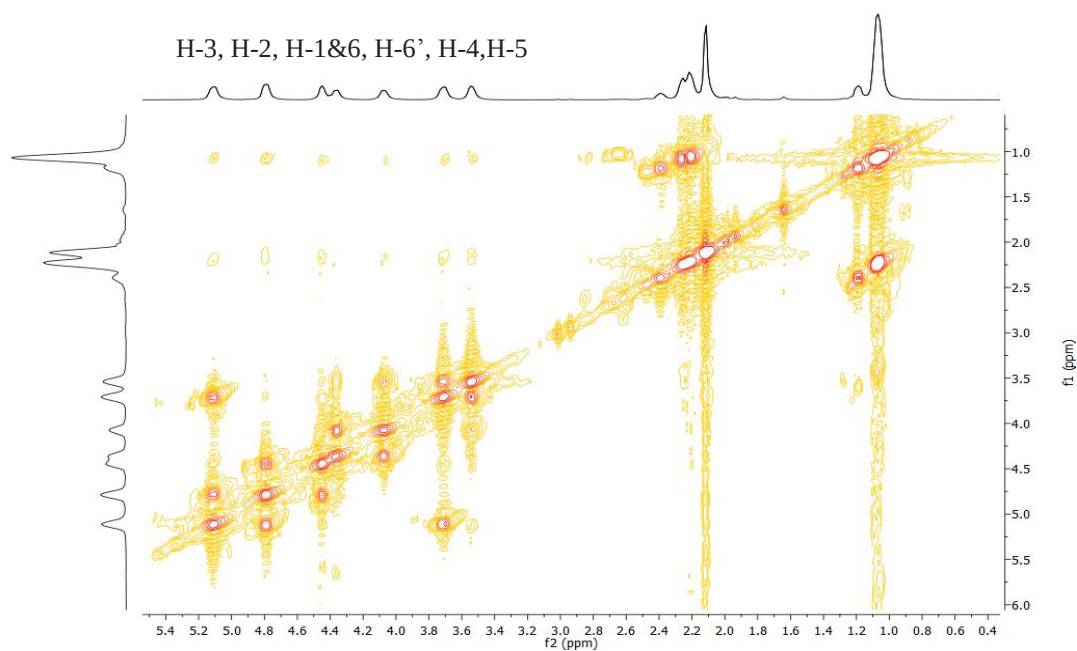


Figure 6.4 ^1H - ^1H COSY spectrum of cellulose diacetate after 2 days TBAF deacylation in THF, followed by perpropionylation (Entry 7, Table 6.2)

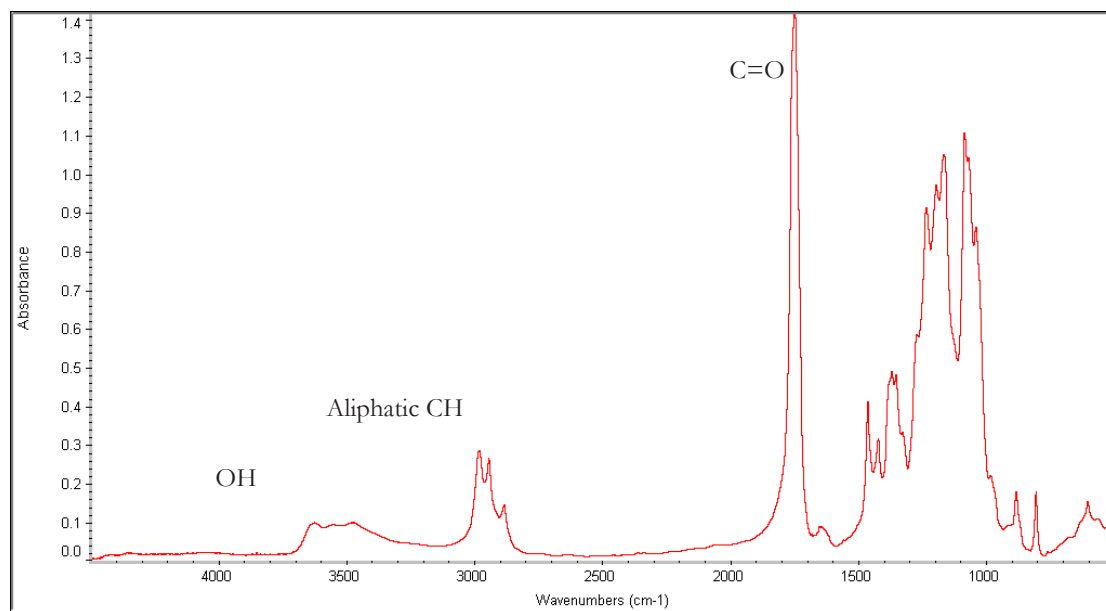


Figure 6.5 FTIR spectrum of cellulose diacetate after 2 days TBAF deacylation in THF, followed by perpropionylation (Entry 7, Table 6.2)

This was a stunning result. We did not anticipate the possibility of deacylation by TBAF. Accepting its occurrence, there was no reason to expect that the deacylation would be regioselective. And, should regioselectivity be observed, the literature would lead one to expect selectivity for deacylation at the less sterically hindered *O*-6 acetate group, not at the more hindered secondary *O*-2 and *O*-3 acetates. Close examination of the literature revealed a few hints of the possibility of fluoride-catalyzed deacylation. Bunton and Fendler investigated the catalysis of acetic and propionic anhydride hydrolyses by fluoride ion (NaF or KF)²³. They presented evidence that the observed rate acceleration was due to general base catalysis, rather than nucleophilic attack by F⁻ to generate acetyl fluoride. As we began this work we found no reports in the literature of deacylation of carbohydrate esters by TBAF, but in 1991 Rinehart and co-workers reported the deacylation of amino acids and peptides containing benzyl and nitrobenzyl ester protecting groups²⁴. They found that TBAF not only catalyzed deacylation, but also provided chemoselectivity, deacylating 4-nitrobenzyl esters selectively in the presence of benzyl esters. Ueki and co-workers observed²⁵ deacylation of phenacyl esters by TBAF and, in the presence of thiols, benzoate esters as well. After the completion of the work reported herein, El Seoud and co-workers²⁶ published a fascinating study that reported the deacylation of cellulose acetate and other cellulose esters catalyzed by tetraallylammonium fluoride in DMSO solvent. The authors did not report the observation of any regioselectivity in this deacylation reaction, and they attributed the deacylation to nucleophilic attack by F⁻ with acetyl fluoride generation.

In order to illuminate the nature of this unexpected deacylation, we carried out several additional experiments (Table 6.2).

Table 6.2 *Results of TBAX-catalyzed deacylation of CA*

Entry	TBAX (mol/AHG)	X	Time (h)	DS _{tot}	DS ₆	DS _{2,3}
1	0	F	24	2.42	0.82	1.60
2	0.008	F	24	2.42	0.82	1.60
3	1.0	F	24	1.56	0.82	0.74
4	2.0	F	24	1.27	0.82	0.45
5	3.0	F	24	1.06	0.82	0.24
6	4.0	F	24	0.92	0.82	0.10
7	4.0	F	48	0.88	0.79	0.09
8	4.0	F	72	0.84	0.76	0.08
9	5.0	F	24	0.63	0.61	0.02
10	6.0	F	24	0.59	0.59	0.00
11	4.0	Cl	24	2.42	0.82	1.60
12	4.0	I	24	2.42	0.82	1.60
13	4.0	OH	24	0	0	0

AHG = anhydroglucose unit. Starting CA DS 2.42, reaction temperature 50 °C

Exposure of CA (DS 2.42) to the chloride and iodide salts of TBA in THF gave no deacylation (entries 11 and 12, respectively). On the other hand, reaction with TBA hydroxide (TBAOH) in THF gave the expected complete deacylation of CA (entry 13). Catalytic TBAF (entry 1) afforded essentially no deacylation, and entries 3-6, 8, 9 show that approximately 4 equiv TBAF/AGU was the ideal amount for near complete deacylation at O-2 and O-3 with preservation of the O-6 acetyl. Higher molar ratios and longer reaction times did lead to partial deacylation at O-6. These results seem to exclude the mechanistic possibility of simple

deprotonation of the water of hydration by F^- followed by OH^- mediated ester hydrolysis; such deacylation in this system is not regioselective, as proven by the TBAOH result.

It was of interest for practical and mechanistic purposes to determine whether this reaction could be extended to cellulose triesters (Table 6.3) such as cellulose triacetate (CTA) and cellulose tripropionate (CTP)^{27, 28}.

