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Cellulose Etherification with Glycidol for Aqueous Rheology Modification

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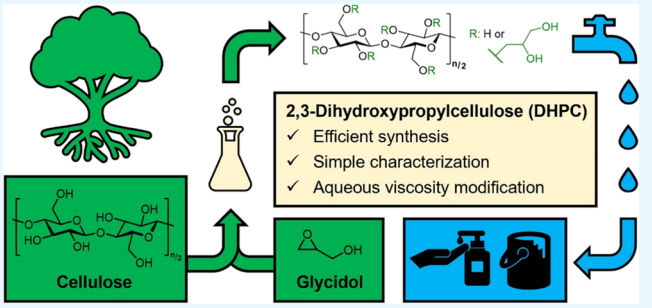
ABSTRACT: Cellulose ethers are an important class of cellulose derivatives extensively used as rheology modifiers in aqueous applications ranging from personal care products and pharmaceuticals to paints and construction materials. 2,3-Dihydroxypropylcellulose (DHPC) is a water-soluble cellulose ether that can be derived from the reaction of cellulose and glycidol in a process that is less hazardous than other cellulose ether syntheses, which use volatile compounds under regulatory scrutiny such as methyl chloride and ethylene oxide. In the present work, the synthesis of DHPC was investigated using cellulose and glycidol under heterogeneous slurry conditions. Cellulose was activated in an organic solvent spiked with aqueous sodium hydroxide and then reacted with glycidol at near-ambient temperatures (30−40 °C) for short reaction times (1−4 h). The products were isolated by filtration and characterized by a variety of commonly available tools including NMR spectroscopy, size-exclusion chromatography, turbidimetry, and rheology. The reaction was optimized to afford a product with good solubility and viscosity in water with minimal input of NaOH and glycidol. Several reaction parameters were investigated including time and temperature, solvent identity and composition, and reagent loading and concentration. While past studies on cellulose etherification have identified some key process parameters, this report leverages modern high-sensitivity instrumentation to develop relationships between the process, chemical structure, and performance. DHPC with moderate levels of substitution by glycidol (molar substitution between 1.0 and 2.0) gave the best balance of solubility and viscosity enhancement. Overall, this work demonstrates that a high-quality cellulose ether can be obtained in mild conditions and high yield without the need for operationally costly procedures such as precipitation or dialysis.



KEYWORDS: *cellulose ether, water solubility, viscosity modification, heterogeneous slurry, glycidol*

1. INTRODUCTION

Lignocellulosic biomass is considered a sustainable natural resource that can support many industries through its structural diversity and widespread availability.[1] The major component of lignocellulosic biomass is cellulose, which is the most abundant polymer in the world and is used as a feedstock in the production of value-added materials such as regenerated cellulose fibers (e.g., Rayon) and cellulose derivatives (e.g., cellulose acetate).[2] Cellulose ethers are an important class of cellulose derivatives and can be produced by modifying the hydroxy groups of the cellulose monomer (the anhydroglucose unit, or AGU) with pendant groups through etherification reactions. Commercially available cellulose ethers tend to be water-soluble products that are used as viscosity modifiers in aqueous applications ranging from food products and paints to personal care products and construction materials.[3] The extent of functionalization can vary significantly within a particular chemistry, leading to dramatic changes in properties like solubility and viscosity.[4] The majority of cellulose ethers are produced via a heterogeneous slurry process that has been the industry standard for decades due to its low cost and reliability.[4,5] This process starts with swelling and activation of semicrystalline cellulose fibers with aqueous NaOH and an organic solvent at high cellulose loading, leading to a heterogeneous slurry that can be reacted with electrophiles such as methyl halides (methylcellulose, MC), sodium chloroacetate (carboxymethylcellulose, CMC), ethylene oxide (hydroxyethyl cellulose, HEC), propylene oxide (hydroxypropyl cellulose, HPC), and sometimes combinations of these reagents. Cellulose etherification is often performed in homogeneous conditions in academic settings, which allows for more control over the reaction compared to the industrially preferred heterogeneous slurry process.[6] Homogeneous

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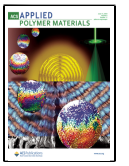

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modification has become increasingly popular due to the development of readily available cellulose solvents such as ionic liquids, concentrated NaOH/urea/water solutions, and mixtures of dimethylacetamide and lithium chloride.[7−10] However, homogeneous methods often require rigorous conditions for cellulose dissolution and reaction, tedious precipitation and purification steps, and expensive reagents. In addition, cellulose loadings must be kept low due to the high viscosity of dissolved cellulose solutions, which leads to processing difficulties at scale. These challenges translate to significant energy and material requirements that are unsustainable, making homogeneous methods difficult for industry to adopt when the infrastructure for reliable heterogeneous methods already exists.

2,3-Dihydroxypropylcellulose (DHPC) can be prepared by the reaction of cellulose with 1-chloro-2,3-propanediol (CPD) or 2,3-epoxy-1-propanol (glycidol).[11] Glycidol is an attractive reagent due to its significantly lower volatility (BP 167 °C) compared to other common epoxides in the cellulose etherification literature such as propylene oxide (BP 34 °C) and ethylene oxide (BP 11 °C), which are under increased regulatory scrutiny due to their toxicity.[12−14] Additionally, glycidol can be synthesized from biomass through glycerol, which is an abundant byproduct of biodiesel production.[15−17] Unlike CPD, glycidol does not generate a chloride salt upon reaction, which allows for lower NaOH loadings and generally milder conditions for corrosion-sensitive reactors, as well as easier purification after the reaction. The first known synthesis of DHPC was mentioned in a 1940 publication, followed by a more descriptive report in 1959 and two patents in the 1970s.[18−21] DHPC synthesis has since been the subject of several academic papers, both in heterogeneous and homogeneous reaction systems.[11,22−27] A notable report from 1992 compared the properties of DHPC synthesized in homogeneous and heterogeneous conditions and found that solubility was enhanced but viscosity was lowered in homogeneous reactions.[28] These analyses provided initial demonstration of DHPC synthesis and properties but did not adequately discuss the importance of the critical reaction parameters on the physicochemical properties of the product.

