# Regioselective Synthesis of Cellulose Esters

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## Abstract

Cellulose is an extraordinarily abundant polymer that can be harvested and purified from trees and other renewable sources. Cellulose derivatives have been widely used as coatings, optical films, fibers, molded objects, and matrices for controlled release. The properties of cellulose derivatives are not only affected by the degree of substitution, but also by the position of substitution. In order to establish the structure-property relationships of cellulose derivatives, it is of great importance to impart regioselectivity into functionalized cellulose. However, regioselective substitution of cellulose is extremely challenging, especially in the synthesis of regioselectively functionalized cellulose esters due to the unstable ester bond under aqueous alkaline or acid conditions.

In this dissertation, the main objective is to search for new tools to synthesize regioselectively substituted cellulose esters, to understand how structural changes impact properties and performance, and thus to design cellulose derivatives delivering high performance. Several strategies for regioselective preparation of cellulose esters are discussed in detail. The obtained regioselective cellulose esters were fully characterized analytically.

Tetrabutylammonium fluoride (TBAF) has been recently discovered to catalyze regioselective deacylation of cellulose esters of the secondary alcohols at C-2 and C-3. The kinetic isotope effects in this deacylation reaction have been investigated to reveal the reaction mechanism. The secondary kinetic isotope effects ($k_H/k_D$=1.26 ± 0.04) measured for the deacylation at C-2/3 suggest that a ketene intermediate mechanism is involved. Inverse kinetic isotope effects ($k_H/k_D$=0.87 ± 0.03) for the deacylation at C-6 are observed, indicating the involvement of a tetrahedral intermediate in the mechanism. Additional studies suggest the possibility that TBAF chelation by neighboring acyl groups may account for the unexpected regioselectivity at the secondary acetates observed in the TBAF deacylation of cellulose esters. In order to expand its utility and understand how to carry it out most efficiently, the scope of TBAF catalyzed deacylation of cellulose acetates has been investigated. Reactions in DMSO, THF, MEK and acetone afforded similar extents of deacylation and regioselectivity. Reaction with TBAF in DMSO at 50 °C for 18 h was the most efficient process providing regioselective deacylation at O-2/3. Furthermore, we demonstrate that TBAF-catalyzed deacylation is also effective and regioselective with cellulose acetate, butyrate, and hexanoate triesters, and even with a cellulose ester devoid of alpha protons, cellulose tribenzoate.

Tetrabuylammonium hydroxides have also been found to mediate regioselective deacylation of cellulose esters. The mechanism for this deacylation was investigated by studying the effect of tetraalkylammonium cation size upon ester deacylation selectivity. We hypothesize that coordination of the tetraalkylammonium cation by the ester oxygen atoms of the vicinal 2,3-acetate groups may drive the unexpected regioselectivity at the secondary alcohol esters.

# Acknowledgements

It would never have been possible to finish my dissertation without the guidance of my advisor and committee members, help from friends, and support from my family.

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# Chapter 1 Introduction

As societal concerns about environmental issues increase, biocompatible and biodegradable polymers, especially those derived from renewable sources, have attracted more attention. As one of the most abundant polymers on earth, cellulose is an important polysaccharide, particularly given societal concerns about declining fossil fuel reserves, and the resulting impact on energy and materials availability. In order to utilize cellulose more effectively, it is widely converted into its organic esters in the laboratory and commercially to improve solubility and processability, by affording materials that are processible into various useful forms. Conversion of cellulose to its esters not only modifies the physical properties of cellulose but also expands the range of applications.

Even though commercially important cellulose esters are randomly substituted, regioselectively substituted cellulose esters have been observed to have notable differences from these randomly substituted derivatives in certain aspects. My doctoral research focuses on synthesis of regioselectively substituted cellulose derivatives. With increased access to regioselectively substituted cellulose esters, we can establish fundamental understanding of the regiochemical structure-property relationships, better predict how structural changes will impact properties, and understand how those property changes will influence their performance in current applications.

Some of the few regioselectively substituted cellulose esters known in the literature have been synthesized on lab scale by protection-deprotection processes employed in modern cellulose solvents. While quite valuable for preparing lab scale samples, this protection-deprotection approach is limited in scope because of the necessity for multi-step, inefficient processes.

Therefore, as one of my basic research projects, interest is focused on the search for new tools for the preparation of regioselectively substituted cellulose esters. This thesis presents a study on the synthesis of regioselectively substituted cellulose esters by using tetrabutylammonium fluoride, investigations of the mechanism, scope and influence of the reaction parameters of this unexpected regioselective deacylation reaction, the first discovery of tetrabutylammonium hydroxide mediated regioselective deacylation of cellulose esters, and the synthesis of novel cellulose levulinates, describing the role of levulinate as a polysaccharide protecting group.

**Chapter 2** gives a comprehensive literature review on regioselective synthesis of cellulose derivatives.

**Chapter 3** discusses attempts to probe the mechanism of TBAF-catalyzed regioselective deacylation of cellulose ester, investigated by methods including kinetic isotope effect studies, effect of added base and acid, and impact of cation nature and size.

**Chapter 4** then investigates the scope of the highly regioselective, TBAF catalyzed deacylation of cellulose acetate, including the influence of key process parameters: solvent, temperature, and water content. The scope of TBAF-catalyzed deacylation with respect to ester type was also studied.

**Chapter 5** describes a new, efficient, flexible, and forgiving one-step method for preparing a wide variety of regioselectively substituted cellulose esters. Tetraalkylammonium hydroxides were found to mediate regioselective deacylation of cellulose esters for the removal of the acyl groups at O-2/3. The mechanism for this deacylation was investigated by studying the impact of tetraalkylammonium cation size upon ester deacylation selectivity. The scope of this deacylation of cellulose esters was investigated to understand how to carry it out more efficiently.

**Chapter 6** covers synthesis of cellulose levulinate in DMAc/LiCl with levulinic acid using different activation methods. The role of levulinate as a protective group was explored.

**Chapter 7** summarizes the research results for each chapter in this dissertation and talks about future experiments.

# Chapter 2 Literature Review

## 2.1 Introduction- Cellulose and Cellulose Derivatives

Cellulose is one of the most common and abundant polysaccharides in nature, and is a major component of the plant cell wall[1] and of many organisms, such as cotton, wood, bacteria, and even some animals[2] (tunicates for example). Cellulose can be obtained in relatively high purity from sources like cotton and trees.

For its biocompatibility and biodegradability, cellulose is gaining increasing interest as society becomes more concerned about environmental issues. Cellulose has a long history of use for producing fibers, films, absorbent products, rayon, and cellophane.[3] With the science of conversion of cellulose into its derivatives, cellulosic derivatives have been applied to cosmetics, agriculture, and pharmacy.[4] Conversion of cellulose into its esters not only improves solubility and processability, but also affords new materials processible into various useful forms. Cellulose esters have been widely used as coatings,[5, 6] matrices for controlled release,[7, 8] binders,[9] fillers,[9] and optical films[10] for decades.

## 2.2 Cellulose Chemistry

### 2.2.1 Cellulose structure and reactivity

Cellulose is a linear homopolysaccharide, consisting of the repeating anhydroglucose unit (AGU) β-D-glucopyronose with 1→4 linkages (**Figure 2.1**), with no branches or substituents. All cellulose hydroxyl groups as well as the anomeric linkage are equatorial.

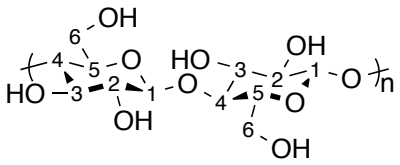


**Figure 2.1** Structure of cellulose

There are three reactive hydroxyl groups in every AGU. The hydroxyl groups of cellulose undergo similar reactions as do other alcohols, such as esterification, etherification, acetylation, oxidation, and displacement, which are critical for cellulose functionalization. Due to different accessibility and other differences in physicochemical properties, each of the three hydroxyl groups has different reactivity. The primary hydroxyl group at C-6 position is least sterically hindered and most accessible compared with the secondary hydroxyl groups at C-2 and C-3 positions. While considering the acidity, the reactivity order of the hydroxyl group is: 2-OH > 3-OH > 6-OH.[11]

However, the uniform molecular structure combined with three hydroxyls per AGU result in extensive inter-molecular and intra-molecular hydrogen bonding (**Figure 2.2**), leading to high crystallinity of cellulose and insolubility in water and other common organic solvents. The major intra-molecular hydrogen bonds occur at $O_3$-H---$O_{anomeric}$ and $O_2$-H---$O_6$, while the major inter-molecular hydrogen bonds occur at $O_6$-H---$O_3$.[12] As a result, the hydroxyl groups of cellulose are poorly accessible, reducing their reactivity. Activation of cellulose by dissolution greatly enhances reactivity by breaking these hydrogen bonds.

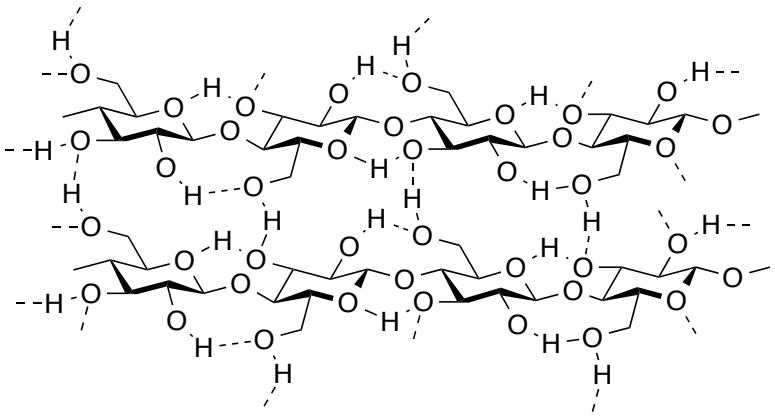


**Figure 2.2** Inter- and intra-hydrogen bonding of cellulose

### 2.2.2 Cellulose dissolution

Advances in dissolution of cellulose in novel solvent systems, including N,N-dimethylacetamide (DMAc)/ LiCl,[13, 14] dimethylsulfoxide (DMSO)/ tetra-n-butylammonium fluoride (TBAF),[15] and ionic liquids[16], enable cellulose to react with a broader range of reagents under milder conditions.

Lithium chloride with amides was first reported to dissolve cellulose. A mixture of cellulose and DMAc was heated to 160 °C, followed by addition of LiCl. Distillate was collected at 170 °C to remove water in DMAc. This solvent system has been proved to be stable and well suited for a variety of reactions of cellulose.

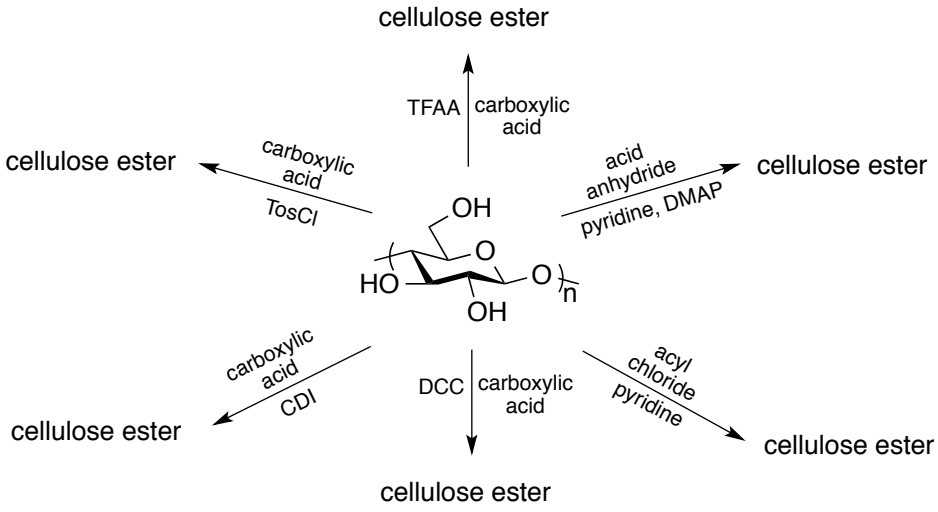
In 2000, Heinze et al.[17] noted that DMSO together with tetrabutylammonium fluoride (TBAF) dissolved cellulose within 15 minutes at room temperature. DMSO with benzyltrimethylammonium fluoride (BTMAF) was later found to dissolve cellulose by treatment at 80°C for 2 hours.[15] The viscosity of cellulose solution in DMSO/ $TBAF{\cdot}3H_2O$ is higher than that in DMSO/ $BTMAF{\cdot}H_2O$.

In addition, there are variety of ionic liquids for dissolution of cellulose, which contain cations such as 1-butyl-3-methylimidazolium ($[Bmim]^+$) and 1-allyl-3-methylimidazolium ($[Amim]^+$), and anions such as $Cl^-$, $Br^-$, and $SCN^-$. Adding cellulose to [Bmim]Cl, followed by heating the solution to 100°C, affords solubility of 10% (wt%).[16] For [Bmim]Br and [Bmim]SCN, the solution needed to be microwaved to afford solubility of 5-7%.

The advent of versatile cellulose solvents makes the synthesis of cellulose derivatives in homogeneous solution possible, and facilitates cellulose functionalization.

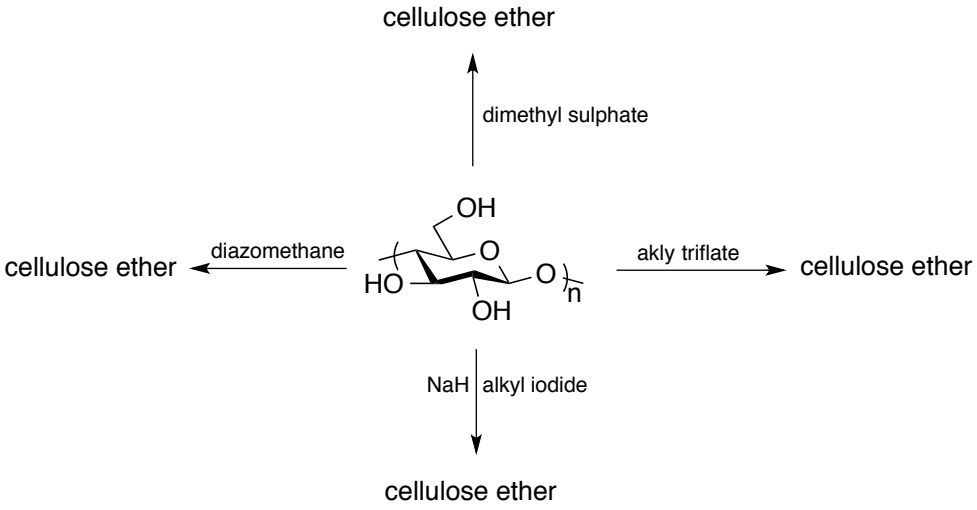
### 2.2.3 Cellulose esterification and etherification reactions

Cellulose esterification is one of the most important methods to functionalize cellulose. Cellulose esters are commonly obtained by esterification of cellulose with a carboxylic acid, acid anhydride, or acyl chloride in the presence of a catalyst. Diverse ways to synthesize cellulose esters are shown in **Scheme 2.1**. Reactions of cellulose with carboxylic acids activated by trifluoroacetic anhydride (TFAA),[18] p-toluenesulfonic acid chloride (TosCl),[19] carbonyldiimidazole (CDI),[19] as well as N-N'-dicyclohexylcarbodiimide (DCC)[20] are efficient methods to synthesize cellulose esters. To simplify the synthesis and diminish the use of toxic reagents, cellulose esters are obtained by esterification of cellulose with acid anhydride and pyridine in the presence of 4-N,N-dimethylaminopyridine (DMAP) as a catalyst.[21] Another effective method is acylation of cellulose with acyl chloride and pyridine.[22]




**Scheme 2.1** Synthesis of cellulose esters

Cellulose etherification is another important way to derivatize cellulose. As shown in **Scheme 2.2**, reactions of cellulose deprotonated with, e.g., sodium hydride (NaH)[23] with dimethyl sulphate,[24] diazomethane,[25] alkyl triflate[26] , and alkyl iodide are important methods for the preparation of cellulose ethers.




**Scheme 2.2** Synthesis of cellulose ethers

## 2.3 Regioselectivity

Regioselective synthesis of cellulose derivatives is important for us to understand their structure-property relationships. The properties of cellulose derivatives with different distributions of functional groups are quite different, such as the melting point and glass transition temperature,[27] crystallinity,[28] solubility,[29] and optical properties.[30] Therefore, it is of great value to impart regioselectivity into functionalized cellulose to better predict the properties of cellulose derivatives.

As to cellulose, the term regioselectivity refers to the selectivity of substitution position among the three reactive sites. If there are n types of substituents (including hydrogen), up to $n^3$ possible monosaccharides can be present. Taking cellulose acetate as an example, including cellulose itself and cellulose triacetate, there are 8 ($2^3$) different monosaccharides (**Figure 2.3**);[31, 32] in the case of cellulose acetate propionate as another example, there are 27 ($3^3$) different monosaccharide possibilities.

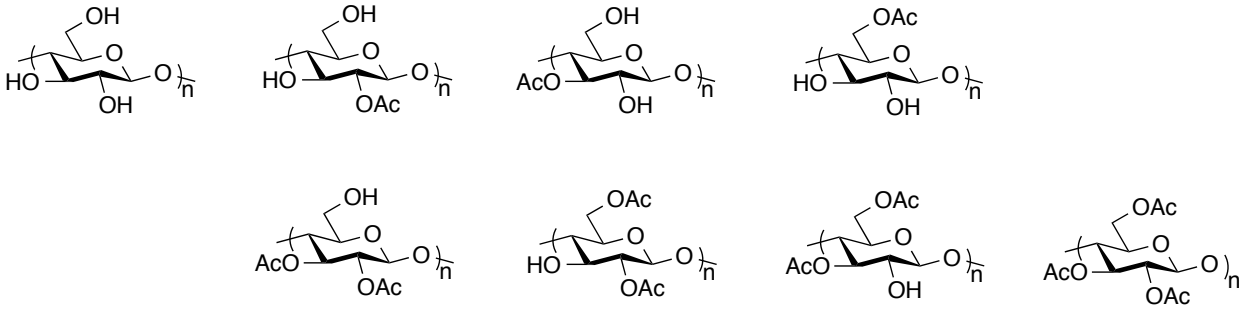
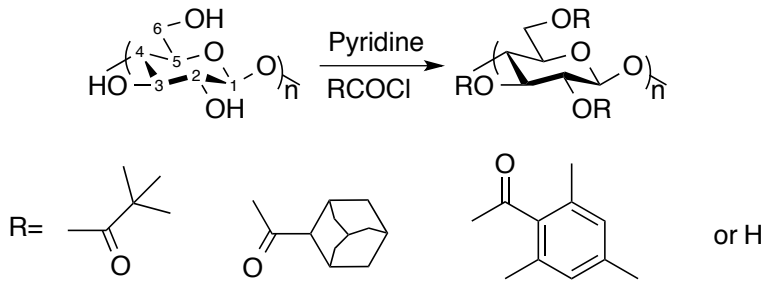


**Figure 2.3** Cellulose acetate isomers

## 2.4 Regioselective syntheses

### 2.4.1 Direct acylation

Direct esterification of cellulose by reaction with several very sterically demanding acyl halides including pivaloyl chloride, adamantoyl chloride, and 2,4,6-trimethylbenzoyl chloride (**Scheme 2.3**) was investigated, trying to achieve regioselective esterification.[33] Functionalization was employed in DMAc/LiCl, DMSO/TBAF, and [Amim]Cl at the lowest practical temperatures. Product analysis indicated that even though esterification of the primary hydroxyl group was consistently preferred, acylation at the secondary alcohols was still observed at significant levels, providing resulting cellulose esters with only modest regioselectivity. No conditions for truly regioselective acylation were identified. It is possible that the intervening carbonyl group creates enough distance between the bulky group of the acylating reagent and the bulky cellulose chain, thereby minimizing selectivity resulting from steric repulsion.




**Scheme 2.3** Direct acylation of cellulose by bulky acyl halides

### 2.4.2 Protection/deprotection schemes

Protection/deprotection chemistry is the most common strategy for preparation of regioselectively substituted cellulose derivatives. Protective groups[34] are introduced to

selectively block reactive hydroxyl groups, followed by functionalization, and then the protective groups are selectively removed. Orthogonal protection is such a strategy to deprotect one of the multiple protective groups at a time under reaction conditions that will not affect the other protective group(s).

#### 2.4.2.1 Triphenylmethyl group

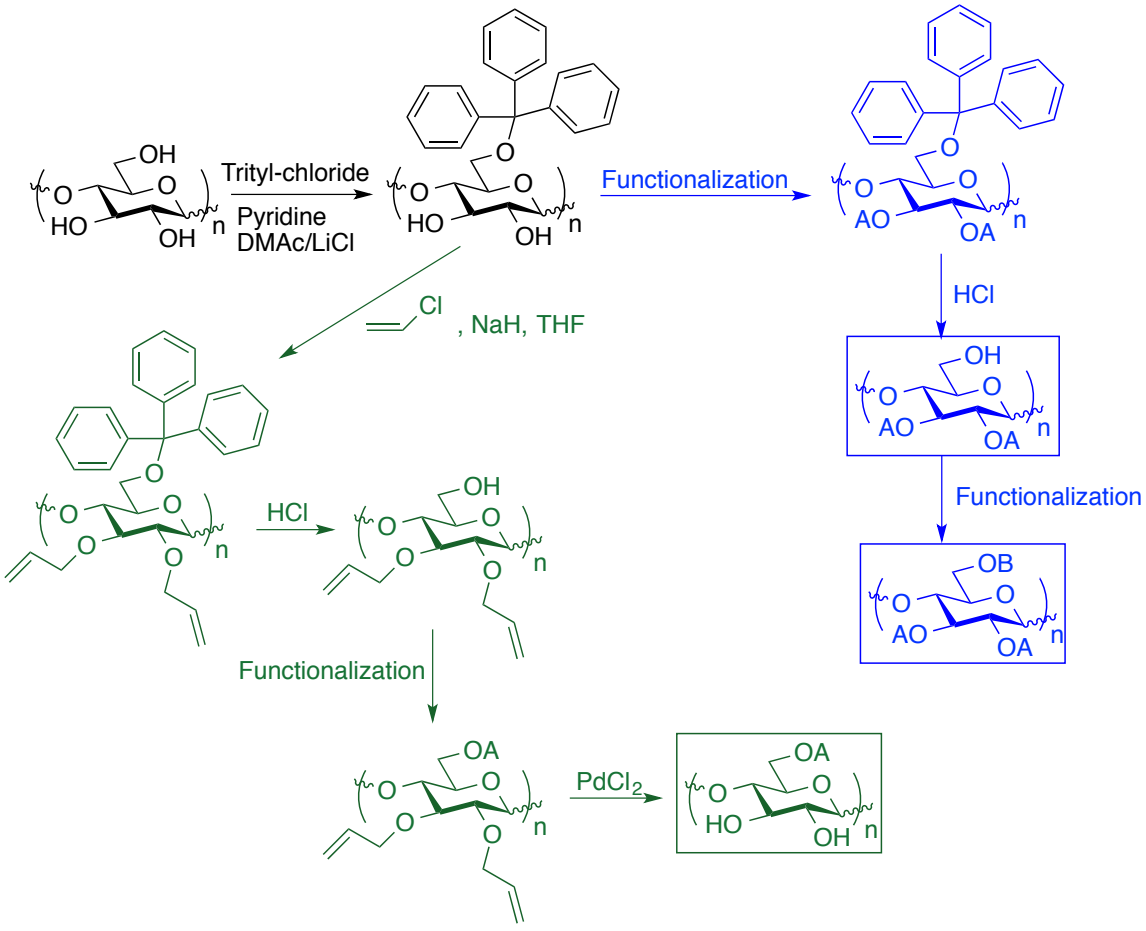
Triphenylmethyl (trityl) is one of the most important protecting groups for the synthesis of regioselectively substituted cellulose derivatives. Trityl chloride was reported to selectively react with the primary hydroxyl group at the O-6 position rather than the secondary hydroxyl groups at O-2 and O-3 positions because of steric demands.[35] 6-O-Trityl cellulose was prepared by the reaction of cellulose with trityl chloride in the presence of pyridine in DMAc/LiCl[36] or ionic liquids.[37] Although a small portion of secondary hydroxyl groups are tritylated, approximately 90 % of the substituents are found at the C-6 position.[38]

Methoxy-substituted trityl chlorides, such as p-monomethoxytriphenyl-methyl chloride, were found to significantly increase the rate and regioselectivity of hydroxyl substitution on cellulose.[39, 40] The rate acceleration was due to the methoxyl group, which is an electron-donating group and can better stabilize the triaryl-methyl cation intermediate. Additionally, the rate of acid-catalyzed deprotection of methoxyl-substituted trityl group is much faster than that of unsubstituted trityl groups.

Tritylation chemistry has facilitated the synthesis of regioselectively substituted cellulose derivatives such as 2,3-O-A-cellulose, 2,3-O-A-6-O-B-cellulose, and 6-O-A-cellulose. As shown in **Scheme 2.4**, 2,3-O-A-cellulose was obtained by modification of the secondary hydroxyl

groups of 6-O-trityl cellulose with acid tolerant functional groups, followed by removal of the trityl group in acidic conditions.[41] Further functionalization of the free primary hydroxyl group of 2,3-O-A-cellulose afforded 2,3-O-A-6-O-B-cellulose.

Synthesis of 6-O-A-cellulose using tritylation chemistry is somewhat more complicated than the synthesis of 2,3-O-A-cellulose. To obtain O-6 substituted cellulose derivatives, the secondary hydroxyls of 6-O-trityl cellulose were protected by allyl groups, which are stable in acidic conditions. The trityl group was then removed by treatment with HCl, and the deprotected primary hydroxyl group was selectively modified, followed by deprotection of the allyl groups in the presence of palladium chloride catalyst.[42]




**Scheme 2.4** Regioselective tritylation and subsequent reactions of cellulose

#### 2.4.2.2 Bulky trialkylsilyl group

Thexyldimethylsilyl chloride (TDMS-Cl) was known to be an effective regioselective protecting group. The regioselectivity of reactions with TDMS-Cl can be higher than those with trityl-Cl,[43] and the specific sites that are protected can be controlled by employing the silyation reaction under different conditions.[44] As shown in **Scheme 2.5**, under heterogeneous conditions, TDMS-Cl exclusively reacted with the primary hydroxyl group at O-6; while the homogeneous solution reaction of cellulose with TDMS-Cl gave O-2 and O-6 selectively protected derivatives. It was reported that cellulose was suspended in N-methylpyrrolidone (NMP) and treated with ammonia at -25 °C, affording 6-O-silyl-cellulose with a DS of 0.99.[45] Homogeneous derivatization of cellulose with TDMS-Cl in DMAc/LiCl in the presence of pyridine at 50 °C gave 2,6-O-silyl-cellulose with DS of 1.90.[46] Imidazole was found to be a more effective base than pyridine for homogeneous reaction of cellulose with TDMS-Cl, affording 2,6-O-silyl-cellulose with DS of 1.99.[47] The analytical difficulties and resultant uncertainties in silyl ether DS and positional DS have been observed by our lab lately. This phenomenon has not been talked about in the open literatures to our best knowledge but is real and important limitation.

The silyl-protected cellulose can be subsequently modified, and the silyl protecting groups can be completely removed by TBAF,[44] making the synthesis of regioselectively substituted 3-O-A-cellulose and 2,6-O-A-3-O-B-cellulose possible. However, it was recently found in our group that TBAF not only cleaves silyl groups but also deacylates certain ester groups,[48] which limits the utility of silyl protected cellulose intermediates for the synthesis of regioselectively substituted cellulose esters.

A variety of 3-O-alkyl cellulose ethers with free 2- and 6-hydroxyl groups have been synthesized through this pathway under homogeneous conditions, by reaction of 2,6-O-silyl-cellulose with

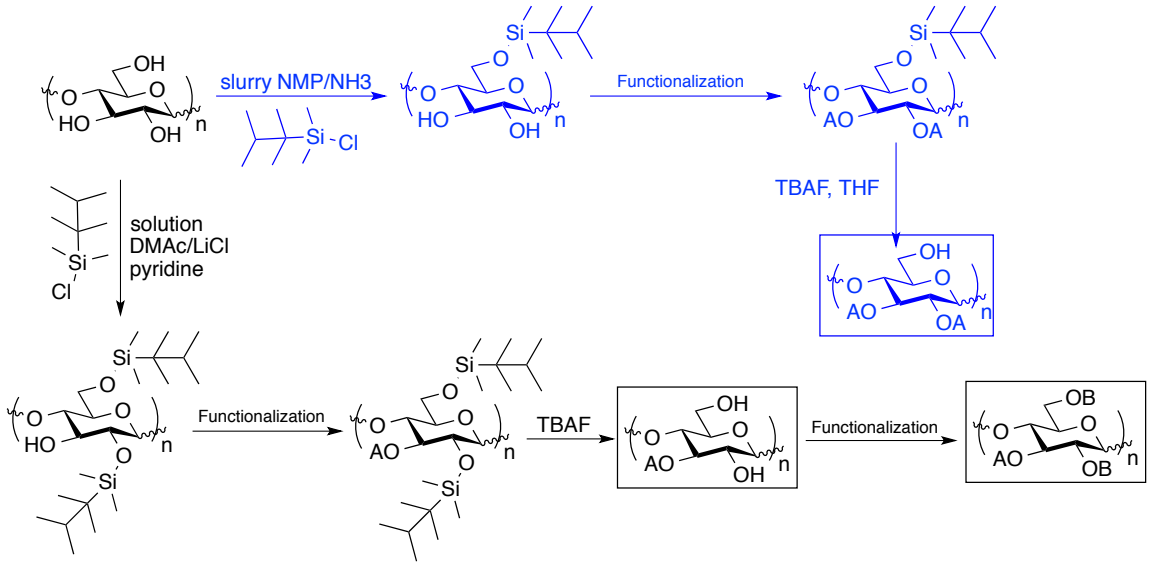
alkyl iodide or bromide in the presence of strong base, followed by removal of silyl groups (**Scheme 2.5**).[47] Solubility of 3-O-substituted ethers with free 2- and 6-OH in various solvents was listed in **Table 2.1**. 3-O-Ethyl, 3-O-n-propyl, 3-O-hydroxyethyl, 3-O-hydroxypropyl, and 3-O-2-methoxyethyl-cellulose are water-soluble. All other 3-O-alkyl ethers reported to date are not soluble in water.

**Table 2.1** Solubility of 3-O-substituted cellulose ethers: "+" soluble, "-" insoluble

| 3-O-substituent | Solubility | | | | |
|---|---|---|---|---|---|
| | Water | Ethanol | THF | DMSO | DMAc |
| Methyl[47] | - | - | - | - | - |
| Ethyl[49] | + | - | - | + | + |
| n-Propyl[50] | + | - | - | + | + |
| n-Butyl[51] | - | - | - | + | + |
| n-Pentyl[52] | - | + | + | + | + |
| i-Pentyl[52] | - | + | + | + | + |
| Dodecyl[52] | - | - | + | - | - |
| Allyl[47] | - | - | - | + | + |
| Hydroxyethyl[53] | + | - | - | - | - |
| Hydroxypropyl[54] | + | - | - | + | + |

| | | | | | |
|---|---|---|---|---|---|
| 2-Methoxyethyl[49] | + | - | - | + | + |
| Propargyl[54] | - | - | - | + | - |

2,6-O-A-cellulose with free 3-OH was obtained by introducing allyl group at O-3 position of 2,6-di-thexyldimethylsilylcellulose,[56] with subsequent removal of silyl groups and derivatization of the free 2,6-OH, followed by deprotection of allyl group by palladium catalyst. Further functionalization of the free 3-OH of 2,6-O-A-cellulose afforded 2,6-O-A-3-O-B-cellulose.

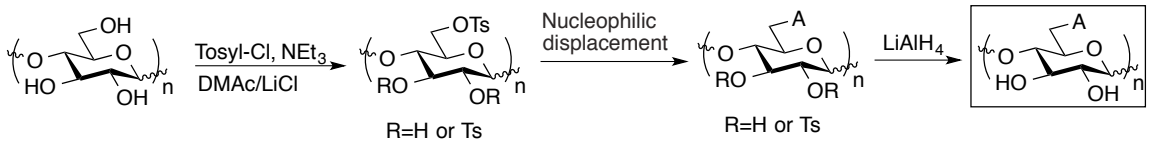



**Scheme 2.5** Regioselective silylation and subsequent reactions of cellulose

### 2.4.2.3 p-Toluenesulfonyl group

Tosyl group serves as both a leaving group and an activating group in chemical modification of cellulose derivatives. The reaction with p-toluenesulfonyl (tosyl) chloride to form cellulose tosyl esters has been widely used to synthesize cellulose derivatives regioselectively substituted at C-6.[57] Soluble in various organic solvents,[58] cellulose tosylate is a very useful intermediate in

cellulose chemistry. Cellulose tosylates can undergo various nucleophilic displacement reactions.[59] Due to the modest steric effect of tosyl group, we must accept partial tosylation in C-2 and C-3 positions when C-6 position is fully tosylated. Even though tosylation is not as selective for O-6 as are reactions with triyl or silyl chlorides, nucleophilic displacement reactions of cellulose tosylates occur exclusively at C-6 due to a $S_N2$ mechanism. Secondary tosylates can be completely removed by reduction at the end of the pathway (in cases where other substituents either are stable to the reduction conditions or provide desired reduction products), affording C-6 selective products (**Scheme 2.6**).




**Scheme 2.6** Synthesis of C-6 substituted cellulose derivatives via cellulose tosylate

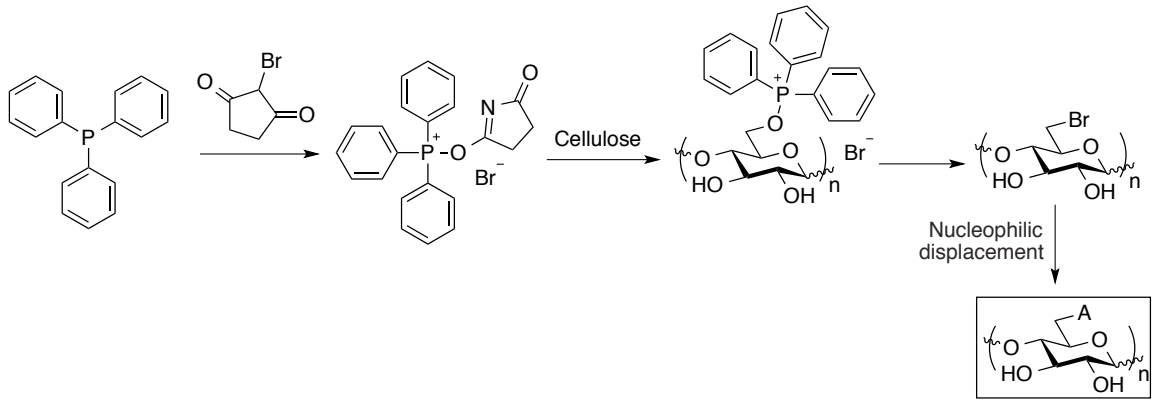
There are reports of heterogeneous cellulose tosylation in pyridine going back several decades,[60] but reaction of cellulose with tosyl chloride in the presence of pyridine in DMAc/LiCl afforded products with higher DS at relatively short reaction times.[61] Despite the relative reactivity increases in the order of C-3 < C-2 < C-6, the differences of the relative DS of the three OH groups are not significant. It was found that using triethylamine as a base in the reaction rather than pyridine resulted in a higher DS for the tosyl group and helped avoid side reactions ($Cl^-$ displacement of tosylate) that formed chlorodeoxycellulose. Using 4-dimethylaminopyridine (DMAP) as a base produced soluble tosylated derivatives with no evidence of side reactions.[62]

In order to evaluate the accessible range of DS, the molar ratio of Tos-C1/ AGU was varied from 0.6 to 9.0, maintaining reaction conditions of 24 h and 8°C.[61] Cellulose tosylates with DS from

0.4 to 2.3 were synthesized. Treatment of cellulose tosylates with iodine at 120°C for 2 h was applied to determine the degree of tosylation at O-6. It was believed that tosylates at C-6 were substituted by iodide with secondary tosylates groups unaffected. It was found that no tosylation was observed at the secondary OH groups for cellulose tosylates with DS of 0.46 or below, and a complete tosylation of the primary hydroxyl group was achieved in derivatives with a total DS of about 1.4.