Table 6.3 *TBAF-catalyzed deacylation of cellulose triesters*

Entry	Ester	TBAF (mol /AHG)	Solvent	Time (h)	DS _{tot}	DS ₆	DS _{2,3}
1	CTA	4.0	DMSO	24	1.37	0.77	0.60
2	CTA	4.0	THF	24	1.41	0.78	0.63
3	CTP	4.0	DMSO	24	1.07	0.91	0.16
4	CTP	4.0	THF	24	1.25	0.95	0.30
5	CTP	4.0	THF	48	1.01	0.80	0.21

Temperature 50°C, TBAF 4.0 mol/AHG

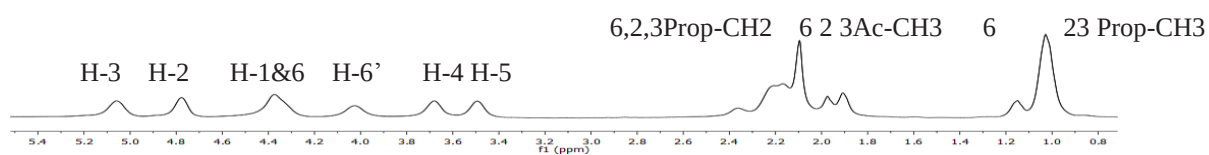


Figure 6.6 ^1H NMR spectrum of cellulose triacetate after 1 day TBAF deacylation in DMSO, followed by by perpropionylation (Entry 1, Table 6.3)

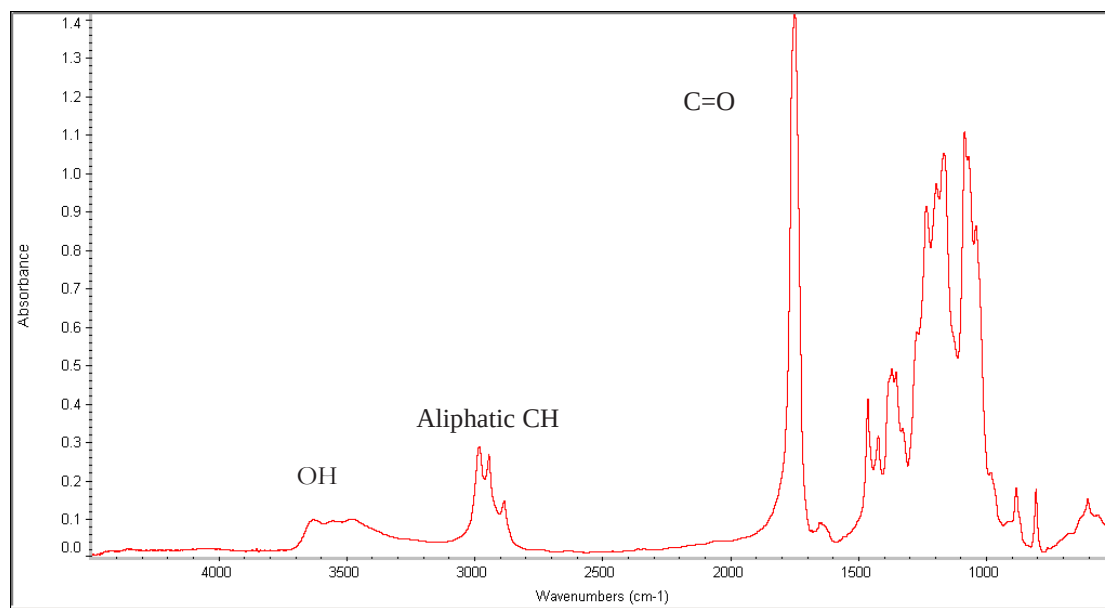


Figure 6.7 FTIR spectrum of cellulose triacetate after 1 day TBAF deacylation in DMSO, followed by perpropionylation (Entry 1, Table 6.3)

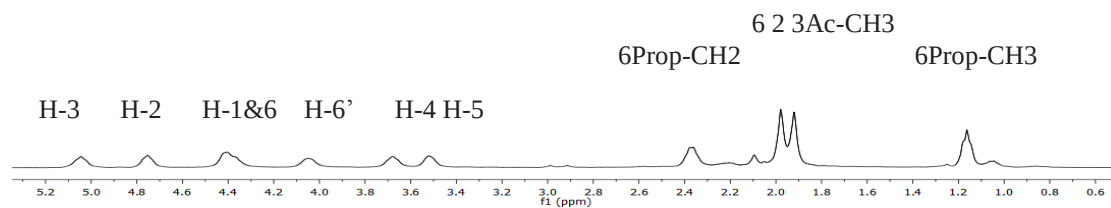


Figure 6.8 ^1H NMR spectrum of cellulose tripropionate after 3 days TBAF deacylation in THF, followed by peracetylation (Entry 5, Table 6.3)

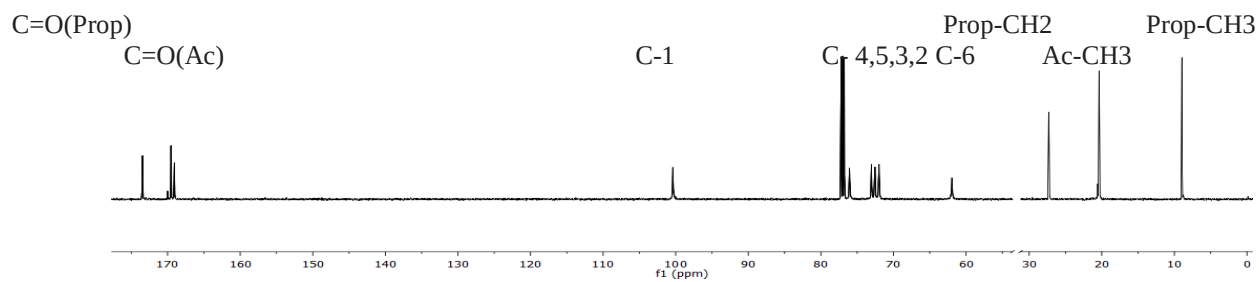


Figure 6.9 ^{13}C NMR spectrum of cellulose tripropionate after 3 days TBAF deacylation in THF, followed by peracetylation (Entry 5, Table 6.3)

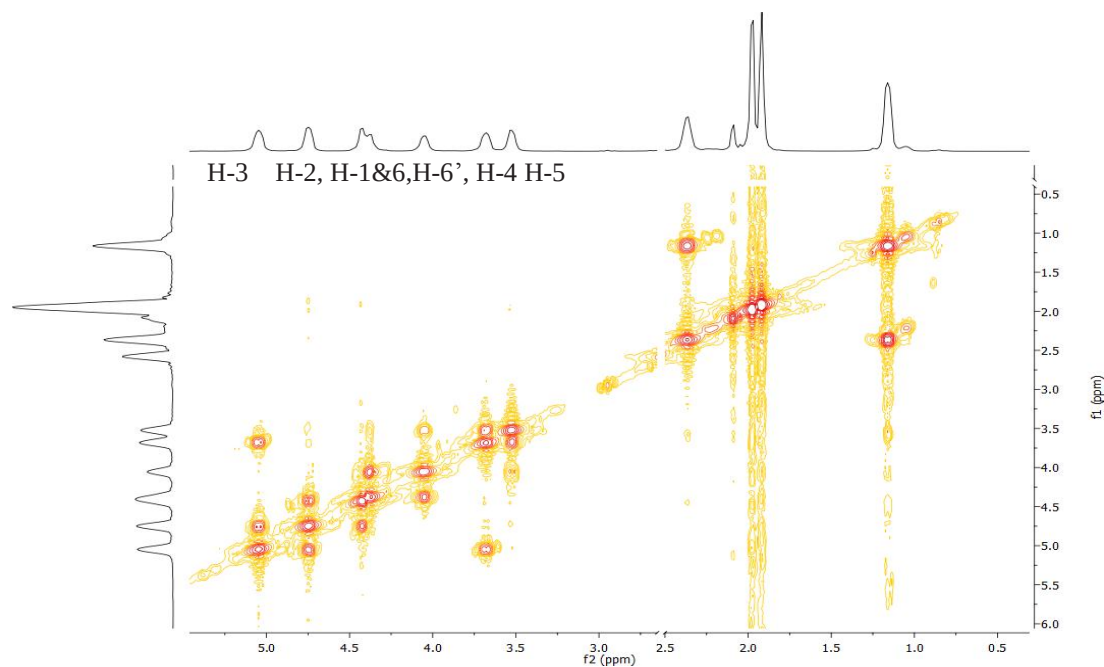


Figure 6.10 ^1H - ^1H COSY spectrum of cellulose tripropionate after 3 days TBAF deacetylation in THF, followed by peracetylation (Entry 5, Table 6.3)

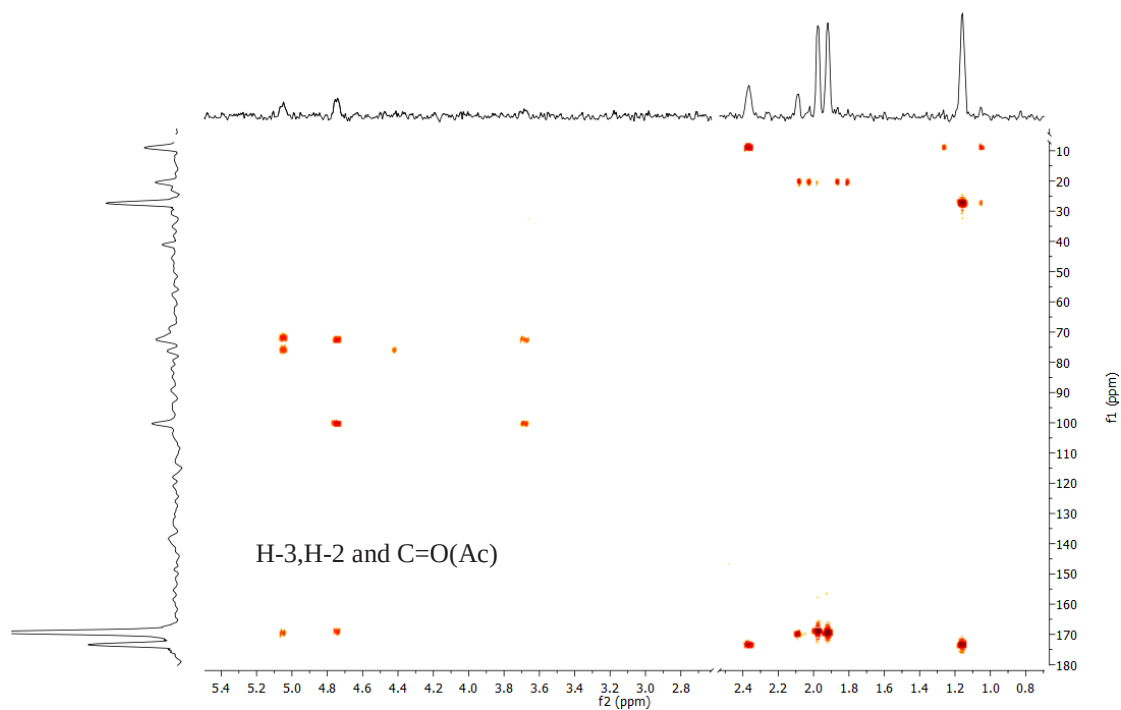


Figure 6.11 HMBC spectrum of cellulose tripropionate after 3 days TBAF deacetylation in THF, followed by peracetylation (Entry 5, Table 6.3)

