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# Remarkably regioselective deacylation of cellulose esters using tetraalkylammonium salts of the strongly basic hydroxide ion

Xueyan Zheng[a,b], Richard D. Gandour[b], Kevin J. Edgar[a,b,c,*]

[a] Department of Sustainable Biomaterials, Virginia Tech, 230 Cheatham Hall, 310 West Campus Drive, Blacksburg, VA 24061, United States
[b] Department of Chemistry, Virginia Tech, 230 Cheatham Hall, 310 West Campus Drive, Blacksburg, VA 24061, United States
[c] Macromolecules and Interfaces Institute, Virginia Tech, 230 Cheatham Hall, 310 West Campus Drive, Blacksburg, VA 24061, United States

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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.



## 1. Introduction

It is 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 (Fox, Li, Xu, & Edgar, 2011). The availability of cellulose solvents like ionic liquids (Pinkert, Marsh, Pang, & Staiger, 2009), DMAc/LiCl (Dawsey & McCormick, 1990), and DMSO/TBAF (Kohler & Heinze, 2007) helps, but high regioselectivity by direct esterification of cellulose has so far been impossible to demonstrate, even in organic solution (Xu, Li, Tate, & Edgar, 2011). Because the direct approach does not work, previous investigators have had to resort to bulky ether protecting groups (Koschella & Klemm, 1997; Petzold, Koschella, Klemm, & Heublein, 2003) to enable selective synthesis of, in the case of ester substituents, 2, 3-diesters (Iwata, Azuma, Okamura, Muramoto, & Chun, 1992) and 2, 6-diesters (Xu, Voiges, Elder, Mischnick, & Edgar, 2012).

These protecting group routes have provided vital insight into structure–property relationships relative to regioselectivity, proving that key properties like crystallinity (Iwata, Okamura, Azuma, & Tanaka, 1996), thermal properties (Iwata, Fukushima, Okamura, & Azuma, 1997), solubility (Kondo, 1994), and optical properties (Buchanan, Buchanan, Guzman-Morales, & Wang, 2010) 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

* Corresponding author at: Department of Sustainable Biomaterials, Virginia Tech, 230 Cheatham Hall, 310 West Campus Drive, Blacksburg, VA 24061, United States. Tel.: +1 540 231 0674; fax: +1 540 231 8176.
*E-mail address:* kjedgar@vt.edu (K.J. Edgar).

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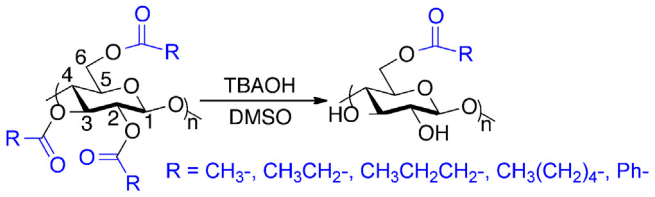
better processes for regioselective synthesis of cellulose esters in order to explore a more expansive structure–property space.

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 (Philipp et al., 1995), providing 64% regioselectivity. Other investigators reacted CTA with dimethylamine and water at 80 °C for 24 h (Wagenknecht, 1996), 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 (Xu & Edgar, 2012; Zheng, Gandour, & Edgar, 2013b). 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, with as high as 97% regioselectivity and 94% conversion at O-2/3. 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 (Hiller, 1953), hydrolysis by hydroxide ion is fast, quantitative, and irreversible (Vos, Burris, & Riley, 1966); 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 (Genung & Mallatt, 1941). 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 1).




**Scheme 1.** TBAOH deacylation of cellulose triesters in DMSO.

## 2. Experimental

### 2.1. 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.

### 2.2. Measurements

$^1H$, $^{13}C$ 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, 6000, 12,800, and 7680 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 (Liebert, Hussain, & Heinze, 2005; Xu et al., 2011). 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.

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

Dissolution of MCC in DMAc/LiCl was performed as previously described (Edgar, Arnold, Blount, Lawniczak, & Lowman, 1995). 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 (Zheng, Gandour, & Edgar, 2013a; Zheng, Gandour, & Edgar, 2013b). 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 vacuum. Yield: 80%. $DS_{Bz}$ = 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).

### 2.4. General procedure for tetraalkylammonium hydroxide deacylation of cellulose triesters

To a solution of cellulose ester in DMSO (40 mL per g of cellulose ester) 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.

### 2.5. General procedure for peracetylation or perpropionylation of deacylated cellulose esters

Deacylated products were peracetylated or perpropionylated for easier NMR analysis, according to previously published procedures (Liebert, Hussain, & Heinze, 2005; Xu et al., 2011). 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 added to 150 mL ethanol to precipitate the product. 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 FTIR spectrum (3460 $cm^{-1}$). The total and partial DS values for the peracetylated or perpropionylated products 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 $\delta$ = 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.

$$DS_{ester} = \frac{3 - 7I_{H,\text{acetyl or propionyl}}}{3I_{H,\ AGU}};\quad I = \text{Integral} \tag{1}$$

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

Subscript definition: S = starting cellulose esters, P = product

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

$$PR = \left[\frac{DS_{2+3(S)} - DS_{2+3(P)}}{DS_{\text{total (S)}} - DS_{\text{total (P)}}}\right] - \left[\frac{DS_{6(S)} - DS_{6(P)}}{DS_{\text{total (S)}} - DS_{\text{total (P)}}}\right] \tag{4}$$

## 3. Results and discussion

A previous publication from our laboratory about TBAF deacylation of cellulose esters (Xu & Edgar, 2012) 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 (Zheng, Gandour, & Edgar, 2013a), 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,

**Table 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 Section 2.
[c] Percent regioselectivity, calculated by equation 4 in Section 2.