### 2.4.3 Direct regioselective halogenation

Reaction of cellulose with triphenylphosphine ($Ph_3P$) and N-bromosuccinimide (NBS) in DMAc/LiCl was reported to afford regioselective halogenation of cellulose at the C-6 position.[63] The remarkable regioselectivity for C-6 is due to the steric bulk of the triphenylphoshonium intermediate and the $S_N2$ mechanism of the subsequent bromide displacement reaction. Like cellulose tosylate, the 6-deoxy-6-bromo-cellulose product can act both as a protecting group and as a good leaving group for substitution chemistry at the C-6 position. Several highly regioselectively substituted cellulose derivatives with substituents at C-6, such as 6-azido-6-deoxy-cellulose,[64] 6-amino-6-deoxy-cellulose,[64] and 6-deoxy-6-thiocyanatocellulose[65] have been synthesized via nucleophilic displacement reactions of 6-deoxy-6-bromo-cellulose.




**Scheme 2.7** Synthesis of C-6 substituted cellulose derivatives via direct regioselective halogenation

The advantage versus tosylation is that the bromination is completely selective for C-6 with no bromination detected at the secondary hydroxyl groups on cellulose. Position of bromination was determined by hydrolysis of bromodeoxycellulose in sulfuric acid, and the resulting saccharides as O-trifluoroacetyl derivatives were analyzed by gas chromatography and gas chromatography-mass spectrometry.[63] No peak was observed from a dibrominated monosaccharide. While the main disadvantage to regioselective bromination compared with tosylation is that the 6-deoxy-6-bromo-cellulose is not soluble in typical aqueous or organic solvents although it can be redissolved in DMAc/LiBr, which limits its reactivity in subsequent reactions. Recently, Fox and Edgar[66] reported a one-pot synthesis of 6-bromo-6-deoxy-cellulose esters, and their solubility was drastically improved. The utility of these compounds by the subsequent nucleophilic displacement of the bromide with cyanide has also been demonstrated.

### 2.4.4 Tetra-n-butylammonium fluoride catalyzed deacylation of cellulose esters

Tetra-n-butylammonium fluoride (TBAF) is a quaternary ammonium fluoride salt and is soluble in common organic solvents, such as THF, MeCN and DMSO, making it a very useful fluoride ion provider. In the laboratory, it has been widely used for a variety of reactions, including cleavage of silyl protecting groups,[67] fluorination,[68] as a phase transfer catalyst, and as a base.[69]

TBAF is available commercially as a trihydrate and is thermally instable. When heated to 77°C, TBAF•$3H_2O$ decomposes to tetra-n-butylammonium bifluoride instead of anhydrous TBAF (**Scheme 2.8**).[70] Even at room temperature it can still slowly undergo a similar decomposition pathway. The basicity and reactivity with regard to nucleophilic fluorination of anhydrous TBAF are much higher for anhydrous TBAF than for its hydrate.[71]

$2(n\text{-}C_4H_9)_4N^+F^- \rightarrow (n\text{-}C_4H_9)_4N^+FHF^- + (n\text{-}C_4H_9)_3N + CH_3CH_2CH{=}CH_2$

**Scheme 2.8** TBAF decomposition

TBAF hydrate was obtained by reaction of tetrabutylammonium bromide with aqueous hydrofluoric acid via ion-exchange.[72] However, it is not possible to prepare anhydrous TBAF by drying due to the decomposition pathway. Sun and co-workers[71] introduced low temperature nucleophilic substitution for the preparation of anhydrous TBAF by reaction of tetrabutylammonium cyanide with hexafluorobenzene at -35°C in polar aprotic solvents.

TBAF together with DMSO is one of the most popular modern solution systems for cellulose. The dissolution mechanism is: the electron negative fluoride ions form strong hydrogen bonding with hydroxyl groups of the anhydroglucose unit (AGU), destroying the hydrogen bonding network of cellulose and imparting negative charge to cellulose chains.[73]

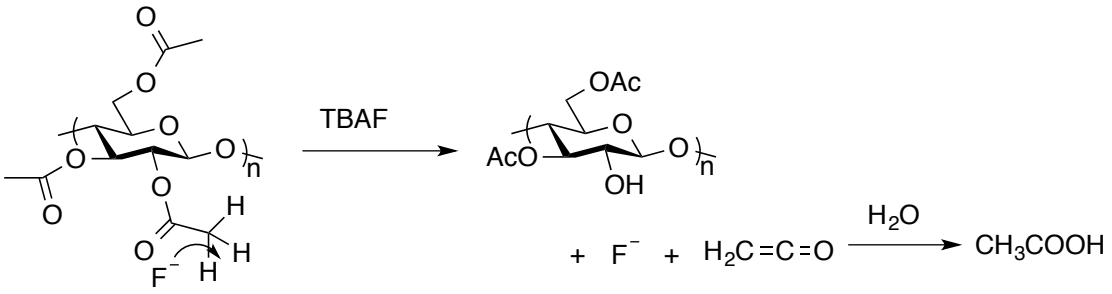
Silyl groups are commonly used as protecting groups for the synthesis of regioselectively substituted cellulose derivatives. An excess or stoichiometric TBAF was reported to completely cleave the silicon-oxygen bond and remove the silyl protective group.[74] Acetic acid was frequently added to the reaction solution to affect the selectivity of silyl ether cleavage by TBAF.[75] It was observed that t-butyldimethylsilyl ether was more labile to hydrolysis by TBAF in the absence of acetic acid, while t-butyldiphenylsilyl ether was more rapidly hydrolyzed in the presence of acetic acid. The mechanism of the selectivity is still under investigation. Recently, DiLauro et al.[76] found that catalytic quantities of TBAF or cesium fluoride (CsF) cleaved the Si-O bond in mixed organic-aqueous buffer solutions, simplifying the work-up procedure and decreasing the expense.

In addition, TBAF has been noted to catalyze deacylation of esters in several literature reports. In 1977, Sieber[77] described the cleavage of an ester group by TBAF during the removal of the 2-trimethylsilylethyl group of 2-trimethylsilylethyl esters of N-protected amino acids. Ueki and co-workers[78] further investigated the ester cleavage reaction with TBAF. They examined hydrolysis of various esters of benzoic acid (including cyclohexyl, benzyl, p-methoxybenzyl, cinnamyl, and t-butyl ester) by TBAF, and found that the percent cleavage was lower with more bulky substituents, with almost no cleavage observed for the t-butyl ester. The mechanism of this ester cleavage reaction was not studied in detail. However, based on the observed substituent effects and the high recovery of benzyl alcohol from benzyl benzoate, they speculated that cleavage occurred by a general base mechanism. TBAF was later found to deprotect 4-nitrobenzyl, 2,2,2-trichloroethyl, and phenacyl esters of amino acids in 1991.[79] The reaction of nitrobenzyl (Nbn) benzoate with TBAF was rather faster than that of benzyl(Bn) benzoate. When running the reaction for 10-30 min at room temperature, the selectivity of TBAF deacylation of Nbn vs. Bn

esters was excellent. However, they failed to explain the selectivity in this paper. In order to achieve selective removal of the phenacyl ester group, combined use of TBAF and 1-octanethiol was established to decrease the basicity of the fluoride ion. TBAF with addition of 1-octanethiol selectively cleaved the phenacyl esters group with benzyl or nitrobenzyl esters unaffected.[80] Recently, Casarano et al.[81] noted that acetylation of cellulose in tetraallylammonium fluoride (TAAF)/DMSO with longer reaction times led to esters with low DS values, which was attributed a general base catalyzed deacylation by TAAF; however the authors did not make any comment about regioselectivity.

Very recently, Xu and Edgar[48] discovered that TBAF regioselectively deacylated cellulose esters at the more hindered ester groups of the secondary alcohols at O-2 and O-3. The reaction of cellulose acetate (DS 2.42) with TBAF in THF proceeded at 50°C within 24 h, affording a cellulose acetate with DS (Ac) at O-6 of 0.80 and DS (Ac) at the secondary alcohols (O-2 and O-3) of 0.10. They suspected that a ketene intermediate mechanism might be involved with the key step being deprotonation of the acyl moieties α to the carbonyl group, followed by elimination of ketene which is then captured by water (water of hydration of TBAF and/or adventitious water) (**Scheme 2.9**).

Deacylation of cellulose esters by TBAF has clear potential as a single-step synthesis of highly regioselectively substituted cellulose 6-O-esters, as well as being a simple route to cellulose-2,3-O-A-6-O-B-esters, without the need of challenging, inefficient protection/ deprotection steps.




**Scheme 2.9** Proposed deacylation reaction[48]

## 2.5 Conclusions

Regioselective substitution of cellulose is extremely challenging, in part due to the low reactivity of cellulosic hydroxyls and the small reactivity differences among them. The advent of modern cellulose solvents and protection/ deprotection schemes have made possible the synthesis of 3-A-cellulose, 6-A-cellulose, 2,3-A-cellulose, 2,3-A-6-B-cellulose, and 2,6-A-B-cellulose, by protection of cellulose with bulky silyl ether group, trityl group, allyl group, or tosyl group. Even so, this strategy has limited utility, due to extra synthetic steps, lost yield at each step, the potential for molecular weight degradation, and the possibility that the reactivity of some protected derivatives may not be as desired.

Regioselective halogenation of cellulose at C-6, followed by selective $S_N2$ substitution reaction, afforded regiospecifically substituted cellulose derivatives like azides and sulfides, without going through protected cellulose intermediates.

The extraordinary, unexpected regioselective deacylation reaction catalyzed by TBAF could facilitate synthesis of regioselectively substituted cellulose esters that complements and in some cases may replace laborious protection/deprotection methods with expensive reagents, affording regioselectively substituted cellulose-6-O-esters in one-step and cellulose-2,3-O-A-6-O-B-

triesters by a single, straightforward additional acylation step.

Having all kinds of regioselectively substituted cellulose esters with one, two, or three ester types at different positions will allow us to establish deep understanding of the structure-property relationships of cellulose derivatives. It will enable us to better predict how structural changes will impact properties and performance in demanding applications, and thus to design cellulose derivatives with higher performance. However, we still have only the most modest tools for the synthesis of regioselectively substituted cellulose derivatives. We can investigate new tools for regioselective synthesis of more cellulose derivatives containing more substituent types.

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# Chapter 3 Probing the Mechanism of TBAF-Catalyzed Deacylation of Cellulose Esters



## 3.1 Abstract

The mechanism of the recently discovered, unusual tetrabutylammonium fluoride (TBAF) deacylation of cellulose esters has been investigated by methods including kinetic isotope effect (KIE) studies. The secondary KIE ($k_H/ k_D$ = 1.26 ± 0.04) measured for deacylation at C-2/3 suggests a mechanism involving a ketene intermediate for those positions. An inverse KIE ($k_H/k_D$ = 0.87 ± 0.03) for the deacylation at C-6 indicates the involvement of a tetrahedral intermediate in the mechanism. Additional studies suggest the possibility that TBAF chelation by neighboring acyl groups may account for the unexpected regioselectivity at the secondary alcohol esters that is observed in the TBAF deacylation of cellulose esters.

## 3.2 Introduction

Utilization of materials based on natural polysaccharides, especially the abundant plant cell wall polysaccharide cellulose, has great currency given societal concerns about declining fossil fuel reserves, energy and materials security, and global climate change. In order to utilize cellulose most effectively, we must develop better methods for converting materials harvested from Nature into readily processed derivatives that provide the high performance needed in demanding applications. A key and difficult aspect of such conversions is control of regiochemistry.

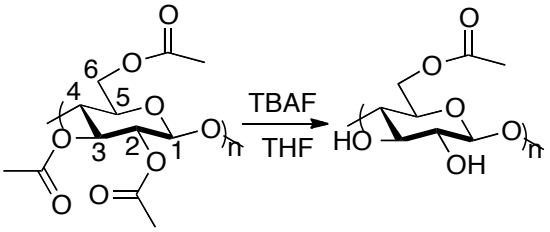
Regioselective substitution of cellulose is extremely challenging, in part due to the low reactivity of cellulosic hydroxyls and the small reactivity differences among them.[1] Regioselectivity is particularly difficult to achieve in acylations, in which direct esterification of cellulose with sterically demanding acylating reagents only provides modest selectivity for acylation at the 6-OH. We suggest that the intervening carbonyl group creates enough distance between the bulky group of the acylating reagent and the bulky cellulose chain[2] to minimize selectivity resulting from steric repulsion. Advances in dissolution of cellulose in organic solvents,[3-5] which enables cellulose to react with a broader range of reagents under milder conditions, have provided a small set of regioselectively substituted cellulose derivatives, usually made by painstaking protection/deprotection chemistry.

Materials made in this way (like cellulose 2,3-*O*-diesters, and cellulose 2,3-*O*-A-6-*O*-B-triesters)[6] have taught us that properties of regioselectively substituted esters and ethers differ sharply from those of more randomly substituted derivatives, including crystallinity,[7] thermal properties,[8] solubility,[9] and optical properties.[10] Very recently, we reported a new protection/deprotection approach, completing the synthesis of cellulose-2,6-*O*-diesters and cellulose-2,6-*O*-A-3-*O*-B-triesters with high regioselectivity by protecting cellulose at both 2- and 6-OH groups using bulky silyl ethers.[11] The thermal and solubility properties of these regioselectively substituted esters diverged noticeably from those of analogous, randomly substituted cellulose esters.

While such protection/deprotection chemistry remains the most common strategy for synthesizing regioselectively substituted cellulose derivatives, the utility of this strategy has limits. It has enabled laboratory-scale determination of several structure–property relationships. However, multi-step protection/deprotection schemes are inevitably time-consuming, expensive,

significantly reduce overall yield, and can cause difficulties due to poor reactivity of some protected intermediates. More efficient methods are needed to help us explore and utilize the key properties of regioselectively substituted cellulosic derivatives. TBAF in combination with dimethylsulfoxide (DMSO), an extraordinary solvent system for cellulosic materials, permits dissolution under exceptionally mild conditions.[12] TBAF efficiently removes silyl ether protecting groups, including the useful thexyldimethylsilyl group; this methodology is a common component of regioselective cellulose ether syntheses.[13] In exploring removal of silyl protecting groups in other common organic solvents, Xu and Edgar[14, 15] have discovered that TBAF smoothly deacylates cellulose esters in THF (**Scheme 3.1**). Remarkably, the highly regioselective deacylation occurs predominantly at the ***more hindered*** ester groups of the secondary alcohols at O-2 and O-3. This relatively simple process provides cellulose-6-*O*-esters with high regioselectivity in one step from commercial or simply synthesized high-DS cellulose esters, and these 6-*O*-esters can be readily converted into cellulose-2,3-*O*-A-6-*O*-B-triesters. For example, reaction of commercially available cellulose acetate (DS 2.42) with TBAF in THF at 50 °C (24 h) affords cellulose acetate with DS (Ac) at O-6 of 0.80 and DS (O-2 plus O-3) of 0.10. The $^{1}H$, $^{13}C$, and HMBC NMR spectra of the resulting cellulose acetate after perpropionylation were shown in **Figure S3.1**, **S3.2**, and **S3.3** (Supporting information), respectively. This surprising regioselective deacylation reaction has no literature precedent (as we were submitting a manuscript on this discovery, El Seoud and coworkers reported deacylation of cellulose acetate by tetraallylammonium fluoride[16]; they did not comment on any observed regiospecificity). Further, the mechanism of this reaction has not been reported. Understanding the mechanism of

such an unpredicted, efficient, and potentially useful regioselective transformation can guide the design of new methods with even greater selectivity.




**Scheme 3.1** TBAF deacylation of CA in THF

In our previous publication,[14] we proposed the possibility of a ketene intermediate mechanism. This would involve deprotonation of the acyl moieties by fluoride ion on the methyl(ene) adjacent to the carbonyl group, with subsequent elimination of a ketene moiety. This ketene moiety would react with water, affording the corresponding carboxylic acid. The source of the water could be adventitious water in the solvent or waters of hydration from TBAF (TBAF as used was roughly a trihydrate; drying the TBAF by breaking the trihydrate is impractical because of concomitant elimination reactions of the butyl groups[17]).

We describe herein our initial investigations of the mechanism of the TBAF regioselective deacetylation of cellulose esters. We study reaction kinetics and the effect of added acid and base in order to provide evidence for or against the ketene intermediate mechanism. Furthermore, we test the hypothesis that chelation of the tetraalkylammonium cation by the ester oxygen atoms of the vicinal 2,3-acetate groups may drive regioselectivity, by studying how tetraalkylammonium cation size affects ester deacylation kinetics and selectivity.

## 3.3 Experimental Section

### 3.3.1 Materials

Microcrystalline cellulose (MCC, Avicel PH-101) and cellulose acetate (CA-398-30, Eastman) were dried under vacuum at 60 °C overnight before use. Tetrabutylammonium fluoride trihydrate (TBAF), tetraethylammonium fluoride hydrate (TEAF), tetramethylammonium fluoride tetrahydrate (TMAF), and potassium fluoride dihydrate (KF) were purchased from Acros Organics and used as received. Dimethyl sulfoxide (DMSO), methyl ethyl ketone (MEK), *N*,*N*-dimethylacetamide (DMAc), and pyridine were obtained from Fisher and dried over molecular sieves (Type 4 Å, 8-12 mesh beads). Acetyl chloride, acetyl chloride-$d_3$, and propionic anhydride were purchased from Aldrich.

### 3.3.2 Measurements

$^1$H, $^{13}$C NMR, HMBC and COSY spectra of the cellulose esters after perpropionylation were acquired in $CDCl_3$ on a Bruker Avance II 500 MHz spectrometer at room temperature or 50 °C. DS values were obtained by calculating the ratio of acetyl or propionyl proton integrals to that of the backbone hydrogens. Molecular weights of the products of cellulose triacetate deacylation (20 equiv TBAF, DMSO, 20 °C) after perpropionylation were measured by size exclusion chromatography (SEC) in chloroform on a Waters Alliance model 2690 chromatograph with Waters 2414 differential refractive index (RI) detector and Viscoteck 270 dual detector, vs. polystyrene standards.

### 3.3.3 Synthesis of protonated and deuterated cellulose triacetates

Synthesis of cellulose triacetates was performed as previously described.[18] Briefly, MCC (5.00 g, 30.8 mmol) and DMAc (187 mL) were kept at 150 °C for 26 min under nitrogen. Anhydrous LiCl (12 g) was added, and the mixture was heated to 165 °C for 8 min. DMAc (25 mL) was

distilled off, and the slurry was cooled to room temperature under stirring overnight. Acetyl chloride [11 mL, 5 mol/mol anhydroglucose unit (AGU)] was added dropwise to the cellulose solution. The solution was allowed to react at 80 °C for 2 h; then kept at room temperature for 24 h. The solution was then added slowly to ethanol (250 mL) under vigorous stirring. The crude product was isolated by filtration and washed several times with ethanol, then dried under vacuum at 50 °C. Deuterated cellulose triacetates were prepared in a similar fashion by using acetyl chloride-$d_3$.

### 3.3.4 Tetraalkylammonium fluoride deacylation of cellulose acetates

To a solution of cellulose acetate in DMSO (40 mL per g of CA) was added tetraalkylammonium fluoride [4 mol/mol AGU, unless otherwise stated] and the reaction solution was kept at 50 °C for 24 h. The solution was then added slowly to water (250 mL), the product was collected by filtration, and then was washed thoroughly with water. After drying under vacuum at 50 °C, the sample was further perpropionylated (details below) for DS and DP determinations. DP by SEC in $CHCl_3$: starting material (CA, DS 2.42) DP 136, product (DS (Ac) 0.92) DP 134.

### 3.3.5 Perpropionylation of the deacylation product

Deacylated products were propionylated for easier NMR analysis, according to literature procedures.[2, 14, 19] 4-(Dimethylamino)pyridine (15 mg) and propionic anhydride (3 mL) were added to the solution of deacylation product in pyridine (3 mL) at 80 °C. After 24 h, the reaction solution was added slowly to ethanol (150 mL); the product was collected by filtration; and it was washed several times with ethanol. The crude product was redissolved in chloroform (5 mL), re-precipitated into ethanol (150 mL), and washed several times with ethanol. The material was dried under vacuum to give the perpropionylated product for NMR analysis.

### 3.3.6 Kinetic experiments

Perprotio or perdeuterio cellulose triacetate (2.50 g, 8.68 mmol AGU) was dissolved in DMSO (100 mL), then TBAF (57.89 g, 20 mol/mol AGU) was added with mechanical stirring at 20 °C. Samples (20 mL) of reaction solution were removed every 15 min and precipitated into water (200 mL). After filtration, the crude product was washed several times with water and dried under vacuum at 50 °C overnight. Perpropionylation of the sample was conducted to enable $^{1}$H NMR measurement of partial and overall DS values, by calculating the ratio of acetyl or propionyl proton integrals to that of the backbone hydrogens. Assignments of the protons and carbons were by COSY and HMBC as previously described.[19, 20] **Figure 3.1** shows the $^{1}$H NMR spectrum of the perpropionylated product from TBAF deacylation of cellulose triacetate (30 min, room temperature). The proton signals have been completely assigned using the COSY NMR spectra in **Figure S3.4** (Supporting information). Signals between 3.45 ppm and 5.20 ppm are the backbone protons. The acetyl protons resonate between 1.88–2.15 ppm. The O-6, O-2 and O-3 acetyl protons are at 2.03–2.15 ppm, 1.95–2.02 ppm, and 1.88–1.95 ppm, respectively. Propionyl methylene and methyl protons are at 2.16–2.44 ppm and 1.01–1.20 ppm, respectively. **Figure 3.2** shows the $^{13}$C NMR spectrum of the resulting cellulose acetate propionate, which shows characteristic signals at δ =173.0 [CO(Prop)], 170.2 [CO(Ac)], 101.1 (C-1), 77.5 (C-4), 73.4 (C-5), 72.1 (C-3), 71.2 (C-2), 62.6 (C-6), 27.4 ($CH_2$), 20.6 [$CH_3$(Ac)] and 8.5 [$CH_3$(Prop)] ppm. The HMBC spectrum (**Figure 3.3**) shows the correlations between the acetyl carbonyl carbons and the H-2, H-3, H-6 and H-6' protons, which confirm acetate substitution at O-2, O-3, and O-6; the correlation between the propionyl carbonyl carbon and the H-2 and H-3 protons confirms propionylation at O-2 and O-3. The correlation cross peak between the propionyl carbonyl C-6 and the H-6/6' is too weak to be observed.

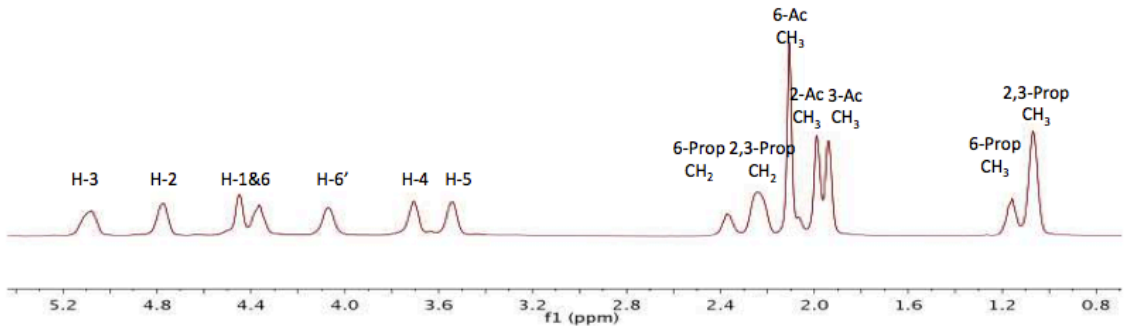



**Figure 3.1** $^{1}$H NMR spectrum of the product of cellulose triacetate deacylation by TBAF (30 min, DMSO, 20 °C) after perpropionylation.

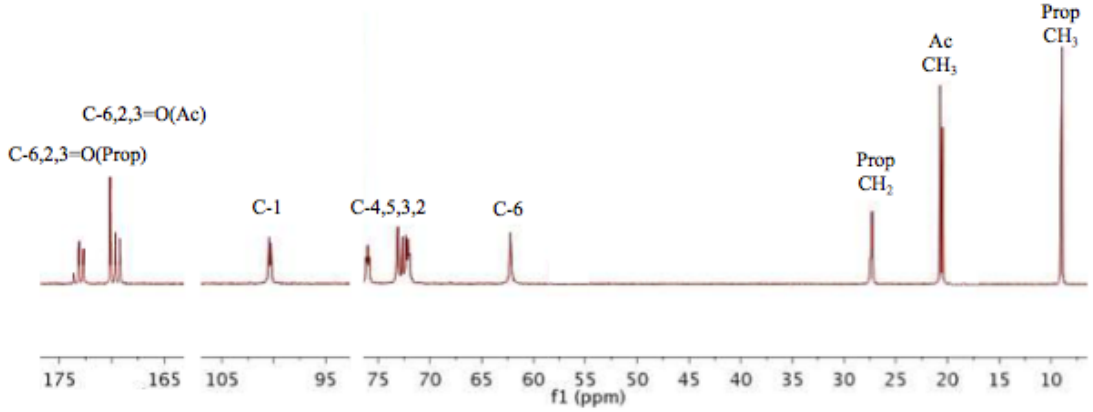



**Figure 3.2** $^{13}$C NMR spectrum of the product of cellulose triacetate deacylation by TBAF (30 min, DMSO, 20 °C) after perpropionylation.

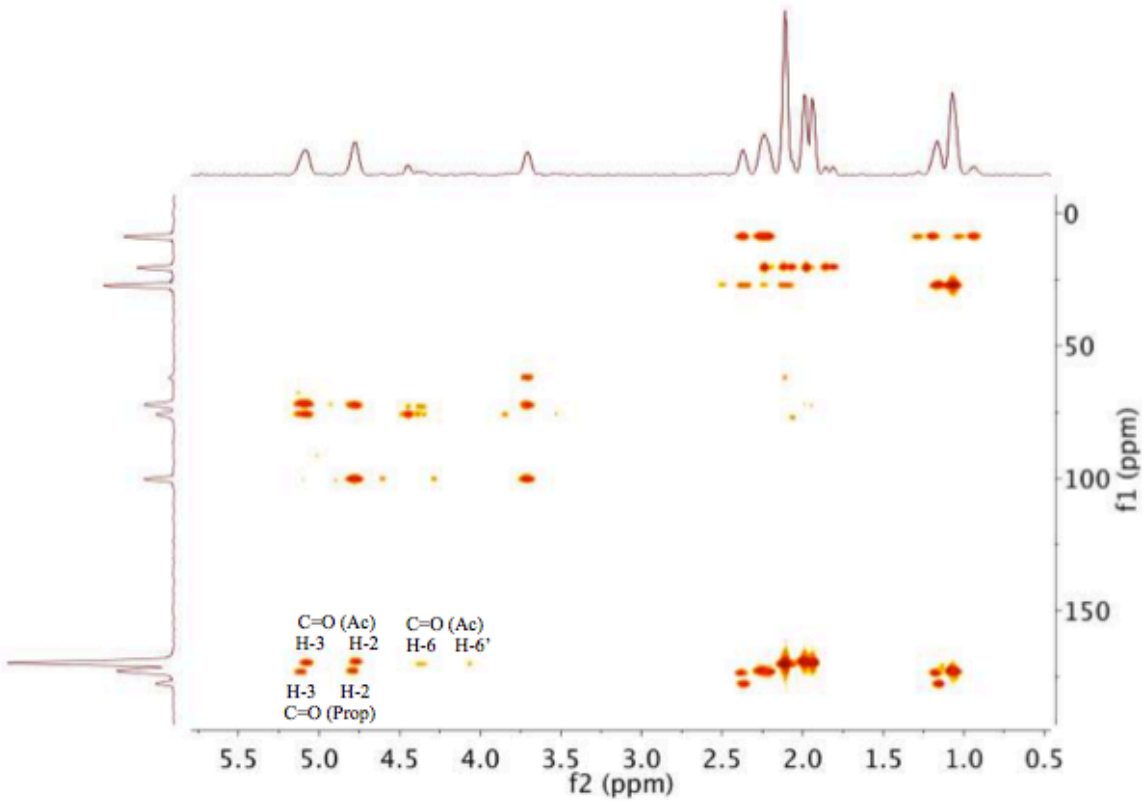



**Figure 3.3** HMBC spectrum of the product of cellulose triacetate deacylation by TBAF (30 min, DMSO, 20 °C) after perpropionylation.

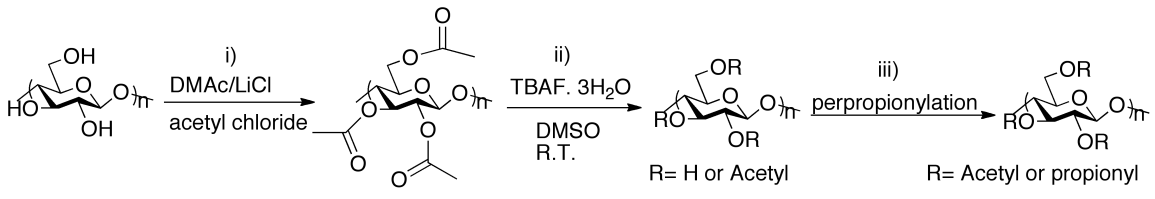
## 3.4 Results and Discussion

### 3.4.1 Kinetic isotope effects

Kinetic isotope effects (KIE) are widely used to elucidate reaction mechanisms by providing information about the transition state of the rate-determining step. For the deacylation, we have postulated a ketene mechanism involving deprotonation of a C—H alpha to the carbonyl. KIE should help determine whether C—H bond breaking is the rate-determining step.

The necessary isotopically-labelled cellulose ester was synthesized by reacting cellulose with the commercially available acetyl-$d_3$ chloride to afford cellulose tri(acetate-$d_3$) with DS 3.0. Similarly, we prepared the protio equivalent by acylation with acetyl-$h_3$ chloride. Fortunately, $^1$H NMR analysis of cellulose acetate position of substitution is well understood.[21, 22] Further, we took advantage of the finding in the Heinze laboratory[19] that peracylation with another ester (typically perpropionylation) affords a simplified set of derivatives, with no spectral complications from polysaccharide OH groups, whose $^1$H NMR spectra are easily interpreted with respect to position of substitution.

We separately carried out TBAF-catalyzed deacylation of deuterio and protio cellulose triacetates, sampling periodically over the reaction course and isolating the reaction products by aqueous quenching and precipitation at each time point. Standard sample workup, perpropionylation, and standard isolation of the resulting triesters, followed by $^1$H NMR analysis of each isolated product gave us detailed information about total DS as well as DS at each individual hydroxyl group. From these analyses, we could determine not only overall reaction kinetics for deuterio vs. protio esters, but also the individual reaction kinetics at each position of the AGU. In order to be certain that extensive base-catalyzed depolymerization had not occurred in the presence of the $F^-$ ion, we used SEC to measure the DP of the cellulose triacetate deacylation products from the kinetics experiment (TBAF (20 mol/mol AGU), DMSO, room temperature) vs. reaction time. Only minor (< 10%) loss of DP was observed (**Figure S3.5**) under these conditions. It is also notable that under preparative conditions (see Experimental section), virtually no DP loss was observed (starting CA (DS 2.42) DP 136, product (CA, DS 0.92) DP 134)).




**Scheme 3.2** Reaction flow: i) synthesis of cellulose triacetates; ii) TBAF deacylation of cellulose triacetates in DMSO; iii) perpropionylation of the deacylation product.

Scheme 3.2 shows the entire process—synthesis of cellulose triacetates, deacylation of cellulose triacetates by TBAF in DMSO, and perpropionylation of the deacylation product. For the TBAF deacylation reaction, the reaction rate has the form (eq. 1):

$$d[\text{acetate}]_t/dt = k[\text{acetate}][\text{TBAF}] \quad (1)$$

Where $k$ is the reaction rate constant that depends on temperature, [acetate] is the concentration of the resulting cellulose acetate, and [TBAF] is the concentration of TBAF. However, measuring the concentration of TBAF can be problematic. We have employed pseudo-first-order conditions (20-fold excess of TBAF) in order to avoid this complication; therefore the concentration of TBAF can be treated as a constant during the reaction (often molar excesses of 100-fold or more are preferred to ensure good pseudo-first order kinetics; this was not possible in this case due to limited solubility of TBAF in DMSO. The linear plots obtained support the notion that 20-fold excess was sufficient in this case). The reaction rate can then be expressed as follows (eq. 2):

$$d[\text{acetate}]_t/dt = k' [\text{acetate}] \quad (2)$$

Where $k'=k[\text{TBAF}]$ (with units $s^{-1}$), $[\text{acetates}] = DS_{\text{acetates}}\ [\text{cellulose triacetates}]_0$

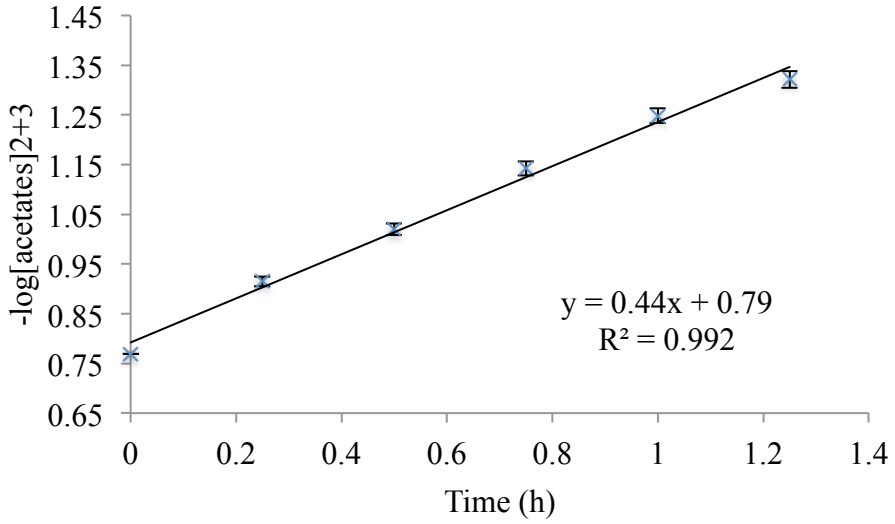
Integration of both sides affords eq 3:

$$-\log[\text{acetates}] = k't - \log[\text{acetates}]_0 \quad (3)$$

Pseudo-first-order rate constants *k'* were obtained from the linear plots of log [acetates] versus time; triplicate runs agreed to within ± 4%.

