

Co-Solvent Facilitated *in situ* Esterification of Cellulose in 1-Ethyl-3-Methylimidazolium Acetate

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The homogeneous conversion of cellulose to cellulose propionate with propionic acid anhydride in the ionic liquid 1-ethyl-3-methylimidazolium acetate and two different co-solvents, dimethyl sulfoxide and 1-methylimidazole, was studied. The software MODDE was used to generate an experimental design and evaluate the significance of the studied parameters. The methods ^1H and ^{13}C nuclear magnetic resonance (NMR) spectrometry and ion chromatography were used to analyze the obtained materials both qualitatively and quantitatively. The NMR spectrometry of dissolved cellulose esters confirmed there was covalent bonding with an even distribution pattern. From both ion chromatography and NMR spectroscopic data, it was concluded that by adding large amounts of co-solvent and using a high reagent-to-anhydroglucose unit ratio, it was possible to reduce the amount of acetylation caused by acetate anions in the ionic liquid. At the same time, it was shown that the reaction time and temperature was not at all significant in this respect. There was no notable difference detected in the degree of substitution between the reactions performed using dimethyl sulfoxide or 1-methylimidazole as a co-solvent.

Keywords: Ionic liquid; Cellulose derivatization; Esterification; Design of Experiment; Co-solvent

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INTRODUCTION

In the last decade, the increasing interest in organic salt melts, commonly referred to as ionic liquids (IL), has played a large role in research on cellulose processing. Though the concept of molten salts as solvents for cellulose was investigated in the 1930s (Graenacher 1934; Graenacher and Sallman 1939) and the 1960s (Husemann and Siefert 1969), the first widely successful IL in this field was 1-butyl-3-methylimidazolium chloride (BMIMCl). This was considered the breakthrough solvent and is still widely used today (Swatloski *et al.* 2002). Ionic liquids can be used for dissolving cellulose, and also as media in cellulose derivatization (Heinze *et al.* 2008; Zhang *et al.* 2015). Again, BMIMCl has proven to be a successful solvent in this case, which for the first time has allowed the large-scale homogeneous acylation of cellulose with different anhydrides and chlorides, as well as carbanilation with good yields (Heinze *et al.* 2005; Barthel and Heinze 2006; Kohler *et al.* 2007). Cellulose fatty esters have also been successfully synthesized in BMIMCl (Singh *et al.* 2015).

Another closely related IL, 1-ethyl-3-methylimidazolium acetate ([EMIm][OAc]), soon proved advantageous as a complementary solvent to BMIMCl. It has a lower melting point, lower viscosity, and it is even liquid at room temperature. Furthermore, [EMIm][OAc] is less toxic than BMIMCl and most importantly displays a superior dissolution power (Kohler *et al.* 2007). These features make it a desirable solvent for

dissolution as well as homogeneous chemical functionalization of cellulose, with an even distribution of substituents along the cellulose chain as well as within each anhydroglucose unit (AGU). However, it has been shown that [EMIm][OAc] is not an inert solvent, but actually reacts with cellulose in some cases. It has been reported that when cellulose, dissolved in [EMIm][OAc], is allowed to react with furoyl-, tosyl-, and trityl- chloride as well as SO_3 -complexes, the result is not the expected esters but rather a cellulose acetate (Kohler *et al.* 2007). It is assumed that the acetate anion reacts with the derivatization agent and forms a very reactive anhydride intermediate, which ultimately is the molecular species that reacts with cellulose. The corresponding side reaction has not yet been noted in BMIMCl. Also, by chemically labeling the acetate anion, it has been possible to detect acetylation of the cellulose backbone with a degree of substitution (DS) of approximately 0.015, even without the addition of any acetylating reagent, except for the solvent itself (Karatzos *et al.* 2012). These side reactions are not always necessarily a drawback because they can be developed to discover new routes for cellulose functionalization. If the reactions are understood, they could potentially lead to a route toward well-defined cellulose derivatives (Gericke *et al.* 2012). However, obvious drawbacks that can never be ignored include an uncertainty in the acylation pattern, problems in the production of pure esters, and the inevitable loss of solvent as the acetate is consumed in the acetylation reaction. In this case, this means that complete recycling of the solvent is not possible. To reduce or potentially avoid these problems, an alternative approach that includes large amounts of a co-solvent is proposed in this study. There are three main advantages to using co-solvents in homogeneous cellulose derivatization in ILs. First, co-solvents lower the viscosity of the solution, which facilitates mixing and mass transfer. Second, in the specific case of using [EMIm][OAc] as a solvent, the addition of large amounts of a co-solvent reduces the amount of acetate ions available for cellulose acetylation as the side reaction. Third, in some cases, secondary solvents are actually required for a successful reaction to take place at all (Kohler *et al.* 2008).