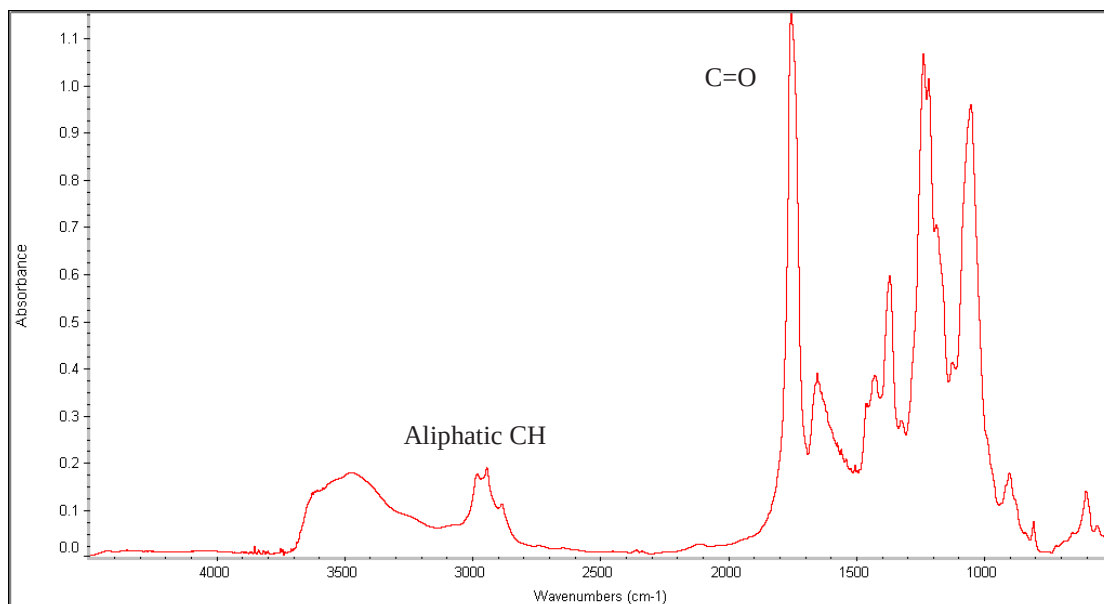


Figure 6.12 FTIR spectrum of cellulose tripropionate after 3 days TBAF deacylation in THF, followed by peracetylation (Entry 5, Table 6.3)

Table 6.4 ^1H NMR Data for cellulose triacetate after 1 day hydrolysis in DMSO and perpropionylation (Entry 1, Table 6.3)

Protons	AGU							Acetyl			Propionyl-CH ₂			Propionyl-CH ₃		
	1	2	3	4	5	6	6'	6	2	3	6	2	3	6	2	3
ppm	4.38	4.78	5.04	3.68	3.49	4.38	4.03	2.10	1.97	1.91	2.36	2.23	2.21	1.15	1.03	1.03

Table 6.5 ^1H and ^{13}C NMR Data for cellulose tripropionate after 3 days hydrolysis in THF and peracetylation (Entry 5, Table 6.3)

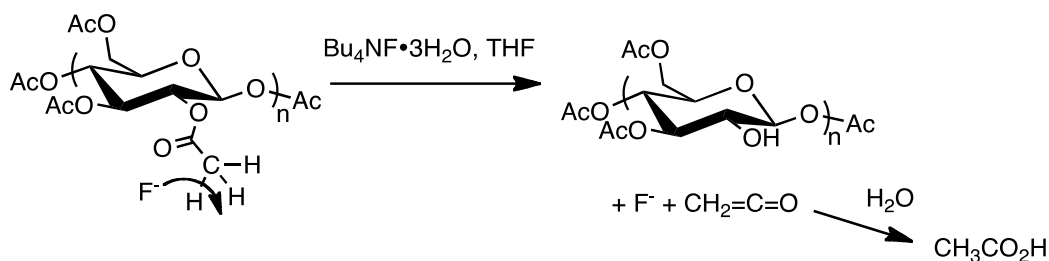
Protons	AGU							Acetyl			Propionyl-CH ₂			Propionyl-CH ₃		
	1	2	3	4	5	6	6'	6	2	3	6	2	3	6	2	3

ppm	4.42	4.75	5.05	3.68	3.53	4.38	4.05	2.09	1.98	1.92	2.36	1.16
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Carbons	AGU						Acetyl	Acetyl-Carbonyl			Propionyl		
	1	2	3	4	5	6	CH3	6	2	3	CH2	CH3	Carbonyl
ppm	100.51	72.01	72.58	76.08	73.03	61.93	20.33	170.02	169.08	169.52	27.41	8.97	173.46

Reaction of CTA with TBAF in DMSO (CTA is not fully soluble in THF) afforded deacylation that was also selective for the secondary acetates, albeit less so than observed in THF with CA of DS 2.42. Reaction of CTA with TBAF in THF (the CTA dissolves as it reacts) was also successful, with similar regioselectivity to that observed in DMSO. Deacylation of CTP by TBAF in THF (in which CTP is soluble) was also effective, as well as regioselective in similar fashion as for the cellulose acetates. In the case of CTP, regioselectivity is high in both THF and DMSO.

It seems likely that this unusual reaction is the result either of nucleophilic attack of F^- upon the acyl carbonyls, producing acyl fluoride as an intermediate that is then hydrolyzed by water (either adventitious, or the TBAF waters of hydration), or by general base catalysis by F^- . The observed regioselectivity, in which deacylation occurs not at the less hindered 6-O-acetate, but rather at the acetates of the secondary alcohols at the 2- and 3-O positions, argues against the nucleophilic displacement mechanism. If such a mechanism were operative, precisely the opposite regioselectivity would be expected. We suspect that a general base-catalyzed mechanism may be occurring, and that the key step is deprotonation of the acyl moieties alpha to the carbonyl group. Subsequent elimination of a ketene, and capturing of the ketene by water affords the carboxylic acid (Scheme 6.3).



Scheme 6.3 *Proposed deacylation mechanism*

This appears to be consistent with our observations. Note that it is also in accord with the chemoselectivity observed by Rinehart and co-workers²²; the acidity of the α -proton in p-nitrobenzyl esters is much higher than that of the benzyl ester α -proton. Very recently Gu et al. described²⁹ the selective removal using TBAF of chloroacetyl ester groups from small molecule carbohydrates, which in some cases also contained acetate and benzoate esters. The acetates and benzoates were not removed, which is consistent with the ketene mechanism we have proposed, since protons alpha to the ester carbonyl in chloroacetate groups are more acidic than those of acetate groups. Another very recent publication from workers at Sanofi-Aventis³⁰ is also pertinent; these researchers reported the $\text{S}_{\text{N}}2$ displacement of a glucose-4-triflate by F^- , producing a galactose-4-fluoride derivative, employing excess TBAF in 2-methyltetrahydrofuran at room temperature. This glucose-4-triflate had all of its other hydroxyl groups protected as benzoate esters, which were not hydrolyzed by the TBAF according to the authors. Since benzoate esters do not have α -protons, this report is also consistent with our proposed mechanism of deacylation by TBAF.

The deacylation reactions all proceed, in THF at equivalent temperature and TBAF/anhydroglucose molar ratio, to similar extent after 24 h; for example, with 4 equiv TBAF at 50°C, approximately 1.5-1.7 DS acyl is removed in each case (entry 6, Table 6.2; entries 1-4,

Table 6.3). This could be the result of increasing moderation of the basicity of the F^- ion as the carboxylic acid co-product is generated. Another limiter for the extent of deacylation could be the availability of water for reaction with the ketene co-product (Scheme 6.3), which if not consumed by hydrolysis would be expected to simply reacylate cellulose. If the TBAF trihydrate is the only source of water, then there are approximately 12 molar equivalents per AGU of water available, or roughly 7.5 equiv (12 mol H_2O /1.6 mol acyls removed) per mol of putative ketene generated. While this is an excess of available water, it is possible that the removal of the second water of TBAF hydration is significantly more energetically unfavorable than removal of the first water of hydration.

While the regioselectivity for deacylation at O-2 and O-3 is not yet fully understood, it would be consistent with the proposed mechanism if relief of steric hindrance in the ground state were a key driver; removal of a proton and generation of a ketene from the O-2- and O-3-esters relieves more ground state steric strain than deacylation of the O-6 ester.

Deacylation of cellulose esters has clear potential as a single-step synthesis of highly regioselectively substituted cellulose 6-O-esters, as well as being a simple route to the cellulose-2,3-O-(ester 1)-6-O-(ester 2) esters (for example, cellulose-2,3-O-dibutyrate-6-O-acetate) which can easily be prepared from them. Application of this deacylation reaction to other polysaccharide and carbohydrate esters also has obvious promise for advancing our understanding of structure/property relationships, analytical characteristics, and for the development of practical syntheses of other highly regioselectively substituted renewable-based materials. In addition, these observations can help us to understand the limitations on product DS observed by most investigators attempting cellulose acylation in DMSO/TBAF. Investigations under way in our laboratory will further explore the mechanism of

this remarkable deacylation reaction and its potential for the synthesis of regioselectively substituted polysaccharide derivatives.