Given the high regioselectivity of TBAF-mediated deacylation for removing secondary alcohol acetate groups at O-2 and O-3, we speculated that the reaction mechanism at O-2/3 could differ from that at O-6. If so, the reaction rate constants at the primary positions would also differ from those at the secondary positions. In order to test this hypothesis, we plotted log [acetates] at O-2/3 and O-6 separately against time. In each plot, linear dependence of log [acetates] on time was observed (**Figure 3.4**). Plotting log $[\text{acetates}]_{2+3}$ versus time yields a straight line of slope 0.44 ± 0.02, while plotting log $[\text{acetates}]_6$ versus time affords a straight line of slope 0.099 ± 0.002. The reaction rate constants at C-2/3 and C-6 differed significantly, supporting the hypothesis that the mechanisms of deacylation of secondary vs. primary alcohol acetates also differed. In the same way, deacylation rate constants for deuterated cellulose triacetates were 0.35 ± 0.02 and 0.109 ± 0.002 for O-2/3 and O-6, respectively. Deacylation of the secondary alcohol acetates (O-2/3) occurred with a small normal KIE of 1.26 ± 0.04; deacylation of the primary alcohol acetates (O-6) gave an inverse secondary KIE of 0.87± 0.03.

(a)




(b)

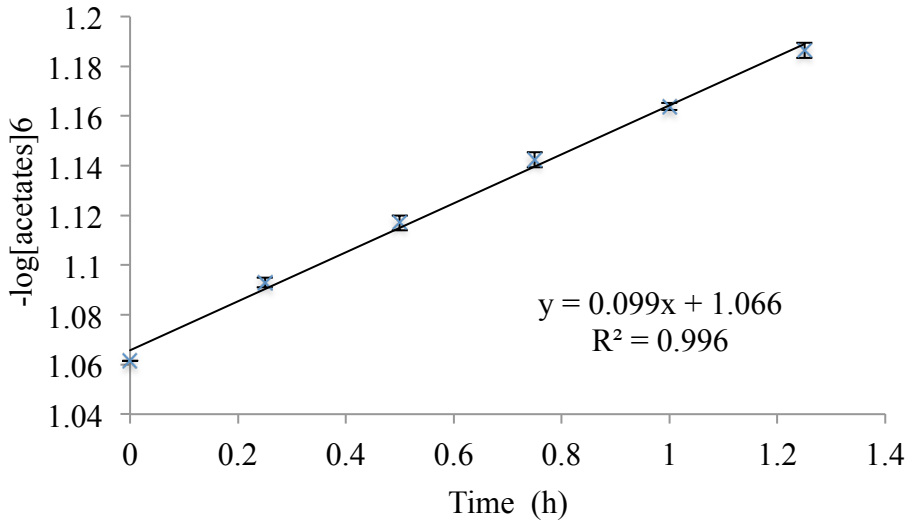
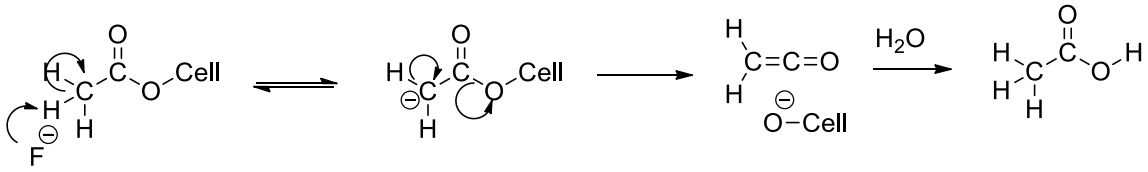



**Figure 3.4** (a) Plot of $-\log[\text{acetates}]_{2+3}$ versus time. (b) Plot of $-\log[\text{acetates}]_{6}$ versus time.

A small normal KIE at C-2/3 (1.3) means that C—H bond-breaking alpha to the carbonyl group is *not* the rate determining step. Primary KIEs typically exceed 2.0.[23-26] The secondary KIE for deacylation at O-2/3 can be attributed to carbon $sp^3 \rightarrow sp^2$ rehybridization. The theoretical maximum KIE resulting from such rehybridization is 1.4;[27] the measured KIE (1.3) at O-2/3 is in this range. We reason that the mechanism of the deacylation reaction at O-2/3 is E1cB elimination (**Scheme 3.3**). In the first step, fluoride anion reversibly abstracts the alpha proton, generating a carbanion. The second, rate-determining step is the elimination reaction, forming ketene and the secondary cellulose hydroxide anion. Ketene condenses quickly with a TBAF water of hydration, affording acetic acid as co-product.




**Scheme 3.3** Ketene intermediate mechanism at C-2/3. (first step reversible, second step rate-determining)

The inverse secondary KIE (0.87) observed at C-6 can be explained by $sp^2 \rightarrow sp^3$ rehybridization at the carbonyl carbon by either of two mechanisms. One mechanism that would involve such rehydridization would be nucleophilic attack of fluoride anion on the acyl carbonyl producing a fluoride-containing, $sp^3$-hydridized tetrahedral intermediate that then collapses to generate the C-6 alcohol plus acetyl fluoride, (which is then hydrolyzed to acetic acid by a TBAF water of hydration). Alternatively a general-base mechanism may operate. Fluoride anion synchronously removes a proton as water attacks the carbonyl carbon to form an anionic $sp^3$-hydridized

tetrahedral intermediate, which then decomposes ultimately to acetate and the C-6 alcohol. In order to provide evidence as to whether the tetrahedral intermediate that forms and decomposes contains fluoride or hydroxide, we evaluated the effects of added base and acid.

### 3.4.2 Effect of added base

To obtain more information about the mechanism at C-6, we investigated whether added base or acid affects deacylation. We reasoned that added base should increase deacylation at C-6 if the mechanism is general base, or should have negligible impact on rates if the mechanism is fluoride nucleophilic attack. As can be seen from **Table 3.1**, adding only $Na_2CO_3$ (entry 3) gave no deacylation of cellulose acetate. Upon adding both $Na_2CO_3$ and TBAF, in comparison to TBAF alone (entry 2), the presence of $Na_2CO_3$ (entries 4 and 5) gave inferior deacylation regioselectivity, with faster removal of the O-6 acyl group, while the rate of O-2/3 deacylation was the same as for entry 2. These results are consistent with a general-base mechanism at O-6 (**Scheme 3.4**).

### 3.4.3 Effect of added acid

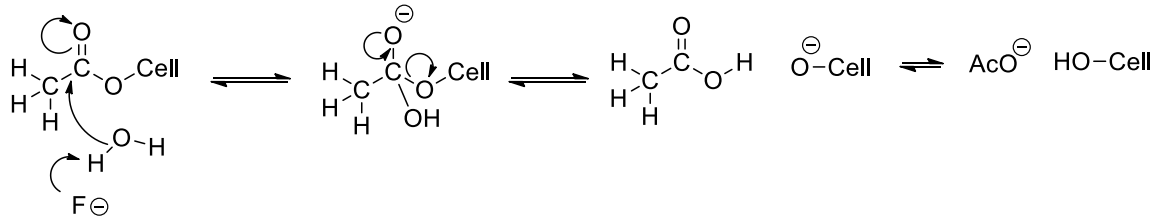
We had noticed from our first observation[14] of the unusual TBAF-catalyzed deacylation that even in the presence of excess TBAF, as the reaction proceeded, the amount of deacetylation plateaued, then the deacetylation rate slowed almost to zero. We suspected that this was due to the generation of co-product acetic acid, which naturally would retard a base-catalyzed reaction. If this were the case, then the presence of excess acetic acid from the start of the reaction should significantly reduce the degree of deacetylation. Indeed, reaction with TBAF in DMSO in the

presence of 4 equiv/AGU added acetic acid (**Table 1**, entry 6) afforded no deacylation at all, while 2 equiv/AGU acetic acid gave little deacylation at O-2/3.

**Table 3.1** Effect of added $Na_2CO_3$ or acetic acid on TBAF deacylation of CA[a]

| Entry | TBAF (mol/AGU) | Acid/ Base | Acid/ Base (mol/AGU) | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ |
|---|---|---|---|---|---|---|
| 1 | 0 | None | 0 | 0.82 | 1.60 | 2.42 |
| 2 | 4 | None | 0 | 0.80 | 0.10 | 0.90 |
| 3 | 0 | $Na_2CO_3$ | 4 | 0.82 | 1.60 | 2.42 |
| 4 | 4 | $Na_2CO_3$ | 1.50 | 0.44 | 0.10 | 0.54 |
| 5 | 4 | $Na_2CO_3$ | 0.75 | 0.57 | 0.11 | 0.68 |
| 6 | 4 | $CH_3CO_2H$ | 4 | 0.82 | 1.60 | 2.42 |
| 7 | 4 | $CH_3CO_2H$ | 2 | 0.82 | 1.47 | 2.29 |

[a]Starting CA DS 2.42, reaction temperature 50 °C, time 24 h, solvent DMSO.




**Scheme 3.4.** General-base mechanism at C-6.

### 3.4.4 Chelation mechanism

The ketene mechanism appears to operate at O-2/3, but it may not be able to explain the high regioselectivity observed for deacylation at these positions. Although steric effects can explain the preference for the ketene mechanism at O-2/3 because of constraints in forming a tetrahedral intermediate, we remain unconvinced that relief of steric strain in the ground state provides adequate driving force for the observed regioselectivity in the deacylation at O-2/3 versus O-6. We speculate that interaction of the bulky tetrabutylammonium cation with the carboxyl oxygen atoms could be a source of regioselectivity. **Figure 3.5** illustrates this hypothesis: the protons alpha to the ammonium nitrogen of TBAF form a complex with the carbonyl oxygens at O-2/3 through hydrogen bonding or ion–dipole interactions. Such a complex would concentrate the accompanying fluoride anion in the vicinity of the O-2/3 acyl groups, providing the impetus for regioselective deacylation at O-2/3.

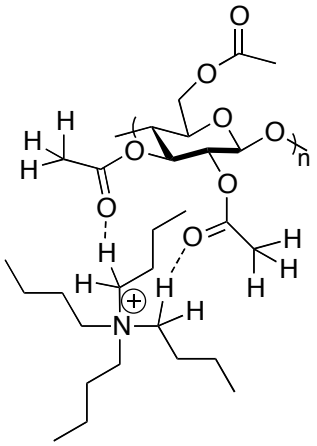


**Figure 3.5** Structure of hypothetical TBAF-acetate complex.

To test the hypothesis that complexation of the tetraalkylammonium cation with the vicinal acetate groups at O-2/3 might control regioselectivity, we carried out several additional experiments (**Table 3.2**). With limited TBAF (entries 2-3), deacylation first occurred at O-2/3 with almost equal DS (Ac) at O-2 and O-3. On the other hand, excess TBAF (entries 4-7) afforded substantial deacylation at O-2/3 and some deacylation at O-6. The fact that deacylation occurs at almost equal rates at O-2 and O-3, and the fact that excess TBAF can eventually cause deacylation at O-6, are consistent with the hypothesis of chelation between the O-2/3 acetates and the ammonium cation, governing the observed regioselectivity.

**Table 3.2** Results of TBAF Deacylation of CA[a]

| **Entry** | **TBAF (mol/AGU)** | **$DS_{total}$** | **$DS_6$** | **$DS_2$** | **$DS_3$** |
|---|---|---|---|---|---|
| 1 | 0 | 2.42 | 0.82 | 0.80 | 0.80 |
| 2 | 1 | 1.54 | 0.82 | 0.35 | 0.37 |
| 3 | 2 | 1.27 | 0.82 | 0.22 | 0.23 |
| 4 | 3 | 1.07 | 0.80 | 0.12 | 0.14 |
| 5 | 4 | 0.90 | 0.80 | 0.05 | 0.05 |
| 6 | 5 | 0.66 | 0.64 | 0.01 | 0.01 |
| 7 | 6 | 0.56 | 0.56 | 0.00 | 0.00 |

[a]Starting CA DS 2.42, reaction temperature 50 °C, time 24 h, solvent DMSO.

### 3.4.5 Impact of cation nature and size

The impact of the nature of the cation was examined in order to provide further evidence about the chelation mechanism (**Table 3.3**). We examined the one alkali metal fluoride (potassium fluoride dihydrate (KF•2 $H_2O$) that was adequately soluble in an appropriate organic solvent (MEK), and two additional tetraalkylammonium fluorides—tetraethylammonium fluoride hydrate (TEAF•$H_2O$) and tetramethylammonium fluoride tetrahydrate (TMAF•4 $H_2O$). No deacylation was observed upon exposure of CA to KF in MEK (entry 2), perhaps due to the reduced dissociation of KF compared to bulky tetraalkylammonium cations; more "naked" anions will be more reactive. Reaction of CA with TEAF (1.6 mol/AGU) in DMSO (entry 4) gave deacylation that was similarly selective at O-6 (virtually no deacylation) but gave slightly less deacylation of the O-2/3 acetates than with TBAF. On the other hand, reaction with TMAF in DMSO (entry 5) showed much poorer regioselectivity than that observed with TBAF, with substantial deacylation at the primary acetate. The different tetraalkylammonium salts have different numbers of waters of hydration; one could speculate that this might cause differences in extent or selectivity of deacylation. In order to test whether these differences in molar equivalents of water available from the salt had significant impact on deacylation extent or regioselectivity, we added the appropriate number of equivalents of water to compensate, such that each experiment had the same number of equivalents of water present (4 mols/mol tetraalkylammonium salt, entries 5-7, **Table 3**). In each case, the added water caused almost no difference in extent or regioselectivity of deacylation; therefore we can interpret differences between entries 1, 3 and 4 as being due to differences in the cation only.

These limited data do not prove the chelation hypothesis, but the TMAF results are consistent with the notion that as cation size declines, the regioselectivity of tetraalkylammonium fluoride-catalyzed deacylation of CA decreases.

**Table 3.3** Effect of cation on CA deacylation selectivity[a]

| Entry | Fluoride source | Solvent | $DS_{total}$ | $DS_6$ | $DS_2$ | $DS_3$ |
|---|---|---|---|---|---|---|
| 1 | TBAF•3 $H_2O$ | MEK | 0.92 | 0.80 | 0.06 | 0.06 |
| 2 | KF•2 $H_2O$ | MEK | 2.40 | 0.80 | 0.80 | 0.80 |
| 3 | TBAF•3 $H_2O$ | DMSO | 0.90 | 0.80 | 0.05 | 0.05 |
| re | TEAF•$H_2O$ | DMSO | 1.05 | 0.80 | 0.12 | 0.13 |
| 5 | TMAF•4 $H_2O$ | DMSO | 0.49 | 0.37 | 0.06 | 0.06 |
| 6 | TBAF•3$H_2O$ + 1 $H_2O$ | DMSO | 0.90 | 0.78 | 0.06 | 0.06 |
| 7 | TEAF•$H_2O$ + 3 $H_2O$ | DMSO | 1.09 | 0.82 | 0.13 | 0.14 |

[a]Starting CA DS 2.42, fluoride salt 4 equiv/AGU, reaction temperature 50 °C, time 24 h.

### 3.5 Conclusions

KIE determination for TBAF-mediated deacylation of cellulose acetate, measured separately for each individual ester group location (O-2, O-3 and O-6), has illuminated the mechanisms of this unusual process. KIE results indicate that deacylation at the secondary O-2/3 positions is by an

E1cB mechanism, while the slower deacylation at the primary O-6 position is by a general base-catalyzed mechanism. We still cannot conclusively pinpoint the source of the remarkable and counterintuitive regioselectivity of this reaction, with deacylation occurring predominantly at the more hindered O-2/3 positions. Evidence from studies of cation effects supports the possibility that coordination of the bulky tetraalkylammonium cations by the vicinal O-2/3 acetates drives the observed selectivity, but we do not consider the currently available evidence definitive. Upcoming studies will further explore the scope of this deacylation reaction, which serves as a valuable one-step method for generating regioselectively substituted cellulose esters without the need of challenging, inefficient protection and deprotection steps.

### 3.6 Supplementary Material

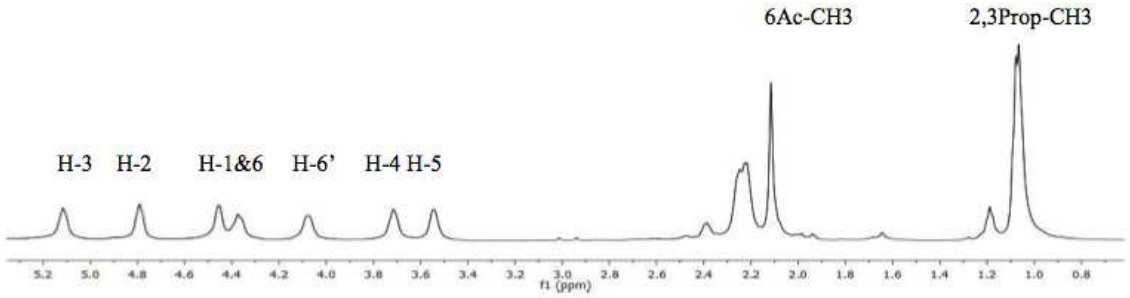



**Figure S3.1** $^{1}$H NMR spectrum of the product of cellulose acetate deacylation by TBAF (4 mol/mol, 24 h, THF, 50 °C)[14] Published with permission from ref 14. Copyright 2012 American Chemical Society.

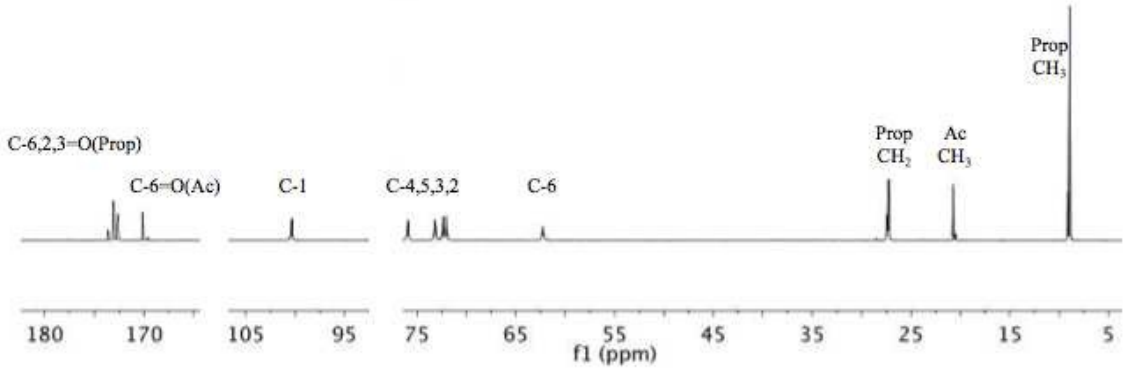



**Figure S3.2** $^{13}$C NMR spectrum of the product of cellulose acetate deacylation by TBAF (4 mol/mol, 24 h, THF, 50 °C)

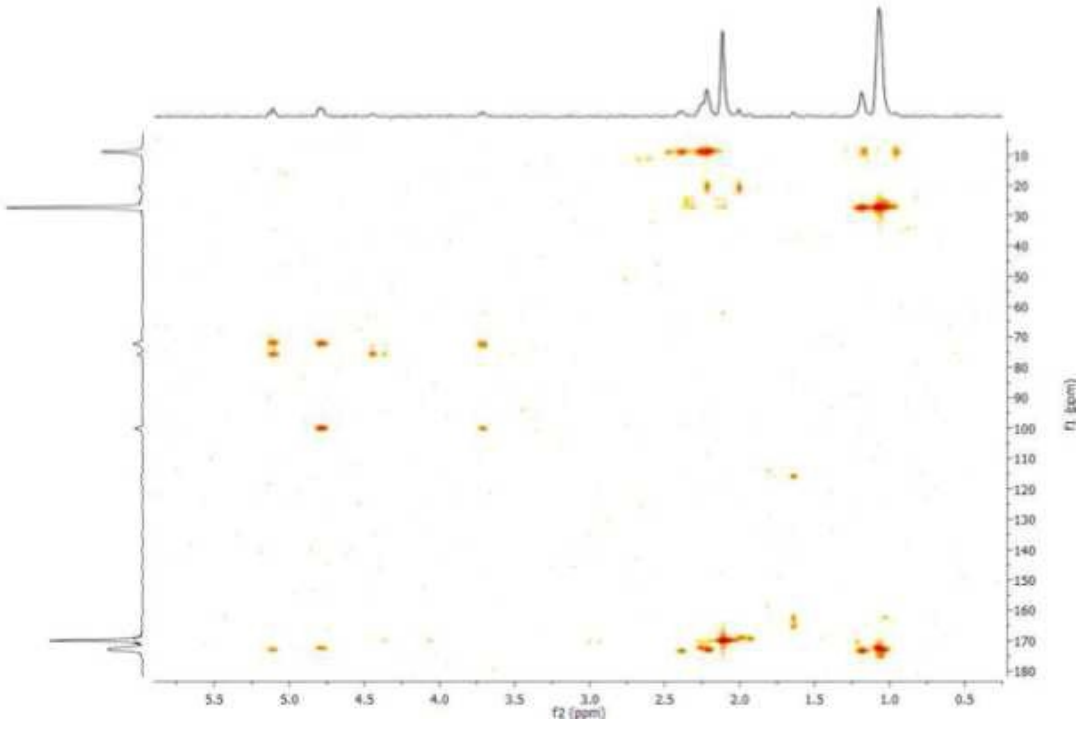



**Figure S3.3** HMBC spectrum of the product of cellulose acetate deacylation by TBAF (4 mol/mol, AGU 24 h, THF, 50 °C)[14] Published with permission from ref 14. Copyright 2012 American Chemical Society.

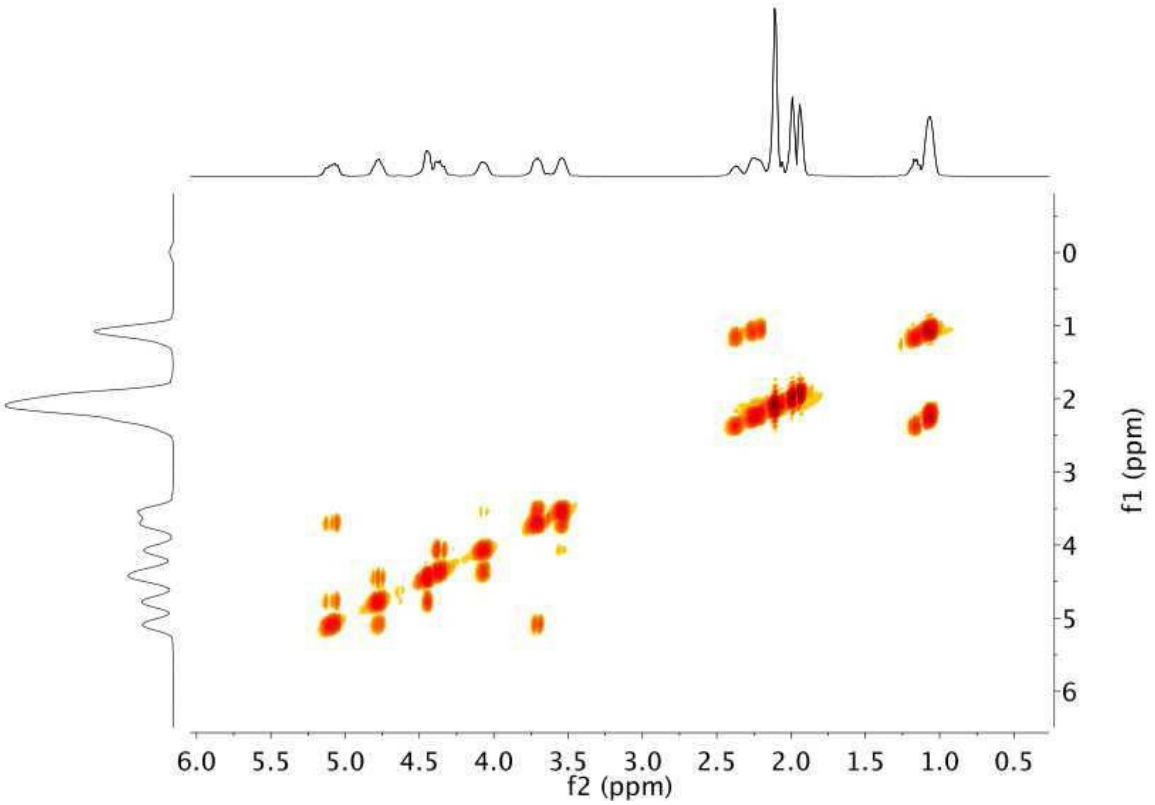



**Figure S3.4** COSY spectrum of the product of cellulose triacetate deacylation by TBAF (20 mol/mol AGU, 30 min, DMSO, 20 °C)

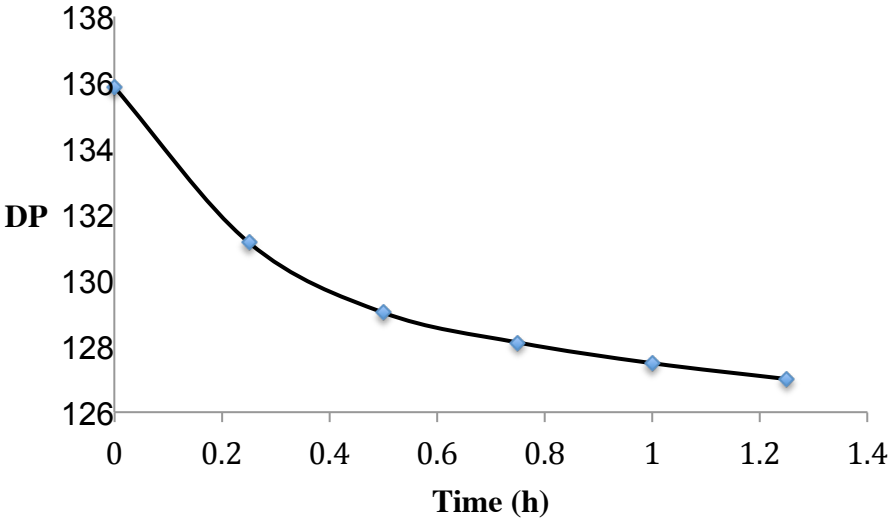


**Figure S3.5** DP of the products of cellulose triacetate deacylation by TBAF (20 mol/mol AGU, DMSO, room temperature) for different reaction times after perpropionylation


### 3.7 Acknowledgements

We thank USDA for their financial support of this study through grant number 2011-67009-20090. We thank the Virginia Tech Institute for Critical Technologies and Applied Science for facility support for this work. We also thank Eastman Chemical Company for their donation of the commercial cellulose acetate samples. We are indebted to Professor James M. Tanko of Virginia Tech, Professor Daniel M. Quinn of the University of Iowa, and Dr. Thomas Elder of the U.S. Forest Service for insightful discussions, and Dr. Sue Mecham for performing SEC measurements.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# Chapter 4 TBAF- catalyzed Deacylation of Cellulose Esters: Reaction Scope and Influence of Reaction Parameters

Adapted with the permission from: Zheng, X.; Gandour, R. D.; Edgar, K. J. Carbohydrate Polymers, 98: 692-698. 

## 4.1 Abstract

In order to expand its utility and understand how to carry it out most efficiently, the scope of the highly regioselective, tetrabutylammonium fluoride (TBAF) catalyzed deacylation of cellulose acetates has been investigated, including the influence of key process parameters: solvent, temperature, and water content. Reactions in DMSO, THF, MEK and acetone afforded similar extents of deacylation and regioselectivity. Reaction with TBAF in DMSO at 50 °C for 18 h was the most efficient process providing regioselective deacylation at O-2/3. All results were consistent with our previous mechanistic proposals. Furthermore, we demonstrate that TBAF-catalyzed deacylation is also effective and regioselective with cellulose acetate, butyrate, and hexanoate triesters, and even with a cellulose ester devoid of alpha protons, cellulose tribenzoate. These reactions displayed regioselectivity for deacylation at O-2/3 similar to that observed earlier with cellulose acetate (DS 2.4).

## 4.2 Introduction

Biocompatible and biodegradable polymers, especially those derived from renewable sources, are of increasing interest as fossil-based feedstocks become increasingly expensive. It thus becomes essential to develop bio-based materials with performance equal to or greater than that

of synthetic materials. Cellulose, an extraordinarily abundant polymer, can be harvested and purified year-round from trees and other renewable sources. The science of conversion of cellulose into derivatives, for example ethers and esters, enables one to create soluble or thermally processable cellulose-based products. These cellulosic derivatives have led to viable commercial applications and thriving industries in cellulosic films, fibers, molded objects, and coatings [1, 2]. Conversion of cellulose into its esters also modifies its physical properties, expanding the range of potential applications. Cellulose esters have been widely used for decades, for example as coatings [3, 4], matrices for controlled release [5, 6], and optical films [7].

Most commercially important cellulose esters are randomly substituted, in so far as one can tell [8] by the available analytical techniques (which are admittedly of limited utility when more than on type of ester group is present, for example in cellulose acetate propionate). In recent years, cellulose solvents like DMAc/LiCl and ionic liquids have enabled more selective derivatization, permitting synthesis of a few regioselectively substituted cellulose esters [9]. These regioselectively substituted cellulose esters commonly have properties that differ remarkably from those of presumably randomly substituted materials, for example in crystallinity [10], thermal properties [11], solubility [12], and optical properties [13]. With our growing appreciation of the power of substitution regioselectivity to modify properties, it becomes all the more informative to establish fundamental understanding of the structure-property relationships with regard to position of substitution. This information will enable us to better predict how structural changes will impact properties and performance in demanding applications, and thus to design cellulose derivatives to deliver high performance.

To date, these regioselective syntheses have almost always involved protection-deprotection schemes that have hygroscopic, multicomponent solvents required for cellulose dissolution.

Examples include cellulose-2, 3-*O*-diesters and cellulose-2, 3-*O*-A-6-*O*-B-triesters synthesized by protecting cellulose with trityl groups at O-6 [11], and cellulose-2, 6-*O*-diesters and cellulose-2, 6-*O*-A-3-*O*-B-triesters synthesized by protecting cellulose with silyl groups at O-2/6 [14]. While invaluable for preparing lab scale samples and carrying out initial structure-property studies of the effects of regiochemistry, this protection-deprotection approach is limited in applicability because of the necessity for multiple steps, yield loss and expense of each step, and the potential for poor reactivity of protected intermediates. These issues make it difficult to make large quantities of regioselectively substituted cellulose derivatives for further study, and certainly prohibit all but the highest value applications for the regioselectively substituted products.

Recently our laboratory has discovered an unexpectedly selective, efficient synthesis of highly regioselectively-substituted cellulose-2, 3-*O*-A-6-*O*-B-triesters without the need for protection/deprotection steps. With commercial cellulose acetate (DS 2.45) as the starting material, reaction with tetrabutylammonium fluoride (TBAF) trihydrate in common organic solvents (e.g. THF) under readily achieved reaction conditions [15] afforded TBAF-catalyzed regioselective deacylation of cellulose acetate at the secondary (2, 3) positions and the retention of the ester group at O-6. The product esters, containing acetate groups regioselectively placed at O-6, can be smoothly acylated with a second acyl type to afford cellulose-2, 3-*O*-alkanoate-6-*O*-acetate triesters. Our proposed mechanism by which TBAF catalyzes this regioselective deacylation of cellulose acetates (Zheng, Gandour & Edgar, 2013[16]. is fluoride-catalyzed deprotonation of the 2, 3-*O*-ester groups at the methylene group alpha to the carbonyl, followed by deacylation by an E1cB mechanism that generates ketene as a co-product (the ketene reacts quickly with adventitious water and/or TBAF water of hydration to produce acetic acid). The slower deacylation at the primary O-6 position occurs by a separate, general base-catalyzed

mechanism. We further suggested that chelation of the TBA cations by the vicinal 2, 3-*O*-acetate groups might be the driving force behind the regioselectivity observed.

The current study explores the scope of the TBAF-catalyzed deacylation of cellulose esters, aiming to learn whether we can make this deacylation process more efficient, flexible and broadly applicable. The influence of TBAF concentration on the deacylation has been investigated in our previous paper [15]; we found that 4 equiv TBAF/ AGU gave the best regioselectivity with almost complete deacylation at O-2/3 while preserving the O-6 acetyl. Herein we study the influence of other key process parameters: solvent, temperature, and added water. Furthermore, we investigate whether TBAF-mediated deacylation can be applied regioselectively to other cellulose esters including the triacetate, tributyrate, trihexanoate and tribenzoate derivatives (**Figure 4.1**).

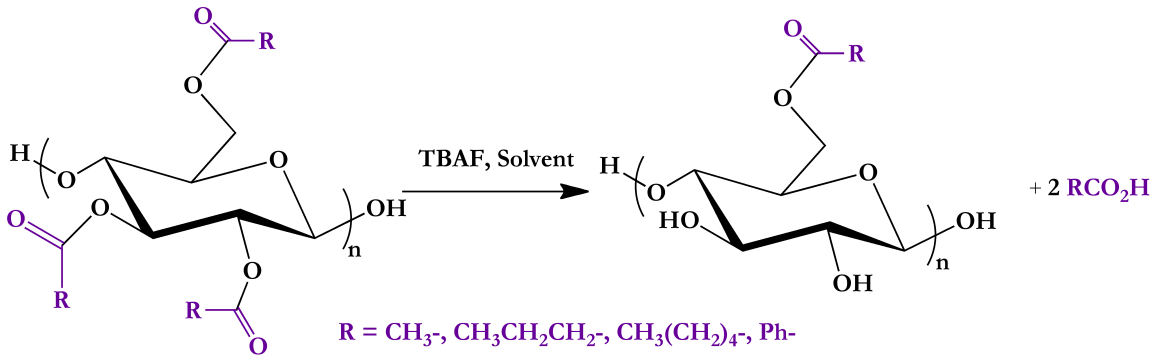


**Figure 4.1** TBAF-catalyzed deacylation of cellulose triesters

## 4.3 Experimental Section

### 4.3.1 Materials

Microcrystalline cellulose (MCC, Avicel PH-101, DP = 260) and cellulose acetate (C CA-398-30, Eastman Chemical Company, DP = 190) were dried under vacuum at 50 °C overnight before use.

*N*,*N*-Dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO), and pyridine were purchased from Fisher and stored over 4 Å molecular sieves. Tetrahydrofuran (THF), acetone, methyl ethyl ketone (MEK), methanol, and reagent alcohol (histological grade) were acquired from Fisher and used as received. n-Butyryl chloride, n-hexanoyl chloride, benzoyl chloride, acetic anhydride, and propionic anhydride were obtained from Aldrich. Tetrabutylammonium fluoride (TBAF, approximately a trihydrate), 4-(dimethylamino) pyridine (DMAP), and lithium chloride (LiCl) were purchased from Acros Organics and used as received.

### 4.3.2 Measurements

$^{1}H$, $^{13}C$, HMBC, and COSY NMR spectra were obtained on a Bruker Avance II 500 MHz spectrometer in $CDCl_3$ at room temperature or 50 °C, with number of scans of 32, 10,000, 19,200 and 9,400 respectively. The total and partial DS (degree of substitution) values of the cellulose ester products after peracetylation or perpropionylation were determined by calculating the ratios of acetyl or propionyl proton integrals to those of the backbone hydrogens [17, 18]. Molecular weights of cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate hexanoate and cellulose propionate benzoate were determined by size exclusion chromatography (SEC) in chloroform on a Waters Alliance model 2690 chromatograph with Waters 2414 differential refractive index (RI) detector and Viscotek 270 dual detector, vs. polystyrene standards.

