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

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

[a] Department of Sustainable Biomaterials, Virginia Tech, 230 Cheatham Hall, Blacksburg, VA 24061, United States
[b] Department of Chemistry, Virginia Tech, 2018 Hahn Hall South, MC 0212, Blacksburg, VA 24061, United States
[c] Macromolecules and Interfaces Institute, Virginia Tech, Blacksburg, VA 24061, United States

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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).

1. 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 commercial applications and thriving industries in cellulosic films, fibers, molded objects, and coatings (Edgar et al., 2001; Klemm, Heublein, Fink, & Bohn, 2005). 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 (Edgar, Arnold, Blount, Lawniczak, & Lowman, 1995; Kosaka et al., 2013), matrices for controlled release (Herrlich, Spieth, Messner, & Zengerle, 2012; Ilevbare, Liu, Edgar, & Taylor, 2012), and optical films (Yamaguchi, Manaf, Songsurang, & Nobukawa, 2012).

Most commercially important cellulose esters are randomly substituted, in so far as one can tell (Buchanan, Edgar, Hyatt, & Wilson, 1991) 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 (Fox, Li, Xu, & Edgar, 2011). These regioselectively substituted cellulose esters commonly have properties that differ remarkably from those of presumably randomly substituted materials, for example in 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). With our growing appreciation of the power of substitution regioselectivity to modify properties, it becomes all the more important 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, using the 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

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

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groups at O-6 (Iwata et al., 1997), 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 (Xu, Voiges, Elder, Mischnick, & Edgar, 2012). 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 (Xu & Edgar, 2012) 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) 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 (Xu & Edgar, 2012); 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 (Fig. 1).

2. Experimental

2.1. Materials

Microcrystalline cellulose (MCC, Avicel PH-101, DP = 260) and cellulose acetate (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.

2.2. 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 9400 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 (Liebert, Hussain, & Heinze, 2005; Xu, Li, Tate, & Edgar, 2011). 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.

2.3. Preparation of cellulose tributyrate

Dissolution of MCC in DMAc/LiCl was by a previously published procedure (Edgar et al., 1995). 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.

2.4. 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. Purification was carried out by re-dissolving the crude product in acetone (50 mL), and re-precipitating by slow addition to methanol (500 mL). After collecting by filtration, the sample was dried under vacuum at 50 °C overnight.

2.5. 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.

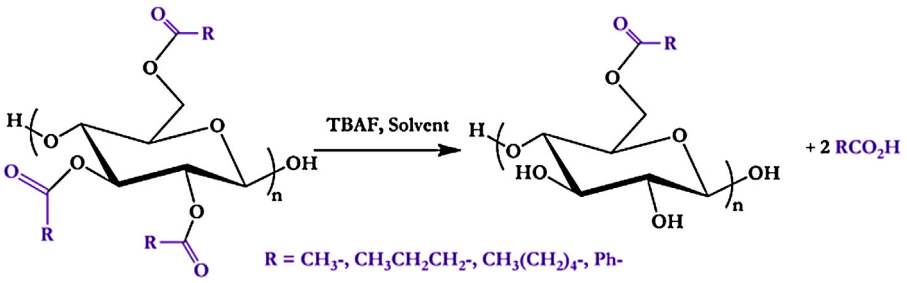

Fig. 1. TBAF-catalyzed deacylation of cellulose triesters.

2.6. 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.

2.7. General procedures for peracetylation or perpropionylation of deacylated cellulose esters

Peracetylation or perpropionylation was carried out according to previously published procedures (Liebert et al., 2005; Xu et al., 2011) 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. Further purification was carried out by re-dissolving the crude product in chloroform and re-precipitating it into ethanol. The sample was dried under vacuum for DS determination. The total and partial DS values for the peracetylated product were determined according to Eqs. (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 Eqs. (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 was determined by Eq. (5), which is the difference between the percent deacylation at O-2/3 and the percent deacylation at O-6.

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

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

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

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

$$\text{Percent regioselectivity} = \left[\frac{DS_{2+3(S)} - DS_{2+3(P)}}{DS_{total(S)} - DS_{total(P)}}\right] - \left[\frac{DS_{6(S)} - DS_{6(P)}}{DS_{total(S)} - DS_{total(P)}}\right]; \quad S = \text{Starting cellulose esters}, \quad P = \text{Product} \tag{5}$$

3. Results and discussion

3.1. Solvent effects on TBAF-catalyzed deacylation of CA

It was of interest to determine the effect of solvent on the TBAF-catalyzed deacylation of CA (DS 2.42), since solvent effects are often important in organic chemistry and can also teach us about the reaction mechanism. It would also be useful to be able to show that a variety of 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 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

Table 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 Eq. (5) in Section 2.

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 O-2/3 but not at O-6. This differs from the result in pyridine. We hypothesize that DMAc may diminish chelation of TBA with the ester groups at O-2 and O-3 by complexing with the tetrabutylammonium ion, thereby reducing the rate of deacylation at those secondary alcohol esters. These 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.

3.2. 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 1, entries 1–3) 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 1, 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 6–11 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 vicinal 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 2).

3.3. 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 (Cox, Terpinski, & Lawrynowicz, 1984). We explored this question by examining 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 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 equiv. 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.

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 could 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 S1) were regioselective for deacylation of the esters of the

Table 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 Eq. (5).