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Chapter 7: Synthesis of Cellulose Levulinate and Its Role as A Protective Group

7.1 Abstract

Cellulose levulinate was synthesized homogenously in DMAc/LiCl by reacting cellulose with different levulinic acid derivatives. Levulinic acid was either converted to levulinoyl chloride prior to reaction or activated *in situ* with N,N'-dicyclohexylcarbodiimide (DCC), p-toluenesulfonyl chloride (tosyl chloride), or 1,1'-carbonyldiimidazole (CDI) respectively. Product DS was determined by ^1H NMR spectroscopy after perpropionylation and the highest DS value reached was around 0.5. The reaction occurred preferentially at primary hydroxyl groups. The new cellulose levulinate after peracetylation or perpropionylation could be hydrolyzed by hydrazine in pyridine. Acetate and propionate esters were stable under such conditions, creating the potential to use levulinate as a protective group for the synthesis of regioselectively substituted cellulose esters.

7.2 Keywords

Cellulose levulinate, levulinic acid, levulinoyl chloride, *in situ* activation, hydrolysis, NMR spectroscopy

7.3 Introduction

Levulinic acid, also known as 4-oxopentanoic acid, is a carboxylic acid containing a γ -ketone group. The general approach to prepare levulinic acid is the dehydration of cellulose under acidic conditions.¹⁻³ Recently, a new industrial process has been developed to produce levulinic acid in higher yield but less cost.⁴ Derived from biomass, levulinic acid and its derivatives find many applications. For example, they have been used to prepare polymers including rubbers⁵, polyamides⁶, copolymers⁷ and epoxy resins⁸; they are also applied in cosmetic areas⁹ and in drug delivery systems¹⁰.

The regioselective synthesis of cellulose derivatives is still a challenge. Up to now, the main strategy for synthesis of regioselectively substituted cellulose derivatives is to use protective groups.^{11,12} Among those protective groups, bulky ether protective groups are of special interest. Thexyldimethylsilyl (TDMS) cellulose has been an important intermediate. Under homogeneous conditions in DMAc/LiCl, both 6 and 2 positions within the AGU can react with thexyltrimethylchlorosilane to form the 2,6-di-*O*-TDMS cellulose ether. On the other hand, if the reaction media is heterogeneous with NMP/NH₃ at -15 °C, the silylation happens exclusively at O-6.^{13,14} Silyl protecting groups can be completely removed by treatment with tetrabutylammonium fluoride, opening up a relatively simple pathway to regioselective synthesis of cellulose derivatives. For example, 3-methylcellulose-2,3-diacetate¹³ and 3-allylcellulose-2,6-diacetate¹⁵ were prepared after deprotection and other functionalization steps. However our group recently found TBAF not only cleaves silyl groups, but also esters¹⁶, which makes the usage of silyl protective group to synthesize regioselective cellulose esters become almost impossible. Levulinate, which could serve as a protective group, has the potential for the synthesis of regioselectively substituted cellulose esters because of the ease of forming and

removal of levulinate. In particular, hydrazine can cleave levulinate in carbohydrates, nucleosides and steroids selectively while alkanoate esters including acetate and propionate are stable under such conditions.^{17,18}

Synthesis of cellulose esters often requires harsh conditions due to the low reactivity of hydroxyl groups of cellulose. The low reactivity is caused by high propensity for both inter- and intramolecular hydrogen bonding. Solvent systems such as DMAc/LiCl have facilitated the synthesis of cellulose esters by permitting acylation of cellulose with reactive agents like acyl halides and carboxylic acid anhydrides in a homogeneous medium.¹⁹ Scientists have used the strategy of activating the carboxylic acids to produce very reactive intermediates, capable of reaction with cellulose to produce the corresponding cellulose esters.²⁰

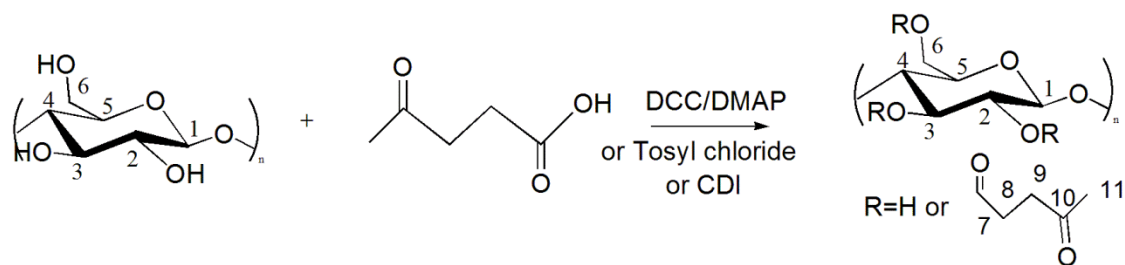
Dicyclohexylcarbodiimide (DCC) in combination with 4-pyrrolidinopyridine (PP) is an effective condensation agent and it has been applied to activate various aliphatic carboxylic acids to form cellulose esters with low DS values.^{21,22} It was also employed to prepare long chain cellulose esters up to eicosanoates within a wide range of DS; even complete substitution was reported.²³

Another method is the *in situ* activation of carboxylic acids with tosyl chloride, forming the mixed anhydride and subsequently the symmetrical carboxylic acid anhydride.²⁴ Recently, it was found the acid chloride is formed in the reaction mixture too.²⁵ Both these acid anhydrides and acid chloride become very reactive intermediates towards esterification of cellulose. It was shown that the conversion of cellulose with 3,6,9-trioxadecanoic acid or 3,6-dioxahexanoic acid via this route could give a wide DS value range from 0.4 to 3.0 depending on reaction conditions.²⁵

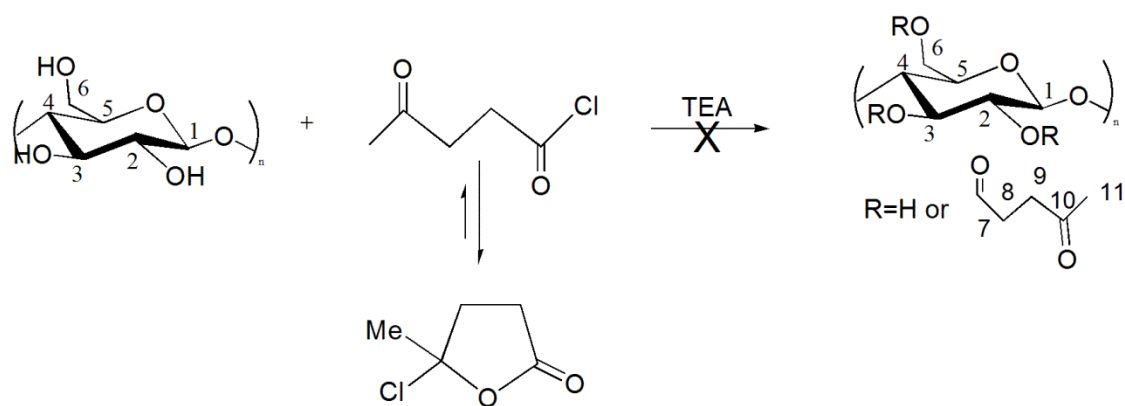
A fairly efficient reagent is 1,1'-carbonyldiimidazole (CDI), which can activate carboxylic acids to form the imidazolides as the acylating reagents.²⁶ This method is more environmentally benign compared with other methods, since the only by products are CO₂ and imidazole, which are non-toxic.²⁷

An important alternative to *in situ* activation is direct acylation with acyl chlorides. Acyl chlorides are highly reactive agents for cellulose esterification. One simple example is cellulose acetate synthesized by reacting cellulose with acetyl chloride in DMAc/LiCl.²⁸ The conversion can be controlled by stoichiometry and a complete substitution can be achieved. A number of bulky acyl chlorides have been applied as well to form cellulose esters and the resulting DS and substitution pattern of these bulky cellulose esters were studied in detail (see Chapter 3).²⁸

Herein we wish to report the protection of cellulosic hydroxyl groups by forming cellulose levulinate esters (see Scheme 7.1 and 7.2) and the successful selective deprotection of the levulinate groups with hydrazine while acetate or propionate are stable under such conditions (see Scheme 7.3). For the activation of levulinic acid, different methods were studied including *in situ* activation with DCC/DMAP, tosyl chloride, or CDI as well as direct conversion of levulinic acid to levulinoyl chloride. The products were characterized by means of IR and NMR spectroscopy and the DS values were calculated by ¹H NMR spectroscopy after perpropionylation.



Scheme 7.1 Conversion of cellulose with levulinic acid and DCC/DMAP, CDI or tosyl chloride in *DMAc/LiCl*



Scheme 7.2 Conversion of cellulose with levulinoyl chloride in *DMAc/LiCl*

7.4 Experimental

7.4.1 Materials

Cellulose (Avicel PH-101, DP=280) was dried under vacuum before use. Other reagents were purchased from Fisher and used without further purification.

7.4.2 Measurements

The FTIR spectra were recorded with a Thermo Electron Nicolet 8700 FT-IR spectrophotometer by using KBr pellets. ^1H spectra were acquired on a Varian INOVA 400 (400 MHz) spectrometer at ambient temperature with 32 scans in CDCl_3 . ^{13}C NMR spectra were acquired on a 500 NMR Bruker Avance II spectrometer (500 MHz) at 50 °C with 15000 scans in CDCl_3 . Chemical shifts are reported relative to the solvent peaks.

7.4.3 General procedure for dissolution of cellulose in DMAc/LiCl

For a typical procedure²⁹, cellulose (1.6 g, 9.88 mmol) was suspended in 60 mL DMAc, the mixture was heated to 150 °C over 26 min. LiCl (3 g) was added and the mixture was heated to 170 °C over 8 min. Distillate (16 mL) was collected at 170 °C. The reaction mixture was finally cooled down to room temperature and stirred overnight.