### 4.3.3 Preparation of cellulose tributyrate

Dissolution of MCC in DMAc/LiCl followed a known method [4]. A mixture of MCC (5.00 g, 30.80 mmol) and DMAc (187 mL) was heated to 156 °C with stirring and kept for 26 min under nitrogen. Anhydrous LiCl (8.5 g) was added and the mixture was stirred at 165 °C for 8 min, then distillate (36 mL) was collected at 165 °C to facilitate water removal. The mixture was

cooled and stirred overnight at room temperature, during which time dissolution occurred. Pyridine (22.38 mL, 10 mol/ mol anydroglucose unit (AGU)) and butyryl chloride (28.38 mL, 10 mol/ mol AGU) were added sequentially, dropwise to the MCC solution. The reaction solution was kept at room temperature for 16 h under vigorous stirring. The reaction mixture was added to water (800 mL), the resulting slurry was filtered, and the solid product was washed several times by methanol. Soxhlet extraction with methanol (300 mL) was carried out to effect further purification. After 12 h, the crude product was collected, redissolved in THF (50 mL), and this solution re-precipitated into methanol (500 mL). The solid product was filtered off, washed several times with methanol, and dried under vacuum at 50 °C overnight.

### 4.3.4 Preparation of cellulose trihexanoate

Pyridine (22.38 mL, 10 mol/ mol AGU) and n-hexanoyl chloride (43.32 mL, 10 mol/ mol AGU) were added to a solution of MCC (5 g, 30.80 mmol) in DMAc/ LiCl solution. The mixture was allowed to react for 24 h at 80 °C. After cooling to room temperature, the product was recovered by slowly adding the reaction solution into water (800 mL), filtering off the solid product, and washing the solid thoroughly by ethanol. Re-dissolving the crude product in acetone (50 mL) and re-precipitating by slow addition to methanol (500 mL) gave purified product. After collecting by filtration, the sample was dried under vacuum at 50 °C overnight.

### 4.3.5 Preparation of cellulose tribenzoate

Pyridine (6 mL, 10 mol/ mol AGU) and benzoyl chloride (14.43 mL, 10 mol/ mol AGU) were added slowly, sequentially to the solution of MCC in DMAc/ LiCl. After heating at 100 °C for 4 h, the reaction solution was cooled to room temperature and kept for 20 h under vigorous stirring. After the reaction mixture was added slowly to water (500 mL), the resulting precipitate was

collected by filtration and then washed several times with water. The product was dried at 50 °C under vacuum.

### 4.3.6 General procedures for deacylation of cellulose esters

TBAF (4 mol/ mol AGU) was added to the solution of cellulose ester (0.5 g) in DMSO (20 mL). After stirring at 50 °C for 24 h, the solution was added slowly to water (250 mL) to precipitate the product, which was collected by filtration, washed several times with water, and dried under vacuum at 50 °C. We had some concern that precipitation could be fractionating the product. For comparison, a duplicate experiment was quenched by acetic acid and the product was isolated by dialysis against water for 3 d, followed by freeze-drying of the retentate. For TBAF deacylation of CA (24 h, DMSO, 50 °C), the percent yield by precipitation is 88% and the percent yield by dialysis is 98%. The total DS and partial positional DS values of the resulting CA samples isolated by the different procedures are the same, with DS of 0.10 at O-2/3 and DS of 0.82 at O-6.

### 4.3.7 General procedures for peracetylation or perpropionylation of deacylated cellulose esters

Peracetylation or perpropionylation was carried out according to previously published procedures [17, 18] in order to obtain products with simplified NMR spectra (no coupling with OH protons, fewer monosaccharide possibilities) for the determination of partial positional DS values of the deacylated product. Deacylated cellulose ester (0.3 g) was dissolved in pyridine (4 mL). DMAP (15 mg) and acetic anhydride (4 mL) or propionic anhydride (4 mL) were added to the solution. After stirring at 80 °C for 24 h, the crude product was obtained by precipitation into ethanol (200 mL) and washed several times by ethanol. Re-dissolving the crude product in chloroform and re-precipitating it into ethanol further purified the product. The sample was dried under vacuum for DS determination. The total and partial DS values for the peracetylated

product were determined according to equation 1 and 2. For example, the partial DS(Ac) values of cellulose acetate butyrate were determined directly by the ratio of the partial acetyl resonances (O-2/3 1.80–1.95 ppm, O-6 2.03–2.08 ppm) to the integrals of the cellulose backbone protons (3.37–5.15 ppm). The partial DS(Ac) value was subtracted from 1 (with successful peracetylation there is a total DS of 1 at each position) to give the DS(Bu) at that position. On the other hand, the total and partial DS values for the perpropionylated product were calculated based on equations 3 and 4 by comparing integrals of the backbone protons with the propionyl methyl protons. The completeness of peracetylation or perpropionylation was confirmed by the disappearance of the OH band in the FITR spectrum (3460 $cm^{-1}$). The percent regioselectivity for the TBAF-catalyzed deacylation were determined by equation 5, which is the difference between the percent deacylation at O-2/3 and the percent deacylation at O-6.

$DS_{ester}=3-7I_{H,\ acetyl}/3I_{H,\ AGU}$; I=Integral (1)

$DS_{ester\ (n)}=1-7I_{H,\ acetyl\ (n)}/3I_{H,\ AGU}$; I=Integral, n=Position 2, 3, 6 (2)

$DS_{ester}=3-7I_{H,\ propionyl}/3I_{H,\ AGU}$; I=Integral (3)

$DS_{ester\ (n)}=1-7I_{H,\ propionyl\ (n)}/3I_{H,\ AGU}$; I=Integral, n=Position 2, 3, 6 (4)

Percent regioselectivity= $[(DS_{2+3(S)}–DS_{2+3(P)})/ (DS_{total(S)}–DS_{total(P)})]-[(DS_{6(S)}–DS_{6(P)})/(DS_{total(S)}–DS_{total(P)})]$; S=Starting cellulose esters, P=Product (5)

## 4.4 Results and Discussion

### 4.4.1 Solvent effects on TBAF-catalyzed deacylation of CA

Solvents can affect outcomes of organic reactions and can also teach us about the reaction mechanism. Determining solvent effects on the TBAF-catalyzed deacylation of CA (DS 2.42) would be useful by showing that various solvents can be used for regioselective cellulose ester deacylation, since cellulose ester solubility can differ markedly according to ester group type and DS.

We investigated TBAF-catalyzed deacylation of CA in solvents in which both polymer and catalyst were soluble, including DMSO, THF, MEK, DMAc, pyridine, and acetone. All six are polar aprotic solvents; five are neutral, while pyridine is a weak base. As can be seen from **Table 4.1**, after treatment of CA with TBAF (4 mol/ mol AGU) at 50 °C for 24 h, deacylation in DMSO (entry 2), THF (entry 3), MEK (entry 4), and acetone (entry 5) produced strikingly similar regioselectivity, removing most of the ester groups at O-2/3, and leaving those at O-6 largely untouched. On the other hand, reaction in the DMAc (entry 6) gave modestly inferior deacylation selectivity; in particular, deacylation at the primary O-6 position was more extensive (DS($Ac_6$) 0.73, vs. 0.80 in THF under otherwise identical conditions). A similar result was observed for deacylation in pyridine, which afforded cellulose acetate with DS($Ac_6$) of 0.75 at O-6 and DS($Ac_{2+3}$) 0.09 at O-2/3. According to our previous results, TBAF deacylation at O-6 is by a general base-catalyzed mechanism; while TBAF deacylation reaction at O-2/3 positions is by an E1cB, ketene intermediate mechanism. The greater extent of deacylation of the O-6 acetate in pyridine could be attributed to acid-base interaction between pyridine and the acetic acid reaction co-product. We demonstrated in our mechanistic paper that the presence of even a few equivalents of acetic acid completely shuts down the TBAF-catalyzed deacylation of CA. Thus,

the presence of basic solvents may promote general base-catalyzed deacylation, reducing regioselectivity. The lower regioselectivity in DMAc results from a decrease in reaction at O2/3 but not at O-6. This differs from the result in pyridine. Possibly, DMAc diminishes the proposed chelation mechanism by complexing with the tetrabutylammonium ion. The results are consistent with our prior conclusions about the mechanisms of TBAF deacylation. Furthermore, we have expanded the range of solvents for the regioselective deacylation of cellulose esters.

**Table 4.1** Effect of solvent on TBAF-catalyzed deacylation of CA[a]

| Entry | Solvent | Time (h) | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ | Percent Regioselectivity[b] |
|---|---|---|---|---|---|---|
| 1 | DMSO | 0 | 0.82 | 1.60 | 2.42 | NA |
| 2 | DMSO | 24 | 0.80 | 0.10 | 0.90 | 97% |
| 3 | THF | 24 | 0.80 | 0.11 | 0.91 | 97% |
| 4 | MEK | 24 | 0.80 | 0.12 | 0.92 | 97% |
| 5 | Acetone | 24 | 0.80 | 0.11 | 0.91 | 97% |
| 6 | DMAc | 24 | 0.73 | 0.12 | 0.85 | 88% |
| 7 | Pyridine | 24 | 0.75 | 0.09 | 0.84 | 91% |

[a]Starting CA DS 2.42, TBAF 4 equiv/ AGU, reaction temperature 50 °C. [b]Calculated by equation 5 in experimental section.

### 4.4.2 Influence of temperature on TBAF deacylation reaction kinetics in DMSO and MEK

Our initial experimentation on TBAF-catalyzed deacylation of CA was carried out at 50 °C for the most part, because reactions in THF or DMSO at that temperature gave convenient reaction rates and remarkable regioselectivity. Since at that temperature regioselectivity was incomplete, we explored temperature effects with the hope that lower temperatures might provide further differentiation in deacylation rates at O-6 vs. O-2/3, affording even higher regioselectivity. We investigated kinetics and selectivity of TBAF-catalyzed deacylation in both DMSO and MEK;

rates and selectivity in these solvents at 50 °C had already been shown to be similar. As the melting point for pure DMSO is 19 °C and the melting point for MEK is -86 °C, TBAF deacylation reaction kinetics in MEK were evaluated at 8 °C (reaction at 0 °C was not possible due to CA precipitation), while kinetics in DMSO were investigated across a range of temperatures from at 15 – 70 °C. Reaction of CA with TBAF in MEK at 8 °C (**Table 4.2**, entries 1 to 3) was very slow, out of the range of practical application, but with complete regioselectivity (as has been observed to be the case for the reaction in MEK at 50 °C at these early reaction stages). After 72 h reaction in MEK (entry 3), there was no deacylation of the O-6 acetate and only 54% deacylation of the O-2/3 acetates, compared with 93% deacylation at O-2/3 for the reaction in MEK at 50 °C for 24 h (**Table 4.2**, entry 4).

Reaction of CA with TBAF in DMSO at 15 °C for 24 h also afforded slower deacylation than at 50 °C in the same solvent, giving CA with $DS_6$ of 0.82 and $DS_{2+3}$ of 0.40 (75% deacylation at O-2/3). Entries 6 to 11 show that deacylation reaction kinetics in DMSO at 25 °C are also relatively slow; after 60 h (entry 10) providing a cellulose acetate with slightly more deacylation at O-6 ($DS_6$ of 0.77) and slightly less deacylation at O-2/3 ($DS_{2+3}$ of 0.21) compared with reaction at 50 °C for 24 h (entry 15). Apparently the rates of decline in reaction rates at O-6 and at O-2/3 with temperature are similar, resulting in small or no gains in selectivity by reducing reaction temperature. Most interestingly, reaction with TBAF in DMSO at 70 °C for 24 h (entry 16) caused increased deacylation of the O-6 acetate ($DS_6$ of 0.60) but reduced deacylation of the O-2/3 acetates ($DS_{2+3}$ of 0.17), in comparison with the control reaction at 50 °C. The enhanced deacylation at O-6 is easy to explain; the general base mechanism at O-6 position is accelerated at higher temperature. The reduced deacylation at O-2/3 might be consistent with our proposed chelation mechanism; at higher temperature, chelation of TBA by the vincinal O-2/3 acyl groups

may be less favorable due to entropic effects. At higher temperatures, increased motion of the smaller TBAF molecules makes such chelation less favorable, reducing the local concentration of fluoride and reducing deacylation at O-2/3. Overall, these results describing the relationship of reaction selectivity and kinetics with temperature are consistent with our earlier mechanistic proposals and data. These kinetic results also indicate that in these solvents, reaction in DMSO at 50 °C is the most efficient process, affording the best regioselectivity at O-2/3 versus O-6 in a manageable 18 h reaction time.

**Table 4.2** Influence of temperature on TBAF-catalyzed deacylation reaction kinetics of CA[a]

| **Entry** | **Solvent** | **Temperature (°C)** | **Time (h)** | **$DS_6$** | **$DS_{2+3}$** | **$DS_{total}$** | **Percent Regioselectivity[b]** |
|---|---|---|---|---|---|---|---|
| 1 | MEK | 8 | 0 | 0.82 | 1.60 | 2.42 | NA |
| 2 | MEK | | 24 | 0.82 | 0.93 | 1.75 | 100% |
| 3 | MEK | | 48 | 0.82 | 0.84 | 1.66 | 100% |
| 4 | MEK | | 72 | 0.82 | 0.79 | 1.61 | 100% |
| 5 | DMSO | 15 | 24 | 0.82 | 0.40 | 1.22 | 100% |
| 6 | DMSO | 25 | 12 | 0.82 | 0.40 | 1.22 | 100% |
| 7 | DMSO | | 24 | 0.82 | 0.28 | 1.10 | 100% |
| 8 | DMSO | | 36 | 0.79 | 0.26 | 1.05 | 96% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9 | DMSO | | 48 | 0.77 | 0.25 | 1.02 | 93% |
| 10 | DMSO | | 60 | 0.77 | 0.21 | 0.98 | 93% |
| 11 | DMSO | | 72 | 0.77 | 0.21 | 0.98 | 93% |
| 12 | DMSO | 50 | 6 | 0.82 | 0.21 | 1.03 | 100% |
| 13 | DMSO | | 12 | 0.80 | 0.17 | 0.97 | 97% |
| 14 | DMSO | | 18 | 0.80 | 0.10 | 0.90 | 97% |
| 15 | DMSO | | 24 | 0.80 | 0.10 | 0.90 | 97% |
| 16 | DMSO | 70 | 24 | 0.60 | 0.17 | 0.77 | 73% |

[a]Starting CA DS 2.42, TBAF 4 equiv/ AGU. [b]Calculated by equation 5 in experimental section.

### 4.4.3. Effect of water content

As the overall stoichiometry of the deacylation is CA + $H_2O$ → CA (lower DS) + $CH_3CO_2H$, we determined whether the reaction rate would be accelerated by added water, and if so whether an impact on selectivity would be observed. This is particularly relevant; since, in the absence of purposely added or adventitious water, the only source of water is the closely held TBAF waters of hydration[19]. We examined the effect of added water on the TBAF deacylation of CA in DMSO; we anticipated that addition of a few equivalents of water to CA in DMSO would be unlikely to precipitate the starting CA, and this was validated in our experiments (**Table 4.3**). Upon adding 1 (entry 2), 3 (entry 3), or 10 (entry 4) equivalents of water, TBAF-catalyzed deacylation occurred with regioselectivity similar to that in the case where no water was

purposely added (entry 1), affording cellulose acetate with similar total and partial DS values. Only the addition of 10 equivalents of water gave slightly more overall deacylation, resulting in additional removal of the O-6 acetate, which is consistent with the general base catalysis mechanism at O-6. Overall, TBAF-catalyzed deacylation of CA in DMSO is rather insensitive to added water; clearly water is not a limiting reagent, despite the energy required to break up the TBAF hydrate.

**Table 4.3** Effect of added water on TBAF-catalyzed deacylation of CA[a]

| Entry | Fluoride Source | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ | Percent Regioselectivity[b] |
|---|---|---|---|---|---|
| 1 | TBAF· $3H_2O$ | 0.80 | 0.10 | 0.90 | 97% |
| 2 | TBAF· $3H_2O$ + 1 eq $H_2O$ | 0.80 | 0.11 | 0.91 | 97% |
| 3 | TBAF· $3H_2O$ + 3 eq $H_2O$ | 0.80 | 0.12 | 0.92 | 97% |
| 4 | TBAF· $3H_2O$ + 10 eq $H_2O$ | 0.75 | 0.12 | 0.87 | 91% |

[a]Starting CA DS 2.42, TBAF 4 equiv/ AGU, reaction temperature 50 °C, reaction time 24 h, solvent DMSO. [b]Calculated by equation 5 in experimental section.

### 4.4.4 Scope of TBAF-catalyzed deacylation with respect to ester type

It is of practical interest to expand TBAF-catalyzed deacylation to other cellulose triesters and to investigate the regioselectivity of these reactions. Since we postulate coordination of the TBA cation with the ester oxygen atoms, and since TBA is quite bulky, one might suspect that

increasing the steric bulk of the ester substituents of the cellulose ester might strongly retard the rate of deacylation. To explore this aspect, we prepared and subjected to TBAF deacylation a series of cellulose triesters; the triacetate (CTA), tributyrate (CTB), trihexanoate (CTH), and tribenzoate (CTBz). We employed the optimal deacylation conditions developed with CA (DS 2.42); 4 equiv TBAF, DMSO solvent, 50 °C. All reactions (**Table S4.1**) were regioselective for deacylation of the esters of the secondary alcohols (O-2/3), as with our previous experiments with CA and CAP. Reaction of CTA in DMSO at 50 °C for 12 h (entry 1c) afforded the resulting CA with DS (Ac) at O-6 of 0.75 and DS (Ac) at O-2/3 of 0.13; this regioselectivity is nearly equivalent to that observed with commercial cellulose diacetate (DS 2.42) and means that the triester (precursor to the diacetate) can be employed as starting material with results nearly identical to those with the diacetate. Exposure of CTB to TBAF for 72 h (entry 2c) gave the resulting cellulose butyrates with DS (Bu) at O-6 of 0.84 and DS (Bu) at O-2/3 of 0.26. **Figure 4.2** shows the $^{1}$H NMR of the peracetylated product from TBAF deacylation of CTB (24 h, DMSO, 50 °C). Proton signals have been completely assigned based on COSY (Supporting information, **Figure S4.1**) and HMBC (**Figure 4.3**) experiments. As shown in **Figure 4.3**, three-bond correlations between the acetyl carbonyl carbons and the H-2 and H-3 protons confirm acetate substitution at O-2 and O-3; correlation between the acetyl carbonyl carbon and the H-6 proton is not observed, which is consistent with minimal deacylation at O-6 (but not conclusive; we find that it is often difficult to observe HMBC correlation peaks between the diastereotopic C-6 protons and the 6-ester carbonyl carbon).

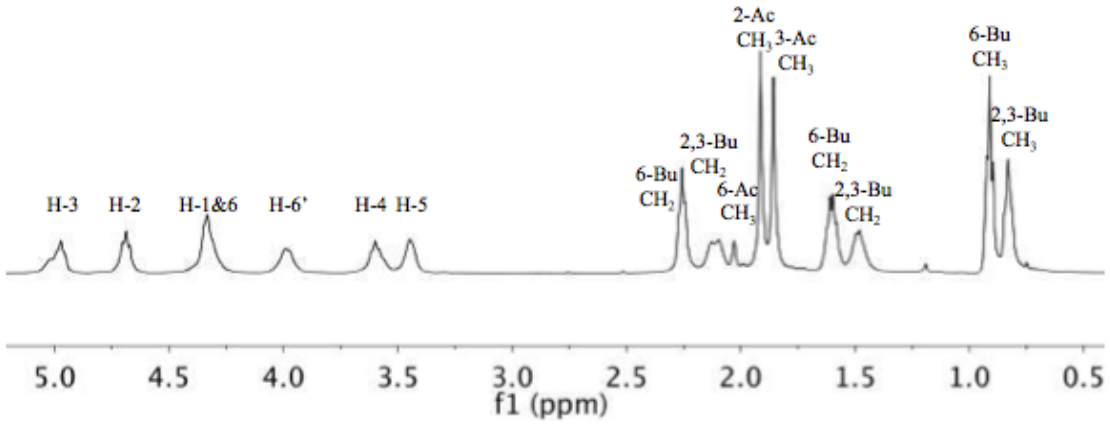


**Figure 4.2.** [1]H NMR spectrum of the product of CTB deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

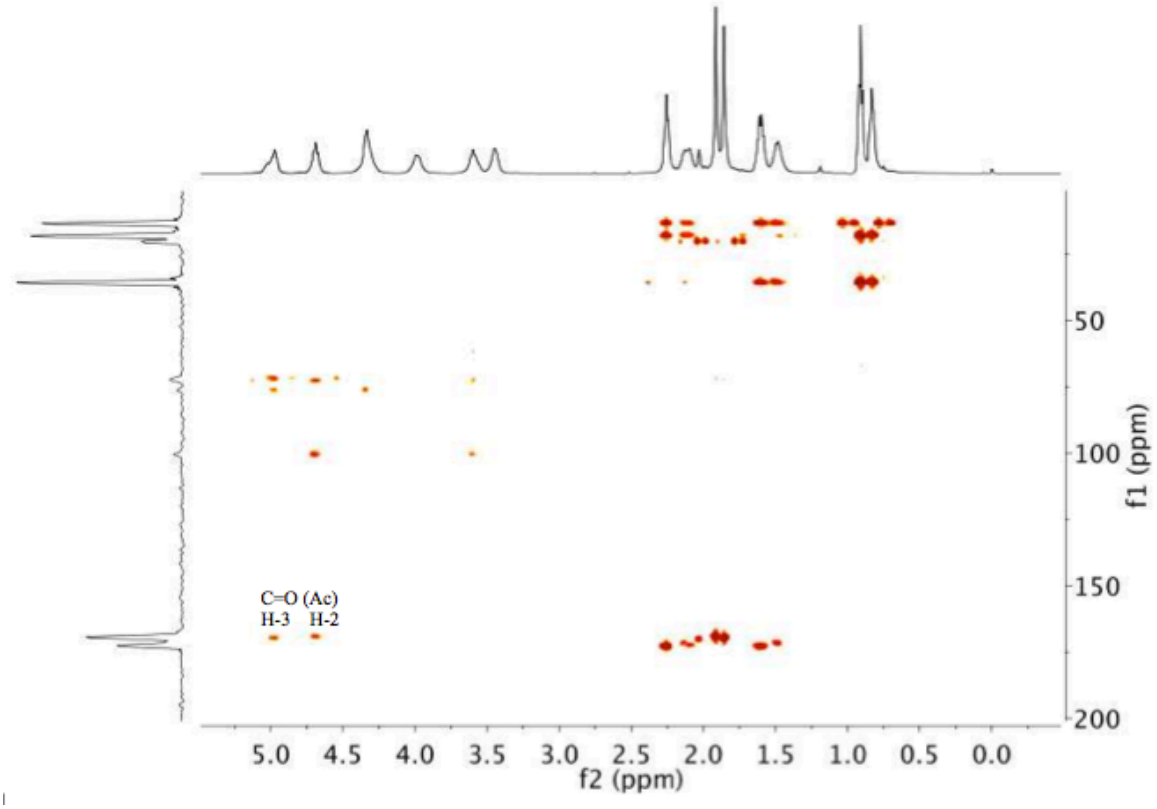


**Figure 4.3.** HMBC spectrum of the product of CTB deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

Reaction of cellulose trihexanoate with TBAF in DMSO for 72 h (entry 3c) afforded similar regioselectivity, providing cellulose hexanoate with DS (Hex) at O-6 of 0.77 and DS (Hex) at O-2/3 of 0.41. The proton NMR spectrum for the product from TBAF deacylation of CTH (24 h, DMSO, 50 °C) following peracetylation is shown in **Fig. S2**. The HMBC spectrum (**Fig. S4**) shows correlation peaks between the acetyl carbonyl carbon and the H-2 and H-3 protons on the cellulose backbone.

As can be seen from the results of the deacylation reactions, as the alkyl chain length of the ester increases, both the rate and regioselectivity of the TBAF-catalyzed deacylation of cellulose esters decline. We reason that with increasing steric demand of the ester group, approach of the fluoride ion (though admittedly it is a small ion) becomes more difficult, and especially approach to the more hindered esters of the secondary OH groups at O-2/3. These results are also consistent with the chelation hypothesis in that the increasing steric hindrance as the ester group becomes more bulky will make it more difficult for TBA to approach and coordinate with the ester oxygens at O-2/3, thus reducing selectivity for and rate of O-2/3 deacylation.

If the proposed ketene intermediate mechanism at O-2/3 (initiated by abstraction of a proton alpha to the ester carbonyl) were exclusively operative in the case of reaction of TBAF with cellulose tribenzoate, we would expect to observe no O-2/3 deacylation. In the event, exposure of CTBz to TBAF under the same reaction conditions as for CTH and CTB afforded deacylation of the O-2/3 benzoates (entries 4a - 4c) with a degree of regioselectivity rivaling that achieved for cellulose acetate (entries 1a - 1c). After 24 h reaction (entry 4a), 72% of the benzoate groups at O-2/3 had been removed, but no deacylation could be observed at O-6. Reaction with TBAF for 72 h (entry 4c) provided cellulose benzoates with DS (Bz) at O-6 of 0.94 and DS (Bz) at O-2/3 of 0.22. The proton (**Figure S4.5**) and carbon (**Figure S4.6**) signals of the perpropionylated

product from TBAF deacylation of CTBz (24 h, DMSO, 50 °C) have been completely assigned based on COSY (Supporting information, **Figure S4.7**) and HMBC (**Figure 4.4**) experiments. The correlations between the propionyl carbonyl carbons and the H-2 and H-3 protons confirm propionyl substitution at O-2 and O-3; only propionyl carbons at O-2 and O-3 were observed (**Figure 4.4**), which is consistent with no deacylation at O-6. Partial DS(Bz) values at each position were determined by difference, with the same methodology as that used with cellulose hexanoate.

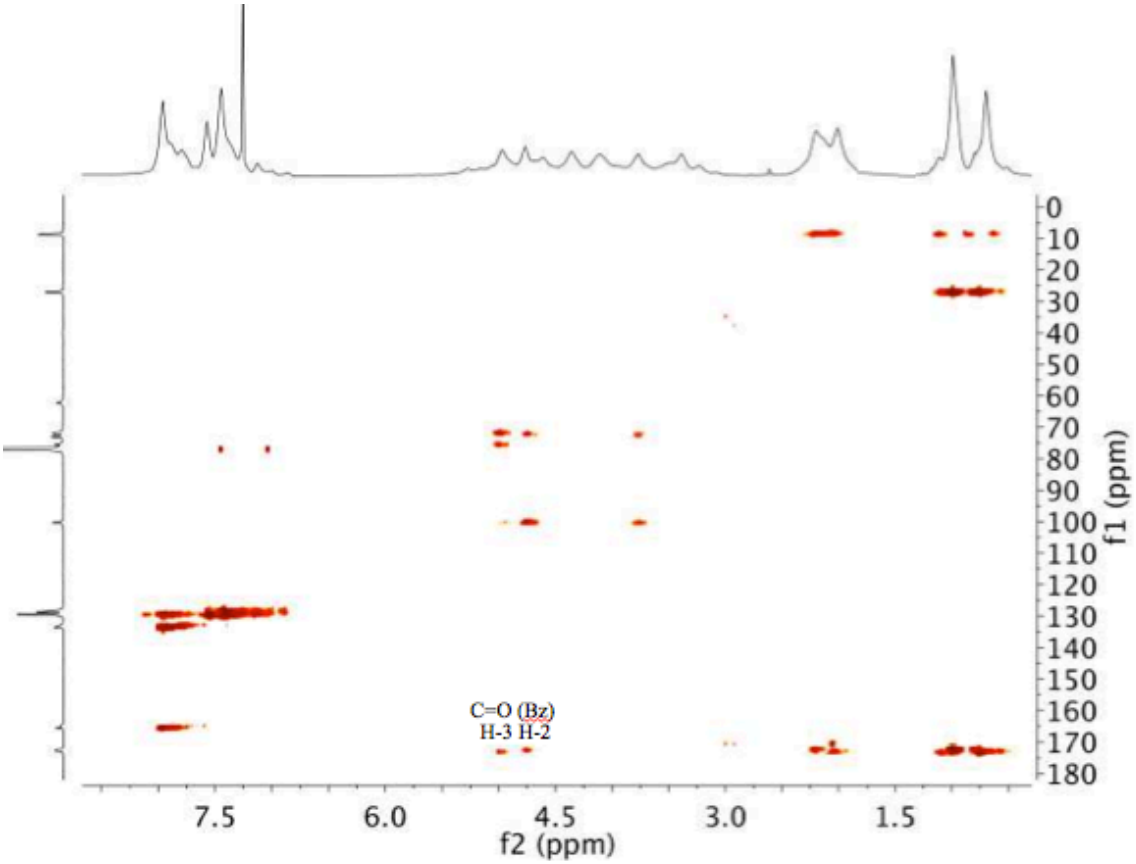


**Figure 4.4.** HMBC spectrum of the product of CTBz deacylation by TBAF (24 h, DMSO, 50 °C), after perpropionylation.

It would appear that the mechanism for TBAF deacylation of cellulose tribenzoates is most likely general base catalysis (since the ketene mechanism is not available); the source of the regioselectivity must be interaction of TBA with the ester oxygens. Compared with the other three TBAF deacylation reactions described in **Table S1**, reaction of cellulose tribenzoate with TBAF afforded surprisingly high regioselectivity with no deacylation at O-6 after 24 h. It will be interesting to further explore the source of this unexpected regioselectivity of benzoate ester deacylation.

### 4.5 Conclusions

Our studies of the effect of solvent on deacylation of CA show gratifying flexibility; the neutral, polar aprotic solvents DMSO, THF, MEK and acetone appear to be nearly equally effective for regioselective TBAF-catalyzed deacylation of cellulose esters. These studies also indicate that pyridine and DMAc are slightly less effective for promoting regioselective deacylation Probably, pyridine accelerates general base-catalyzed deacylation at O-6; while DMAc competes for TBA and reduces the chelation mechanism. Studying the effect of temperature on TBAF-catalyzed deacylation of CA shows a surprising insensitivity of regioselectivity to temperature; reaction at our original temperature of 50 °C gives perhaps the best combination of regioselectivity and conversion. The deacylation reaction is also relatively insensitive to the effects of added water, despite its role as a stoichiometric reagent and the fact that the only (non-adventitious) source of water in the original reaction is the tightly bound waters of TBAF hydration. Added water does not accelerate the reaction to any appreciable degree, and at higher water levels (10 eq / AGU) slightly decreases regioselectivity for deacylation at O-2/3. We have demonstrated that TBAF is an effective catalyst not only for regioselective deacylation of cellulose diacetate and cellulose

tripropionate, but also for regioselective deacylation of CTA, long chain cellulose esters, and cellulose benzoate. TBAF-catalyzed deacylation for all of these esters occurs regioselectively at O-2/3, although the rate of deacylation and the degree of regioselectivity decline somewhat as ester chain length increases. The selectivity of TBAF-catalyzed deacylation of cellulose tribenzoate is surprisingly good, among the best examples we have seen, which is especially interesting given that benzoate has no hydrogen atoms alpha to the ester carbonyl and so cannot participate in the ketene (E1cB) mechanism observed in the case of the esters of the secondary (O-2/3) hydroxyls of cellulose diacetate. Taken together, the results of these explorations of the scope of this unusual deacylation reaction show that it is a flexible, forgiving, and efficient one-step method for preparing a wide variety of regioselectively substituted cellulose esters.

### 4.6 Supplementary Material

Supplementary information available for this chapter includes $^{1}H$, $^{13}C$, HMBC, and COSY NMR spectra of the peracetylated or perpropionylated products of TBAF deacylation of cellulose triacetate, cellulose tributyrate, cellulose trihexoanoate, and cellulose tribenzoate.