In this project, the aim was to evaluate the effect of co-solvents on the acylation of cellulose in [EMIm][OAc]. It has been shown that this can produce cellulose acetate instead of the intended ester, and by adding co-solvents in large amounts, the hypothesis is that this can be circumvented or at least diminished. Two different co-solvents were used, dimethyl sulfoxide (DMSO) and 1-methylimidazole (MIM). DMSO is a well-known co-solvent for cellulose and has been used in homogeneous derivatization, *e.g.*, in combination with tetrabutylammonium fluoride (Ass *et al.* 2004; Ramos *et al.* 2005) or ILs (Liu *et al.* 2006). The co-solvent MIM has many interesting properties and has been reported to act as a catalyst in cellulose chemistry (Kohler *et al.* 2008).

EXPERIMENTAL

The homogeneous acylation of cellulose in mixtures of IL and co-solvents was performed according to an experimental plan designed using the software MODDE 9.0 (Umetrics, Umea, Sweden). The design parameters were the reaction time (t), reaction temperature (T), the molar ratio of the reagent to AGU (rr), and the solvent composition (% IL), as shown in Table 1. The experiments were performed equally for the two co-solvents, MIM and DMSO, in a total of 18 samples. In addition, three replicate samples using DMSO as the co-solvent were performed. The results of the experimental work were evaluated in MODDE and a Multiple Linear Regression (MLR) was carried out.

Table 1. Parameters and their Quantities in the Experimental Design

Time (min)	Temperature (°C)	Reagent: AGU (mol/mol)	Solvent Composition (% IL)
5	30	3	10
30	50	5	50
60	70	10	100

Materials

Microcrystalline cellulose (MCC, Avicel PH101, M_w = 53470, M_n = 24235) (FMC biopolymers, Cork, Ireland) was dried at 60 °C overnight and then stored in a desiccator until use. Sigma Aldrich (Saint Louis, USA) provided the reagents 1-methylimidazole (99%), propionic anhydride (> 99%) and dimethyl sulfoxide ($\geq$ 99.5%). BASF (Ludwigshafen, Germany) provided 1-ethyl-3-methylimidazolium acetate ($\geq$ 90%, LOT STBC9122V). All chemicals were stored dry and used without further purification. The Karl Fisher titration method detected only a very small amount of water (< 0.3%) in the ionic liquid. DMSO- d_6 , DMF- d_7 , and CDCl₃ were purchased from ARMAR chemicals (Döttingen, Switzerland) in ampoules and used immediately after opening.

Methods

Dissolution of cellulose and synthesis of cellulose esters

The microcrystalline cellulose (1.0 g) was dispersed in mixtures of [EMIm][OAc] and the co-solvent at room temperature and then stirred until dissolved at 30, 50, or 70 °C to produce 10 wt.% solutions that were visually clear and without any remaining particles.

Propionic anhydride was added to the clear cellulose solutions in amounts according to the experimental design. The reaction was allowed to proceed for 5, 30, or 60 min before it was quenched by adding the reaction mixture to 200 mL of methanol. The product was then separated by filtration, washed, and finally dialyzed against deionized water for 10 days before lyophilization (freeze-drying) and analysis.