7.4.4 Synthesis of cellulose levulinate via levulinic acid/DCC

Cellulose (1.6 g, 9.88 mmol) was dissolved in DMAc/LiCl by the general procedure. DCC (6.11 g, 29.64 mmol, 3 mol/mol AGU) was then added to the solution followed by the addition of levulinic acid (3.44 g, 29.64 mmol, 3 mol/mol AGU). DMAP (0.05 g) was then added as catalyst. The mixture was allowed to react at 40 °C for 24 h under an N_2 atmosphere. The homogeneous mixture was precipitated in 200 mL methanol and washed with 3×500 mL methanol, and dried under vacuum at 40°C to yield product (sample 1).

Yield: 1.28 g, 65 %.

Degree of substitution (DS): 0.36 (determined by ^1H NMR spectroscopy after perpropionylation).

FT-IR (cm^{-1}): 3447 $\nu(\text{OH})$, 2924 $\nu(\text{C-H})$, 1425 $\nu(\text{CH}_2)$, 1637 $\nu(\text{ketone carbonyl})$, 1761 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 2.14-2.90 (levulinate), 2.18, 2.36 (CH_2 -propionate), 1.03, 1.16 (CH_3 -propionate), 3.49-5.06 (AGU).

^{13}C NMR (in CDCl_3): δ (ppm) = 205.94-207.20 (ketone carbon-levulinate), 172.46-173.31 (CO), 100.18 (C^1), 71.71-72.90 (C^2 , C^3 , C^5), 75.95 (C^4), 61.92 (C^6), 27.66 (C^8), 37.56, 38.09 (C^9), 29.69 (C^{11}), 27.19 (CH_2 -propionate), 8.92 (CH_3 -propionate).

7.4.5 Synthesis of cellulose levulinate via levulinic acid/tosyl chloride

Cellulose (1.6 g, 9.88 mmol) was dissolved in DMAc/LiCl by the general procedure. Levulinic acid (10.45 g, 6.96 mmol, 6 mol/mol AGU) dissolved in 10 ml DMAc and tosyl chloride (11.44 g, 6.96 mmol, 6 mol/mol AGU) dissolved in 10 mL DMAc were added to cellulose solution. The mixture was allowed to react at 80 $^{\circ}\text{C}$ for 24 h under N_2 . The homogeneous mixture was precipitated in 200 mL ethanol and washed with 500 mL ethanol for three times, then dried under vacuum at 40 $^{\circ}\text{C}$ to yield product (sample 4).

Yield: 1.46 g, 70 %.

Degree of substitution (DS): 0.50 (determined by ^1H NMR spectroscopy after perpropionylation).

FT-IR (cm^{-1}): 3451 $\nu(\text{OH})$, 2923 $\nu(\text{C-H})$, 1423 $\nu(\text{CH}_2)$, 1638 $\nu(\text{ketone carbonyl})$, 1760 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 2.14-2.90 (levulinate), 2.18, 2.36 (CH_2 -propionate), 1.03, 1.16 (CH_3 -propionate), 3.49-5.06 (AGU).

^{13}C NMR (in CDCl_3): δ (ppm) = 205.80-207.48 (ketone carbon-levulinate), 169.11-172.31 (CO), 100.43 (C^1), 71.57-72.78 (C^2 , C^3 , C^5), 76.15 (C^4), 62.06 (C^6), 29.78 (C^8), 37.56, 38.07 (C^9), 29.55 (C^{11}), 27.19 (CH_2 -propionate), 8.92 (CH_3 -propionate).

7.4.6 Synthesis of cellulose levulinate via levulinic acid/CDI

Cellulose (1.6 g, 9.88 mmol) was dissolved in DMAc/LiCl by the general procedure. Levulinic acid (3.44 g, 29.64 mmol, 3 mol/mol AGU) was dissolved in 10 mL DMAc, followed by the addition of CDI (4.80 g, 29.64 mmol, 3 mol/mol AGU). The mixture was added to the cellulose solution, which was then stirred at 80 °C for 24 h under N_2 . The homogeneous mixture was precipitated into 200 mL ethanol, filtered, and the precipitate was washed with 3×500 mL ethanol. It was dried under vacuum at 40 °C to yield product (sample 5).

Yield: 1.20 g, 60 %.

Degree of substitution (DS): 0.44 (determined by ^1H NMR spectroscopy after perpropionylation).

FT-IR (cm^{-1}): 3447 $\nu(\text{OH})$, 2924 $\nu(\text{C-H})$, 1425 $\nu(\text{CH}_2)$, 1637 $\nu(\text{ketone carbonyl})$, 1761 $\nu(\text{CO}_{\text{Ester}})$.

^1H NMR (in CDCl_3): δ (ppm) = 2.14-2.90 (levulinate), 2.18, 2.36 (CH_2 -propionate), 1.03, 1.16 (CH_3 -propionate), 3.49-5.06 (AGU).

^{13}C NMR (in CDCl_3): δ (ppm) = 205.94-207.20 (ketone carbon-levulinate), 172.46-173.31 (CO), 100.18 (C^1), 71.71-72.90 (C^2 , C^3 , C^5), 75.95 (C^4), 61.92 (C^6), 27.66 (C^8), 37.56, 38.09 (C^9), 29.69 (C^{11}), 27.19 (CH_2 -propionate), 8.92 (CH_3 -propionate).

7.4.7 Synthesis of levulinoyl chloride

A solution of levulinic acid (10 g, 0.086 mol) and DMF (1 drop) in dichloromethane was cooled to 0 °C, and oxalyl chloride (22.3 ml, 0.258 mol) was slowly added. After 60 min at 15 °C, the solvent was removed under reduced pressure. The acid chloride was produced as oil that was not purified further.

7.4.8 Synthesis of cellulose levulinate via levulinoyl chloride

Cellulose (1.6 g, 9.88 mmol) was dissolved in DMAc/LiCl by the general procedure. Et₃N (8.25 mL, 59.28 mmol, 6 mol/mol AGU) was added all at once; then, levulinoyl chloride (6.5 g, 49.4 mmol, 5 mol/mol AGU) was added dropwise. The mixture was allowed to react at 60 °C for 24 h under N₂. The homogeneous mixture was precipitated into 200 mL methanol and washed with 3×500 mL methanol, and dried under vacuum at 40 °C to yield product (sample 7).

Yield: 1.35 g, 53 %.

Degree of substitution (DS): 0 (determined by ¹H NMR spectroscopy after perpropionylation).

¹H NMR (in CDCl₃): δ (ppm) = 2.18, 2.36 (CH₂-propionate), 1.03, 1.16 (CH₃-propionate), 3.49-5.06 (AGU).

7.4.9 Peracetylation

Cellulose levulinate (0.3 g) was put into a solution of 5 mL pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL acetic anhydride. After stirring for 24 h at 80 °C, the mixture was cooled down and poured into 100 mL water with rapid stirring. The crude product was collected by filtration, and washed several times with excess water. It was redissolved in 5

mL CHCl_3 . This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C.

7.4.10 Perpropionylation

Cellulose levulinate (0.3 g) was dissolved in a mixture of 5 mL pyridine, 20 mg 4-(dimethylamino)pyridine, and 5 mL propionic anhydride. After stirring for 24 h at 80 °C, the product was cooled down and poured into 100 mL water with rapid stirring, washed several times with water. The crude product was collected by filtration, then was redissolved in 5 mL CHCl_3 . This solution was added slowly with rapid stirring to 100 mL ethanol. After filtration and washing with excess ethanol several times, the sample was dried under vacuum at 40 °C.

7.4.11 General procedure for hydrolysis of levulinic acid esters¹⁸

Peracetylated cellulose levulinate (0.4 g) was dissolved in 14 mL pyridine and 3.6 mL AcOH. Hydrazine monohydrate (0.5 mL, 8.89 mol/mol AGU) was added and the solution was allowed to stir at room temperature for 24 h. The product was poured into 100 mL water, washed several times with water, and dried under vacuum at 40 °C. The product was then perpropionylated in order to permit a better resolved NMR spectra.

FT-IR (cm^{-1}): 3478 $\nu(\text{OH})$, 2984 $\nu(\text{C-H})$, 1770 $\nu(\text{CO}_{\text{Ester}})$.

^{13}C NMR (in CDCl_3): δ (ppm) = 169.51-173.95 (CO), 100.65 (C^1), 71.45-72.93 (C^2 , C^3 , C^5), 75.82 (C^4), 61.99 (C^6), 20.30 (CH_3 -acetate), 27.35 (CH_2 -propionate), 8.80 (CH_3 -propionate).

7.5 Results and Discussion

7.5.1 Synthesis of cellulose levulinate via levulinic acid/DCC

In situ activation of levulinic acid is possible with DCC. DCC is well known in peptide and protein chemistry as an agent for the coupling of amino functions and carboxylic acid groups. It was first used together with 4-pyrrolidinopyridine (PP) by Glasser et al. for the synthesis of cellulose esters with various carboxylic acids.²¹ Other long chain cellulose esters up to eicosanoic acid ester were produced by this method with a wide range of DS values.²³ DMAP has been proven to be more effective than PP for this coupling reaction. Together with DCC, DMAP has been used to synthesize unsaturated and aromatic cellulose esters.³⁰ The advantage of this method lies in the high reactivity of the mixed anhydride formed as an intermediate and a completely homogeneous reaction condition in DMAc/LiCl. However, the highly toxic DCC needs to be recycled carefully.

Cellulose levulinate was successfully synthesized in DMAc/LiCl with DCC/DMAP and a representative ¹H NMR spectrum of cellulose levulinate after perpropionylation is shown in Figure 7.1. A rather small DS value of 0.36 was obtained at a molar ratio of levulinic acid /AGU of 3 mol/mol within a reaction time of 24 h at 40 °C. With a higher reaction temperature at 80 °C, an increase of the molar ratio levulinic acid/AGU from 1:3 to 1:6 yields a product with DS of 0.5, which is still quite low. The product with such a low DS is not soluble in chloroform or DMSO.