We hypothesized that precise control over the functionalization of cellulose with glycidol could lead to efficient synthesis of a product with high solubility and viscosity in water with more benign reactants. To this end, we performed systematic studies of the important reaction parameters in industrially relevant heterogeneous conditions and optimized the reaction using the principles of green chemistry as a guide.[29] These experiments showed that the levels of NaOH, water, and glycidol must be precisely controlled to achieve a more sustainable DHPC synthesis and that a moderately polar organic solvent (or mixtures of solvents) can minimize byproduct formation and maximize atom economy. This work also showed that under-functionalized DHPC has low solubility and low viscosity in water, while over-functionalized DHPC has good solubility but similarly poor viscosity. Moderate levels of functionalization (at least one and no more than two glycidol units per AGU) resulted in the desired properties of high solubility and high viscosity and could be accessed with high yields, mild reaction conditions, and efficient use of reagents.

Herein, analytical methods have also been developed for DHPC characterization, including optimized NMR spectroscopy techniques for determining the level of glycidol substitution across the cellulose backbone. We complemented these NMR methods with other tools like powder X-ray diffraction (PXRD), size-exclusion chromatography (SEC), turbidimetry, and rheology to highlight the interplay of process, structure, and properties. The insights gained in this work offer an optimized synthesis of DHPC with benign and abundant solvents, a short reaction time and low temperature, and minimal loadings of NaOH and glycidol. The methods and trends highlighted in this work can be generalized to other cellulose derivatives and provide a starting point for future research and development of cellulosic materials with greener syntheses, tunable properties, and accurate characterization methods for use in a variety of aqueous applications.

2. EXPERIMENTAL SECTION

2.1. Materials. Microcrystalline cellulose (MCC, 93%) was purchased from Sigma-Aldrich. High-molecular-weight cellulose-dissolving pulp from wood (GP, 94%) was purchased from GP Cellulose. Isopropyl alcohol (IPA), acetone, ethanol, acetic acid, *tert*-butanol (*t*-BuOH), 2-methyl-2-butanol (2-Me-2-BuOH), 2-methyl-2-pentanol (2-Me-2-PeOH), 2-butanol (2-BuOH), 2-pentanol (2-PeOH), methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), dimethyl sulfoxide (DMSO), dimethylacetamide (DMAc), and acetonitrile (MeCN) were purchased from commercial suppliers and used without further purification. Pyridine (Sigma-Aldrich, 99%), dimethylaminopyridine (DMAP, Oakwood Chemical, 98%), D_2O (Cambridge, 99.9%), glycidol (Sigma-Aldrich, 96%), propionic anhydride (Sigma-Aldrich, 99%), acetic anhydride (Sigma-Aldrich, 98%), $NaNO_3$ (Sigma-Aldrich, 99%), and NaN_3 (RPI, 99%) were used without further purification. NaOH was purchased from Sigma-Aldrich as a 50 wt % solution in water and diluted to 40 wt % prior to use. NaOD was purchased from Sigma-Aldrich as a 40 wt % solution in D_2O and was diluted to 2 wt % in D_2O prior to use. Grade 1 qualitative cellulose filter paper (11 μm pore size) was purchased from Whatman and 0.45 μm nylon syringe filters were purchased from Fisher Scientific.

2.2. Synthesis. *2.2.1. Synthesis of 2,3-Dihydroxypropylcellulose (DHPC).* DHPC was synthesized under heterogeneous slurry conditions (see Figure 1 for an illustration) with NaOH as the catalyst and glycidol as the reactant in a variety of organic solvents (IPA, 2-BuOH, 2-PeOH, acetone, MEK, MIBK, ethanol, DMSO, *t*-BuOH, 2-Me-2-BuOH, 2-Me-2-PeOH). In a representative synthesis, a 40 mL scintillation vial was charged with a stir bar, 1.0 g of cellulose, 15 mL of acetone, and 0.70 mL of water. This mixture was stirred under N_2 at 20 °C for 10 min and then 0.81 mL of aqueous NaOH

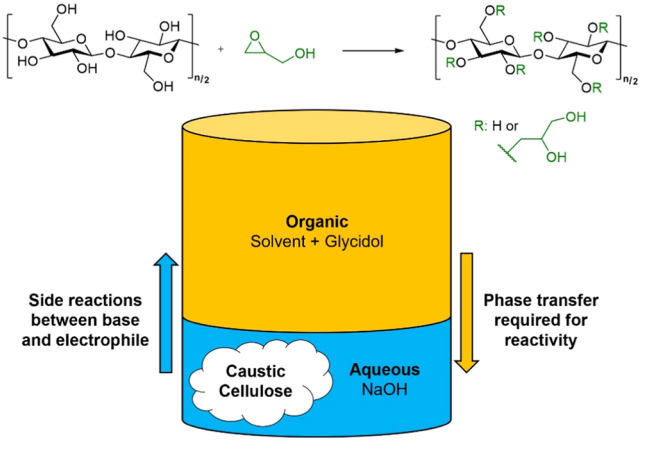

Figure 1. Top: General scheme for DHPC synthesis from cellulose and glycidol with unspecified level of substitution. Bottom: Illustration showing the three-phase slurry and the consequences of reagent transfer between phases.