Table 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 equiv. H_2O	0.80	0.11	0.91	97
3	TBAF·$3H_2O$ + 3 equiv. H_2O	0.80	0.12	0.92	97
4	TBAF·$3H_2O$ + 10 equiv. 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 Eq. (5).

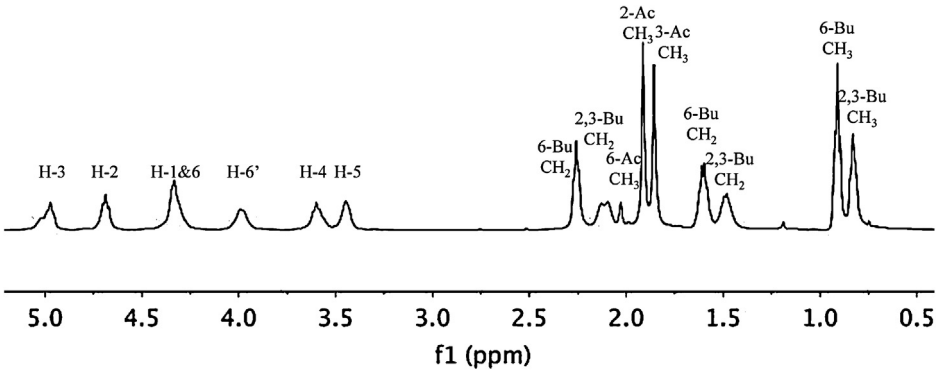

Fig. 2. ^{1}H NMR spectrum of the product of CTB deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

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. Fig. 2 shows the ^{1}H NMR spectrum of the peracetylated product from TBAF deacylation of CTB (24 h, DMSO, 50 °C). Proton signals have been completely assigned based on COSY (Fig. S1) and HMBC (Fig. 3) experiments. As shown in Fig. 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 in and of itself; we find that it is often difficult to observe HMBC correlation peaks between the diastereotopic C-6 protons and the 6-ester carbonyl carbon).

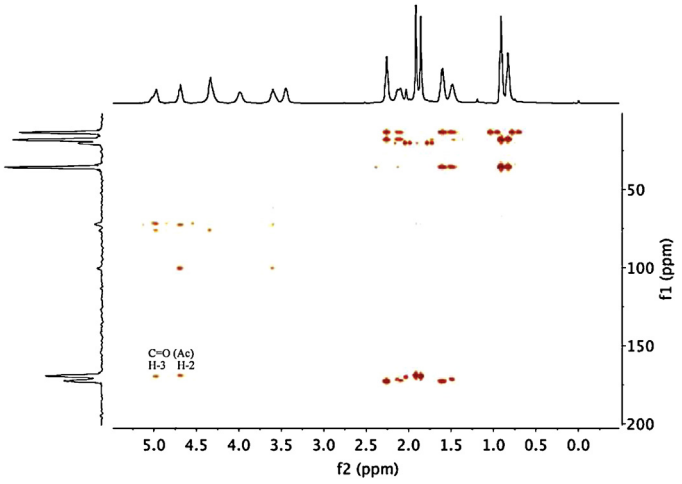

Fig. 3. HMBC spectrum of the product of CTB deacylation by TBAF (24 h, DMSO, 50 °C), after peracetylation.

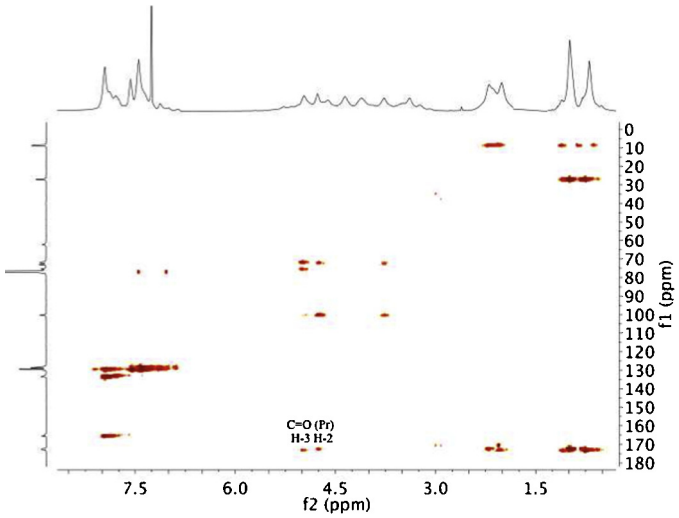

Fig. 4. HMBC spectrum of the product of CTBz deacylation by TBAF (24 h, DMSO, 50 °C), after perpropionylation.

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 the large TBA cation 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–c) with a degree of regioselectivity rivaling that achieved for cellulose acetate (entries 1a–c). 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 (Fig. S5) and carbon (Fig. S6) signals of the perpropionylated product from TBAF deacylation of CTBz (24 h, DMSO, 50 °C) have been completely assigned based on COSY (Fig. S7) and HMBC (Fig. 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 (Fig. 4), which is consistent with no deacylation at O-6. Partial DS(Bz) values at each position were determined by difference, using the same methodology as that used with cellulose hexanoate.

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.

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. It is likely that pyridine accelerates general base-catalyzed deacylation at O-6; while DMAc may compete for TBA and thus inhibit the chelation-driven deacylation at O-2/3. 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 equiv./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.

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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.2013.06.010.

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