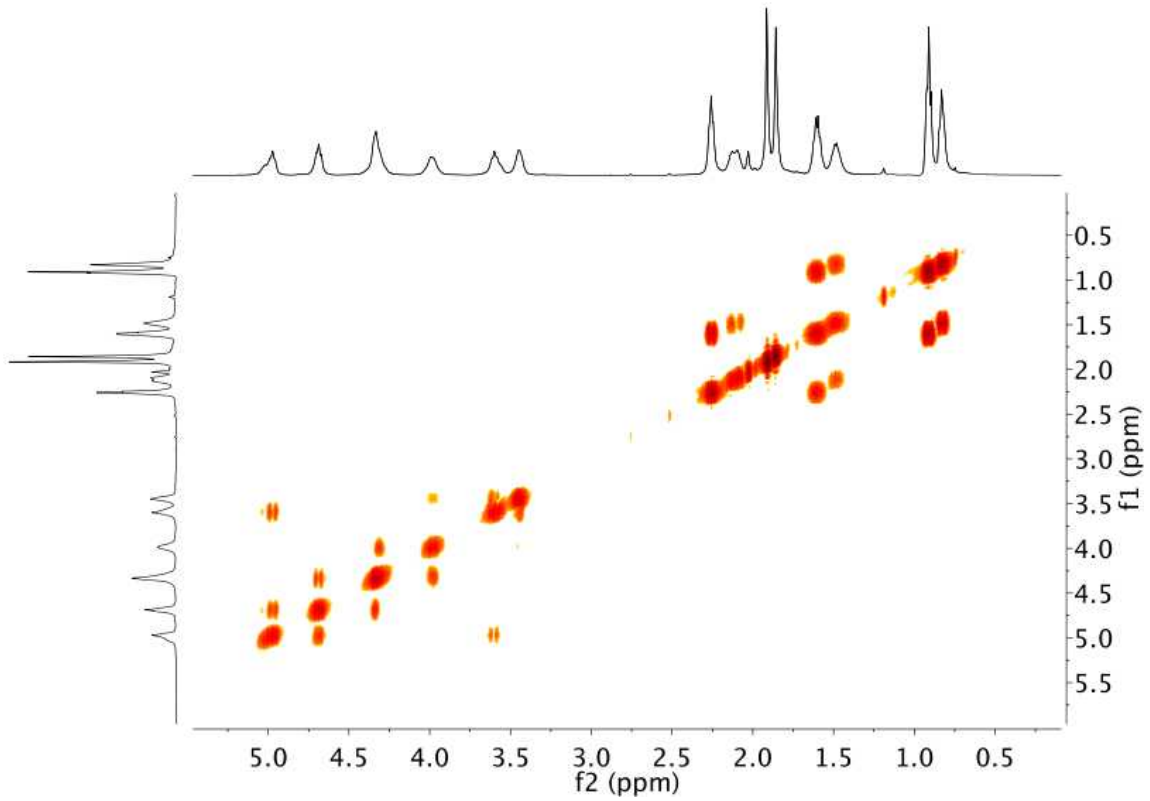


**Figure S4.1** COSY spectrum of the product of CTB deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

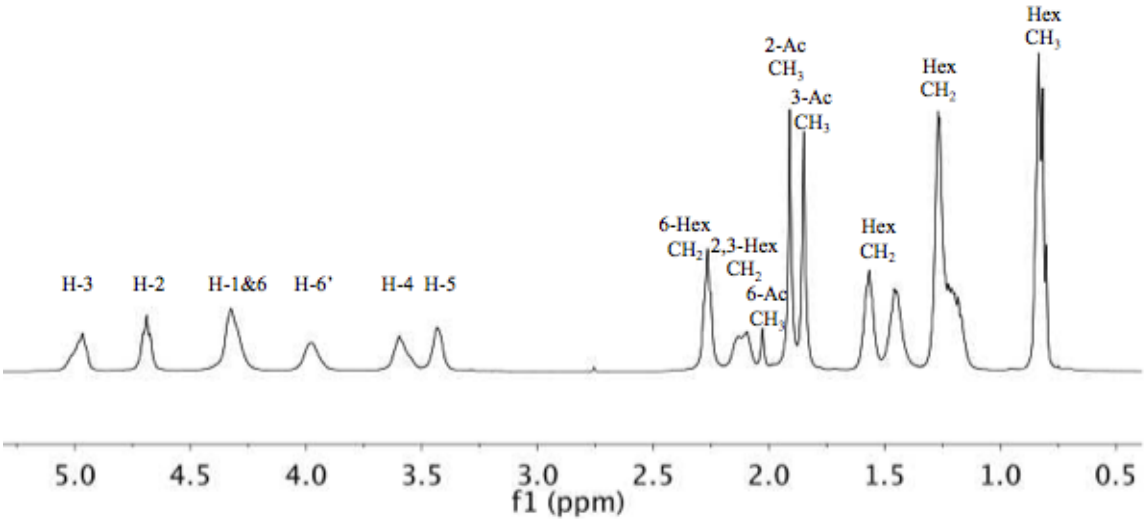

**Figure S4.2** $^{1}$H NMR spectrum of the product of CTH deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

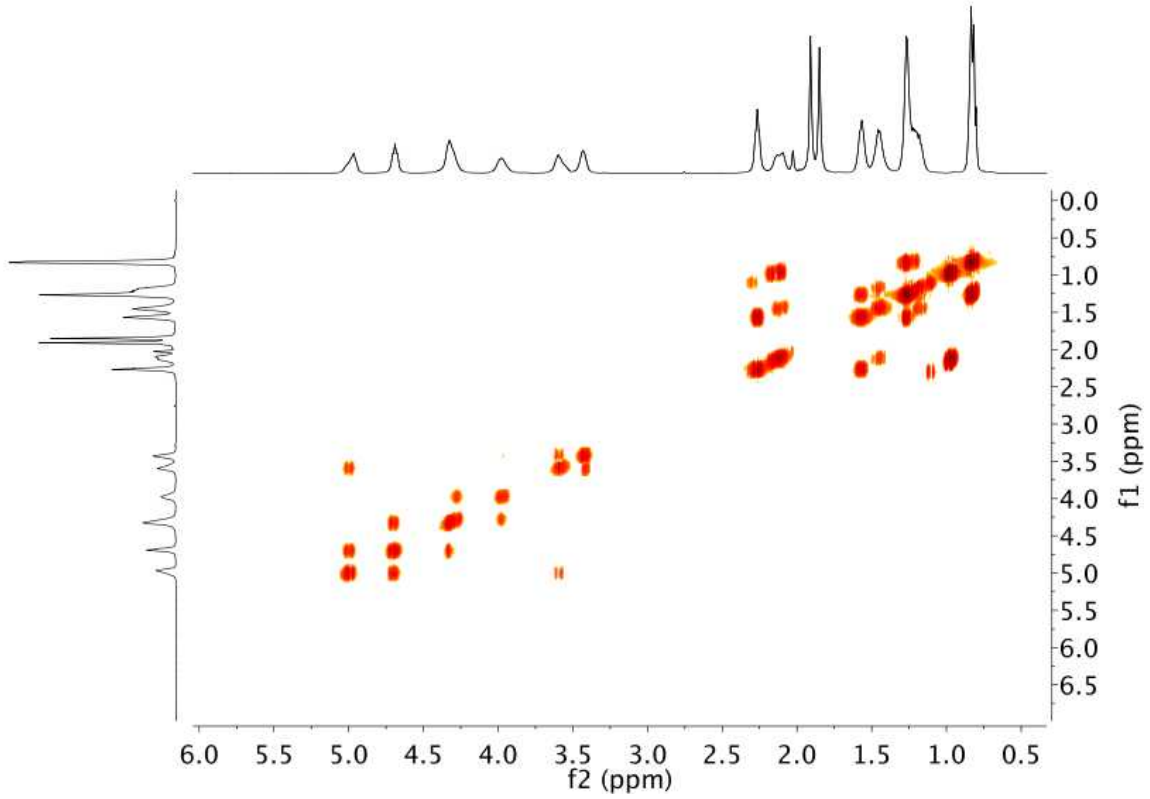


**Figure S4.3** COSY spectrum of the product of CTH deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

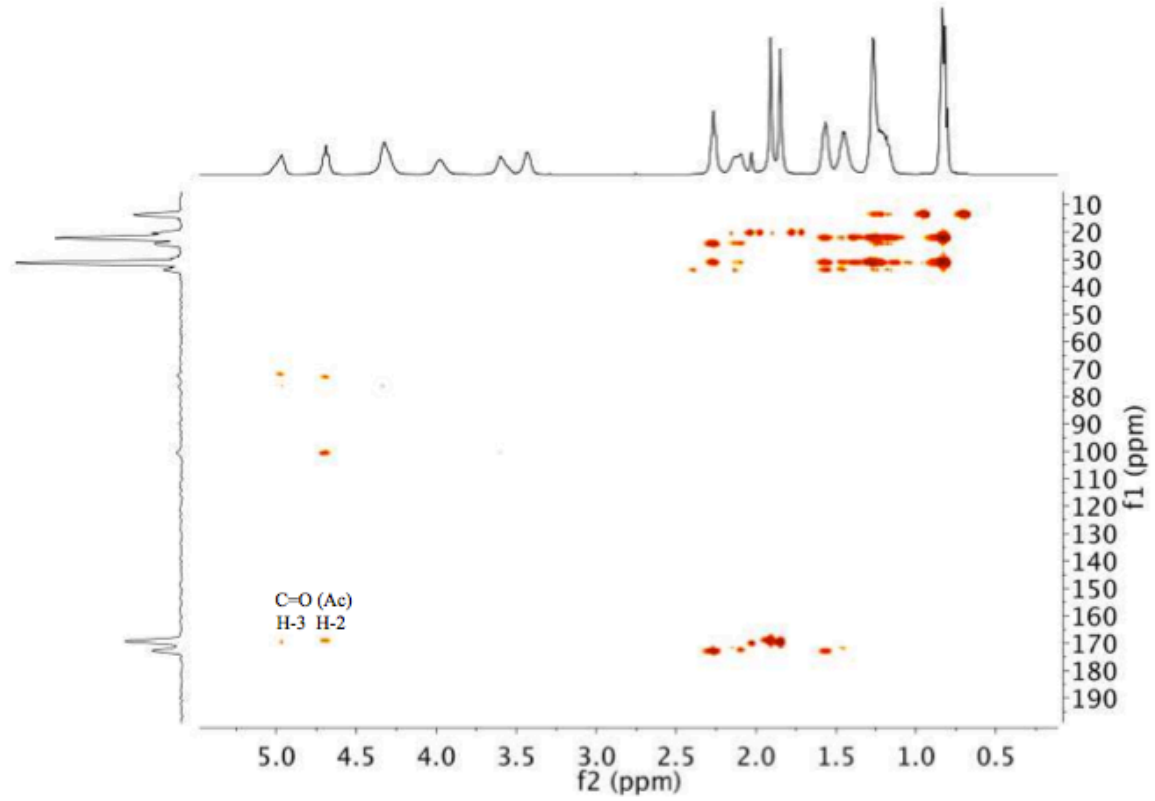


**Figure S4.4** HMBC spectrum of the product of CTH deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

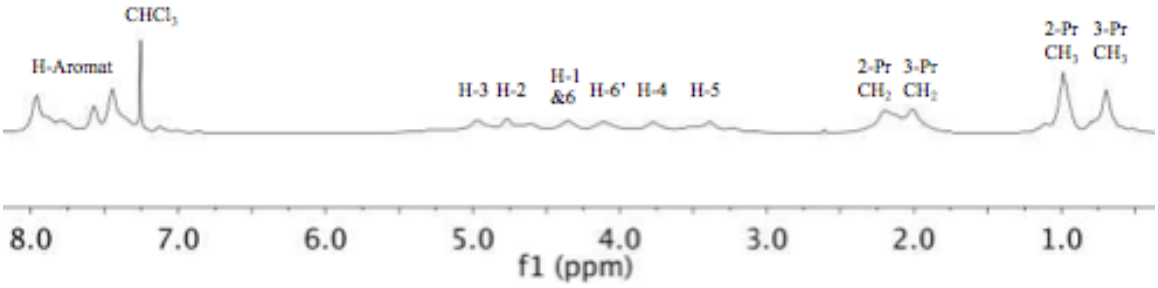


**Figure S4.5** $^{1}$H NMR spectrum of the product of CTBz deacylation by TBAF (24 h, DMSO, 50 °C), after perpropionylation.

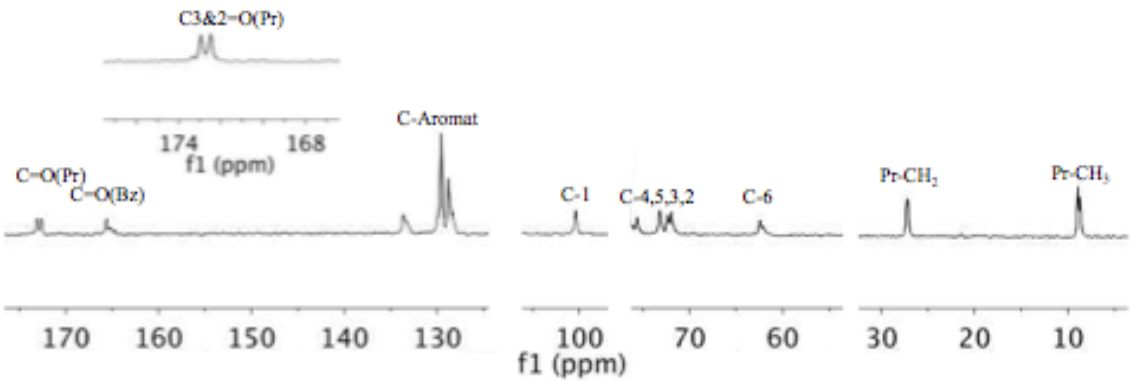


**Figure S4.6** $^{13}$C NMR spectrum of the product of CTBz deacylation by TBAF (24 h, DMSO, 50 °C), after perpropionylation.

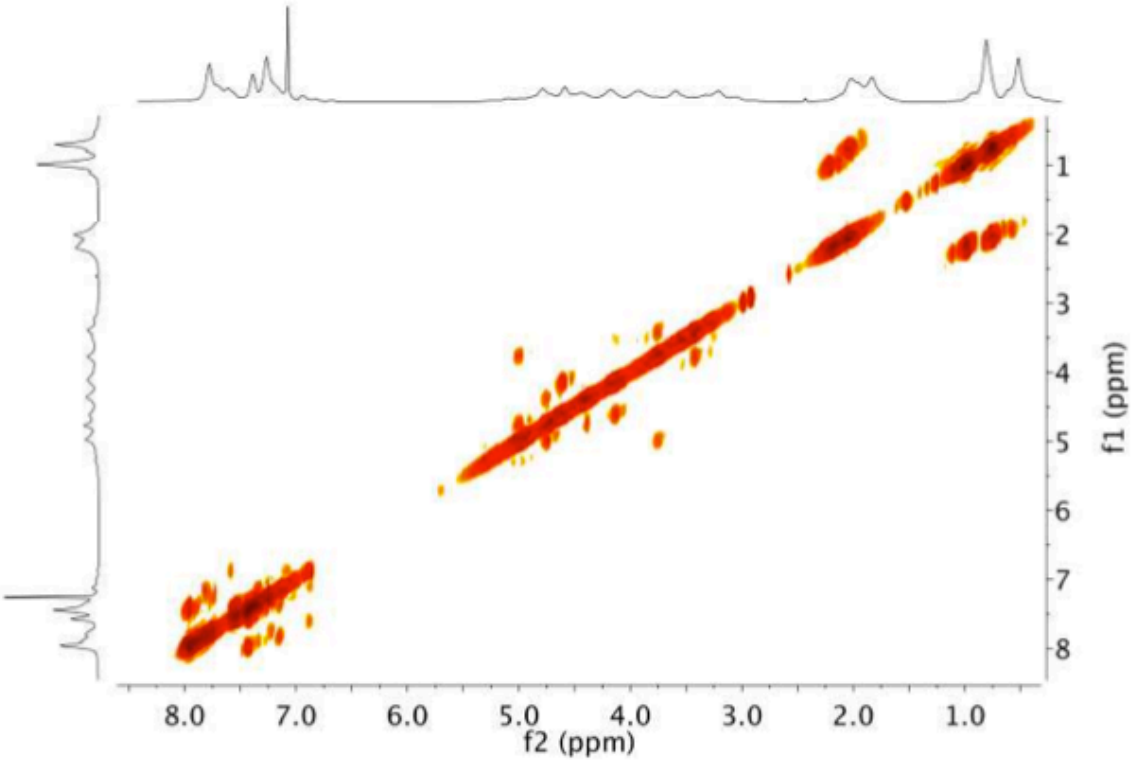

**Figure S4.7** COSY spectrum of the product of CTBz deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

**Table S4.1** TBAF-catalyzed deacylation of cellulose triesters[a]

| Entry | Ester Type | Time (h) | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ | PC[b] | PR[c] | DP |
|---|---|---|---|---|---|---|---|---|
| 1a | CTA DP 136 | 6 | 0.75 | 0.15 | 0.90 | 95% | 76% | 127 (18 h) |
| 1b | | 12 | 0.75 | 0.13 | 0.88 | 96% | 76% | |
| 1c | | 18 | 0.75 | 0.13 | 0.88 | 96% | 76% | |
| 2a | CTB DP 147 | 24 | 0.88 | 0.72 | 1.60 | 64% | 83% | 139 (24 h) |
| 2b | | 48 | 0.86 | 0.38 | 1.21 | 81% | 83% | |
| 2c | | 72 | 0.84 | 0.26 | 1.10 | 87% | 83% | |
| 3a | CTH DP 132 | 24 | 0.88 | 0.73 | 1.61 | 64% | 83% | 121 (24 h) |
| 3b | | 48 | 0.80 | 0.50 | 1.30 | 75% | 76% | |
| 3c | | 72 | 0.77 | 0.41 | 1.18 | 80% | 75% | |
| 4a | CTBz DP 140 | 24 | 1.00 | 0.36 | 1.36 | 82% | 100% | 133 (24 h) |
| 4b | | 48 | 0.96 | 0.26 | 1.22 | 87% | 96% | |
| 4c | | 72 | 0.94 | 0.22 | 1.16 | 89% | 93% | |

[a]Solvent DMSO, TBAF 4 equiv/ AGU, reaction temperature 50 °C. [b]Percent conversion at O-2/3, calculated by equation 5 in experimental section. [c]Percent regioselectivity, determined by equation 6 in experimental section.

**4.7 Acknowledgements**

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# Chapter 5 Remarkably Regioselective Deacylation of Cellulose Esters using Tetraalkylammonium Salts of the Strongly Basic Hydroxide Ion

Adapted with permission from Zheng, X.; Gandour, R. D.; Edgar, K. J. Carbohydrate Polymers, 111: 25-32. 

## 5.1 Abstract

Tetraalkylammonium hydroxides have been found to mediate regioselective deacylation of cellulose esters. This deacylation surprisingly shows substantial selectivity for the removal of the acyl groups at O-2/3, affording cellulose-6-O-esters by a simple, efficient one-step process. The mechanism for this deacylation was investigated by studying the effect of tetraalkylammonium cation size upon ester deacylation selectivity. We hypothesize that coordination of the tetraalkylammonium cation by the ester oxygen atoms of the vicinal 2,3-acetate groups may drive the unexpected regioselectivity at the secondary alcohol esters. Broad scope with respect to ester type was demonstrated; regioselective O-2,3 deacylation was observed with cellulose acetate, propionate, butyrate, hexanoate and benzoate triesters. The scope of this deacylation of cellulose acetates has been investigated to understand how to carry it out most efficiently. Reaction with TBAOH in pyridine was the most effective process, providing the highest selectivity.

## 5.2 Introduction

It's very challenging to synthesize polysaccharide derivatives with regioselective substitution patterns; indeed it is one of the great remaining challenges in polysaccharide chemistry. Regioselective synthesis of cellulose derivatives is hindered by the fact that cellulose has poor organic solubility, by its great propensity to hydrogen bond to itself, and by the high steric hindrance caused by the stiff and bulky cellulose main chain. As a result cellulose hydroxyl groups are relatively poor nucleophiles, resulting in a requirement for fairly harsh reaction conditions for esterification and other modification reactions; these harsh conditions make it difficult to take advantage of the relatively small reactivity differences between the 2-, 3- and 6-OH groups [1]. The availability of cellulose solvents like ionic liquids [2], DMAc/LiCl [3], and DMSO/TBAF [4] helps, but high regioselectivity by direct esterification of cellulose has so far been impossible to demonstrate, even in organic solution [5]. Because the direct approach doesn't work, previous investigators have had to resort to bulky ether protecting groups [6, 7] to enable selective synthesis of, in the case of ester substituents, 2, 3-diesters [8] and 2, 6-diesters [9].

These protecting group routes have provided vital insight into structure-property relationships relative to regioselectivity, proving that key properties like crystallinity [10], thermal properties [11], solubility [12], and optical properties [13] are quite sensitive to position of substitution. An important goal of studies of the cellulose ester regiochemical structure-property relationship is to provide guidance to more conventional, commercially practical cellulose ester syntheses. In principle, if we know which substituted monosaccharide provides the most desirable properties, and if we know the analytical characteristics of that monosaccharide (learned from homopolymer spectra) so that we can quantify it in commercial co-polymers, we can seek to adjust its content through modification of synthesis conditions. Protection/deprotection chemistries have limited

effectiveness because they involve many steps, yields may be low in some steps, and desired reactivity of intermediates cannot be guaranteed. We need better processes for regioselective synthesis of cellulose esters in order to explore a more expansive structure-property space.

The approach of deacylating fully substituted cellulose esters in order to synthesize regioselectively substituted products has received some attention by earlier investigators, but they have observed only limited success with this approach. Reaction of cellulose esters with aliphatic amines was found to afford deacylated cellulose esters, but with only modest regioselectivity. For example, exposure of cellulose triacetate (CTA) to hexamethylenediamine at 60 °C for 24 h gave the resulting cellulose acetate with DS (Ac) at O-6 of 0.60 and DS (Ac) at O-2/3 of 0.15,[14] providing 64 % regioselectivity. Other investigators reacted CTA with dimethylamine and water at 80 °C for 24 h,[15] which afforded improved regioselectivity (86 %), but with rather incomplete deacylation at O-2/3 (65 %). Despite extensive variation of reaction conditions and deacylating reagents, these investigators did not report high regioselectivity at high conversion.

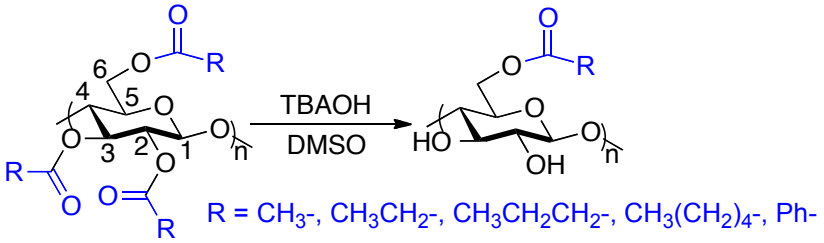
Our group has focused substantial effort on the search for new tools for the preparation of regioselectively substituted cellulose esters. We discovered an unexpected, versatile, and efficient process for the synthesis of highly regioselectively substituted cellulose esters without the need for protection/deprotection steps, using commercial cellulose esters as starting materials, and requiring only common organic solvents [16, 17]. The process involves tetrabutylammonium fluoride-mediated deacylation of cellulose esters. Reaction of cellulose acetate (DS 2.42) with TBAF in DMSO, for example, proceeds at 50 °C within 24 h to afford a cellulose acetate with DS (Ac) at O-6 of 0.80, while the total residual DS at the secondary alcohols (O-2 and O-3) is

only 0.10. Thereby TBAF was exploited for the synthesis of cellulose-6-O-esters and cellulose-2, 3-O-A-6-B-triesters, starting from commercial or simply synthesized high-DS cellulose esters.

The TBAF chemistry is an appealing new approach to certain regioselectively substituted cellulose esters, but we had some concerns that the difficulty of recycling TBAF might detract from the efficiency and utility of the method. We hypothesized that the more convenient tetraalkylammonium hydroxides might exhibit similarly enhanced reactivity towards deacylation of esters of the secondary cellulose hydroxyl groups. This hypothesis seems counterintuitive at first glance. Those experienced in the hydrolysis of polysaccharide esters know that while acid catalyzed hydrolysis is relatively slow and reversible [18], hydrolysis by hydroxide ion is fast, quantitative, and irreversible [19]; indeed, hydrolysis with aqueous NaOH has been a standard method for quantitative cellulose ester hydrolysis in order to liberate and quantify the acids as part of a total degree of substitution (DS) determination [20]. Successful regioselective deacylation of cellulose esters by tetraalkylammonium hydroxide would not only be interesting, counterintuitive chemistry given the considerations above, but hydroxides have major practical advantages vs. fluoride salts for ester deacylation. They are much less expensive, but more importantly they could in principle be recycled after the reaction by simple ion exchange, with the result that the only reagent consumed in the transformation would be a number of equivalents of sodium hydroxide equal to the number of acyl groups removed. This would have considerable practical significance for potential large-scale preparation of these regioselectively substituted cellulose esters.

Herein we describe initial investigations of this hypothesis. We investigate how $R_4NOH$ complexation may drive regioselectivity by studying the influence of tetralkylammonium cation size. Key process parameters are explored in order to maximize efficiency and scope of the

process, including potential application to other cellulose esters; triacetate, tributyrate, trihexanoate and tribenzoate derivatives (**Scheme 5.1**).




**Scheme 5.1** TBAOH deacylation of cellulose triesters in DMSO

## 5.3 Experimental Section

### 5.3.1 Materials

Microcrystalline cellulose (MCC, Avicel PH-101, DP= 260) and cellulose acetate (CA-398-30, Eastman, DP = 190) were dried under vacuum at 60 °C overnight before use. Tetrabutylammonium hydroxide (TBAOH, 40 wt% in water), tetraethylammonium hydroxide (TEAOH, 25 wt% in water), tetramethylammonium hydroxide (TMAOH, 25 wt% in water), 4-(dimethylamino)pyridine (DMAP), and lithium chloride (LiCl) were purchased from Acros Organics and used as received. Dimethyl sulfoxide (DMSO), N, N-dimethylacetamide (DMAc), 1,3-dimethyl-2-imidazolidinone (DMI), 1,4-dioxane, sulfolane and pyridine were obtained from Fisher and dried over molecular sieves (Type 4 Å, 8-12 mesh beads). Tetrahydrofuran (THF), acetone, methanol, reagent alcohol (histological grade), and chloroform were supplied by Fisher and used as received. Acetyl chloride, propionyl chloride, n-butyryl chloride, n-hexanoyl chloride, benzoyl chloride, acetic anhydride and propionic anhydride were purchased from Aldrich.

### 5.3.2 Measurements

$^{1}H$, $^{13}C$ NMR, HMBC, and COSY spectra of cellulose esters after peracetylation or perpropionylation were acquired in $CDCl_3$ on a Bruker Avance II 500 MHz spectrometer at 50 °C, employing 16, 6,000, 12,800, and 7,680 scans, respectively. The total and partial DS values were obtained by calculating the ratio of acetyl or propionyl proton integrals to those of the backbone hydrogens.[5, 21] Molecular weight determination was achieved by size exclusion chromatography (SEC) in chloroform on a Waters Alliance model 2690 chromatograph with Waters 2414 differential refractive index (RI) detector and Viscotek 270 dual detector, vs. polystyrene standards.

### 5.3.3. General procedures for preparation of cellulose triesters

Dissolution of MCC in DMAc/ LiCl was performed as previously described [22]. A mixture of MCC (5.00 g, 30.8 mmol) and DMAc (187 mL) was kept at 150 °C for 26 min with vigorous stirring under nitrogen. Anhydrous LiCl (8.5 g) was added, and the mixture was stirred at 165 °C for 8 min. DMAc (25 mL) was distilled off to facilitate water removal. The slurry was cooled to room temperature and stirred overnight, during which time dissolution occurred.

Synthesis of cellulose triesters was performed by a previously published procedure [17, 23]. Briefly, cellulose triacetate (CTA) was prepared by adding acetyl chloride (5 mol/mol anhydroglucose unit (AGU)) to the cellulose solution. The solution was kept at 80 °C for 2 h; then maintained at room temperature for 24 h. The solution was added slowly to ethanol (1000 mL) under vigorous stirring. The crude product was isolated by filtration and washed several times with ethanol, then dried under vacuum at 60 °C.

Yield: 84 %. $DS_{Ac}$ = 2.98 by $^{1}H$ NMR. $^{1}H$ NMR (DMSO-$d_6$): 1.88- 2.03 ppm ($CH_3$-acetate), 3.45- 5.20 (cellulose backbone).

Cellulose tripropionate was synthesized by adding pyridine (10 mol/mol) and propionic anhydride (10 mol/ mol AGU) to the MCC solution in DMAc/ LiCl. After being kept at 80 °C for 24 h, the reaction solution was slowly added to ethanol (1000 mL). The crude product was filtered, washed several times with ethanol, and dried under vacuum at 60 °C overnight.

Yield: 82 %. $DS_{Pr}$ = 3.00 by $^{1}H$ NMR. $^{1}H$ NMR (DMSO-$d_6$): 1.01-1.20 ppm ($CH_3$-propionate), 2.16-2.44 ppm ($CH_2$-propionate), 3.45-5.20 (cellulose backbone).

Cellulose tributyrate (CTB) was prepared by adding pyridine (10 mol/mol AGU) and butyryl chloride (10 mol/mol AGU) to a solution of MCC in DMAc/ LiCl. The mixture was allowed to react for 24 h at room temperature. The product was recovered by slowly adding the reaction solution into water (1000 mL), filtering off the solid product, and washing the solid thoroughly with ethanol. Purification was carried out by redissolving the crude product in THF (50 mL), and re-precipitating by slow addition to methanol (1000 mL). After collecting by filtration, the sample was dried under vacuum at 60 °C overnight.

Yield: 80 %. $DS_{Bu}$ = 3.00 by $^{1}H$ NMR. $^{1}H$ NMR (DMSO-$d_6$): 0.80-0.96 ppm ($CH_3$-butyrate), 1.40-1.70 ppm ($CH_2$-butyrate), 2.08-2.35 ppm ($CH_2$-butyrate), 3.45-5.20 (cellulose backbone).

Cellulose trihexanoate (CTH) was obtained by adding pyridine (10 mol/mol AGU) and n-hexanoyl chloride (10 mol/mol AGU) sequentially to the MCC solution. The reaction solution was kept at 80 °C h for 24 h under vigorous stirring. The reaction mixture was added to water (1000 mL), the resulting slurry was filtered, and the solid product was washed several times by methanol. The crude product was collected, redissolved in acetone (50 mL), and this solution re-

precipitated into methanol (1000 mL). The solid product was filtered off, washed several times with methanol, and dried under vacuum at 60 °C overnight.

Yield: 78 %. $DS_{He}$ = 3.00 by $^1$H NMR. $^1$H NMR (DMSO-$d_6$): 0.75-0.85 ppm ($CH_3$-hexanoate), 1.12-1.35 ppm ($CH_2$-hexanoate), 1.37-1.50 ppm ($CH_2$-hexanoate), 1.52-1.65 ppm ($CH_2$-hexanoate), 2.05-2.35 ppm ($CH_2$-hexanoate), 3.45-5.20 (cellulose backbone).

Cellulose tribenzoate (CTBz) was prepared by adding pyridine (10 mol/mol AGU) and benzoyl chloride (10 mol/mol AGU) to a solution of MCC in DMAc/ LiCl. After reacting for 24 h at 100 °C, the reaction solution was cooled to room temperature and kept for 20 h under vigorous stirring. The product was obtained by slowly adding the reaction solution into water (1000 mL), filtering off the solid product, and washing the solid thoroughly with water. The sample was dried at 60 °C under vaccum.

Yield: 80 %. $DS_{He}$ = 2.98 by $^1$H NMR. $^1$H NMR (DMSO-$d_6$): 3.45-5.20 (cellulose backbone), 7.35-8.05 ppm (CH-aromatic).

### 5.3.4. General procedures for tetraalkylammonium hydroxide deacylation of cellulose triesters

To a solution of cellulose ester in DMSO (40 mL per g of cellulose esters) was added tetraalkylammonium hydroxide or sodium hydroxide (2 mol/mol AGU, unless otherwise stated), and the reaction solution was kept at 50 °C for 24 h. The solution was then added slowly to water (250 mL), the product was collected by filtration, washed several times with water, and dried under vacuum at 60 °C. The sample was further peracetylated or perpropionylated (details below) for DS and DP determinations.

### 5.3.5 General procedures for peracetylation or perpropionylation of deacylated cellulose esters.

Deacylated products were peracetylated or perpropionylated for easier NMR analysis, according to previously published procedures [5, 21]. 4-(Dimethylamino)pyridine (20 mg) and acetic anhydride (4 mL) or propionic anhydride (4 mL) were added to the solution of deacylated product (0.3 g) in pyridine at 80 °C. After stirring for 24 h, the reaction solution was precipitated into 150 mL ethanol. The product was collected by filtration and was washed several times with ethanol. The crude product was redissolved in chloroform (10 mL), reprecipitated into ethanol (150 mL), and washed several times with excess ethanol. The peracetylated or perpropionylated sample was dried under vacuum at 60 °C for analysis. The completeness of peracetylation or perpropionylation was confirmed by the disappearance of the OH band in the FITR spectrum (3460 $cm^{-1}$). The total and partial DS values for the peracetylated or perpropionylated product were determined according to equations 1 and 2 by $^{1}H$ NMR. The positional percent conversion (PC) and the percent regioselectivity (PR) for TBAOH catalyzed deacylation were calculated based on equations 3 and 4, respectively. Carbon signals were completely assigned based on $^{1}H$, COSY, and HMBC experiments. Signals at δ =77.5 (C-4), 73.4 (C-5), 72.1 (C-3), 71.2 (C-2), and 62.6 (C-6) ppm are the backbone carbons. The propionyl carbonyl carbons resonate between 172.5 and 173.5 ppm. The O-6, O-3, and O-2 propionyl carbonyl carbons are at 173.5, 173 and 172.5 ppm, respectively. The acetyl carbons are at 169-170 ppm. The O-6, O-3, and O-2 acetyl carbons are at 170, 169.5, and 170 ppm, respectively. Propionyl methylene, acetyl methyl, and propionyl methyl carbons resonate at 27.2, 20.5 and 8.9 ppm, respectively.

$$DS_{ester}=3-7I_{H,\ acetyl\ or\ propionyl}/3I_{H,\ AGU};\ I=Integral \quad (1)$$

$$DS_{ester\ (n)}=1-7I_{H,\ acetyl\ or\ propionyl\ (n)}/3I_{H,\ AGU};\ I=Integral,\ n=Position\ 2,\ 3,\ 6 \quad (2)$$

Subscript Definition: S=Starting cellulose esters, P=Product

$$PC_{(n)}=(DS_{(n),(S)}-DS_{(n),(P)})/DS_{(n),(S)};\ n=\text{Position } 2, 3, 6 \quad (3)$$

$$PR=[(DS_{2+3(S)}-DS_{2+3(P)})/(DS_{total(S)}-DS_{total(P)})]-[(DS_{6(S)}-DS_{6(P)})/(DS_{total(S)}-DS_{total(P)})] \quad (4)$$

**5.4 Results and Discussion**

A previous publication from our laboratory about TBAF deacylation of cellulose esters[16] reported that treatment of cellulose acetate (CA, DS 2.45) with excess TBAOH (4 mol/mol anhydroglucose unit (AGU)) afforded the expected complete deacylation. We did not examine deacylation with limited equivalents of TBAOH in that study, so did not observe whether deacylation under such reagent-limited conditions was regioselective. In the current study we hypothesized that hydroxide ion coupled with the same bulky cation as in our TBAF deacylation might exhibit similar regioselectivity, driven perhaps by a similar chelation mechanism. Our chances might be enhanced if we limited the amount of reagent and kept temperature and reaction times to the minimum necessary. In our previous publication [23], we proposed a possible mechanism by which TBAF catalyzes regioselective deacylation of cellulose esters. Evidence from those studies supports the possibility that the bulky tetrabutylammonium cation, which has the positive charge distributed on the hydrogen atoms, forms ion-dipole complexes with the vicinal O-2/3 esters analogous to those formed with maleate [24] and interaction of quaternary ammonium ions with cellobiose [25] (**Figure 5.1**), followed by fluoride-catalyzed deacylation at the secondary O-2/3 positions by an E1cB mechanism, with the slower deacylation at the primary O-6 position occurring by a separate, general base-catalyzed mechanism. Could similar complexation also drive tetraalkylammonium hydroxide ester deacylation regioselectivity?

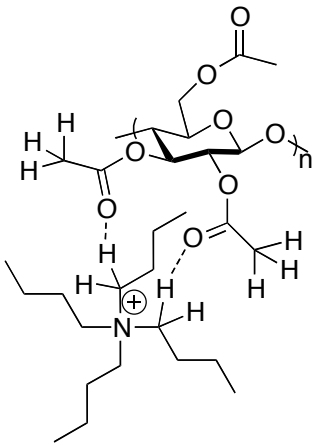


**Figure 5.1** Structure of hypothetical TBA–cellulose acetate ion–dipole complex[23]

### 5.4.1 TBAOH-catalyzed deacylation of CA

We began by carrying out experiments in which CA was exposed to TBAOH, examining the effect of TBAOH/CA stoichiometry (**Table 5.1**). Treatment of CA (DS 2.42) with 1 equiv/AGU TBAOH in DMSO (entry 2) for 24 h remarkably afforded 100% regioselectivity with no deacylation at O-6 and partial deacylation at O-2/3 (58% conversion). After 24 h reaction of CA with 1.6 equiv. TBAOH (entry 3), the DS acetate was reduced from 2.42 to 0.88, with DS (Ac) at O-2/3 of 0.16 (90% conversion) and DS (Ac) at O-6 of 0.72. Such treatment with limited quantities of TBAOH afforded almost equal levels of deacylation at O-2 and O-3. This TBAOH mediated regioselective deacylation of cellulose acetate is very surprising and without literature precedent. On the other hand, excess TBAOH (4 equiv.) led to complete deacylation of CA (entry 4) as we had previously observed.