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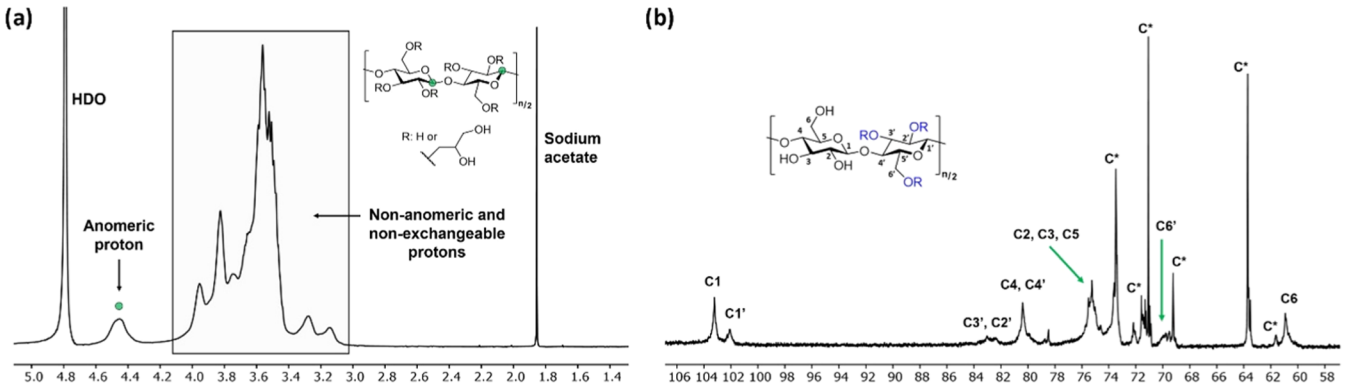

Figure 2. (a) ^{1}H NMR of a representative DHPC sample in D_2O + 2.0 wt % NaOD, where the anomeric proton is highlighted by the green circle. (b) ^{13}C NMR of a representative DHPC sample on a Bruker 850-MHz Avance III spectrometer equipped with a 5 mm triple resonance cryoprobe. CX (C1 = carbon 1, C2 = carbon 2, etc.) represents carbons of the AGU that have no substituents on their adjacent hydroxy group, and CX′ represents carbons that have at least one substituent attached to their adjacent hydroxy group. C* represents carbons of the glycidol appendages that are not included in the calculation.

(40 wt %) was added dropwise over 60 s. Upon introduction of NaOH, the reaction mixture formed three distinct phases consisting of the organic solvent, aqueous NaOH, and solid cellulose undergoing mercerization. The stirring speed was increased to the point that phase separation was not visible and the system became an off-white free-flowing suspension. After continuous stirring for 20 min, 1.6 mL of glycidol was added and the mixture was heated to 40 °C. After 4 h of reaction at 40 °C, the mixture was cooled to room temperature, opened to air, and diluted with 10 mL of ethanol. 1.6 mL of aqueous acetic acid (50 wt %) was added and stirred for 15 min to fully neutralize the remaining base. The reactions were conducted under a N_2 atmosphere to limit oxygen-mediated degradation of cellulose which is possible under elevated temperatures and highly basic conditions. The DHPC product was collected by filtration and washed with 20 mL of ethanol/water in the following volume ratios: 70:30, 80:20, 90:10, 100:0. Finally, the washed DHPC was rinsed with pure acetone and dried at 50 °C in a vacuum oven overnight to afford a free-flowing off-white powder.

2.2.2. Per-Acetylation of DHPC with Acetic Anhydride. In a typical synthesis, a 40 mL scintillation vial was charged with a stir bar, 0.50 g of DHPC (2.0 mmol, 1.0 equiv), 15 mL of acetonitrile, 0.92 mL of pyridine (9.9 mmol, 5.0 equiv), and 1.9 mL of acetic anhydride (20 mmol, 10 equiv). This mixture was stirred under N_2 at 20 °C for 5 min and then heated to 70 °C and held overnight. After 18 h, the mixture was cooled to room temperature and precipitated in 400 mL of a 50:50 (by volume) mixture of ethanol and water. An off-white solid was collected by filtration and washed with 20 mL of ethanol twice and 20 mL of isopropanol twice. The acetylated DHPC was transferred to a glass vial and then dried at 50 °C in a vacuum oven overnight to afford a crispy white powder. The reaction is conducted at lower temperature than the previously published method (70 vs 100 °C) and substitutes acetonitrile for DMAc, which is the preferred solvent according to the CHEM21 solvent selection guide. In addition, pyridine is substituted for DMAP, which is considered less acutely toxic according to the European Chemical Health Agency (ECHA). The ECHA ranks DMAP as a class 2 hazard (fatal) for dermal exposure and a class 3 hazard (toxic) for inhalation and ingestion, while pyridine is ranked as a class 4 hazard (harmful) for all three routes of exposure.[30]