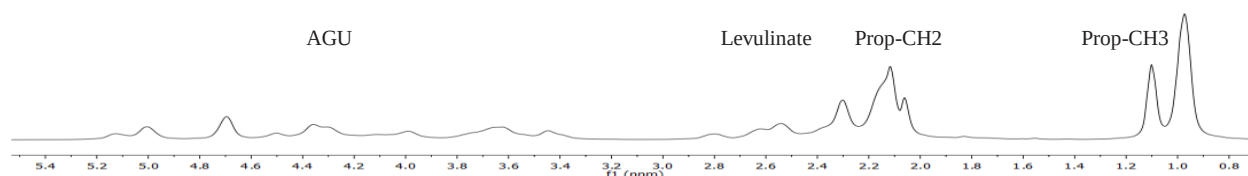


Figure 7.1 ^1H NMR spectrum of cellulose levulinate after perpropionylation (sample 2)

7.5.2 Synthesis of cellulose levulinate via levulinic acid/tosyl chloride

Another efficient reagent for the *in situ* activation of carboxylic acids is p-toluenesulfonyl chloride (tosyl chloride). It was first applied to synthesize cellulose acetates.²⁴ Long chain or bulky cellulose esters were also produced via this path.^{24,27} The advantage of tosyl chloride lies in the fact that esterification can occur without addition of a base and that DS of 3,6,9-trioxadecanoic acid ester up to 3 can be achieved.²⁵ Synthesis of cellulose levulinate using tosyl chloride was previously reported in a Japanese patent application; however, no detailed results were published.³¹

Although the reactive intermediates formed *in situ* during this reaction are still under discussion, it is generally accepted that both acid anhydride and the mixed anhydride of carboxylic acid and toluene sulfonic acid become reacting sites.^{24, 27}

We examined the reaction of levulinic acid with cellulose in the presence of tosyl chloride. Cellulose levulinate was produced when treating cellulose dissolved in DMAc/LiCl with levulinic acid in the presence of tosyl chloride leading to the levulinic acid ester. A rather low DS

of 0.10 was achieved at a molar ratio of AGU/ levulinic acid/Tos-Cl of 1/3/3 within 24 h at 80 °C. A further increase of the molar ratio to 6 mol levulinic acid/mol AGU still does not form a high DS product, only DS 0.50.

7.5.3 Synthesis of cellulose levulinate via levulinic acid/CDI

Comparable results were obtained by reacting cellulose with levulinic acid/CDI. This method is of special interest for cellulose modification, since the pH stays almost the same during the reaction and cellulose polymer chain degradation can be avoided.²⁷ Cellulose levulinate with a DS of 0.44 can be achieved by treating cellulose with 3 equiv levulinic acid/AGU in the presence of 3 equiv CDI at 80 °C for 24 h. A molar ratio of AGU/levulinic acid/CDI of 1/6/5 leads to a sample with a DS of 0.55.

From the results above, esterification of cellulose with levulinic acid in the presence of CDI gave a higher DS than the other two *in situ* activation methods under comparable conditions.

Possible explanations for such a low DS via DCC/DMAP, tosyl chloride or CDI *in situ* activation could result from the inherent equilibrium between levulinic acid and its lactone form via intramolecular transfer of the proton from the carboxy group to the carbonyl oxygen.³² This will decrease the efficiency of levulinic acid *in situ* activation significantly, limiting the DS of levulinate.

7.5.4 Synthesis of cellulose levulinate via levulinoyl chloride

Acyl chlorides are highly efficient and reactive agents for cellulose esterification. Cellulose levulinate was synthesized before by esterification of cellulose with levulinoyl chloride in a heterogenous state, resulting in a low DS of 0.10-0.45.³³ We want to run this reaction in a homogeneous system, so a higher DS value can be expected.

Levulinic acid was converted to levulinoyl chloride by using oxalyl chloride. Oxalyl chloride is very effective to prepare acyl chloride from the corresponding acids.³⁴ Levulinoyl chloride was then added drop by drop into cellulose solution in DMAc/LiCl with TEA as base. Perpropionylation was applied on the crude product. Surprisingly, no levulinate was detected from NMR spectra. Pyridine was used instead of TEA and the reaction temperature was increased from 60 °C to 80 °C. However, no acylation occurred between cellulose and levulinoyl chloride either.

When levulinic acid was converted to levulinoyl chloride, 5-chloro- γ -valerolactone was produced spontaneously (see Scheme 7.2).³⁵ This compound can be predominant, even with a yield up to 100 %.³⁶ It is so stable that it can't react with cellulose under such acylation conditions, explaining why no levulinate moiety was found.

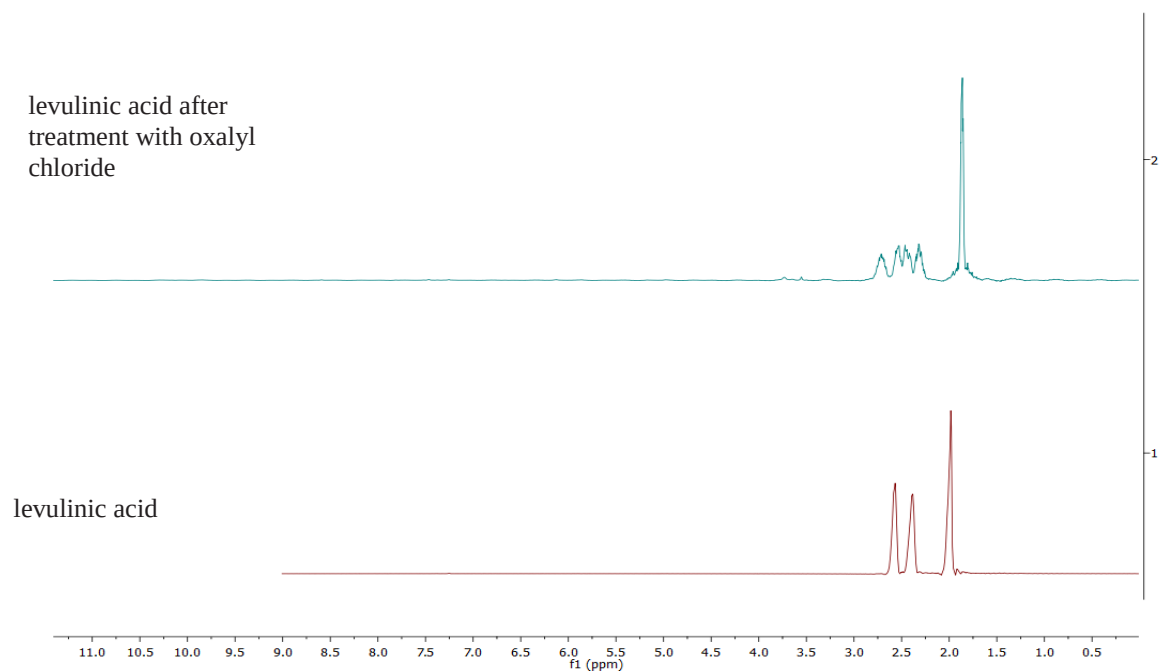


Figure 7.2 ^1H NMR spectrum of levulinic acid and its derivative

Table 7.1 Conditions and results of the homogeneous reaction of cellulose with levulinic acid after in situ activation with DCC/DMAP, tosyl chloride, CDI or with levulinoyl chloride.

Method	Molar ratio ^a	Time (h)	Temperature(°C)	Sample	DS ^b
DCC/DMAP	1:3	24	40	1	0.36
DCC/DMAP	1:6	24	80	2	0.51
Tos-Cl	1:3	24	80	3	0.11
Tos-Cl	1:6	24	80	4	0.50
CDI	1:3	24	80	5	0.44
CDI	1:6	24	80	6	0.55

Lev-Cl	1:5	24	60	7	0
Lev-Cl ^c	1:5	24	80	8	0

^aMol levulinic acid per mol anhydroglucose unit.

^bDegree of substitution of levulinate moieties determined after perpropionylation by ¹H NMR spectroscopy.

^cPyridine was used as the base instead of TEA.

7.5.5 Solubility of new cellulose levulinate

Table 7.2 summarizes the solubility of cellulose levulinate. We found little dependence of solubility on preparation methods; low DS (less than 0.60) cellulose levulinate was insoluble in all common organic solvents. We would predict that a higher DS of cellulose levulinate could lead to more organic solubility.

Table 7.2 *Solubility of cellulose levulinate vs. DS*

Sample	DS	Solubility				
		DMSO	Pyridine	THF	CHCl ₃	NMP
1	0.36	-	-	-	-	-
2	0.51	-	-	-	-	-
3	0.11	-	-	-	-	-
4	0.50	-	-	-	-	-
5	0.44	-	-	-	-	-
6	0.55	-	-	-	-	-
7	0	-	-	-	-	-

7.5.6 NMR spectra of cellulose levulinate

Figure 7.3 shows a typical ^{13}C NMR spectrum of cellulose levulinate after perpropionylation, recorded in CDCl_3 . The peaks were assigned by analogy to previous studies.⁷ The levulinoyl moieties gave clear signals due to two methylene carbons at 27.66 ppm and 38.09 ppm and to one methyl carbon at 29.69 ppm. The signals for propionate methyl and methylene are also detectable at δ (ppm) = 8.92 and 27.19. The peaks of the carbon atoms of the AGU are found in the region δ = 61.92-100.18. The only peak for C-6 showed up at δ = 61.98, shifting to downfield by 1.9 ppm compared to unfunctionalized cellulose, which means that all O-6 has been substituted by ester moiety. Moreover, the downfield signals at δ = 205.94 - 207.20 correspond to ketone carbon of levulinate while the peaks overlapped at δ = 172.46-173.31 belong to the carbonyl carbon of levulinate and propionate. A comparable ^{13}C NMR spectrum of cellulose levulinate after peracetylation was shown in Figure 7.4. A more pronounced splitting of the signals in the carbonyl region at 169.11-172.31 ppm can be observed. The signals at δ = 169.11, 169.86 and 170.33 result from acetyl carbonyl carbon within three reacting sites. The peaks at 206.03 ppm are from the ketone carbon of the levulinate group. For the methylene and methyl region of levulinate, the signals at δ = 29.78 and 38.07 are attributable to methylene carbons while 29.55 ppm is from methyl carbon. Compared with cellulose levulinate after perpropionylation, the peracetylated derivative displays more distinct peaks for methylene carbons since they are not overlapped with propionate methylene any more. The assignment of propionate methyl peaks in the ^1H NMR spectrum (see Figure 7.1) is possible by comparing with the work of Heinze.³⁷ The ^1H NMR spectrum showed that the peaks for propionyl methyl group at 1.10 ppm (O-2/3) are much stronger than that at 1.23 ppm (O-6), indicating that the

esterification with levulinic acid occurred at all three hydroxyl groups but with preference for O-6. All three methods afforded the same substitution pattern.