**Table 5.1** Results of TBAOH Deacylation of CA[a]

| Entry | TBAOH (mol/AGU) | $DS_6$ | $DS_2$ | $DS_3$ | $DS_{total}$ | $PC_{2+3}$[b] | PR[c] |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0.82 | 0.80 | 0.80 | 2.42 | NA | NA |
| 2 | 1 | 0.82 | 0.33 | 0.34 | 1.49 | 58 % | 100 % |
| 3 | 1.6 | 0.72 | 0.08 | 0.08 | 0.88 | 90 % | 87 % |
| 4 | 4 | 0 | 0 | 0 | 0 | 100 % | NA |

[a]Starting CA DS 2.42, solvent DMSO, reaction temperature 50 °C, time 24 h. [b]Percent conversion at O-2/3, determined by equation 3 in experimental section. [c]Percent regioselectivity, calculated by equation 4 in experimental section.

### 5.4.2 Impact of cation size

To help illuminate the nature of this surprisingly regioselective deacylation, the impact of cation size was evaluated (**Table 5.2**). We examined one alkali metal hydroxide (sodium hydroxide) and two commercially available tetraalkylammonium hydroxides: tetramethylammonium hydroxide (TMAOH) and tetraethylammonium hydroxide (TEAOH). Reaction of CA with TEAOH (1.6 mol/mol AGU) in DMSO (entry 2) afforded deacylation with similar selectivity for O-2/3 but with slightly more deacylation of the O-6 acetate than with TBAOH. Furthermore, reaction with TMAOH (entry 3) gave poorer regioselectivity than that observed with TEAOH, with even more deacylation at the primary acetate. As can be seen from the results of the deacylation reactions, as the alkyl chain length of the tetraalkylammonium decreases, more

deacylation occurs at the O-6 acetate and the regioselectivity declines. At this point, we offer two possible explanations: (1) chelation of the smaller tetraalkylammonium hydroxide to the vicinal O-2, 3 carbonyl oxygens may be less selective than that of the bulky tetrabutylammonium cation, thereby reducing the local concentration of hydroxide at O-2/3, correspondingly increasing the "free" hydroxide concentration, and increasing the amount of deacylation at O-6, and (2) chelation occurs at any of the acetates but the bulkier alkylammonium cation retards hydrolysis at the O-6 acetate more than at the O-2/3 acetates. Existing evidence cannot rule out a combination of the two explanations.

The regioselectivity of the TBAOH deacylation is quite surprising given the extensive literature about quantitative deacylation of polysaccharide esters with hydroxide base, but at least our earlier TBAF work did provide some precedent. However, we obtained yet another unexpected result upon treatment of CA with NaOH (1.6 mol/mol AGU) in DMSO (entry 4); these conditions also provided unexpectedly highly regioselective deacylation of the secondary acetates with percent regioselectivity of 82 %, which is even higher than that of TEAF and TMAF catalyzed-deacylation of CA. While in some sense the impact of tetraalkylammonium cation size on regioselectivity displayed in **Table 2** is expected, given our previous TBAF results and our hypotheses about the cause of selectivity in $R_4N^+OH^-$ hydrolyses, the NaOH result is quite surprising and we do not yet have enough mechanistic understanding to fully explain the regioselectivity observed. Our hypotheses have been focused on the structure of a single AGU. Given the complex structure of a polymer, especially CA with its high density of functional groups and potential binding sites for chelation, we may have to consider a model involving two or three AGUs to find the correct explanation.

**Table 5.2** Effect of Cation on CA Deacylation Selectivity[a]

| Entry | Hydroxide Source | $DS_6$ | $DS_2$ | $DS_3$ | $DS_{total}$ | $PC_{2+3}$[b] | PR[c] |
|---|---|---|---|---|---|---|---|
| 1 | TBAOH | 0.72 | 0.08 | 0.08 | 0.88 | 90 % | 87 % |
| 2 | TEAOH | 0.67 | 0.08 | 0.08 | 0.83 | 90 % | 81 % |
| 3 | TMAOH | 0.60 | 0.07 | 0.07 | 0.74 | 91 % | 74 % |
| 4 | NaOH | 0.68 | 0.10 | 0.11 | 0.89 | 87 % | 82 % |

[a]Starting CA DS 2.42, hydroxide source 1.6 equiv/AGU, solvent DMSO, reaction temperature 50 °C, time 24 h. [b]Percent conversion at O-2/3, calculated by equation 3 in experimental section. [c]Percent regioselectivity, determined by equation 4 in experimental section.

### 5.4.3 Scope of TBAOH-catalyzed deacylation with respect to ester type

We wished to determine whether the observed regioselective TBAOH-catalyzed deacylation of CA could also be effectively applied to a broader range of cellulose esters. Toward that end, we prepared a series of cellulose triesters by solution acylation of MCC in DMAc/LiCl, including CTA, CTB, CTH, and CTBz. All cellulose triesters were deacylated under the same conditions; 2 equiv TBAOH, DMSO solvent, 50 °C, 24 h. As can be seen from **Table 5.3**, these reactions were regioselective for deacylation of the esters of the secondary alcohols (O-2/3), as we observed with CA. The degree of polymerization (DP) of the products from cellulose ester deacylation was measured by SEC. All cellulose triesters as well as CA DS 2.42 experienced only minor (< 10 %) loss of DP during deacylation (see **Table S5.1**).

Exposure of CTA to TBAOH for 24 h (entry 1) gave the resulting CA with DS (Ac) at O-6 of 0.82 and DS (Ac) at O-2/3 of 0.13; this percent regioselectivity is nearly equivalent to that observed with commercial cellulose diacetate (DS 2.42) but with slightly higher DS values at each position. **Figure 5.2** shows the $^{13}C$ NMR spectrum of the perpropionylated product from TBAOH deacylation of CTA (24 h, DMSO, 50 °C). Carbon signals have been completely assigned based on $^{1}H$ (**Figure S5.1**), COSY (**Figure S5.2**), and HMBC (**Figure 5.3**) experiments. The HMBC spectrum (**Figure 5.3**) shows correlation peaks between the propionyl carbonyl carbon and the H-2 and H-3 protons on the cellulose backbone; correlation between the propionyl carbonyl carbon and the H-6/6' protons is too weak to be observed, which is consistent with minimal deacylation at O-6.

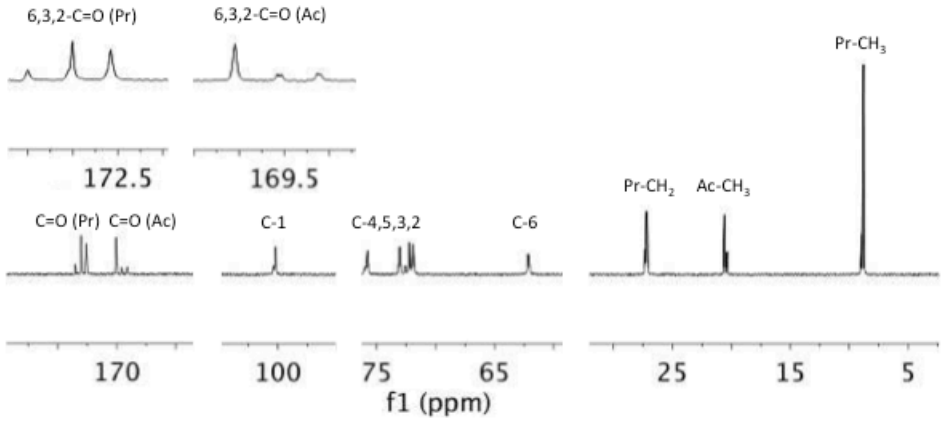



**Figure 5.2** $^{13}C$ NMR spectrum of the product of CTA deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

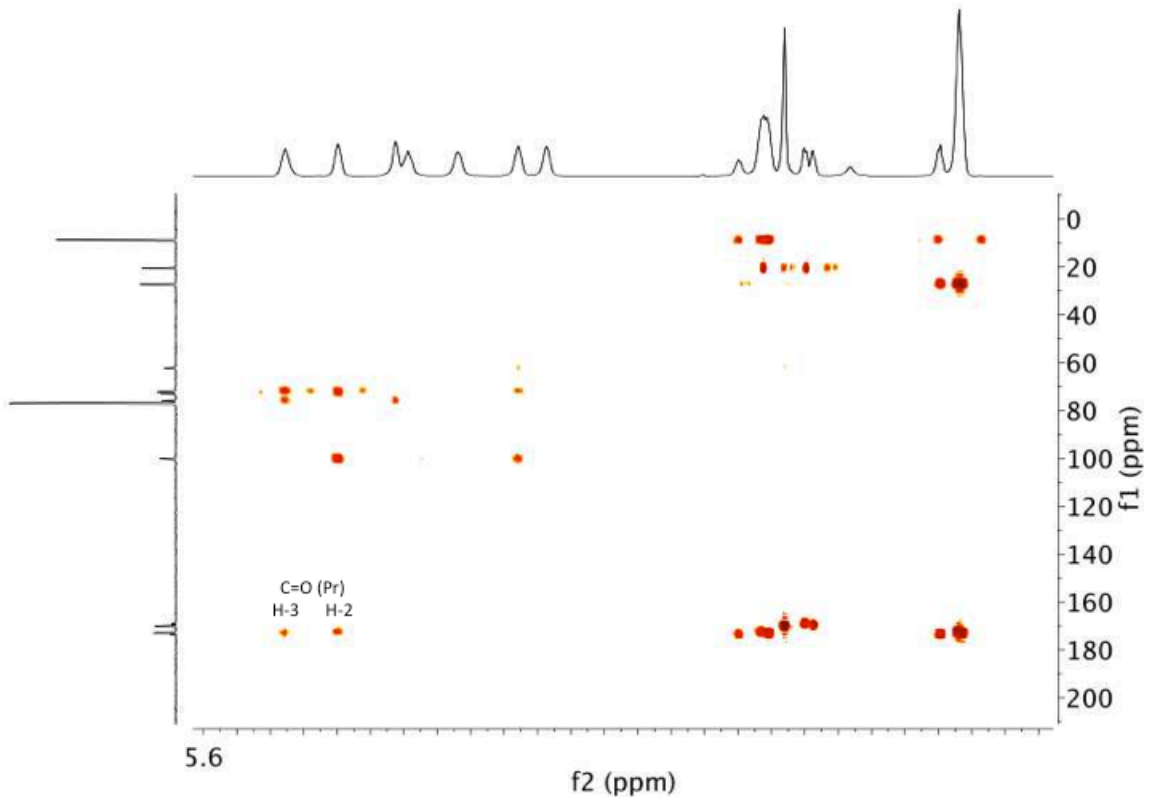



**Figure 5.3** HMBC NMR spectrum of the product of CTA deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

Reaction of CTP at 50 °C for 24 h (entry 2) afforded cellulose propionates with DS (Pr) at O-6 of 0.84 and DS (Pr) at O-2/3 of 0.30. The proton and carbon NMR spectra for the product from TBAOH deacylation of CTP (2 equiv, 24 h, DMSO, 50 °C) following peracetylation are shown in **Figure S5.3** and **S5.4**, respectively. As shown in **Figure S5.5**, three-bond correlations between the acetyl carbonyl carbons and the H-2 and H-3 protons confirm propionyl substitution at O-2 and O-3. Reaction of CTB with TBAOH in DMSO for 24 h (entry 3) afforded similar regioselectivity, providing cellulose butyrates with DS (Bu) at O-6 of 0.80 and DS (Bu) at O-2/3

of 0.36. On the other hand, exposure of CTH to TBAOH for 24 h (entry 4) gave the resulting cellulose hexanoates with DS (Hex) at O-6 of 0.77 and DS (Hex) at O-2/3 of 0.40.

The results clearly suggest that as the alkyl chain length of the ester increases, the regioselectivity of TBAOH-catalyzed deacylation declines. It may be that with increasing steric demand of the ester group, coordination of the TBA cation at O-2/3, O-6, or both becomes more difficult, thus reducing selectivity for O-2/3 deacylation.

Besides the aliphatic cellulose triesters, we also investigated the regioselectivity of TBAOH deacylation of cellulose tribenzoates. Reaction of CTBz with TBAOH under the same reaction conditions as for CTA afforded cellulose benzoates (entry 5) with DS (Bz) at O-6 of 0.86 and DS (Bz) at O-2/3 of 0.15. The regioselectivity surprisingly was slightly better than that achieved for the best aliphatic cellulose triester case (CTA). After 24 h reaction, 92 % of the benzoate groups at O-2/3 had been removed and 86 % of the benzoate group at O-6 was retained. The proton (**Figure S5.6**) and carbon (**Figure 5.4**) signals of the perpropionylated product from TBAOH deacylation of CTBz (2 equiv, 24 h, DMSO, 50 °C) have been completely assigned based on COSY (**Figure S5.7**) and HMBC (**Figure S5.8**) experiments. The correlations between the propionyl carbonyl carbons and the H-2 and H-3 protons confirm propionyl substitution at O-2 and O-3.

The similarity between the regioselectivity of CTBz debenzoylation and that of CTA deacylation presents a mechanistic conundrum. The lack of alpha hydrogens on the benzoate esters removes the E1cb mechanism from consideration. As stated above, the E1cb mechanism is likely to occur for deacylation of CTA and, perhaps, the other esters with alpha hydrogens. The likely mechanisms for hydrolysis of benzoate are specific base (direct attack of hydroxide on the ester carbonyl) catalysis or general base catalysis (hydroxide-catalyzed attack of water on the ester

carbonyl). A third mechanism that involves hydroxide attack at the para or ortho positions on the aromatic ring to form a carbanion and subsequent loss of the alkoxide and formation of a ketene-like intermediate appears to energetically unlikely. Consequently, the same percentage regioselectivity is preserved even though different mechanisms operate. A simple explanation resides in the complexation of the alkylammonium cation to the esters. Whether this complexation accelerates hydrolyses at O-2/3 or retards hydrolysis at O-6, it does so regardless of which mechanism operates.

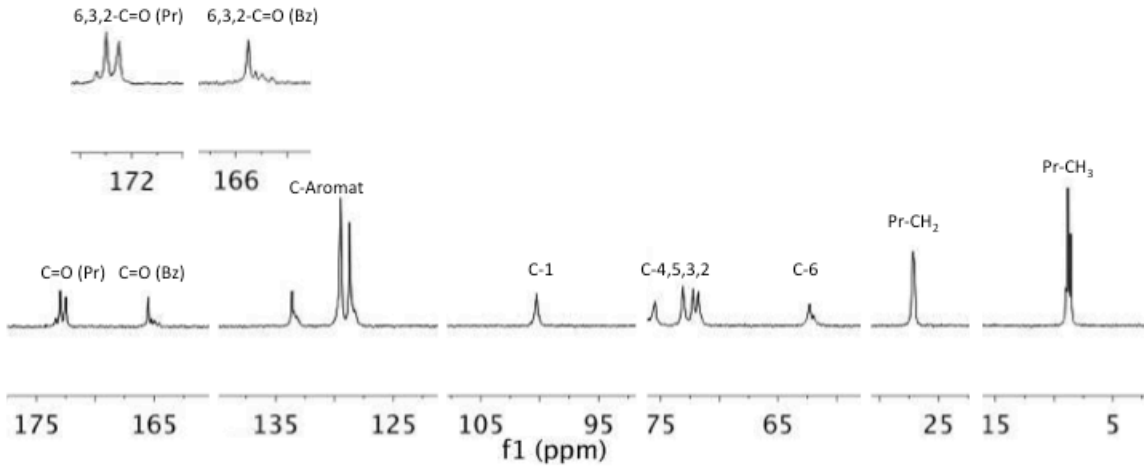



**Figure 5.4** $^{13}C$ NMR spectrum of the product of CTBz deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

**Table 5.3** TBAOH-Catalyzed Deacylation of Cellulose Triesters[a]

| Entry | Ester Type | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ | PC[b] | PR[c] |
|---|---|---|---|---|---|---|
| 1 | CTA | 0.82 | 0.20 | 1.06 | 90 % | 84 % |
| 2 | CTP | 0.84 | 0.30 | 1.14 | 85 % | 83 % |
| 3 | CTB | 0.80 | 0.36 | 1.16 | 82 % | 78 % |
| 4 | CTH | 0.77 | 0.40 | 1.17 | 80 % | 75 % |
| 5 | CTBz | 0.86 | 0.15 | 1.01 | 92 % | 86 % |

[a]Solvent DMSO, TBAOH 2 equiv/ AGU, reaction temperature 50 °C, time 24h. [b]Percent conversion at O-2/3, calculated by equation 3 in experimental section. [c]Percent regioselectivity, determined by equation 4 in experimental section.

### 5.4.4 Solvent effects on TBAOH-catalyzed deacylation of CA

Choice of solvent can significantly influence reaction outcome; exploring solvent effects on TBAOH-catalyzed deacylation of CA (DS 2.42) might uncover solvents that provide even higher regioselectivity as the strength of chelation will depend on solvent. This commercially available CA is soluble in a variety of solvents, including DMSO, DMAc, DMI, pyridine, THF, 1,4-dioxane, and sulfolane. Upon addition of aqueous TBAOH, the reaction solutions in DMSO, DMAc and pyridine remained homogeneous, while the reaction solutions in THF, 1,4-dioxane and sulfolane became heterogeneous. As can be seen from **Table 5.4**, treatment of CA with TBAOH (1.6 mol/mol AGU, 50 °C, 24 h) in DMSO (entry 2) and DMAc (entry 3) gave similar selectivity for deacylation of the O-2/3 acetates, with percent regioselectivities of 87 % and 85 %,

respectively. Reaction in DMI (entry 4) gave reduced total extent of deacylation but better regioselectivity (PR of 92 %) vs. DMSO, with the same extent of deacylation at O-2/3 but more acetate retention at O-6. On the other hand, reaction in pyridine (entry 4) did not increase the total amount of deacylation but gave superior deacylation selectivity, with less deacylation at O-6 ($DS(Ac_6)$ 0.77, vs. 0.72 in DMSO under otherwise identical conditions) and more deacylation at O-2/3 ($DS(Ac_{2+3})$ 0.11, vs. 0.16 in DMSO). Interestingly, heterogeneous deacylation in THF (entry 5) gave less total deacylation ($DS_{total}$ 0.93, vs. 0.86 in DMSO) and provided no regioselectivity at all, producing a randomly substituted cellulose acetate with $DS_6$ of 0.35 and $DS_{2+3}$ of 0.58 at O-2/3. Heterogeneous deacylation in sulfolane (entry 6) and dioxane (entry 7) provided regioselectivity values of 68 % and 78 %, respectively. Overall, the reaction in pyridine at 50 °C at afforded the best regioselectivity at O-2/3 versus O-6. These enhanced results in homogeneous solution can be interpreted as being due either to acceleration of deacylation at O-2/3 or retardation of deacylation at O-6. In the case of the poorer results in heterogeneous media, the complexity of the heterogeneous mixtures makes it difficult to interpret the results with the data available. The exciting aspect of these solvent results, however, is the increased regioselectivity in pyridine. Increasing the regioselectivity from 87% to 94% requires a > 2-fold change in the ratio of rate constants.

**Table 5.4** Effect of Solvent on TBAOH-Catalyzed Deacylation of CA[a]

| Entry | Solvent | Time (h) | Phase | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ | $PC_{2+3}$[b] | PR[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | Starting CA | NA | NA | 0.82 | 1.60 | 2.42 | NA | NA |
| 2 | DMSO | 24 | Homogeneous | 0.72 | 0.16 | 0.88 | 90 % | 87 % |
| 3 | DMAc | 24 | Homogeneous | 0.70 | 0.14 | 0.84 | 91 % | 85 % |
| 4 | DMI | 24 | Homogeneous | 0.76 | 0.16 | 0.92 | 90 % | 92 % |
| 5 | Pyridine | 24 | Homogeneous | 0.77 | 0.11 | 0.88 | 93 % | 94 % |
| 6 | THF | 24 | Heterogeneous | 0.35 | 0.58 | 0.93 | 64 % | 37 % |
| 7 | Sulfolane | 24 | Heterogeneous | 0.58 | 0.33 | 0.91 | 79 % | 68 % |
| 8 | Dioxane | 24 | Heterogeneous | 0.65 | 0.21 | 0.86 | 87 % | 78 % |

[a]Starting CA DS 2.42, TBAOH 1.6 equiv/ AGU, reaction temperature 50 °C. [b]Percent conversion at O-2/3, calculated by equation 3 in experimental section. [c]Percent regioselectivity, determined by equation 4 in experimental section.

### 5.4.5 Influence of temperature on TBAOH-catalyzed deacylation of CA in DMSO, DMAc and pyridine

We initially explored TBAOH-catalyzed deacylation of CA at 50 °C in DMSO for 24 h, conditions similar to those used for TBAF-catalyzed reactions. These conditions with TBAOH afforded 87% regioselectivity. Given the general ease of hydrolysis of polysaccharide esters by

hydroxide, it was of interest to determine whether reduced reaction temperature might enhance reaction regioselectivity. Deacylation selectivity was examined in the homogeneous reaction solvents DMSO, DMAc, and pyridine. As the selectivities in DMSO and DMAc at 50 °C were similar, and the melting points for DMSO and DMAc are 19 °C and –20 °C respectively, TBAOH deacylation reactions at 25 °C and 50 °C were evaluated in DMSO, while 8 °C and 15 °C reaction temperatures were investigated in DMAc (a homogeneous reaction at lower temperature in DMAc was not possible due to CA precipitation). Because TBAOH deacylation of CA in pyridine gave the best regioselectivity, the temperature effect in pyridine was evaluated from 0 to 50 °C. Neither solvent freezing nor CA precipitation occurred in pyridine across this temperature range.

As can be seen from **Table 5.5**, reactions of CA with TBAOH in DMSO and DMAc at 50 °C (entry 1), 25 °C (entry 2), 15 °C (entry 3) and 8 °C (entry 4) afforded similar regioselectivity and reaction rate. Reactions of CA with TBAOH in pyridine at 50 °C (entry 5), 25 °C (entry 6), 15 °C (entry 7) and 0 °C (entry 8) also afforded the same regioselectivity and reaction rate. All the reactions were completed within an hour and lower temperatures did not afford further differentiation in deacylation rates at O-6 vs. O-2/3. The complete lack of influence of temperature on regioselectivity within the temperature range studied is remarkable. TBAOH-catalyzed deacylation reaction is quite efficient and fast even at the lowest practical temperatures in these solvents. Further studies into how quickly this reaction occurs are planned.

The remarkable insensitivity of regioselectivity and conversion to changes in temperature suggests a very rapid reaction. Having observed an E1cb mechanism with TBAF promoted deacylation of CA, we would expect a similar mechanism for TBAOH because hydroxide is a stronger base than fluoride. The p$K_a$ of water in DMSO is 31.4 [26]; p$K_a$ values of the alpha

hydrogens in acetate esters range from 29.5 to 30.3 [27]. These data suggest that the cellulose ester/hydroxide equilibrium favors formation of the ester carbanion. Complexation of an ester with a cation would further favor formation of the carbanion. With the carbanion as the reactive intermediate, the reaction barrier would be decomposition of the carbanion to form ketene and alkoxide. This unimolecular process would be favored by entropy. As such, the observation of no changes in conversion or regioselectivity with decreasing temperature may reflect entropy-driven reactions. Elucidation of the mechanism of this interesting reaction is worthy of and will require much additional study.

**Table 5.5** Influence of Temperature on TBAOH-Catalyzed Deacylation Reaction Kinetics of CA[a]

| Entry | Solvent | Temperature (°C) | Time (h) | $DS_6$ | $DS_{2+3}$ | $DS_{total}$ | PC[b] | PR[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | DMSO | 50 | 1 | 0.70 | 0.16 | 0.86 | 90 % | 85 % |
| 2 | DMSO | 25 | 1 | 0.70 | 0.16 | 0.86 | 90 % | 85 % |
| 3 | DMAc | 15 | 1 | 0.70 | 0.18 | 0.88 | 89 % | 84 % |
| 4 | DMAc | 8 | 1 | 0.70 | 0.20 | 0.90 | 88 % | 84 % |
| 5 | Pyridine | 50 | 1 | 0.77 | 0.11 | 0.88 | 93 % | 94 % |
| 6 | Pyridine | 25 | 1 | 0.77 | 0.11 | 0.88 | 93 % | 94 % |
| 7 | Pyridine | 15 | 1 | 0.77 | 0.11 | 0.88 | 93 % | 94 % |
| 8 | Pyridine | 0 | 1 | 0.77 | 0.11 | 0.88 | 93 % | 94 % |

[a]Starting CA DS 2.42, TBAOH 1.6 equiv/ AGU. [b]Percent conversion at O-2/3, calculated by equation 3 in experimental section. [c]Percent regioselectivity, determined by equation 4 in experimental section.

**5.5 Conclusions**

We have described in this account an unexpectedly efficient synthetic method for preparing highly regioselectively substituted cellulose-6-O-esters in one-step from commercial and other easily prepared cellulose esters (including triesters). The product cellulose-6-O-esters can be readily converted into cellulose-2, 3-O-A-6-O-B-triesters by a single, straightforward additional acylation step. This new chemistry facilitates synthesis of regioselectively substituted cellulose esters that complements and in some cases may replace laborious protection/deprotection methods with expensive reagents. The effectiveness of these methods is quite unexpected, causing scientists to revisit the long standing paradigm in polysaccharide ester chemistry that base-catalyzed hydrolysis of polysaccharide esters is fast, non-selective, irreversible, and quantitative; the "non-selective" part at least is clearly untrue, under the proper conditions. Quite apart from the unexpected nature of these findings, this methodology is highly practical; employing easily synthesized cellulose triesters, conventional organic solvents, and a single-step conversion; using amounts of base that are nearly stoichiometric per ester group removed; and appearing to lend itself to recycling of the expensive tetraalkylammonium cations via ion-exchange.

Evidence from studies of tetraalkylammonium cation size effects supports a chelation mechanism; selective interaction of the bulky tetrabutylammonium cation with the carbonyl oxygen atoms could be the source of regioselectivity, but our evidence on this point is not yet

conclusive. The cation may be accelerating reactions at O-2/3 or retarding reaction at O-6. The surprising regioselectivity observed when employing limited quantities of NaOH in place of the tetraalkylammonium hydroxides complicates mechanistic analysis, necessitating further study, but also opens up intriguing synthetic possibilities. TBAOH is an effective catalyst not only for regioselective deacylation of CA, but also for regioselective deacylation of CTA, CTP, CTB, CTH, and CTBz, providing regioselective deacylation at O-2/3, although percent regioselectivity declines as ester chain length increases in the alkanoyl series. TBAOH-catalyzed benzoylation of CTBz is surprisingly regioselective, more so than any alkanoate we examined, indicating that CTBz debenzoylation could be a promising pathway to novel and useful regioselectively substituted esters. Solvent and temperature effect studies show that the organic base pyridine is the most effective solvent for promoting regioselective $R_4NOH$ deacylation and that changing temperature within the studied range does not impact regioselectivity. These syntheses of regioselectively substituted cellulose esters will permit deeper understanding of cellulose ester structure-property relationships with regard to position of substitution, providing the ability to better predict how structural changes will affect properties and performance in demanding applications. Application of this deacylation reaction to other polysaccharide esters for the development of practical syntheses of other highly regioselectively substituted renewable-based materials is under investigation in our lab and will be reported in an upcoming manuscript.

### 5.6 Supporting Information

$^{1}H$, $^{13}C$, HMBC and COSY spectra of the products of TBAOH deacylation of CTA, CTP, and CTBz after peracetylation or perpropionylation.

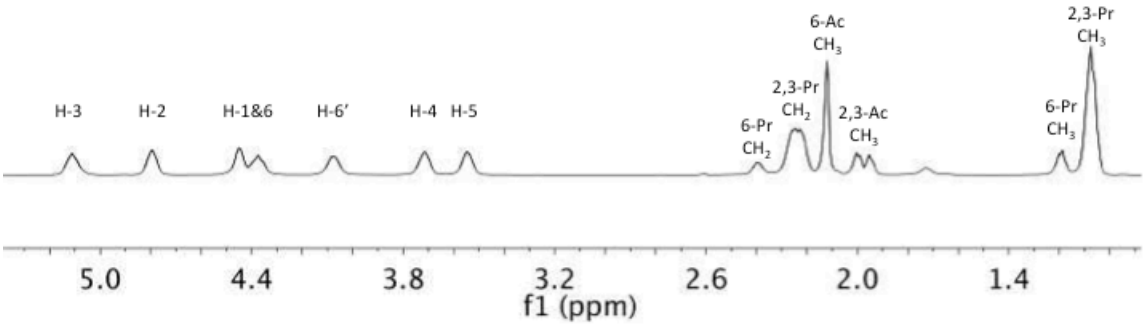



**Figure S5.1** $^{1}$H NMR spectrum of the product of CTA deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

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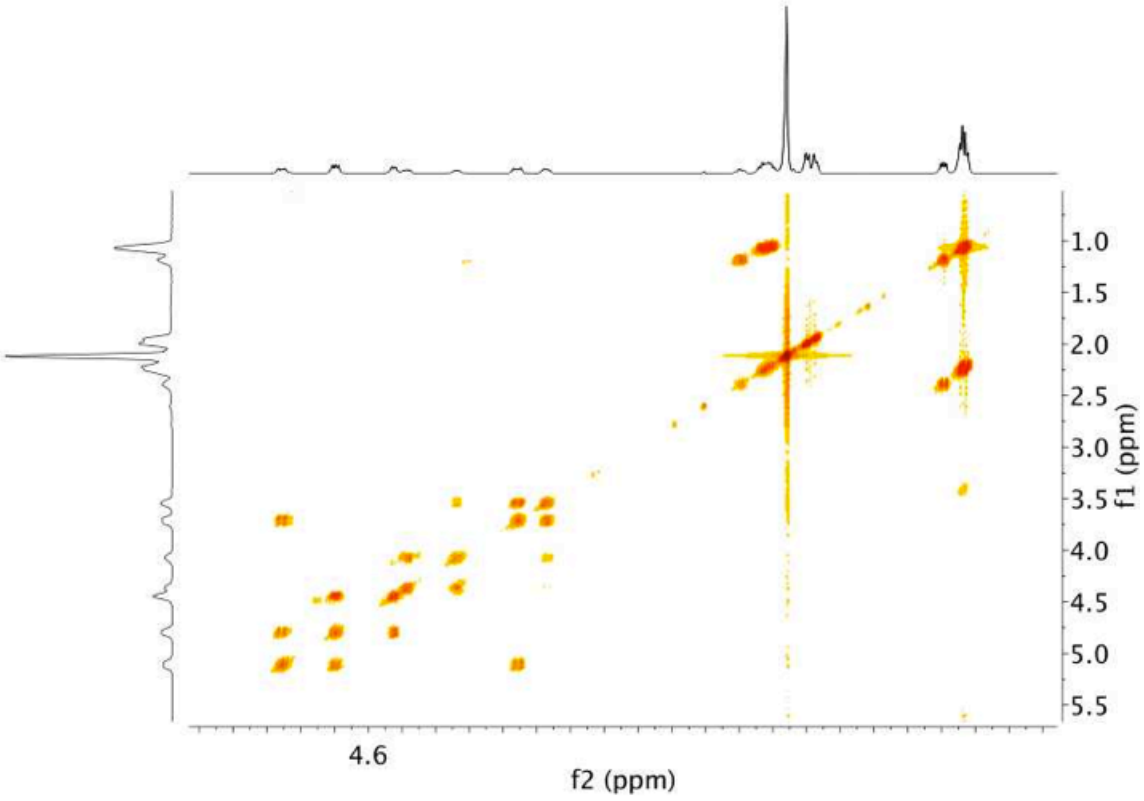


**Figure S5.2** HMBC NMR spectrum of the product of CTA deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

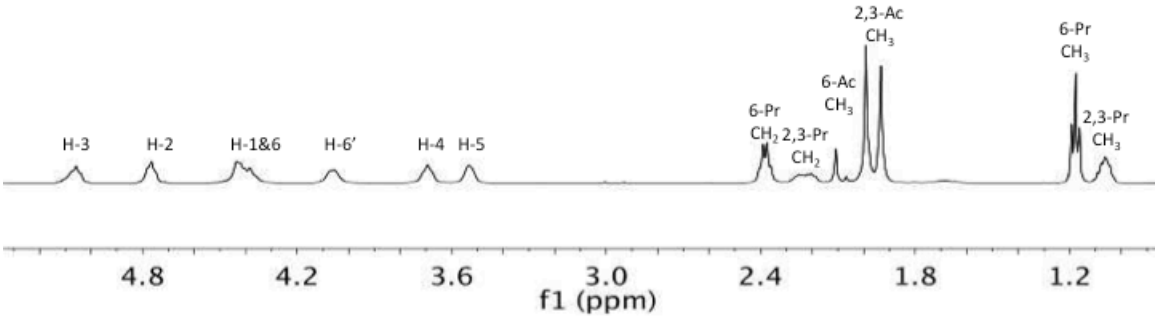


**Figure S5.3** $^{1}$H NMR spectrum of the product of CTP deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after peracetylation.

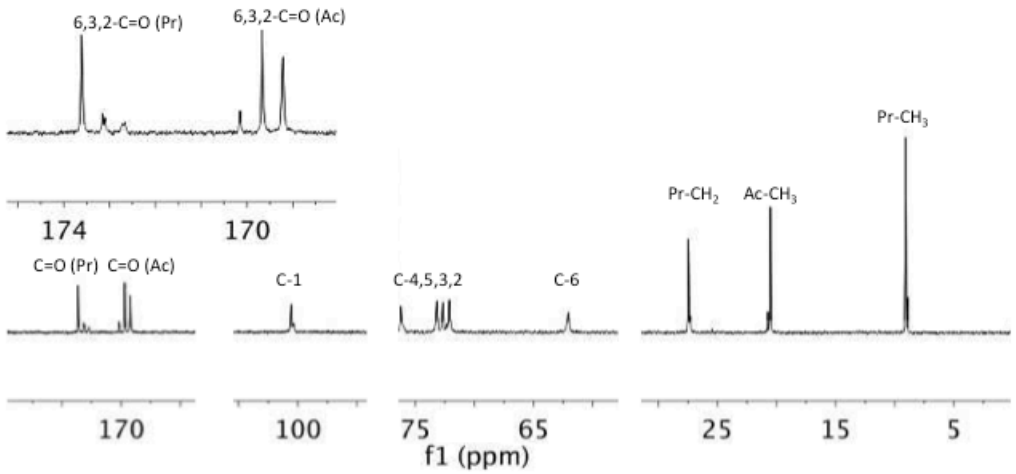


**Figure S5.4** $^{13}$C NMR spectrum of the product of CTP deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after peracetylation.