2.3. Characterization. *2.3.1. Molar Substitution (MS) Estimation of DHPC by ^{1}H NMR.* In a typical procedure, 10 mg of DHPC was dissolved in 1.0 mL of D_2O with 2.0 wt % NaOD and mixed for at least 2 h prior to analysis via ^{1}H NMR spectroscopy (Bruker Avance III HD; 400 MHz). The spectra were referenced to the residual solvent peak and the anomeric proton (4.3−4.6 ppm) was compared to nonexchangeable protons of the rest of the polymer (3.0−4.1 ppm). A molar substitution (MS) was estimated by eq 1. The numerator represents the nonexchangeable protons added to cellulose by the introduction of glycidol, and the denominator represents the nonexchangeable protons present in glycidol. $I_{3.0-4.1}$ refers to the integration of peaks from 3.0 to 4.1 ppm and $I_{4.3-4.6}$ refers to the integration of the anomeric proton peak from 4.3 to 4.6 ppm

$$\mathrm{MS} = \frac{(I_{3.0-4.1} - 6)}{(I_{4.3-4.6}) \times 5} \tag{1}$$

2.3.2. MS Estimation of Acetylated DHPC by ^{1}H NMR. In a typical procedure, 10 mg of acetylated DHPC was dissolved in 1.0 mL of $CDCl_3$ and mixed for at least 2 h prior to analysis via ^{1}H NMR spectroscopy (Bruker Avance III HD; 400 MHz). The spectra were referenced to the residual solvent peak and the proton attached to the C2 carbon of the AGU (4.8 ppm) was compared to the methyl groups introduced by acetylation (1.8−2.2 ppm). The peak assignment for the proton on C2 was given in a previous report of propionylated DHPC.[25] MS was estimated by eq 2 where I_{Me} refers to the integration of the methyl peaks from 1.8 to 2.2 ppm and $I_{\mathrm{C2-H}}$ refers to the integration of the C2 proton at 4.8 ppm

$$\mathrm{MS} = \frac{I_{\mathrm{Me}}}{3} - (3 \times I_{\mathrm{C2-H}}) \tag{2}$$

2.3.3. Degree of Substitution (DS) Estimation by ^{13}C NMR. In a typical procedure, 60 mg of dried sample was dissolved in 1.0 mL of DMSO-d_6 and mixed overnight at room temperature prior to analysis via ^{13}C NMR spectroscopy (Bruker Avance II; 850 MHz) at 60 °C with an inverse-gated pulse sequence, 5000 scans, and a relaxation delay (d1) of 2 s. We did not find significant differences in MS or DS by lengthening the relaxation delay (d1), despite the expected differences in relaxation time between core glucan protons and external protons introduced by glycidol. Elevated temperatures can enhance relaxation rates which lead to a lower dispersion of relaxation times between chemically distinct fragments.[31] The peak assignments used to calculate the degree of substitution (DS) in eq 3 were given in a previous report of DHPC synthesis.[25] The carbons are numbered according to Figure 2 with C1 referring to carbon number one where the adjacent hydroxy group is unsubstituted by glycidol, and C1′ referring to carbon number one where the adjacent hydroxy group is substituted. In eq 3, I_{C1} refers to the integration for C1. The other carbons follow the same format as C1 and C1′

$$\begin{aligned}\mathrm{DS} &= \mathrm{DS_{C2}} + \mathrm{DS_{C3}} + \mathrm{DS_{C6}} \\ &= \frac{I_{\mathrm{C1'}} + (I_{\mathrm{C2'}} + I_{\mathrm{C3'}} + I_{\mathrm{C1'}}) + (I_{\mathrm{C1}} + I_{\mathrm{C1'}} - I_{\mathrm{C6}})}{I_{\mathrm{C1}} + I_{\mathrm{C1'}}}\end{aligned} \tag{3}$$

2.3.4. Turbidity Measurement. DHPC (0.75 g) was dispersed in deionized water (23 g) at 3.0 wt % and mixed overnight at room temperature. The impurities were not accounted for when preparing

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samples, but all samples should be at least 90% pure according to NMR, SEC, and thermogravimetric analysis (TGA), which measure sodium acetate, polyglycidol, and water, respectively. The resulting mixtures were transferred to the analysis vial and gently mixed to ensure a homogeneous suspension without any bubbles. These samples were then placed in a Lovibond TL250-LW turbidimeter and turbidity values were reported in nephelometric turbidity units (NTU).

2.3.5. Viscosity Measurement. DHPC (0.75 g) was dispersed in deionized water (23 g) at 3.0 wt % and mixed overnight at room temperature. The impurities (water, polyglycidol, sodium acetate) were not accounted for when preparing samples, but all samples should be at least 90% pure by NMR, SEC, and TGA (see the Supporting Information (SI) for more information). The resulting mixtures were analyzed by a TA Instruments DHR-3 rheometer with DIN concentric cylinders configuration and a shear rate sweep between 1 and 100 rad/s at 25 °C. Viscosity values in centipoise (cP) were reported at 10 rad/s, which is within the Newtonian regime for this polymer at 3.0 wt %.