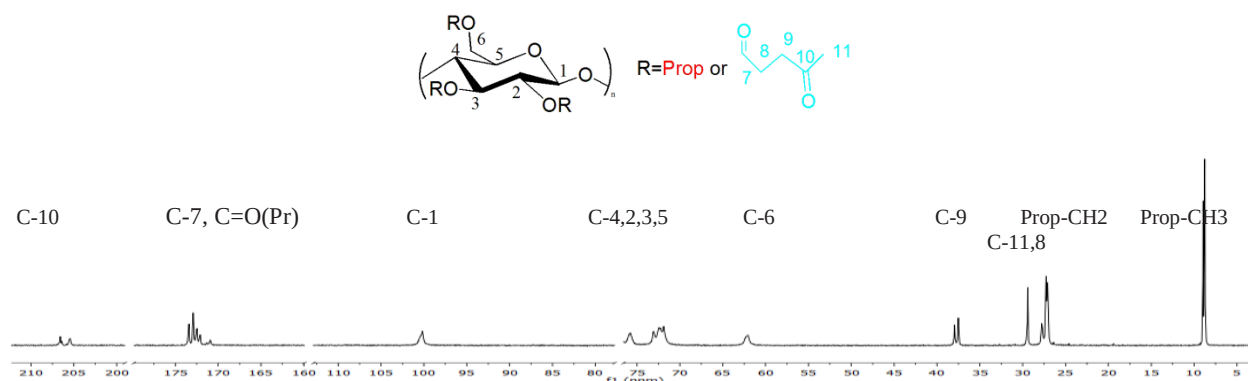


Figure 7.3 ^{13}C NMR spectrum of cellulose levulinate after perpropionylation (sample 2).

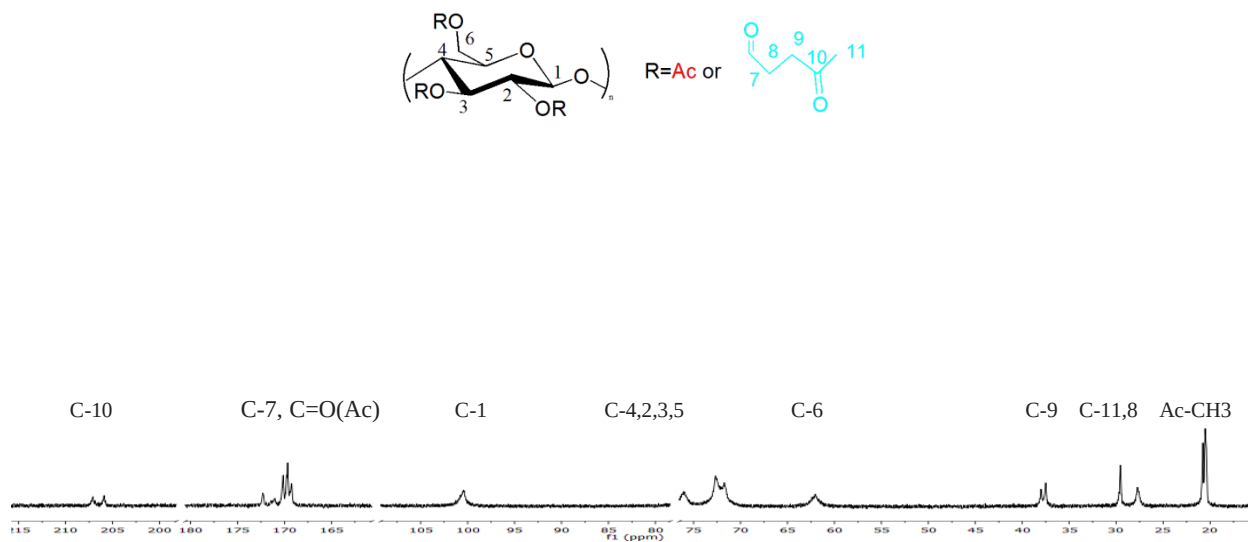
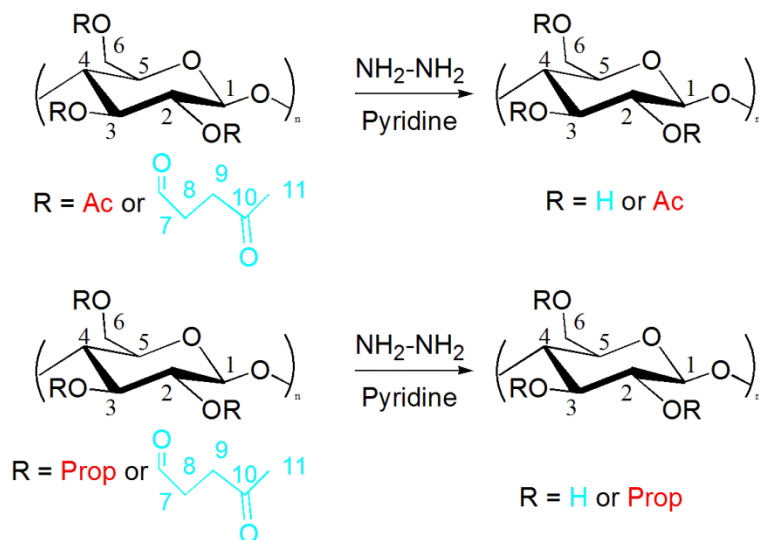


Figure 7.4 ^{13}C NMR spectrum of cellulose levulinate after peracetylation (sample 2)

7.5.7 Selective hydrolysis of cellulose levulinate acetate and cellulose levulinate propionate with hydrazine

Levulinate, as a protective group, can be removed by several methods such as Grignard reagent³⁸, hydrazine¹⁷, sodium bisulfite³⁹, and sodium borohydride⁴⁰, among which, hydrazine is the most interesting one to us since it can cleave levulinate selectively while alkanoate esters including acetate and propionate are stable under such conditions.^{17,18}

After peracetylation or perpropionylation, cellulose levulinate was redissolved in pyridine and treated with hydrazine at room temperature for 24 h. The product was recovered by precipitating into water. The ¹H NMR spectrum of the product confirmed peaks for acetyl or propionyl groups, but no peaks for levulinate groups, indicating hydrolysis of levulinate by hydrazine was complete. In order to have better resolved NMR spectra, the product was either peracetylated or perpropionylated accordingly. From the ¹³C NMR spectra of the peracetylated or perpropionylated sample (Figure 7.5), no levulinoyl moieties were detectable. The DS value was determined by the ratio of the integrals of the protons of AGU and the methyl moiety of propionate. The DS of the acetyl group or propionyl group stays the same after the addition of hydrazine, in other words, there was no cleavage of the acetate or propionate. This is quite important for the regioselective synthesis of cellulose esters because such a protective group is stable under most esterification conditions but it can be cleaved off by hydrazine selectively while acetate or propionate is stable. The application of levulinate as a protective group for the regioselective synthesis of cellulose esters is still under investigation in our group.



Scheme 7.3 *Hydrolysis of cellulose levulinate acetate or propionate with hydrazine in pyridine*

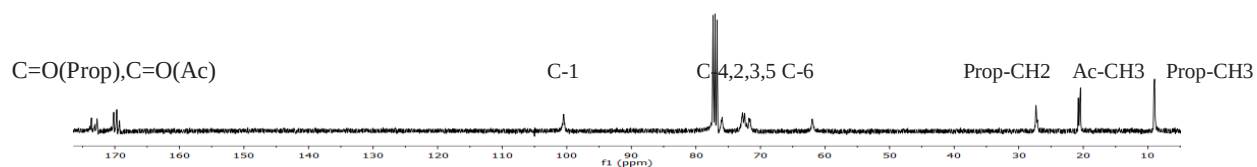


Figure 7.5 *^{13}C NMR spectrum of cellulose levulinate propionate after hydrolysis with hydrazine (peracetylation was applied)*

7.6 Conclusions

Cellulose levulinate derivatives were successfully synthesized by reaction of cellulose in DMAc/LiCl solution with levulinic acid in the presence of DCC/DMAP, CDI or TosCl.

Comparing the three methods used, the *in situ* activation of the levulinic acid gave derivatives with DS from 0.1 to 0.5 depending on reaction conditions. Surprisingly, levulinoyl chloride failed to react with cellulose, which could be explained by the by-product 5-chloro- γ -valerolactone formed spontaneously when converting levulinic acid to levulinoyl chloride. None of the methods tried give complete substitution of cellulose. Cellulose levulinate synthesized by three methods all had similar substitution patterns, with acylation occurring preferentially at O-6. Cellulose levulinate after peracetylation or perpropionylation that can be reacted with hydrazine at room temperature, resulting in complete levulinate deprotection, gives mixed triesters, while the acetate or propionate groups were stable under these conditions. Further applications of levulinate as a protective group for the regioselective synthesis of cellulose derivatives are still under investigation.