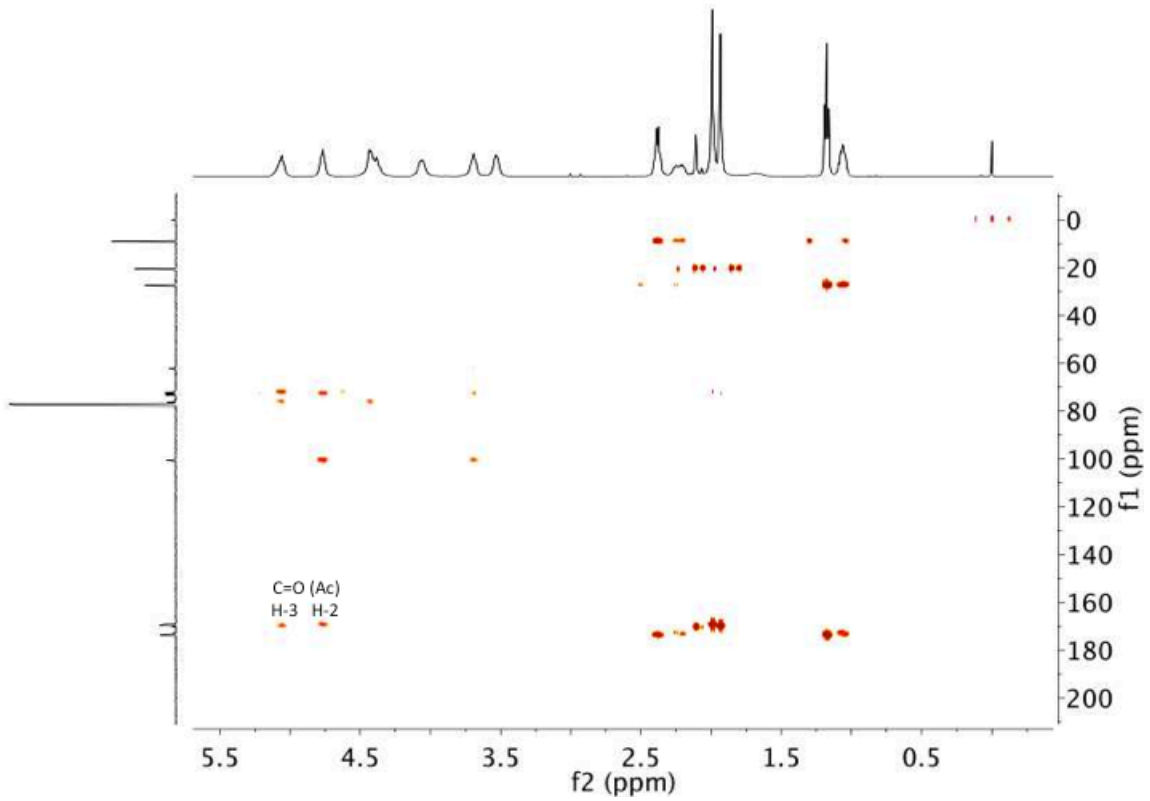


**Figure S5.5** HMBC NMR spectrum of the product of CTP deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after peracetylation.

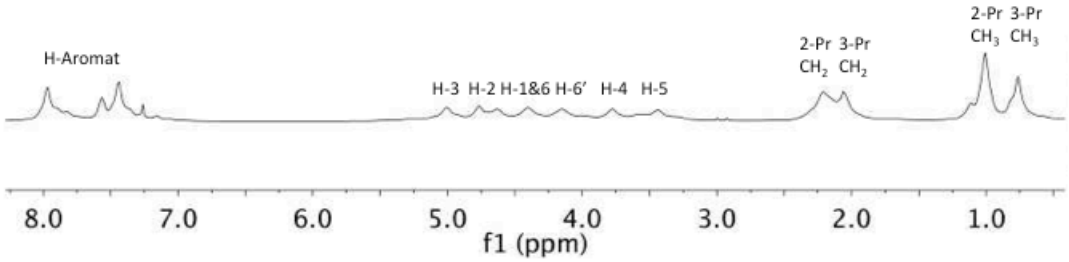


**Figure S5.6** $^{1}$H NMR spectrum of the product of CTBz deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

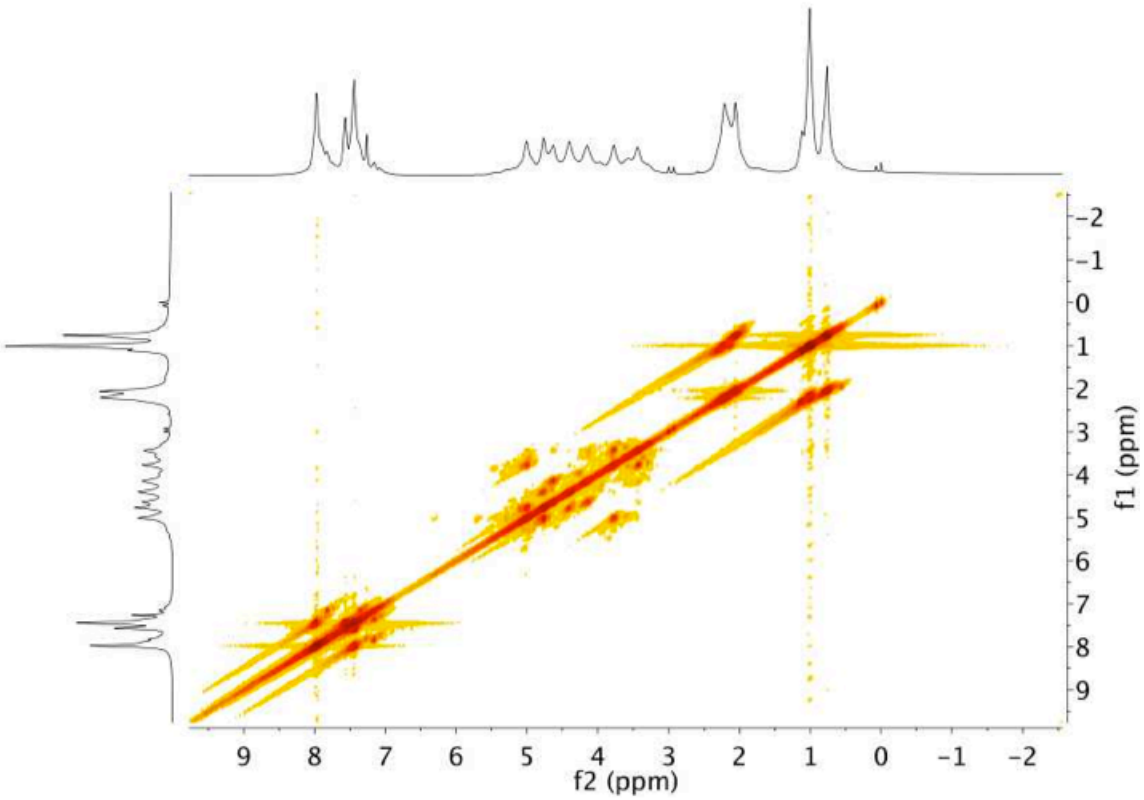


**Figure S5.7** COSY NMR spectrum of the product of CTBz deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

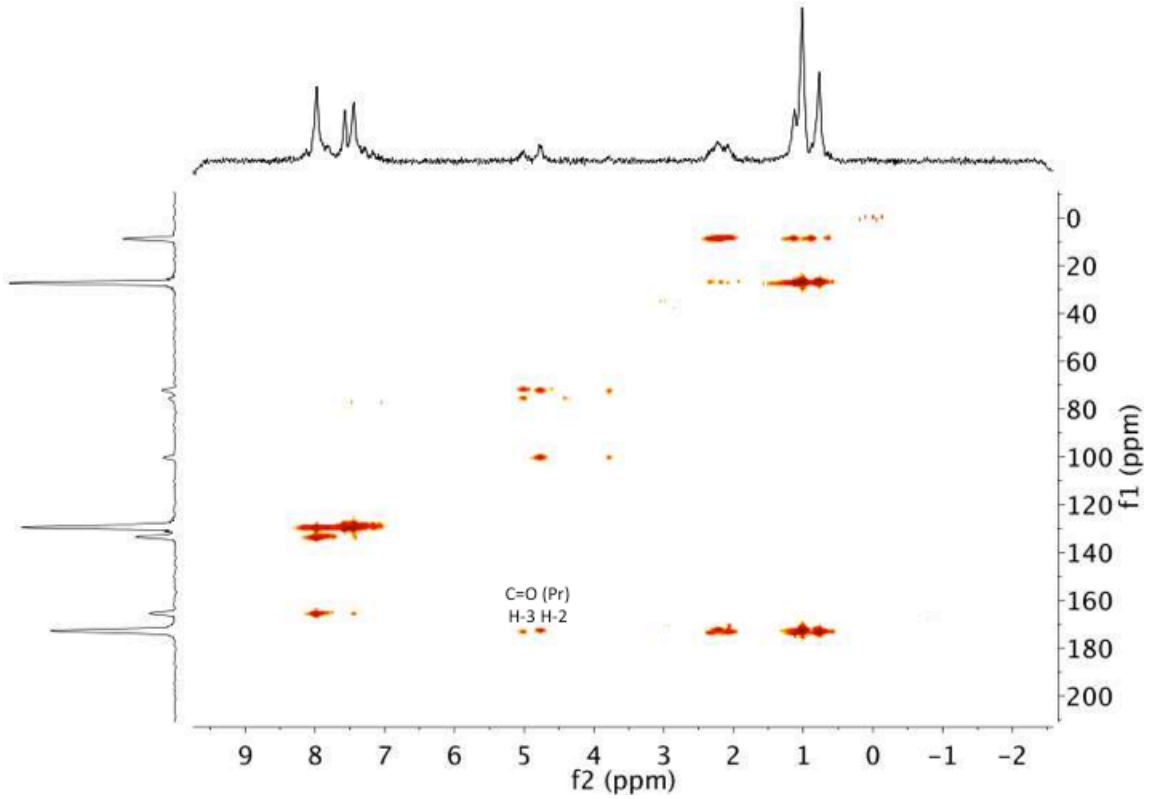


**Figure S5.8** HMBC NMR spectrum of the product of CTBz deacylation by TBAOH (2 equiv, 24 h, DMSO, 50 °C), after perpropionylation.

**5.7 Acknowledgements**

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# Chapter 6 Cellulose Levulinate: a New Protecting Group for Cellulose that can be Selectively Removed in the Presence of Other Ester Groups


## 6.1 Abstract

Levulinate is an important hydroxyl protecting group in carbohydrate chemistry but has not previously been employed in cellulose chemistry, perhaps because of challenges involved in synthesis of cellulose levulinates. Herein we describe homogeneous acylation of cellulose in *N*, *N*-dimethylacetamide /LiCl using differently activated levulinic acid derivatives, including *in situ* activation with dicyclohexylcarbodiimide, *p*-toluenesulfonyl chloride, 1,1'-carbonyldiimidazole, or trifluoroacetic anhydride, providing the first access to cellulose levulinates. Degree of substitution (DS) has been determined by $^{1}$H NMR spectroscopy using perpropionylated cellulose levulinates, showing that. DS values as high as 2.42 are attainable. Cellulose levulinate esters were hydrolyzed selectively by hydrazine without detectable loss of other alkanoate ester groups (acetate or propionate), indicating strong promise for levulinate as a useful protecting group for the synthesis of regioselectively substituted cellulose and other polysaccharide derivatives.


## 6.2 Introduction

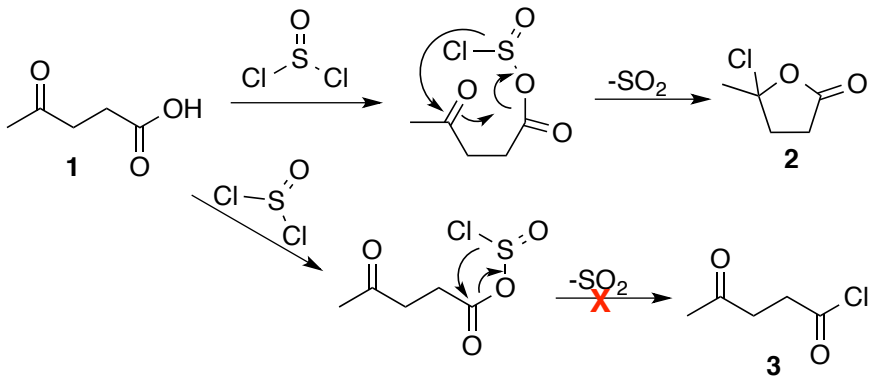
Advances in the past two decades against the difficult problem of regioselective synthesis of polysaccharide derivatives, especially derivatives of cellulose [1, 2], have taught us that regioselectively substituted cellulose derivatives have properties that are often quite distinct from their randomly substituted equivalents. For example, key properties like crystallinity [3, 4], thermal

properties [5], solubility [6], and optical properties [7] depend strongly on position of substitution. Initial regioselective syntheses employed protecting group chemistry, in particular exploiting the generally higher reactivity of the primary OH group at C-6 of cellulose to protect that position [8, 9]; this methodology provided access to 2,3-disubstituted derivatives [10] and through them to 2,3-A-6-B trisubstituted derivatives. Recently, we have developed routes to the same families of derivatives with similar regioselectivity but avoiding the necessity of protection/deprotection steps by regioselective 2,3-deacylation of cellulose (and amylose) esters using tetrabutyl ammonium fluoride (TBAF) or hydroxide (TBAOH) bases [11, 12]. While this provides an efficient route to these derivatives, full exploration of structure-property relationships will require synthetic access to other cellulose derivative homopolymers, such as cellulose 3,6-diesters and –diethers. This will require differentiation of the very similarly reactive 2-OH and 3-OH groups, and almost certainly will require the development of new protecting group chemistry. Sterically demanding silyl ethers like thexyldimethylsilyl have shown some promise for selective reaction at O-2 vs. O-3, as pioneered by the Klemm and Heinze groups [13-15]. However, quantitative analysis of positional degree of silylation has proven difficult. Of equal importance, removal of these silyl ethers requires treatment with fluoride salts like TBAF [16]; as we note above TBAF is not compatible with ester substituents as it catalyzes their deacylation [17]. As an illustrative example, in an attempt to deprotect the silyl ether group of 3-allyl-2-thexyldimethylsilylcellulose-6-O-acetate with TBAF in tetrahydrofuran (THF) [17], the reaction did not provide the expected product 3-O-allyl-6-O-acetyl-cellulose, but rather 3-O-allyl-cellulose (Scheme S1); TBAF removed not only the silyl group but also the acetate group.

It is of importance to develop better polysaccharide protective groups, which can be readily, ideally regioselectively, reacted with polysaccharide hydroxyl groups, and can then be removed

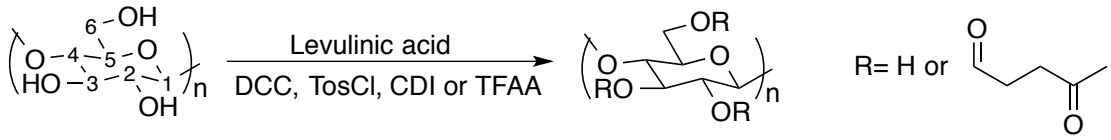
chemoselectively without affecting other groups, especially rather sensitive ester groups, to permit regioselective synthesis of polysaccharide esters. For this purpose, our attention was drawn to levulinate esters, which are commonly used as protective groups in small molecule carbohydrate chemistry to protect hydroxyls. Derived from the acid hydrolysis of cellulose [18], levulinic acid contains two reactive functional groups, a carboxylic acid and a ketone. Esters of levulinic acid are widely used in drug delivery systems, and as solvents, additives, plasticizers [18], and as protecting groups applied in synthetic organic chemistry [19]. More importantly, levulinate esters are acid stable and can, in small molecule chemistry, be removed by hydrazine selectively with respect to other esters [20], due to the potential for reaction of a single hydrazine molecule with both the ketone and ester carbonyls of the levulinate group. These characteristics raised our interest in levulinate as a potential protecting group for the synthesis of regioselectively substituted cellulose esters. However, synthesis of polysaccharide levulinates has not been reported, despite the fact that alkyl and carbohydrate levulinates, such as ethyl [21, 22] n-butyl,[23], benzyl [24, 25], and oligosaccharide levulinates [26] have been well explored. While those experienced with synthesis of polysaccharide derivatives will hardly be surprised that some reactions of small molecule carbohydrates don't work on the more unreactive, less soluble polysaccharides, especially the insoluble, crystalline, heavily hydrogen-bonded cellulose, still we were surprised at the lack of prior literature on the subject. Besides the poor reactivity of cellulose and to a lesser extent other polysaccharides, there is also the issue of the interesting cyclization chemistry available to levulinic acid. Exposure of levulinic acid to reagents like thionyl chloride does not result in the expected simple conversion to the acid chloride, but rather in chlorination of a cyclic intermediate, affording 5-chloro-5-methyl-dihydrofuran-2(3H)-one (2, **Scheme 6.1**) [27]. These chlorolactones are much less reactive towards hydroxyl acylation than are most acid chlorides.

There is surprisingly little discussion of these issues with regard to acylation of carbohydrates with levulinate in that body of literature, however as we will see, the issues impact reaction with polysaccharides significantly and may help to explain the paucity of previous studies of polysaccharide levulinates.




**Scheme 6.1** Reaction of levulinic acid with thionyl chloride

We report herein initial studies of methods for synthesis and characterization of levulinic acid esters of cellulose. We attempt to synthesize cellulose levulinates of different degrees of substitution and avoid issues arising from levulinate cyclization to lactone species by using various methods for mild activation of levulinic acid, including dicyclohexylcarbodiimide (DCC), *p*-toluenesulfonyl chloride (TosCl), 1,1'-carbonyldiimidazole (CDI), and trifluoroacetic anhydride (TFAA) (**Scheme 6.2**). In addition to the essential issue of whether levulinates can be practically attached as polysaccharide esters, we also address the other critical issue of whether levulinate esters can be selectively removed in the presence of other alkanoate ester groups.




**Scheme 6.2** Reaction of cellulose with levulinic acid and DCC, TosCl, CDI or TFAA in DMAc/LiCl

## 6.3 Experimental

### 6.3.1 Materials

Microcrystalline cellulose (MCC, Avicel PH-101, DP 260) was vacuum-dried before use. 4-Dimethylaminopyridine (DMAP), levulinic acid, DCC, TosCl (99+ %), CDI (97 %), and TFAA were purchased from Acros Organics. *N*, *N*-Dimethylacetamide (DMAc), lithium chloride (LiCl), acetic anhydride, propionic anhydride, and pyridine (anhydrous) were purchased from Fisher; all reagents were used without further purification.

### 6.3.2 Measurements

$^{1}H$, $^{13}C$ NMR, HMBC and COSY spectra of the cellulose esters after peracetylation or perpropionylation were acquired in $CDCl_3$ on a Bruker Avance II 500 MHz spectrometer at room temperature or 50 °C, with number of scans of 32, 10,000, 19,200 and 9,400 respectively. DS values were determined by means of $^{1}H$ NMR spectroscopy. DS values for the peracylated product were calculated based on the following equations by calculating the ratio of acetyl or propionyl proton integrals to the backbone hydrogens integral [28, 29].

$DS_{Ac} = 7I_{Ac\text{-}CH_3} / 3I_{backbone}$; I= Integral

$DS_{Lev} = 3- DS_{Ac}$

$DS_{Pr} = 7I_{Pr\text{-}CH_3} / 3I_{backbone}$; I= Integral

$DS_{Lev} = 3- DS_{Pr}$

Product yields were calculated using the following equation:

$Yield= 162B / (162+98 \times DS_{Lev})A$

A is the mass of cellulose, and B is the mass of the product cellulose levulinate.

Molecular weight of perpropionylated cellulose levulinate was determined by size exclusion chromatography (SEC) in chloroform on a Waters Alliance model 2690 chromatograph with Waters 2414 differential refractive index (RI) detector and Viscotek 270 dual detector, vs. polystyrene standards.

### 6.3.3 General procedure for dissolution of cellulose in DMAc/LiCl

Following a known procedure [30], a mixture of MCC (2.00 g, 12.32 mmol) and DMAc (74.8 mL) was heated to 156 °C over 26 min under nitrogen. Anhydrous LiCl (3.4 g) was added and the mixture was stirred at 165 °C for 8 min. Distillate (14.4 mL) was collected at 165 °C. The mixture was cooled down to room temperature and stirred overnight.

### 6.3.4 Synthesis of cellulose levulinate via *in situ* activation of levulinic acid with DCC

A solution of levulinic acid and DCC with stated molar ratio (**Table 1**) in DMAc was stirred for 30 min at 80 °C under $N_2$. The mixture was slowly added to the pre-dissolved cellulose. DMAP (100 mg) was added as a catalyst, then the reaction mixture was stirred for 24 h at 80 °C. The

reaction solution was cooled to room temperature and then precipitated into 200 mL ethanol. The product was isolated by filtration, washed several times with ethanol, collected, and dried under vacuum at 40 °C overnight. Yield: 82 %.

### 6.3.5 Synthesis of cellulose levulinate via *in situ* activation of levulinic acid with TosCl

Levulinic acid and TosCl with stated molar ratio (**Table 1**) were dissolved in DMAc. The reaction solution was stirred for 30 min at 80 °C under $N_2$. The reaction mixture was then added dropwise into the pre-dissolved cellulose solution over 30 min and allowed to react at 80 °C for 24 h. The product was isolated by adding the reaction mixture slowly to ethanol (200 mL). The precipitate was isolated by filtration, washed with ethanol (3 X 100 mL), then dried under vacuum at 40 °C to yield the product. Yield: 80 %.

### 6.3.6 Synthesis of cellulose levulinate via *in situ* activation of levulinic acid with CDI

A solution of levulinic acid and CDI with stated molar ratio (**Table 1**) in DMAc was stirred for 30 min at 80 °C under $N_2$. The mixture was added dropwise from an addition funnel to the pre-dissolved cellulose solution and allowed to stir for 24 h at 80 °C. The homogeneous mixture was slowly added to ethanol (200 mL) to precipitate the product. The product was isolated by filtration and washed several times with ethanol. It was dried under vacuum at 40 °C overnight. Yield: 84 %.

### 6.3.7 Synthesis of cellulose levulinate via *in situ* activation of levulinic acid with TFAA

A solution of TFAA and levulinic acid with stated molar ratio (Table 1) was stirred at 50 °C for 30 min under $N_2$ and was immediately added dropwise into the pre-dissolved cellulose solution. The solution was stirred at 50 °C for 24 h. After cooling to room temperature, the reaction solution was slowly added to ethanol (500 mL) under vigorous stirring. The product was isolated by filtration, washed with ethanol several times, and dried under vacuum at 40 °C overnight. Yield: 78 %.

### 6.3.8 General procedures for peracetylation or perpropionylation

Cellulose levulinates were peracylated for easier NMR analysis, according to literature procedures [17, 28, 29]. Cellulose levulinate (0.3 g), DMAP (15 mg) and acetic anhydride or propionic anhydride (4 mL) were added to pyridine (4 mL). After stirring at 80 °C for 24 h, the crude product was obtained by precipitation into ethanol (200 mL) and washed with several times by ethanol. The product was then re-dissolved in chloroform (5 mL), re-precipitated into ethanol (200 mL), and dried under vacuum to give the perpropionylated product for NMR analysis.

### 6.3.9 General procedure for the hydrolysis of peracylated cellulose levulinate with hydrazine

Peracylated cellulose levulinate (0.3 g) was dissolved in pyridine (5 mL) and propionic acid (1 mL). Hydrazine monohydrate (0.3 mL, 7.11 mol/mol anhydroglucose unit (AGU)) was added

and the solution was allowed to stir at room temperature for 24 h. The product was dialyzed against DI water for 4 days and then freeze-dried.

### 6.3.10 Solubility test

Samples (10 mg) were dissolved in a solvent (1 mL) under vigorous stirring at room temperature. Tetrahydrofuran (THF), chloroform, dimethyl sulfoxide (DMSO), pyridine and ethanol were used for this test. Solubilities were determined by visual inspection.

## 6.4 Results and Discussion

### 6.4.1 Approaches

We chose initially to explore the straightforward approach of reaction of levulinic acid with thionyl chloride, to see whether acylation via the chlorolactone intermediate **2** (**Scheme 6.1**) might be feasible. Levulinic acid was reacted with thionyl chloride, and the product solution was then added dropwise to cellulose solution in DMAc/LiCl, with pyridine as base. However, no levulinate signals were detected in the $^{1}$NMR spectra of the perpropionylated product. The chlorolactone is predominant and stable with respect to levulinoyl chloride formation; our observation indicates that direct acylation of cellulose with this reagent is not practical, consistent with experience in small molecule carbohydrate chemistry [27, 31].

Therefore, we explored other, milder activating reagents such as DCC, TosCl, CDI and TFAA in hope of changing the levulinate/lactone equilibrium, and/or enhancing reactivity towards cellulose hydroxyls (**Scheme S6.2**). DCC is a popular condensation reagent, which has been frequently applied to activate carboxylic acids and thereby prepare other types of cellulose esters.

Acid anhydrides have been shown to be reactive intermediates in these reactions [32]. In our case, levulinic acid was allowed to react with DCC for 30 min under $N_2$; this reaction mixture and DMAP were then added to cellulose DMAC/ LiCl solution, and the resulting mixture was allowed to react for 24 h.

TosCl is another useful carboxyl activation reagent. It has been shown that both mixed anhydrides and acid chlorides are formed when carboxylic acids were treated with TosCl [33]. Acylation of cellulose by TosCl activation of levulinate was also performed in two steps. TosCl and levulinic acid were stirred at 80 °C for 30 min and the resulting mixture was added slowly to cellulose solution.

Activation of the carboxylic acid with CDI provides another mild method for ester synthesis. The imidazolide [34] of levulinic acid was firstly formed by reaction of levulinic acid with CDI at 80 °C for 30 min, which was then added to a cellulose solution. This method is of great interest for cellulose esterification, because the only by-products are readily removed $CO_2$ and imidazole [35].

Reaction of carboxylic acids with TFAA has been demonstrated to be an efficient esterification system for cellulose by producing a mixture of acid anhydrides [36], even though the strongly acidic conditions may in some cases cause significant polymer chain degradation. In our case, levulinic acid and TFAA were stirred at 50 °C for 30 min. The pre-mixed solution was then added to the cellulose solution, followed by reaction for 24 h at 50 °C.

### 6.4.2 Preparation of cellulose levulinate with different DS values

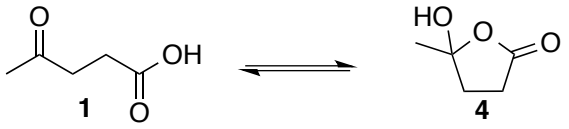
Across the range of acylation approaches attempted, it quickly became clear that efficiency of acylation with levulinate is much inferior to that achievable with simple alkanoates like acetate

or propionate; very high efficiencies are possible with simple alkanoyl chlorides or alkanoic anhydrides under the proper conditions [30]. In order to determine whether synthesis of high DS cellulose levulinates was possible, we explored preparation using different activating reagents using a range of reagent equiv / AGU (**Table 6.1**). Reaction of cellulose with levulinic acid in the presence of DCC leads to the cellulose levulinates 1-3. At a molar ratio of 3 equiv each of levulinic acid and DCC per AGU, a rather small $DS_{Lev}$ of 0.34 was reached within a reaction time of 24 h at 80 °C. Even treatment of cellulose with 6 equiv levulinic acid and DCC per AGU for 24 h at 80 °C afforded cellulose levulinate with a disappointing $DS_{Lev}$ of 0.46. Fortunately, we found that 24 h reaction of cellulose with a large excess of both levulinic acid and DCC (20 equiv) afforded the potentially useful $DS_{lev}$ of 1.53 (generally for use of levulinate as a hydroxyl protecting group, DS 1.0 or 2.0 would be the target).

We sought to understand whether other activation methods could more efficiently afford cellulose levulinates with higher DS values, beginning by employing similar reaction conditions for TosCl-mediated activation of levulinic acid. Treating cellulose with 3 or 6 equiv TosCl-activated levulinate per AGU again provided a relatively low acylation extent, with $DS_{Lev}$ below 0.5 (samples 4 and 5). Practical $DS_{Lev}$ levels (1.51, sample 6) were again only achieved when cellulose was exposed to a large excess of reagent (20 equiv/AGU each of levulinic acid and TosCl, 24 h, 80 °C).

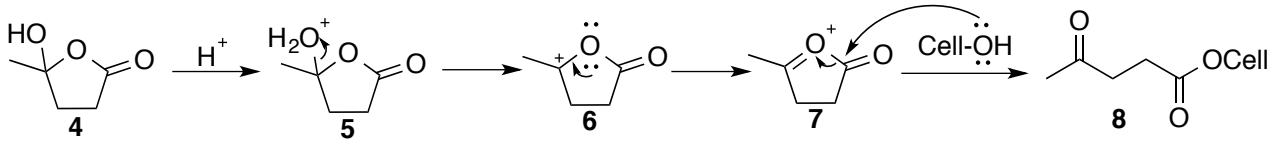
Somewhat disappointingly, even reaction of dissolved cellulose with levulinic acid imidazolide proceeded with rather low efficiency, leading to the corresponding cellulose levulinates with $DS_{Lev}$ of 0.40, 0.48 and 1.64 at molar ratios of AGU/levulinic acid/CDI of 1/3/3, 1/6/6, and 1/20/20, respectively (24 h, 80 °C, samples 7-9). Thus, these three different activation methods (DCC, TosCl and CDI) all gave similar results: with fewer than 6 equiv of coupling reagents,

low DS (below 0.5) cellulose levulinates were obtained; excess activation reagent (20 equiv) afforded cellulose levulinate with DS about 1.5-1.6. At this point we do not know the extent to which activated levulinates arise from the ring open form (**1**) and to what extent from the lactone form (**4, Scheme 6.3**). It is possible that low reactivity of the activated lactone form is the source of the low DS observed when using only moderate activated levulinic acid excess.




**Scheme 6.3** Equilibrium in solution between levulinic acid and its lactone form

Interestingly, activation by the (more acidic) TFAA method provided the highest DS. Only 3 equiv of reagent/AGU was enough to approach DSLev of 1 (0.96), while 6 equiv afforded $DS_{Lev}$ 1.68 (24 h, 50 °C). Reaction of cellulose with 20 equiv/ AGU TFAA and levulinic acid afforded the highest $DS_{Lev}$ we observed under any reaction conditions, providing cellulose levulinate with $DS_{Lev}$ of 2.42. It may be that higher DS values can be obtained using TFAA because, under acidic conditions, both activated levulinic acid and its lactone form react with cellulose. We suspect that the protonated hydroxyl group of 5-OH-γ-valerolactone may act as a leaving group, thereby creating a resonance-stabilized cation (**6**). Subsequent attack by a cellulose hydroxyl group on the carbonyl carbon results in ring opening and affords cellulose levulinate (**Scheme 6.4**).




**Scheme 6.4** Proposed reaction of 5-OH-γ-valerolactone with cellulose in the presence of acid

**Table 6.1** Conditions and results of cellulose reaction with levulinic acid after *in situ* activation

| **Methods** | **Reaction conditions** | | | **Cellulose levulinate** | | **DP** |
|---|---|---|---|---|---|---|
| | **Molar ratio**[a] | **Time (h)** | **Temperature (°C)** | **Sample** | **$DS_{Lev}$** | |
| **DCC** | 1: 3: 3 | 24 | 80 | **1** | 0.34 | 132 (Sample **3**) |
| | 1: 6: 6 | 24 | 80 | **2** | 0.46 | |
| | 1: 20: 20 | 24 | 80 | **3** | 1.53 | |
| **TosCl** | 1: 3: 3 | 24 | 80 | **4** | 0.22 | 128 (Sample **6**) |
| | 1: 6: 6 | 24 | 80 | **5** | 0.44 | |
| | 1: 20: 20 | 24 | 80 | **6** | 1.51 | |
| **CDI** | 1: 3: 3 | 24 | 80 | **7** | 0.40 | 139 (Sample **9**) |
| | 1: 6: 6 | 24 | 80 | **8** | 0.48 | |
| | 1: 20: 20 | 24 | 80 | **9** | 1.64 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **TFAA** | 1:3:3 | 24 | 50 | **10** | 0.96 | 96 (Sample **12**) |
| | 1:6:6 | 24 | 50 | **11** | 1.68 | |
| | 1: 20: 20 | 24 | 50 | **12** | 2.42 | |

[a]Mol AGU/mol levulinic acid/mol (DCC, TosCl, CDI, or TFAA).

### 6.4.3 NMR analysis and DS determination

For determination of $DS_{Lev}$ values, the products 1-12 (see tables 6.1) were treated with propionic anhydride in pyridine in the presence of DMAP catalyst, yielding fully substituted cellulose levulinate propionates with simplified spectra. The perpropionylated products are readily soluble in chloroform. **Figure S6.1** shows the $^1$H NMR spectrum of cellulose levulinate **9** after perpropionylation in $CDCl_3$. Proton peaks were assigned based on previous studies, 2D spectra, and long-range correlation spectra [11, 12, 37]. The protons of the methyl group of the propionate moiety are located at δ = 0.95-1.25 ppm and the propionate methylene protons are at δ = 2.19 ppm. The levulinate methyl protons resonate at δ = 2.12 ppm and four levulinate methylene protons are visible at δ = 2.29-3.07 ppm. The signals between 3.35 and 5.30 ppm are the backbone protons. Propionate and levulinate DS values were determined by means of $^1$H NMR spectroscopy, according to the equations in the Experimental Section.

It was important to determine regioselectivity, although our previous results with much more sterically demanding acylating reagents suggested that high O-6 selectivity was not to be expected [29]. Reaction of cellulose with 20 equiv/ AGU CDI and levulinic acid at 50 °C for 24 h afforded a randomly substituted cellulose levulinate with $DS_{Lev}$ at O-2/3 of 1.03 and $DS_{Lev}$ at O-6 of 0.51. Partial $DS_{Pr}$ values of cellulose propionate levulinate were determined directly by the

ratio of partial propionate methyl resonances (O-2/3 1.10-1.25 ppm, O-6 0.95- 1.10 ppm) to the integrals of the cellulose backbone protons (3.35- 5.30 ppm). The partial $DS_{Lev}$ value was subtracted from 1 (with successful perpropionylation there is a total DS of 1 at each position) to give the $DS_{Lev}$ at that position.

Carbon signals were completely assigned by analogy to previous work.[37] Signals at δ = 62.0 ppm (C-6), between 70.2 and 73.5 ppm (C-2, C-3 and C-5), at δ = 77.5 ppm (C-4), and at δ = 100.0 ppm (C-1) are the backbone carbons. The propionate methyl, methylene, and carbonyl carbons resonate at 8.9, 27.4, and 169.8-172.5 ppm, respectively. Two levulinate methylene carbons are at 28.8 and 39.9 ppm, and the levulinate methyl carbon is at 28.9 ppm. The levulinate ketone carbon and ester carbonyl carbon are at 206.8 and 173.2 ppm, respectively.

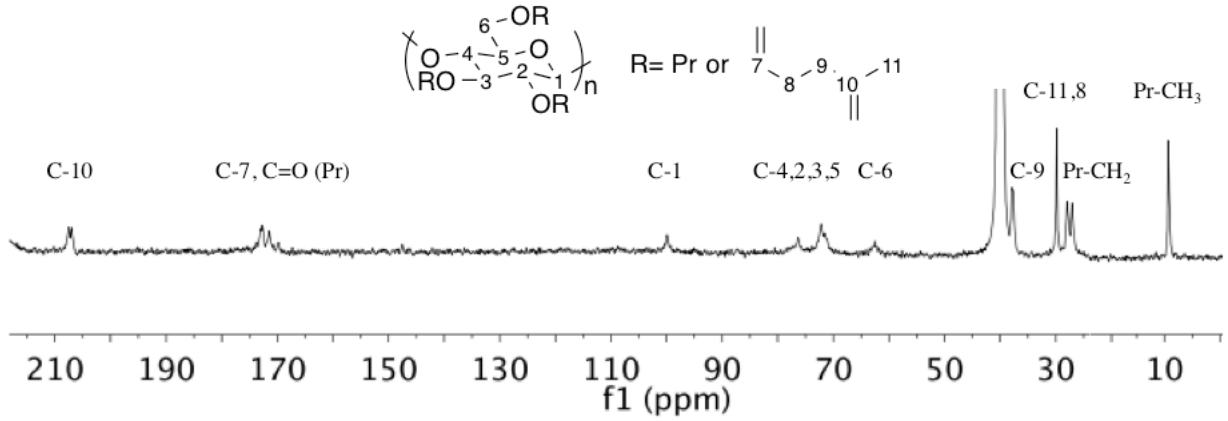



**Figure 6.1** $^{13}C$ NMR spectrum of cellulose levulinate **9** after perpropionylation.

### 6.4.4 Solubility of cellulose levulinates vs. DS

Solubilities of cellulose levulinates with different DS values were investigated and the results are listed in **Table 6.2**. Compound 4, 1, and 8 with $DS_{Lev}$ below 0.5 were insoluble in any common organic solvents. Cellulose levulinate samples with DS values of 1.51 (sample 6) and 1.64

(sample 9) had better solubility in THF, DMSO and pyridine. Compound 12 with the highest DS of 2.42 was soluble in THF, chloroform, pyridine, and DMSO. Solubility of cellulose levulinates depends predictably (based on extensive literature precedent with simple cellulose alkanoates) on the DS values; higher $DS_{Lev}$ leads to more organic solubility. Peracylation consistently improved solubility in organic solvents since the resulting cellulose alkanoate levulinates were more hydrophobic and not prone to intramolecular or intermolecular hydrogen bonding.