2.3.6. SEC Measurement. DHPC (4.5 mg) was dispersed in 1.5 mL of an aqueous SEC mobile phase consisting of 0.2 M $NaNO_3$ and 0.1 wt % NaN_3 and filtered through a 0.45 μm nylon syringe filter. Solutions were analyzed by aqueous size-exclusion chromatography (SEC) in an Agilent Technologies (Santa Clara, CA) 1260 Infinity system with a flow rate of 0.8 mL/min through a single Tosoh TSKgel GMPWxl column with injection volumes of 100 μL. A Wyatt HELEOS II light scattering detector (λ = 662 nm) and Optilab T-rEX refractometer (λ = 658 nm; Wyatt technologies; Santa Barbara, CA) were used as in-line light scattering and differential refractive index detectors, respectively. Astra VII software (Wyatt Technologies; Santa Barbara, CA) was used for the determination of M_n, M_w, and $Đ$ assuming a dn/dc of 0.14, which was confirmed by static light scattering on two representative DHPC samples and similar to values used previously in the literature for other cellulose ethers.[32]

2.3.7. Thermogravimetric Analysis (TGA). TGA was performed on a TA Instruments SDT Q500 in air from room temperature to 600 °C at a ramping rate of 10 °C/min.

2.3.8. Powder X-ray Diffraction (PXRD). Powder X-ray diffraction patterns were taken from powder samples using a Rigaku Smartlab SE diffractometer with a nickel-filtered Cu Kα radiation beam (40 kV, 30 mA).

2.3.9. Fourier Transform Infrared Spectroscopy (FTIR). An attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) instrument (Bruker Alpha Platinum), fitted with a diamond single-bounce crystal, was used to record FTIR spectra with 16 scans and a 4 s acquisition time.

2.3.10. Glycidol and Glycerol Partitioning Study. The portioning of glycidol and glycerol between organic and aqueous NaOH layers was determined using three ketone solvents: acetone, MEK, and MIBK. In the partitioning measurement, the concentration of each component (water, NaOH, ketone, glycidol, and glycerol) was set as close as possible to those in the DHPC synthesis conditions outlined in Table 2. The weight ratio of water to organic solvent was 10:90. The molar ratios of water to NaOH to glycidol and water to NaOH to glycerol were 12:1.5:4 and 12:1.5:2, respectively. In a typical procedure, 1.2 g of 22 wt % aqueous NaOH solution was mixed with 10.8 g of organic solvent. To this mixture, 1.2 mL of glycidol or 0.6 mL of glycerol was added at once, and the resultant mixture was then vigorously shaken by hand for 1 min to facilitate partitioning. After shaking, the mixture was left to sit undisturbed for a short time until the emulsion disappeared. Subsequently, 0.1 mL of the organic layer containing the partitioned glycidol or glycerol was carefully decanted and mixed with 0.9 mL of an NMR solvent consisting of D_2O with 1 wt % phenol as a standard. Before transferring this mixture into an NMR tube, it was thoroughly shaken by hand. Finally, the ^{1}H NMR spectrum was measured to calculate the glycidol/glycerol partitioning in the organic layer. Throughout the experiment, every step following the addition of glycidol to the bilayer solvent was conducted as quickly as possible to minimize epoxide ring-opening reactions of glycidol.

3. RESULTS AND DISCUSSION

3.1. Synthesis of 2,3-Dihydroxypropylcellulose (DHPC). Understanding the important process parameters in the synthesis of DHPC is the first step toward designing reactions with higher efficiency and better product properties. The first phase of classic heterogeneous etherification of cellulose is called mercerization, during which the cellulose is suspended in a moderately polar organic solvent and reacted with NaOH (aq).[5] This caustic solution does not dissolve the polymer but instead activates the crystalline domains through swelling and deprotonates the hydroxy groups of cellulose for subsequent reactions.[33,34] In the second step, the activated (mercerized) cellulose is reacted with an electrophile at elevated temperature, followed by neutralization with acid and washing with mixtures of organic solvents and water.[5,20]

In this work, microcrystalline cellulose (MCC) and acetone were selected as the cellulose starting material and organic solvent, respectively, due to their low price and frequent use in the literature. Glycidol was selected as the reactant due to its low volatility, biobased synthesis routes, and polar hydroxy group, which should give the final product good solubility in water. Similar to the synthesis of HEC from ethylene oxide and HPC from propylene oxide, DHPC synthesis is complicated by side reactions including self-oligomerization and solvolysis of the epoxide.[35] Figure 1 depicts a simplified reaction scheme and illustration of the heterogeneous slurry process that consists of solid cellulose surrounded by caustic water, and an organic phase that contains most of the glycidol. The phase transfer of glycidol into the aqueous phase is an equilibrium process, and some glycidol will always be present in both phases. As the reaction progresses, glycidol is depleted from the reactive aqueous phase that drives more glycidol into the aqueous phase from the organic phase. The reaction scheme in Figure 1 shows two AGUs of cellulose to differentiate it from other glucose-based polymers, but all molar equivalences in this work are referenced to a single AGU.

The parameters of the initial reactions were based on the previously published patent literature for DHPC to act as a baseline for further study.[20,21] MCC was mercerized at 20 °C for 20 min followed by the introduction of glycidol and reaction at 40 °C for 4 h. MCC loading was set at 6.0 wt %, the solvent was 90:10 acetone/water by weight, and the molar ratios of NaOH and glycidol to the AGU were 1.5 and 4.0, respectively. Because water is added to the reaction mixture, the effect of any adventitious water inherent to the reagents or the atmosphere should be negligible. Prior to any of the postsynthetic characterization, DHPC samples were purified from significant side products that include polyglycidol and sodium acetate from neutralization. We confirmed by ^{1}H NMR and SEC that washing with ethanol/water mixtures was effective at removing most of the polyglycidol compared to other washing solvents such as acetone/water. However, sodium acetate had limited solubility in ethanol/water mixtures. Increasing the water content of the solvent mixture removed more of the salt but using more than 30 vol % water led to dissolution of highly functionalized DHPC. The washing process was optimized with a solvent gradient of ethanol/water to pure acetone (Section 2.2.1) so that our products had less than 5 wt % sodium acetate according to NMR and less than 5 wt % polyglycidol by SEC (Table S1 and Figure S10). After purification, the free-flowing off-white powder was analyzed by