Analysis of cellulose esters

The ¹H and ¹³C NMR spectra of the cellulose esters were recorded in DMSO- d_6 , DMF- d_7 , or CDCl₃ (20 mg/mL) depending on the DS, with a Varian 400-MR spectrometer (Oxford, UK) running at 400 MHz at room temperature using 32 scans. The cellulose derivatives were further hydrolyzed in 72% H₂SO₄ according to a procedure based on previous literature (Theander and Westerlund 1986). The hydrolysates were analyzed for anions, and quantified using acetate and propionate standards (Sigma Aldrich, Saint Louis, USA) by ion chromatography (IC) in aqueous Na₂CO₃ (3.6 mM) at 45 °C on a Metrohm 850 Professional IC Anion MCS (Herisau, Switzerland), equipped with a Metrosep A Supp 7 column, and using MagIC Net 3.0 software (Herisau, Switzerland).

RESULTS AND DISCUSSION

The homogeneous reactions of the cellulose with the propionic acid anhydride in [EMIm][OAc] with and without a co-solvent were studied and the degree of propionate over acetate substitution was calculated after the ion chromatography of hydrolyzed

products. A multiple linear regression was calculated on the accumulated results for both DMSO and MIM to predict the propionate degree of substitution (DS_{prop}) as a function of the parameters listed in Table 1. It was found that the amount of co-solvent significantly predicted the value of DS_{prop} ($\beta = -0.168$, $p = 4.08 \times 10^{-6}$), as did the reagent ratio ($\beta = 0.0926$, $p = 1.62 \times 10^{-3}$). Time or temperature were not significant. The overall model fit was $R^2 = 0.879$, with $F(2,16) = 29.05$, $p < 0.000$. As expected, this means that by increasing the amount of the propionic anhydride reagent the resulting product will have a higher propionate DS. Furthermore, and more importantly, it shows that a decreased relative amount of IL, *i.e.*, an increased relative amount of co-solvent, also yields a higher propionate DS, and thus plays an important role.

Fig. 1 shows the DS of propionate, relative to the DS of acetate, in the hydrolyzed products, as quantified by IC, for both the sample series with DMSO and that with MIM as the co-solvent. It indicates that for samples without a co-solvent (% IL = 100), all samples showed low propionate contents. For the samples with 50% IL, the results were more varied, but still very low in propionate content. For the samples prepared in 10 mol% [EMIm][OAc] and 90 mol% co-solvent (% IL = 10), the propionate content was higher. There is also a wide distribution in the propionate:acetate ratio, which is directly linked to the amount of propionate anhydride added in the reaction, expressed as the molar ratio anhydride per anhydroglucose unit AGU ($rr = 10$, $rr = 5$, or $rr = 3$). This shows, again, the positive correlation for the amount of reagent and the negative correlation for the amount of [EMIm][OAc].

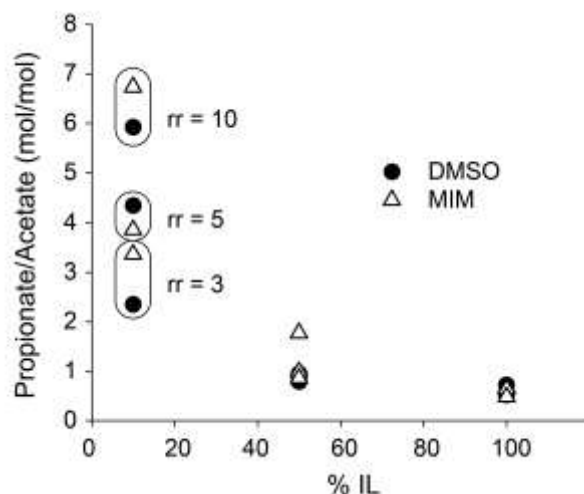


Fig. 1. Amounts of propionate, relative to acetate, in cellulose derivatives produced in either [EMIm][OAc]/DMSO or [EMIm][OAc]/MIM, with the % IL in the solvent being 10%, 50%, and 100%