**Table 6.2** [a]Solubility of cellulose levulinates vs. $DS_{lev}$

| **Sample** | **$DS_{Lev}$** | **Solubility** | | | | |
|---|---|---|---|---|---|---|
| | | **THF** | **$CHCl_3$** | **DMSO** | **Pyridine** | **Ethanol** |
| **4** | 0.22 | - | - | - | - | - |
| **1** | 0.34 | - | - | - | - | - |
| **8** | 0.48 | - | - | - | - | - |
| **6** | 1.51 | + | - | + | + | - |
| **9** | 1.64 | + | - | + | + | - |
| **12** | 2.42 | + | + | + | + | - |

[a]+ soluble; - insoluble.

### 6.4.5 Selective deprotection of levulinate using hydrazine

The ability to selectively remove potential alcohol protecting groups is also an essential feature if they are to be useful. As we demonstrate above, protection of cellulose free hydroxyl groups as levulinate esters can be achieved, and accessability of either DS 1.0 or DS 2.0 means that sufficient DS may be attainable for most practical situations. The small molecule literature indicates that levulinate can be removed by several reagents, including (a) Grignard reagents [38], (b) sodium bisulfite [39], (c) sodium borohydride [31], and (d) hydrazine [24, 40], among which, hydrazine was reported to selectively deprotect levulinate in the presence of other ester groups (O-acetyl, O-propionyl, O-benzoyl) [20, 24]. However, precedent for deacylation of cellulose alkanoates may not provide encouragement; Miyamato et al. has described [41] that hydrazine catalyzes deacylation of cellulose acetate.

In order to investigate whether hydrazine can selectively deacylate cellulose levulinate esters in the presence of acetate or propionate esters, peracetylated or perpropionylated cellulose levulinates were treated with hydrazine in pyridine and propionic acid at room temperature for 24 h. The product was collected by precipitation in water and filtration, and was peracylated (with an alkanoate not present in the starting ester) to afford a well-resolved NMR spectrum for DS determination. **Scheme S6.1** shows the reaction schemes.

The $^{13}C$ NMR spectrum of the product of cellulose levulinate propionate **12** hydrolysis by hydrazine after peracetylation is shown in **Figure 6.2**. No carbon signals of levulinate moieties are observed, confirming the complete removal of levulinate by hydrazine. DS values for the products of cellulose acetate levulinate or cellulose levulinate propionate hydrolysis by hydrazine after peracylation were determined by $^{1}H$ NMR. As shown in **Figure S6.3**, peaks between 1.80 and 2.15 ppm confirm acetate substitutions; peaks at 0.95-1.25 ppm and 2.18-2.42

ppm are propionate methyl protons and propionate methylene protons. Peaks for levulinate protons are absent. $DS_{Ac}$ values were determined directly by the ratio of the acetyl resonances (1.80-2.08 ppm) to the integrals of the cellulose backbone protons (3.30-5.50 ppm). $DS_{Pr}$ was calculated similarly by comparing integrals of the backbone protons with the propionyl methyl protons (0.95-1.25 ppm). As shown in **Table S6.1**, the starting DS acetyl or propionyl, respectively, remains the same after treatment with hydrazine, proving selective deacylation of levulinate by hydrazine in the presence of acetate and propionate.

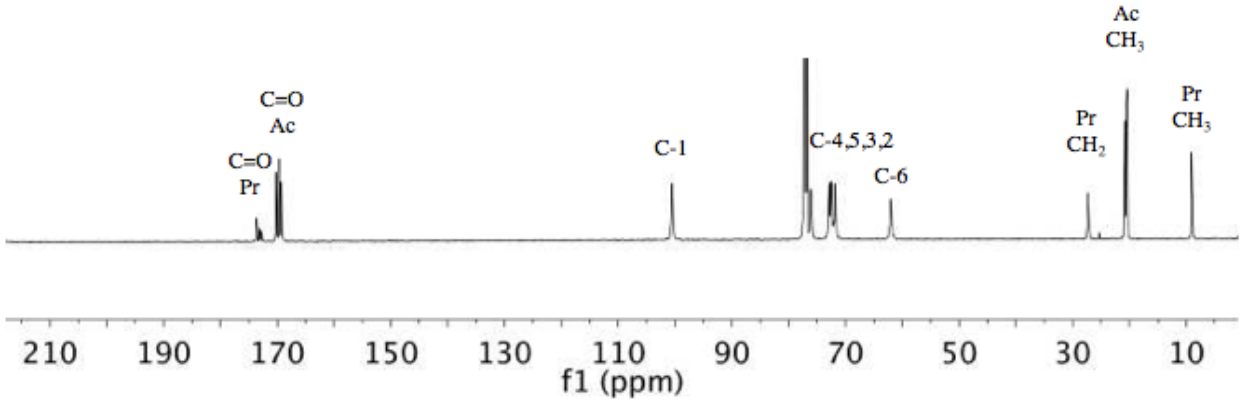


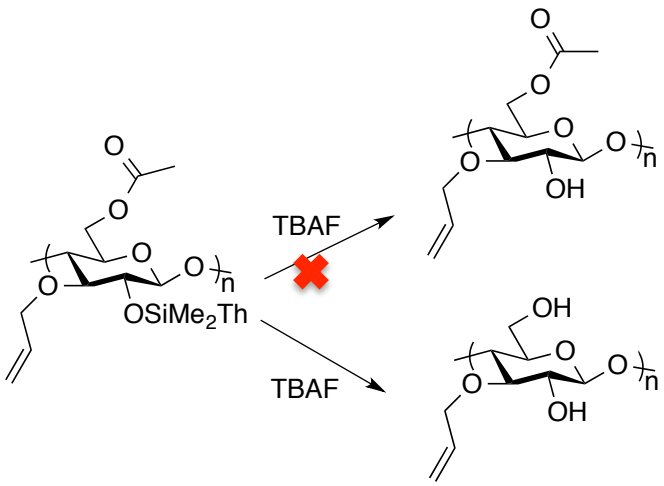

**Figure 6.2** $^{13}C$ NMR spectrum of the product of cellulose levulinate propionate **12** hydrolysis by hydrazine after peracetylation.

### 6.5 Conclusions

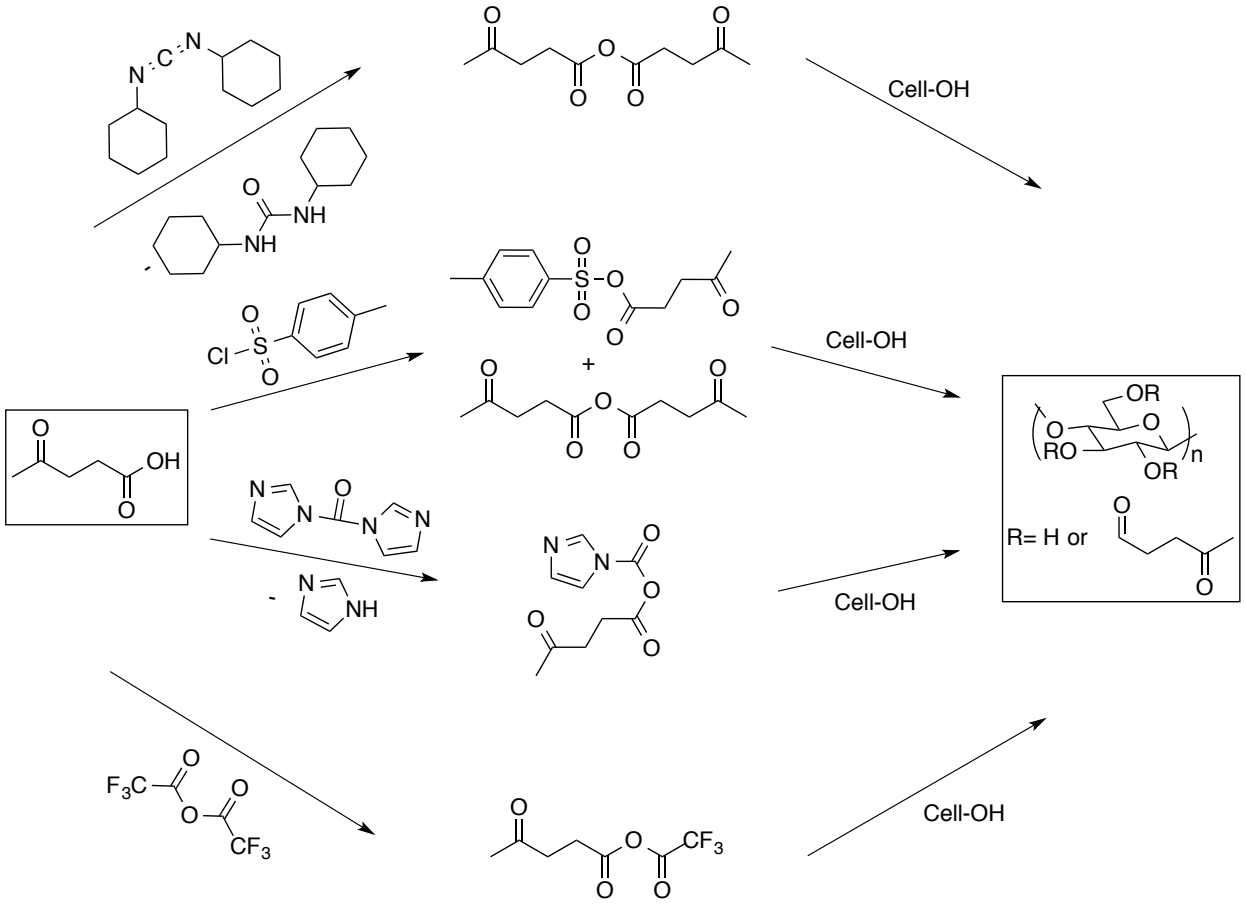
Cellulose levulinates with a wide range of DS values (0.22-2.42) were successfully prepared by esterification of cellulose in DMAc/LiCl with levulinic acid in the presence of activating agents DCC, TosCl, CDI or TFAA. Comparing these four methods investigated, *in situ* activation of levulinic acid with TFAA provided the highest $DS_{Lev}$ of 2.42 under comparable conditions. Efficiency is modest, but for the purposes of making cellulose ester homopolymers for initial structure-property investigations, is sufficient. $^{1}H$ and $^{13}C$ NMR spectra of cellulose levulinate

propionate were assigned in detail based up on previous literature. Solubility of cellulose levulinate depends in predictable fashion on $DS_{Lev}$. Hydrazine can selectively cleave the levulinate groups of cellulose acetate levulinate and cellulose levulinate propionate while leaving acetates and propionates unscathed. With the availability of these methods for protection and mild deprotection of alcohols, levulinate shows great potential as protecting group for synthesis of regioselectively substituted derivatives of cellulose and is likely to be of general use in polysaccharide chemistry. Further studies of subsequent modifications of the new cellulose esters and applications of levulinate as protecting group for regioselective synthesis of cellulose esters are under way.

## 6.6 Supporting information




**Scheme S6.1** TBAF-catalyzed deacylation of 3-allyl-2-thexyldimethylsilylcellulose-6-O-acetate




**Scheme S6.2** Reaction of cellulose with levulinic acid applying in situ activation with DCC, TosCl, CDI or TFAA in DMAc/LiCl

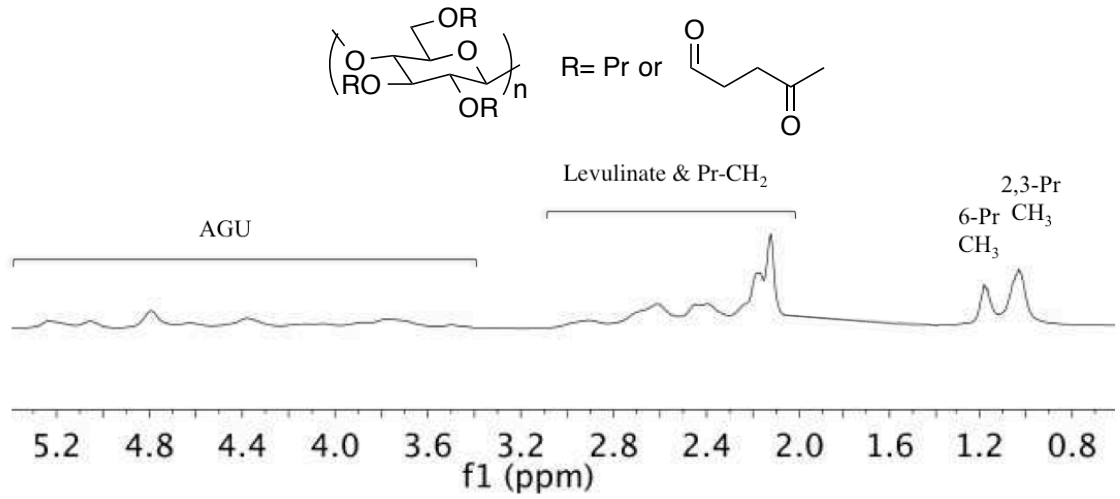



**Figure S6.1** [1]H NMR spectrum of cellulose levulinate **9** after perpropionylation.

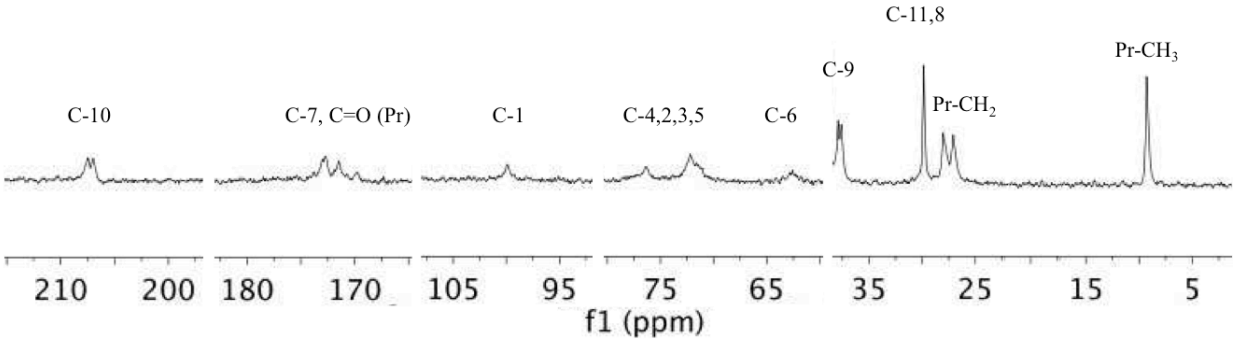
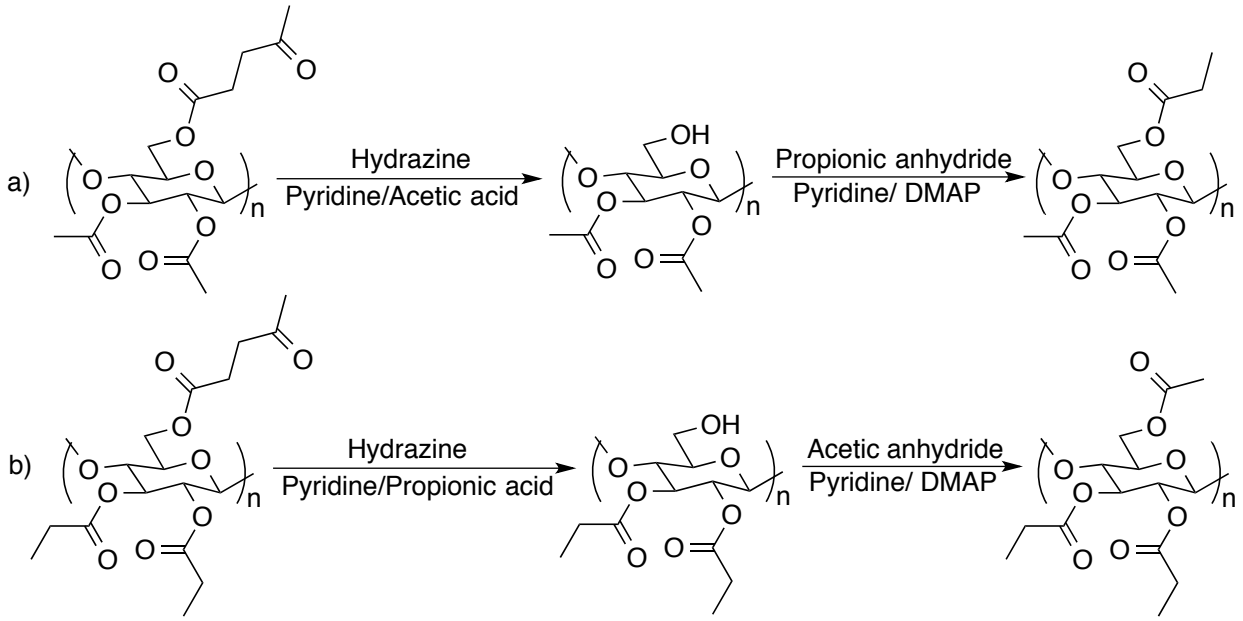


**Figure S6.2** $^{13}C$ NMR spectrum of cellulose levulinate (20 equiv/AGU TFAA, 24 h, 50 °C) after perpropionylation.




**Scheme S6.3** Hydrolysis of cellulose levulinate acetate or propionate with hydrazine, followed with perpropionylation or peracetylation

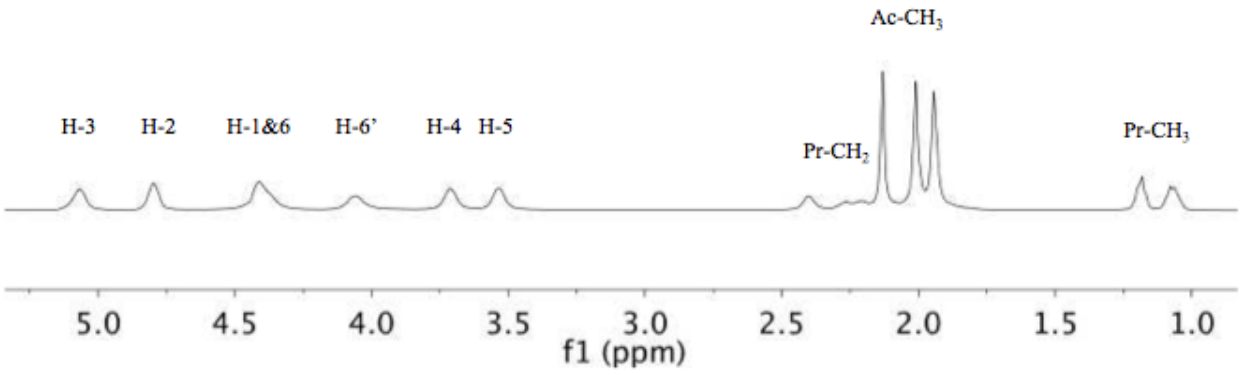



**Figure S6.3** $^{1}$H NMR spectrum of the product of cellulose levulinate **10** propionate hydrolysis by hydrazine after peracetylation

**Table S6.1** DS values of the product of hydrolysis of cellulose levulinate acetate or propionate after perpropionylation or peracetylation.

| Sample | Reaction scheme[a] | DS | | |
|---|---|---|---|---|
| | | Levu | Ac | Pr |
| **7** | NA | 0.40 | 2.61 | 0 |
| **7** | a | 0 | 2.58 | 0.40 |
| **7** | NA | 0.40 | 0 | 2.59 |
| **7** | b | 0 | 0.43 | 2.62 |
| **9** | NA | 1.64 | 1.33 | 0 |
| **9** | a | 0 | 1.31 | 1.64 |

| | | | | |
|---|---|---|---|---|
| **9** | NA | 1.64 | 0 | 1.38 |
| **9** | b | 0 | 1.66 | 1.36 |
| **10** | NA | 2.42 | 0.59 | 0 |
| **10** | a | 0 | 0.60 | 2.45 |
| **10** | NA | 2.42 | 0 | 0.60 |
| **10** | b | 0 | 2.41 | 0.57 |

[a]Reaction schemes a and b were shown in **Scheme S6.1**.

[b]Degree of substitution were determined by $^{1}$H NMR spectroscopy.


### 6.7 Acknowledgement

This project was supported by a grant from the U.S. Department of Agriculture (USDA, grant number 2011-67009-20090). We thank the Department of Sustainable Biomaterials, the Chemistry Department, and the Institute for Critical Technologies and Applied Science at Virginia Tech for their financial, facilities, and educational support.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# Chapter 7 Summary and Future Work

Even though extremely challenging, regioselective functionalization of cellulose esters is very important for us to establish a fundamental understanding of structure-property relationships of cellulose derivatives with regard to the position of substitution. Protection and deprotection chemistry is the most common strategy for the preparation of regioselectively substituted cellulose derivatives, which however is time consuming and expensive, significantly reduces the overall yield, and can cause difficulties due to poor reactivity of some protected intermediates. As one of the most important protecting groups, the thexyldimethylsilyl group can be deprotected by TBAF. Recently, it was found in our group that TBAF not only cleaves silyl groups but also deacylates certain ester groups, limiting the utility of silyl protected cellulose intermediates for the synthesis of regioselectively substituted cellulose esters.

My doctoral research has been focused on the development of new tools for the regioselective synthesis of cellulose esters. We described extensive studies on synthesis and characterization of regioselectively substituted cellulose esters.

## 7.1 Probing the mechanism of TBAF-catalyzed deacylation of cellulose esters

TBAF was discovered to regioselectively deacylate cellulose esters in THF at the more hindered ester groups of the secondary alcohols at O-2 and O-3. The mechanism of this reaction was investigated to guide the design of new methods with even greater selectivity. Kinetic isotope effects (KIE) were measured separately for each ester group location (O-2/3 and O-6). Deacylation at O-2/3 shows a secondary KIE ($k_H/k_D$= 1.26 ± 0.04), suggesting an E1cB

mechanism. An inverse KIE ($k_H/k_D = 0.87 \pm 0.03$) for the slower deacylation at the primary O-6 position indicates the involvement of a tetrahedral intermediate in the mechanism. Further investigation on the effect of added base and acid supports a general base-catalyzed mechanism at O-6. We still cannot conclusively pinpoint the source of the counterintuitive regioselectivity of this reaction. Evidence from studies of cation effects supports the possibility that coordination of the bulky tetraalkylammonium cations by vicinal O-2/3 acetates drives the observed selectivity, but we do not consider the currently available evidence definitive.

### 7.2 Reaction scope and influence of reaction parameters of TBAF-catalyzed deacylation of cellulose esters

The scope of the highly regioselective, TBAF-catalyzed deacylation reaction was further explored to expand its utility and understand how to carry it out most efficiently. It is demonstrated that TBAF-catalyzed deacylation is also effective and regioselective with cellulose acetate, propionate, butyrate, and hexanoate triesters, and even with a cellulose ester devoid of alpha protons, cellulose benzoate.

The effect of solvent on deacylation shows exceptional flexibility; DMSO, THF, MEK and acetone are nearly equally effective for regioselective deacylation of cellulose acetate; while DMAc and pyridine are slightly less effective. Regioselectivity of TBAF-catalyzed deacylation shows a surprising insensitivity to temperature; reaction at 50 °C gives the best combination of regioselectivity and conversion. The deacylation reaction is also relatively insensitive to the effects of added water.

The results of these explorations of the scope of this unusual deacylation reaction show that it is a flexible, forgiving, and efficient one-step method for generating regioselectively substituted cellulose esters without the need of challenging, inefficient protection/deprotection steps.

### 7.3 Remarkably regioselective deacylation of cellulose esters using tetraalkylammonium hydroxide.

Based on the proposed chelation mechanism for TBAF-catalyzed decylation of cellulose esters in **chapter 3**, we hypothesized that tetralkylammonium hydroxide might also exhibit similarly enhanced reactivity towards deacylation of esters of the secondary cellulose hydroxyl groups. We carried out experiments in which CA was exposed to TBAOH, examining the effect of TBAOH/ CA stoichiometry. Limited quantities of TBAOH show substantial selectivity for the removal of the acyl groups at O-2/3. The effectiveness of these methods is quite unexpected, counterintuitive, and causing scientists to revisit the long-standing paradigm that base-catalyzed hydrolysis of polysaccharide esters is non-selective.

Evidence from studies of tetraalkylammonium cation size effects supports a chelation mechanism, but our evidence on this point is not yet conclusive. TBAOH is an effective catalyst not only for regioselective deacylation of CA, but also for regioselective deacylation of CTA, CTP, CTB, CTH, and CTBz, although percent regioslectivity declines as ester chain length increases in the alkanoyl series, similar to the trend observed in TBAF deacylation. Solvent and temperature effect studies show that the organic base pyridine is the most effective solvent for promoting regioselective deacylation and that changing temperature within the range studied does not impact regioselectivity.

TBAOH deacylation is a far more economical and practical one-step method for making regioselectively substituted cellulose-6-O-esters, employing only common organic solvents, using no protective groups, and creating the possibility of recycling the reagent by simple ion-exchange.

### 7.4 Synthesis of novel cellulose levulinates using differently activated levulinic acid derivatives and the role of levulinate as a polysaccharide protective group

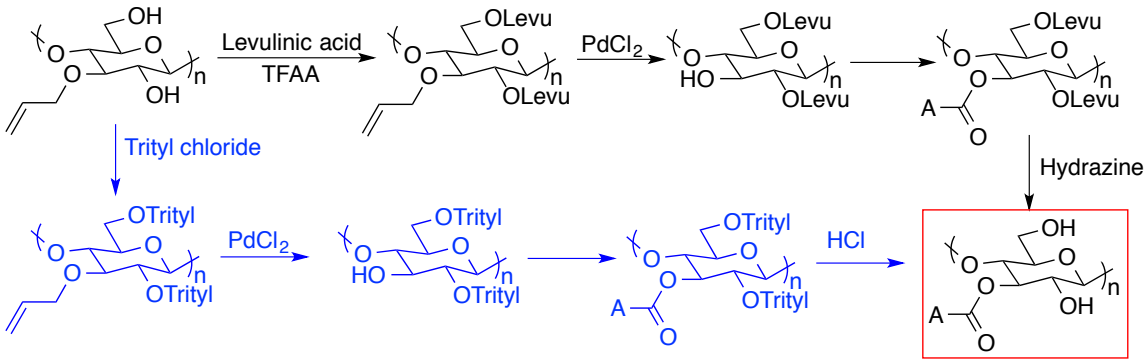
New cellulose levulinates with a wide range of DS values (0.22-2.42) were synthesized homogeneously in DMAc/LiCl by reaction with levulinic acid activated in several different ways, including in situ activation with dicyclohexylcarbodiimide, toluenesulfonyl chloride, 1,1'-carbonyldiimidazole, and trifluoroacetic anhydride. A DS value as high as 2.42 was obtained by the method of activation of levulinic acid with TFAA. Cellulose levulinate esters were found to be selectively hydrolyzed by hydrazine in the presence of acetate and propionate esters, and without removing acetate or propionate, making levulinate a promising protecting group for the regioselective synthesis of cellulose esters.

### 7.6 Proposed future work

Cellulose-6-O-A-2,3-O-B esters (prepared by derivatization of cellulose with bulky ether protective groups at C-6, followed by esterification and deprotection chemistries),[1-3] and cellulose-3-O-A-2,6-O-B esters (synthesized by protection of cellulose at both 2- and 6-OH groups using bulky silyl ethers)[4] are the only regioselectively substituted cellulose esters that have been successfully prepared. By using the knowledge generated in this thesis work, we can

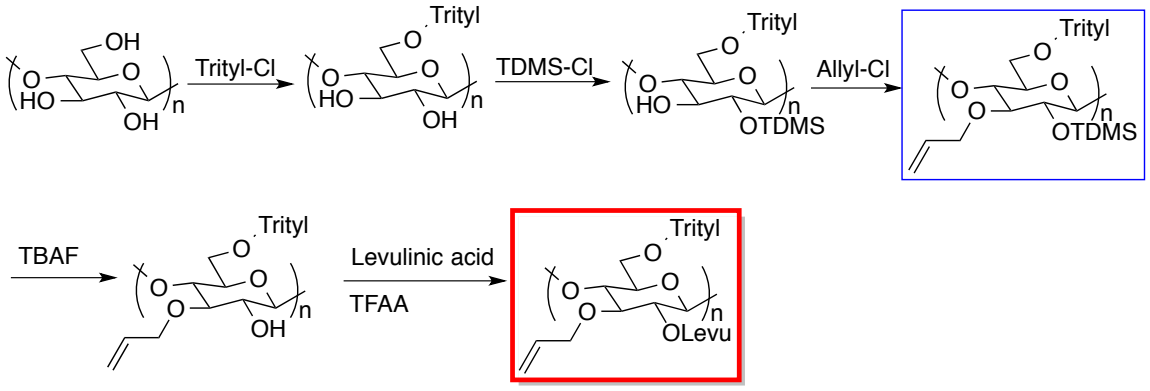
now propose the synthesis of cellulose esters with full control of ester type at each position to establish a comprehensive understanding of structure-property relationship of the full range of cellulose ester homopolymers.

The proposed scheme employs 3-O-allyl cellulose[5] as a key protected precursor, from which cellulose-3-O-A-monoesters would be synthesized by two methods (**Scheme 7.1**). One is the use of the levulinoyl group for the protection of the free hydroxyl groups at C-2/6, followed by cleavage of the allyl group, esterification, and deprotection of the levulinoyl groups by hydrazine; the other is the exploitation of the trityl group for the derivatization of hydroxyl groups at C-2/6, followed by removal of the allyl group, acylation, and deprotection of the trityl group by HCl.




**Scheme 7.1** Synthesis of cellulose-3-O-A-monoester

As shown in **Scheme 7,2**, 2-O-silyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose, serving as an important intermediate for the regioselective synthesis of cellulose esters, would be synthesized by protection of the 6-OH by a trityl group, the 2-OH by a silyl group, and the 3-OH by an allyl group. Orthogonal protection is a strategy allowing individual selective deprotection of the functional groups without affecting each other.




**Scheme 7.2** Synthesis of orthogonally protected cellulose intermediates 2-O-silyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose and 2-O-levulinoyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose

Regioselectively substituted cellulose esters (including cellulose-2-O-A-monoester, cellulose-2-O-A-3-O-B-diester, cellulose-2-O-A-6-O-B-diester, cellulose-2-O-A-3,6-O-B-triester, and cellulose-2-O-A-3-O-B-6-O-C-triester (**Figure 7.1**)) would then be synthesized by individual selective deprotection reactions of the silyl group, allyl group, and trityl group of 2-O-silyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose, followed by esterification. For example, cellulose-2-O-A-3-O-B-6-O-C-triester could be prepared by the following steps: (1) deprotection of the silyl group by TBAF, followed by esterification; (2) cleavage of allyl group by $PdCl_2$, followed by esterification; (3) removal of trityl group by HCl, followed by esterification.

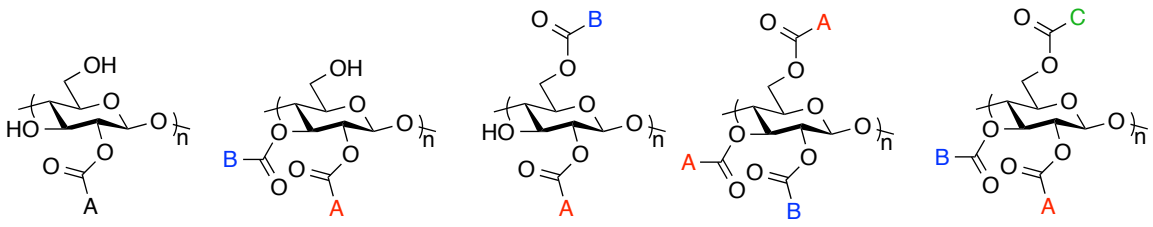


**Figure 7.1** Regioselectively substituted cellulose esters prepared from 2-O-silyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose

However, as we know, deprotection of the silyl group by TBAF may also cause deacylation of any secondary ester groups present, which makes it unlikely that synthesis of cellulose-3-O-A-monoester, cellulose-3,6-O-A-diester, and cellulose-3-O-A-6-O-B-diester (**Figure 7.2**) by using 2-O-silyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose as protected cellulose intermediate would be successful. To conquer this problem, we would substitute the silyl group at C-2 with a levulinoyl group. The deprotection of levulinoyl group by hydrazine has been shown in our work not to affect other ester group types. 2-Levulinoyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose would be obtained by cleavage of the silyl group by TBAF, followed by protection of the free hydroxyl group at C-2 by levulinate (**Scheme 7.2**). Thereafter, the protecting groups would be selectively removed followed by esterification for the synthesis of cellulose-3-O-A-monoester, cellulose-3,6-O-A-diester, and cellulose-3-O-A-6-O-B-diester. For instance, cellulose-3-O-A-6-O-B-diester could be prepared by removal of allyl group at C-3 by $PdCl_2$, acylation of the free hydroxyl group at C-3, deprotection of trityl group at C-6 by HCl, esterification of the free hydroxyl group at C-6, and cleavage of levulinate at C-2 by hydrazine. If this approach is successful, all kinds of regioselectively substituted cellulose esters with one, two, or three ester types at different positions could be synthesized from either single intermediate; 2-O-silyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose or 2-O-levulinoyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose.

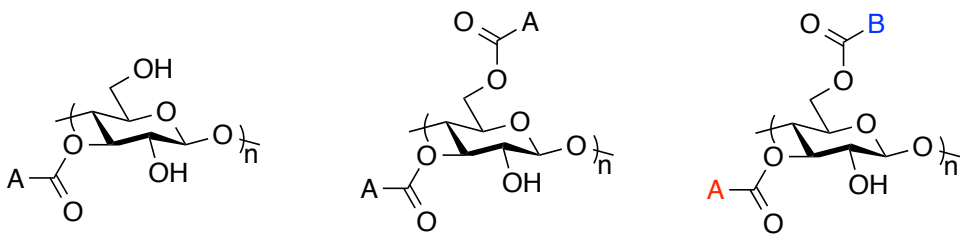



**Figure 7.2** Regioselectively substituted cellulose esters prepared from 2-levulinoyl-3-O-allyl-6-O-(4-methoxy)-trityl cellulose

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