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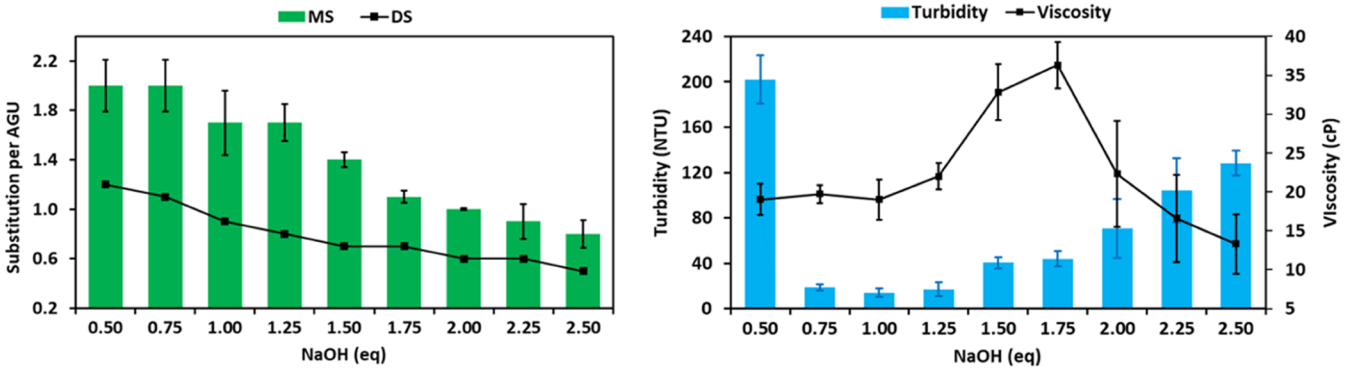

Figure 3. DHPC synthesis: 6.0 wt % cellulose in 90:10 acetone/water with 4.0 equiv of glycidol. Mercerization for 20 min at 20 °C, reaction for 4 h at 40 °C. Reactions were run in triplicate and error bars refer to standard deviation. Left: MS determined by ^{1}H NMR in D_2O + 2% NaOD (green bars). DS determined by ^{13}C NMR in DMSO-d_6 (black lines); only one representative sample was measured. Right: Turbidity reported for DHPC samples at 3.0 wt % in water at room temperature (blue bars). Viscosity data reported for DHPC samples at 3.0 wt % in water with shear rate of 10 rad/s at 25 °C (black lines). Raw data can be found in Tables S3 and S7.

^{1}H NMR and ^{13}C NMR, which is shown for a representative DHPC sample in Figure 2.

NMR characterization of cellulose derivatives is generally challenging due to difficulties in purification, solubility, and signal overlap. When the product is soluble in D_2O, the appearance of the residual H_2O peak immediately downfield from the anomeric proton can also contribute to poor peak separation in ^{1}H NMR. This could be resolved by spiking the solvent with 2.0 wt % sodium deuteroxide (NaOD), which shifts the solvent peak away from the anomeric proton (Figure S1).[36] Using NaOD also tends to increase the solubility of DHPC, leading to optically clear solutions that give a more realistic approximation of the structure of the entire sample. This simple solvent system allowed us to integrate the anomeric proton against the rest of the AGU to give an estimate of the average number of glycidol substituents per AGU (eq 1 in Section 2.3.1). This is referred to as the molar substitution (MS) in the cellulose literature, which must be differentiated from the degree of substitution (DS). The DS is defined as the average number of hydroxy groups substituted per AGU and has a maximum of three. There is no theoretical maximum to the MS and the MS is always equal to or greater than the DS. Figure S2 shows an illustration of a theoretical DHPC polymer where MS is 2.5 and DS is 1.0. The most common methods to estimate MS and DS of cellulose ethers involve either full functionalization of the remaining hydroxy groups to give an organic-soluble polymer, acid digestion of the polymer's acetal linkages followed by gas chromatography-mass spectrometry (GC-MS) of the resulting hydrolysate, a combination of ^{1}H and ^{13}C NMR spectroscopy with very long experiment times, or other complicated postfunctionalization schemes.[9,37,38] Spiking the solvent with 2.0 wt % NaOD rendered these procedures unnecessary for MS estimation of DHPC, which significantly simplified the process and allowed for high-throughput experimentation.

We validated this method by comparing it to a technique used in a previous report of DHPC synthesis. Chang et al. measured MS by functionalizing DHPC with propionic anhydride at 100 °C in dimethylacetamide with dimethylaminopyridine as the catalyst.[25] In our laboratory, this reaction yielded a product with significant discoloration, which is likely the result of degradation due to the production of acid during the reaction with anhydride. To avoid degradation of our products, the procedure was modified to proceed in milder conditions with less toxic reagents as described in Section 2.2.2. Briefly, DHPC was reacted with acetic anhydride overnight at 70 °C in acetonitrile and pyridine. A representative ^{1}H NMR spectrum of the off-white product in $CDCl_3$ can be found in Figure S3, and complete acetylation of all DHPC hydroxy groups was confirmed by the absence of OH stretching in the FTIR spectrum shown in Figure S4.