The DS followed the same trend as noted in Fig. 1. This might be related to the lower solution viscosity, which will contribute to higher mass transfer rates in the reaction mixture. The co-solvent MIM is known to catalyze some reactions. For the trimethylsilylation of cellulose in imidazolium based ionic liquids, it was found that the amount of MIM, which is a starting molecule for the synthesis of the solvent, had an impact on the degree of substitution in the final product (Kohler *et al.* 2008). Furthermore, in DMAc/LiCl, the esterification of cellulose by carboxylic acid anhydrides is efficiently catalyzed by imidazole (Nawaz *et al.* 2013). Thus, it seems that MIM (and its analogues)

can have an impact on different kinds of cellulose derivatization routes. In Fig. 1, there seems to be no difference when using DMSO or MIM as the co-solvent in this case, which to some degree seems surprising. However, it must be emphasized that a crude quality of [EMIm][OAc] was used in these experiments, which is known to contain some trace of MIM. Therefore, the potential catalytic effect of MIM might in this case be noticed even in the case where no extra MIM is added.

The cellulose acetate propionate samples were dissolved in their appropriate deuterated solvents, and the NMR spectra were recorded. In the ^1H NMR spectrometry, the propionate and acetate signals can be readily separated. Well-resolved NMR spectrometry can often be utilized to follow derivatization patterns, *e.g.*, preferences of acetylation/propionation on the different hydroxyl groups. Fig. 2 shows three samples, from a highly substituted cellulose propionate (Fig. 2a) to a very low amount of propionate compared to acetate (Fig. 2c). The peak integrals fully coincide with the results from the ion chromatography.

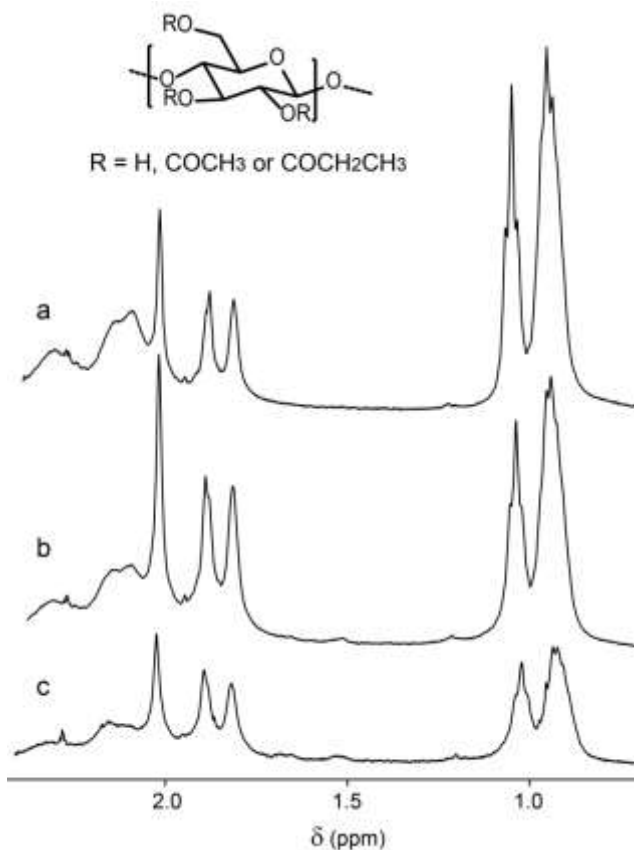


Fig. 2. The ^1H NMR spectra of cellulose acetate propionate prepared with a propionic anhydride to AGU ratio (rr) of 10 in a binary solvent of [EMIm][OAc] and DMSO comprising: a) 10% IL, b) 50% IL, and c) 100% IL

The peaks in the cropped NMR spectra in Fig. 2 originate from the overlapping propionate CH_2 signals ($\delta \approx 2.2$ to 2.4 ppm), the acetate CH_3 signals ($\delta \approx 2.1$ to 1.8 ppm), and finally the overlapping propionate CH_3 signals ($\delta \approx 1.1$ to 0.8 ppm) (Cheng *et al.* 2011). The acetate CH_3 has three peaks, originating from the C6, C2, and C3 site on the glucose unit, respectively, which confirm covalent bonding. Both the propionate CH_3 and the

propionate CH₂, however, only display two peaks because of the overlap between the C2 and C3 site signals.

The ¹³C NMR spectrometry was able to resolve the propionate peaks and confirm an even distribution on C6, C2, and C3, as shown in the ¹³C NMR spectrum in Fig. 3.