7.7 Acknowledgements

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Chapter 8: Summary and Future Work

Regiocontrol in cellulose chemistry is still a difficult, mostly unconquered frontier. We have described extensive studies on regioselective synthesis of cellulose derivatives, focusing on synthesis, characterization and structure-property relationships.

In **Chapter 3**, cellulose esters with bulky acyl groups including pivalate, adamantate, and 2,4,6-trimethylbenzoate were successfully prepared by acylation of cellulose with the corresponding acid chlorides. The esterification was in most cases selective for the primary hydroxyl groups as expected, but even with these bulky acyl groups, acylation at the secondary alcohols O-2 and O-3 was still observed. ***No conditions for truly regiospecific acylation were identified.*** The novel cellulose pivalates and mesitylates of this study have interesting properties and will be further studied in our laboratory.

In **Chapter 4**, we have developed general synthetic methods, based on computational studies of models of potential synthetic intermediates, for the successful regioselective synthesis of cellulose-2,6-di-O-esters and cellulose-2,6-di-O-(ester A)-3-O-(ester B) derivatives. We report also the first analytical studies of these regioselectively substituted cellulose esters. The structure-property relationships were investigated in regarding to solubility and thermal properties.

This strategy can also be applied to syntheses of a broad range of regioselective cellulose derivatives including cellulose esters and ethers, for example, 2,6-di-O-butyrate cellulose, 2,6-di-O-acetate-3-O-butyrate cellulose, 2,6-di-O-propionate-3-O-butyrate cellulose, and 2,6-di-O-ethyl-3-O-methyl cellulose can all be synthesized. These regioselective derivatives are

very important resources which can not only serve as analytical standards with regard to NMR spectra, but can also help to understand the structure-property relationships.

In **Chapter 5**, subsequent reactions were carried out on remaining hydroxyl groups of 3-*O*-benzyl and 3-*O*-allyl cellulose towards bulky ether protective groups in order to achieve regioselective substitution of primary hydroxyl groups. 3-*O*-Benzyl cellulose showed surprisingly low reactivity for silylation reactions while 3-*O*-allyl cellulose can undergo all reactions tested. We compared the effects on substitution of using different bulky reagents. Several important protective intermediates were successfully synthesized via 3-*O*-allyl cellulose with high potential for the synthesis of regioselectively substituted cellulose esters and ethers. For example, 2-*O*-methyl cellulose has been synthesized via these intermediates (after deprotection and functionalization steps) and analysis of the distribution of methyl groups will be our future work.

We have already known that protective groups can strongly affect the reactivity of cellulose intermediates compared with unfunctionalized cellulose, based on computational studies. Instead of applying allyl protective group at C-3, we can explore other protective groups, among which, 4-methoxybenzyl and 2,4-methoxybenzyl group are most interesting. Because they are more bulky than allyl group, affording higher selectivity for O-6 substitution, at the same time, the involvement of electron donating moiety on phenyl ring can increase the reactivity of 3-*O*-substituted cellulose towards subsequent reactions with other bulky ether protective groups. The removal of methoxylbenzyl group could be also easier than benzyl group.

In **Chapter 6**, tetrabutylammonium fluoride has been found to catalyze the deacylation of cellulose esters including cellulose diacetate (CA-398-30), cellulose triacetate, and cellulose tripropionate in either THF or DMSO. Surprisingly, the deacylation is highly regioselective at

C-2 and C-3, affording cellulose-6-*O*-esters by a simple one-step process employing no protective groups.

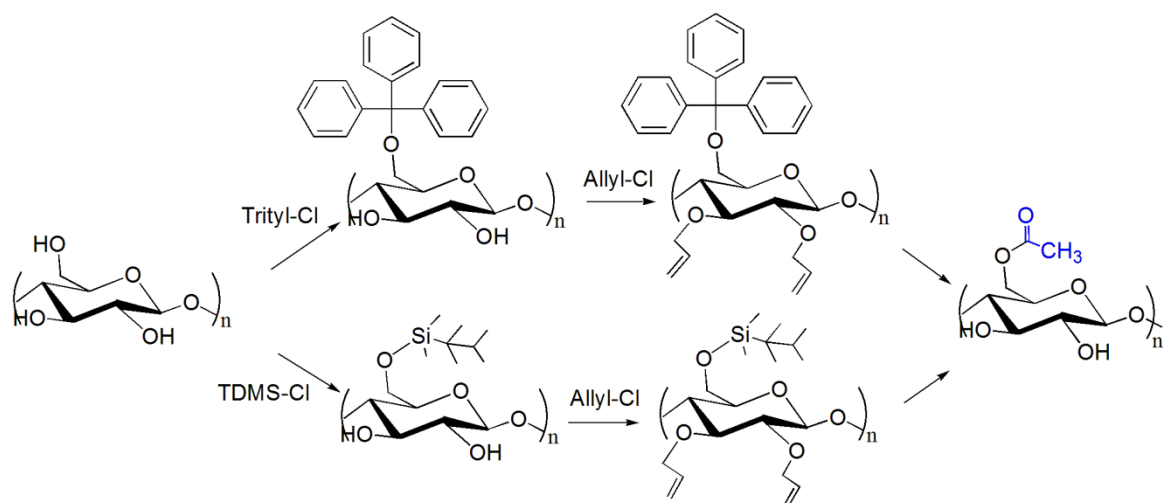
In the future, we will continue to investigate the mechanism of this remarkable deacylation reaction. Meanwhile, we will synthesize a series of regioselective cellulose esters (6-*O*-ester A and 6-*O*-ester A-2,3-di-*O*-ester B) via this deacylation route. We then will fully characterize the regioselective cellulose esters obtained and carry out studies on their properties including solubility, thermal properties, and optical properties, allowing us to better understand structure-property relationships.

In **Chapter 7**, cellulose levulinate was synthesized homogeneously in DMAc/LiCl using different activating levulinic acid derivatives. A DS value as high as 0.55 was reached. The new cellulose levulinate, after peracetylation or perpropionylation, could be hydrolyzed by hydrazine in pyridine but acetate or propionate was stable under such conditions.

One problem for using levulinate as a protective group is the low DS value. We need to optimize reaction conditions so as to achieve a full substitution. Then we can apply levulinate together with the silyl and trityl group to synthesize regioselective cellulose derivatives.

Up to now, the main strategy to synthesize regioselective cellulose derivatives is to use protection-deprotection routes. Some preliminary results are very promising, which are worthy of comprehensive studies.

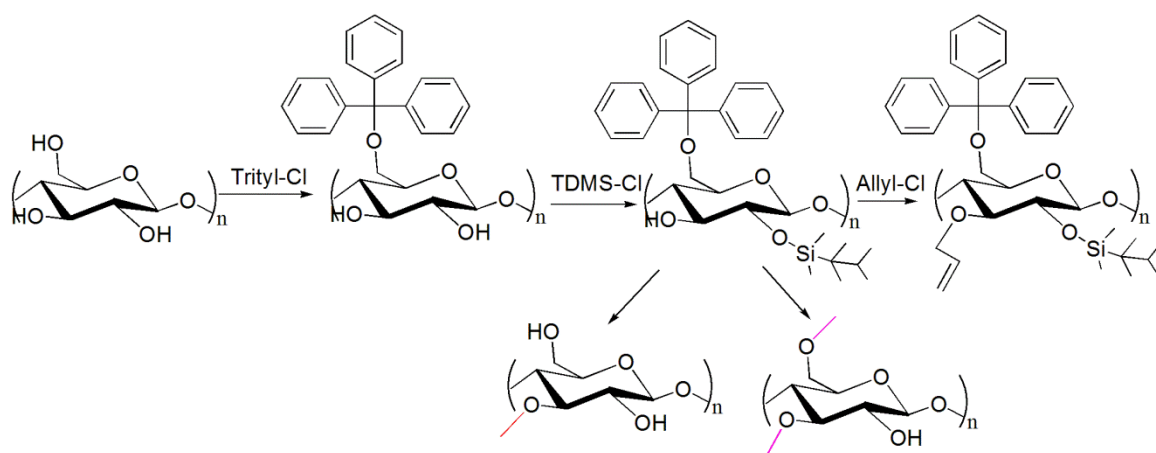
6-*O*-Acetyl cellulose was synthesized via two routes (Scheme 8.1). The properties of 6-*O*-acetyl cellulose obtained by these two methods will be tested and compared, leading to deeper understanding of structure-property relationships with respect to synthetic strategies.



Scheme 8.1 *Synthesis of 6-O-acetyl cellulose via two different routes*

Finally, some preliminary results showed that 6-O-(4-methoxy)-trityl-2-O-thexyldimethylsilyl cellulose which was synthesized by orthogonally protecting cellulose (Scheme 8.2) could be a very interesting intermediate. After it was synthesized, we could selectively deprotect the trityl and silyl group followed by other functionalization steps, so as to form other regioselective cellulose derivatives. For example, 3-O-methyl cellulose and 3,6-di-O-methyl cellulose have been synthesized. Quantitative analysis of the degree of regioselectivity and structure-property relationships of these two methyl cellulose ethers will be investigated in the future. To move further, the only free hydroxyl group of 6-O-(4-methoxy)-trityl-2-O-thexyldimethylsilyl cellulose was protected as an allyl ether to form a fully functionalized cellulose derivative (6-O-(4-methoxy)-trityl-2-O-thexyldimethylsilyl-3-O-allyl cellulose). This intermediate is very important to synthesize other regioselective cellulose acetate or methyl cellulose isomers. For example, after the removal of silyl group at C-2 by TBAF, the free hydroxyl group could then be

acylated, followed by the deprotection and other functionalization steps, leading to 2-*O*-substituted cellulose esters.



Scheme 8.2 *Synthesis of orthogonally protective cellulose intermediates*