A third method for estimating MS is by mass gain, in which the purified DHPC product is weighed and compared to the amount of cellulose put into the reaction. We confirmed that our products were generally around 90% pure by a combination of NMR, TGA, and SEC, which measures the leftover sodium acetate, water, and polyglycidol, respectively. Assuming 90% purity and 90% yield, we were able to calculate a rough mass gain estimate for four DHPC samples. It should be noted that the mass gain method is highly dependent on yield and purity and should not be trusted when more rigorous methods are available. Table S2 shows the comparison of these mass gain MS values to the NMR methods previously described. Due to the slight differences in MS for each method, we chose to use the simple NMR method of adding 2.0 wt % NaOD to D_2O throughout this report so that all samples could be compared to each other.

To further improve our understanding of the distribution of glycidol across the cellulose backbone, we optimized a quantitative ^{13}C NMR method for DS that has been used previously in the literature.[23,25] The experiments were performed at 60 °C and a DHPC concentration of 60 mg/mL in DMSO-d_6 (Section 2.3.3), which allowed for fewer scans and reduced d1 relaxation time.[31] These conditions required only 4 h for spectra with much better signal-to-noise than in the previous reports of DHPC synthesis. Figure 2 shows a representative ^{13}C NMR spectrum of our DHPC products along with the peak assignments that have been used previously.[23,25] This technique allows for the determination of the DS at each hydroxy group, which have different reactivity based on the accessibility and acidity of the various protons. It is generally accepted that the order of reactivity is C6 > C2 ≫ C3, although the relative reactivity of the C6 and C2 hydroxy groups can change depending on the chemistry.[37]

The DS and MS are useful metrics but are not sufficient to fully describe the extent of cellulose functionalization. Because they are average values, it is expected that there are both inter- and intrachain heterogeneities present on the cellulose chains

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within the sample.[37] A solubility test provided an estimate of the amount of the water-insoluble product, which tends to have a low MS and DS. Figure S5 shows the appearance of several DHPC samples in water at 3.0 wt %, which ranged from hazy to optically clear. We developed an assay to quantify the solubility of our samples using a turbidimeter (Section 2.3.4) so that minor differences between samples could be quantified. Herein, DHPC samples with turbidity less than 100 nephelometric turbidity units (NTU) were considered mostly soluble, while samples with turbidity greater than 1100 NTU (which was the upper limit for the turbidimeter) were considered insoluble.

Because cellulose ethers are often used as rheology modifiers, the viscosity of our DHPC samples at 3.0 wt % in water was measured using a rheometer. Figure S6 shows the slight shear-thinning behavior of a representative DHPC sample at 25 and 40 °C, which is typical of a cellulose ether in water.[39] Because of the dependence of viscosity on shear rate, all measurements were performed at 25 °C and a shear rate of 10 rad/s (95 rotations per min), which is within the Newtonian range for this polymer and gives a reasonable estimate of viscosity in relevant applications. Other reports of water-soluble cellulose ethers discuss the ability of these products to act as rheology modifiers, but do not quantify the changes in solubility and viscosity based on the reaction parameters and chemical structure.[28,33,40] Overall, these purification and characterization techniques significantly simplify the workflow of cellulose etherification and will provide the broader cellulosics field with accurate, reproducible methods to probe synthesis−structure−property relationships for water-soluble cellulose ethers.

3.2. Effect of NaOH Concentration in DHPC Synthesis.

The literature shows that NaOH concentration has an impact on the synthesis of other cellulose ethers, so we conducted a series of model reactions with various NaOH loadings.[5,33,34] Figure 3 shows the results of this study that was performed in triplicate due to the proclivity of cellulose and DHPC to aggregate under some reaction conditions. DS determination was only performed on a representative sample within each condition due to the long experiment times required for high-quality data.

We observed that MS and DS decreased with higher NaOH loadings, which could be attributed to increased side reactions with excess hydroxide. Since glycidol is an epoxide, it is susceptible to hydrolysis and oligomerization in the presence of NaOH.[35] A similar trend was also found in a report of HPC synthesis.[33] Functionalization with glycidol drives the polymer into solution by disrupting the highly ordered crystalline network in pristine cellulose, and so samples with higher MS and DS generally showed lower turbidity in water. The exception to this trend was in the samples prepared with 0.5 equiv of NaOH, which showed high turbidity even though the apparent MS was quite high. This may be due to insufficient swelling during mercerization, leading to over-functionalized domains that contribute to the high MS and under-functionalized domains that contribute to the high turbidity.

The viscosity of the DHPC mixtures was highest at moderate MS values between 1.1 and 1.4. The low MS samples (MS < 1.1) had low viscosity due to the relative insolubility of these samples, leading to fewer polymer chains in solution that could contribute to viscosity.[41] The high MS samples (MS > 1.4) prepared with 0.75−1.25 equiv of NaOH also showed lower viscosity, indicating that there may be an upper limit to the amount of glycidol that should be introduced to cellulose for maximum viscosity enhancement. However, these data did not show any clear correlation between the MS/DS ratio and viscosity. Rather, viscosity decreased outside the narrow MS range of 1.1−1.4 and DS range of 0.6−0.8 (Table S3). Statistical analysis was able to demonstrate a linear relationship between viscosity and turbidity, MS, and DS (Figure S12). The relationship between NaOH input and the various outputs (MS, DS, viscosity, turbidity) was further elucidated by PXRD analysis of the cellulosic crystal structure after the mercerization process. A series of samples were aged under varying NaOH loadings, neutralized, washed, and dried prior to analysis (Figure 4). The