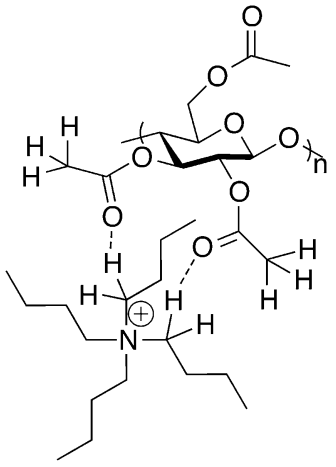


**Fig. 1.** Structure of hypothetical TBA–cellulose acetate ion–dipole complex (Zheng, Gandour, & Edgar, 2013a).

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 (Bach, Dmitrenko, & Glukhovtsev, 2001) and interactions of quaternary ammonium ions with cellobiose (Casarano, Pires, Borin, & El Seoud, 2014) (Fig. 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?

### 3.1. 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 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.

### 3.2. Impact of cation size

To help illuminate the nature of this surprisingly regioselective deacylation, the impact of cation size was evaluated (Table 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

**Table 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 Section 2.
[c] Percent regioselectivity, determined by equation 4 in Section 2.

**Table 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 24 h.
[b] Percent conversion at O-2/3, calculated by Eq. (3) in Section 2.
[c] Percent regioselectivity, determined by Eq. (4) in Section 2.

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.

### 3.3. 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 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 S1).

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. Fig. 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 $^{1}H$ (Fig. S1), COSY (Fig. S2), and HMBC (Fig. 3) experiments. The HMBC spectrum (Fig. 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.

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

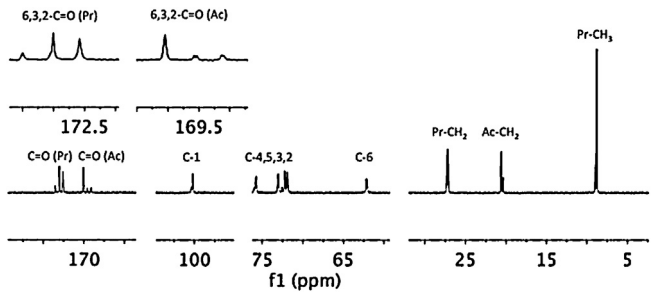



**Fig. 2.** $^{13}C$ NMR spectrum of the product of CTA deacylation by TBAOH (2 equiv., 24 h, DMSO, 50 °C), after perpropionylation.

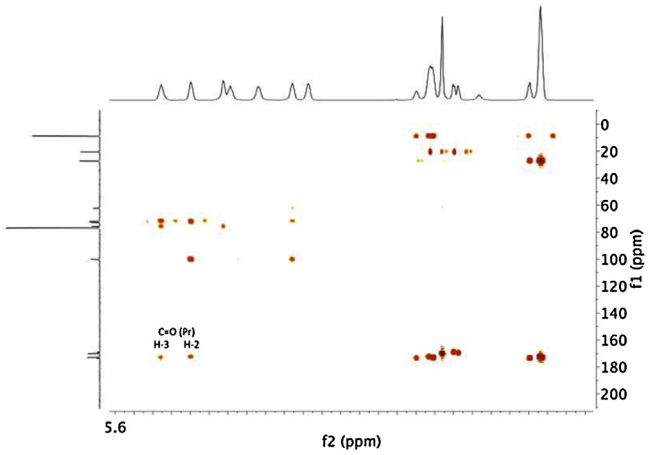



**Fig. 3.** HMBC NMR spectrum of the product of CTA deacylation by TBAOH (2 equiv., 24 h, DMSO, 50 °C), after perpropionylation.

peracetylation are shown in Figs. S3 and S4, respectively. As shown in Fig. S5, 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 groups at O-6 were retained. The proton (Fig. S6) and carbon (Fig. 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 (Fig. S7) and HMBC (Fig. S8) 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

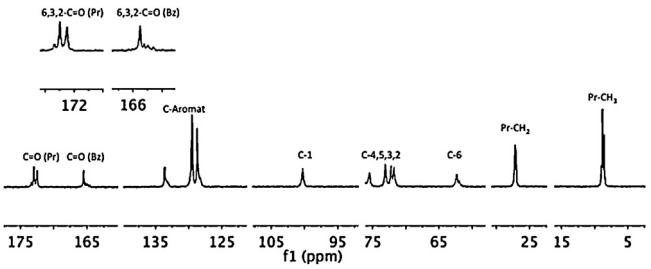



**Fig. 4.** $^{13}C$ NMR spectrum of the product of CTBz deacylation by TBAOH (2 equiv., 24 h, DMSO, 50 °C), after perpropionylation.

**Table 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 Eq. (3) in Section 2.
[c] Percent regioselectivity, determined by Eq. (4) in Section 2.

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.

### 3.4. 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 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 vs. 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.

### 3.5. 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

**Table 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 Eq. (3) in Section 2.
[c] Percent regioselectivity, determined by Eq. (4) in Section 2.

nor CA precipitation occurred in pyridine across this temperature range.

As can be seen from Table 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 (Olmstead, Margolin, & Bordwell, 1980); p$K_a$ values of the alpha hydrogens in acetate esters range from 29.5 to 30.3 (Zhang, Bordwell, Van Der Puy, & Fried, 1993). 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.

## 4. 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.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2014.04.014.

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