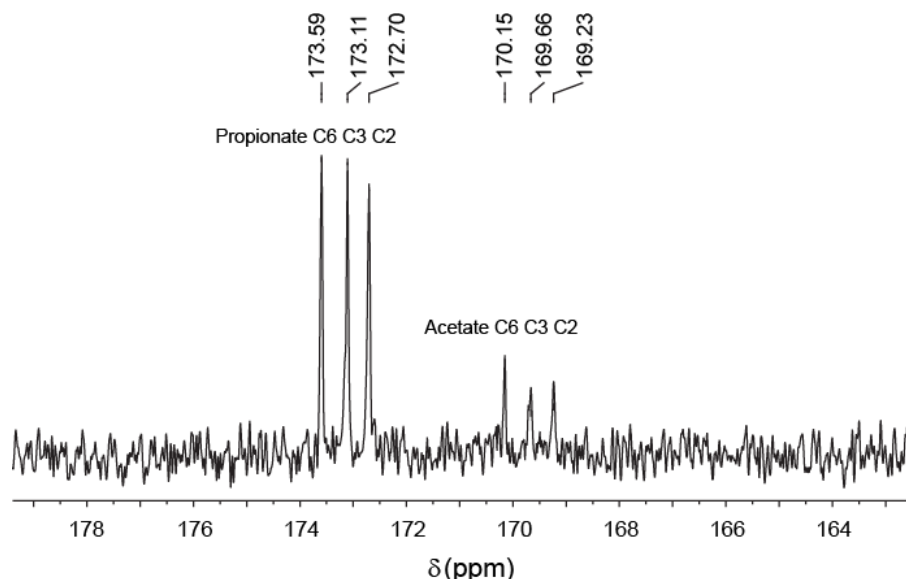


Fig. 3. ¹³C NMR spectrum of cellulose acetate propionate prepared in 10% [EMIm][OAc], *rr*= 5

The proposed mechanistic steps for the reactions leading to the cellulose acetate propionate product are depicted in Fig. 4. First, a reaction is proposed between some of the acetate in the IL with propionic anhydride, forming an asymmetric propionic acetic anhydride, and second the reaction is proposed between any anhydride and cellulose, forming the corresponding cellulose ester.

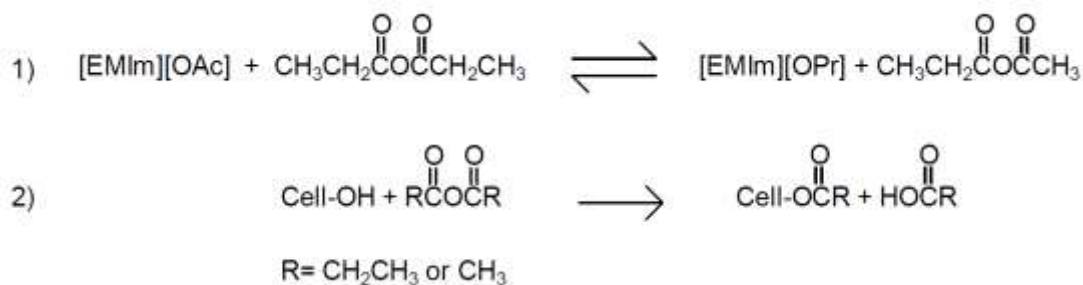


Fig. 4. Proposed reactions for (1) formation of an asymmetric anhydride and (2) esterification of cellulose

CONCLUSIONS

1. The amount of co-solvent (DMSO or MIM) and the amount of reagent turned out to be significant parameters ($p < 0.01$) for diminishing acetylation, while the time and the temperature of the reaction were not. A low amount of IL and a high amount of reagent gave the highest propionyl:acetyl ratio, *i.e.*, the targeted ester and very little unwanted acetylation.

2. The ^1H and ^{13}C NMR spectrometry of the dissolved polymer confirmed the presence of covalent bonding with an even distribution pattern, as well as the trend already established by IC. In no case was acetylation fully avoided.
3. There was no notable difference detected in the degree of substitution between the reactions performed using dimethyl sulfoxide or 1-methylimidazole as a co-solvent.

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