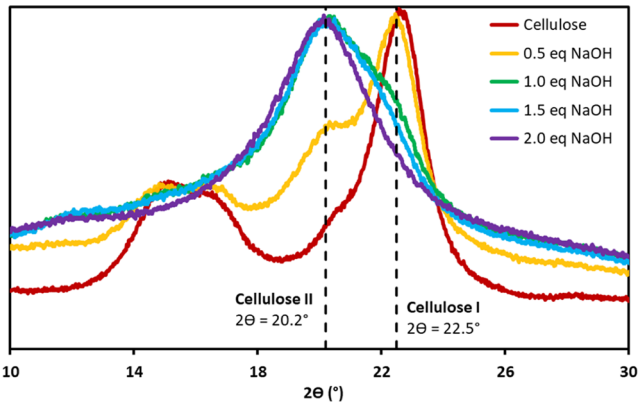

Figure 4. Powder X-ray diffraction of cellulose mercerized with 0.5−2.0 equiv of NaOH in 90:10 acetone/water at a cellulose concentration of 6.0 wt %.

PXRD pattern for pristine cellulose primarily showed the reflections corresponding to cellulose I, which is the dominant crystalline structure of cellulose in nature.[42] Cellulose I consists of alternating parallel polymer chains, while the more stable cellulose II consists of alternating antiparallel polymer chains. Cellulose II can be obtained by regeneration of cellulose after sufficient swelling by NaOH or molecular dissolution in a cellulose solvent.[43] There are also some amorphous domains present in the regenerated samples that are largely silent or contribute to broadening of peaks in the PXRD patterns.

The data in Figure 4 confirmed that 0.5 equiv of NaOH was insufficient for mercerization as many of the polymer chains remained crystalline cellulose I. A distinct change in the PXRD pattern was observed with 1.0 equiv of NaOH, indicating that much of the sample had been converted to cellulose II. The width of the major cellulose II reflection peak decreased up to 2.0 equiv of NaOH, indicating that swelling may improve slightly above 1.0 equiv of NaOH. To determine whether it was the absolute amount of NaOH or the concentration of NaOH that was important, a series of experiments were conducted where 1.5 equiv of NaOH was diluted with varying amounts of water. The syntheses were fixed at 6.0 wt % cellulose to minimize mass transport effects, so the acetone/water ratio (by weight) was changed to vary the NaOH concentration. Table 1 shows the results of these experiments, with Entry 1B representing a comparison to the reactions in Figure 3 where the acetone/water ratio was fixed at 90:10 by weight with 12 mol equiv of water and an NaOH concentration of 22 wt %.

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Table 1. Varying the Acetone/Water Ratio in the Reaction of Cellulose with Glycidol

sample[a]	acetone/water (w/w)	equiv water	[NaOH] (wt %)	MS[b]	DS[c]	turbidity (NTU)[d]	viscosity (cP)[e]
1A	95:5	6	35	1.7	0.8	241	18
1B	90:10	12	22	1.4	0.7	41	33
1C	85:15	18	16	1.3	0.7	49	24
1D	80:20	24	12	1.1	0.7	91	17
1E	70:30	30	8	0.8	0.6	>1100	4

[a]DHPC synthesis: 6.0 wt % cellulose in acetone/water with 1.5 equiv of NaOH and 4.0 equiv of glycidol. Mercerization for 20 min at 20 °C, reaction for 4 h at 40 °C. [b]MS determined by ^{1}H NMR in D_2O + 2% NaOD. [c]DS determined by ^{13}C NMR in DMSO-d_6. [d]Turbidity of 3.0 wt % DHPC samples at room temperature. [e]Viscosity of 3.0 wt % DHPC samples at 25 °C.

Entry 1A provided a high MS of 1.7 but the 90:10 ratio in Entry 1B achieved lower turbidity and higher viscosity, despite the lower MS. PXRD data in Figure S7 showed that the 95:5 acetone/water ratio did not undergo significant swelling during mercerization with 1.5 equiv of NaOH, which explains the sample's relative insolubility. Meanwhile, the same PXRD data showed that all other solvent compositions in Table 1 achieved full cellulose swelling. The insolubility of Entry 1E (and to a lesser extent 1D) was due to aggregation during the reaction, which limited accessibility of much of the polymer to glycidol. Overall, these data showed that both the amount of NaOH and the amount of water contributed to swelling and reactivity in this heterogeneous reaction system. These results agreed with a previous study on the synthesis of carboxymethylcellulose (CMC), in which the authors found that NaOH concentrations between 10 and 30 wt % gave the best CMC solubility.[34]

3.3. Effect of Hydrophilicity of the Organic Solvent in DHPC Synthesis. While previous reports of cellulose etherification in heterogeneous slurry conditions used an organic solvent, there has been little attention given to the role and identity of the solvent in the process. The foundational DHPC patents describe a wide variety of solvents but only state that they should not be reactive toward glycidol and should be at least partially miscible with water.[20,21] We found that the polarity and functionality of the organic solvent had a significant effect on the extent of functionalization of cellulose with glycidol. The highly polar solvents ethanol and DMSO did not phase-separate from the aqueous layer at any point during mercerization or functionalization, which led to a diluted system with poor NaOH penetration into the cellulose fibers and no soluble DHPC. Alternatively, the nonpolar solvent 1-octanol caused the cellulose, water, and NaOH to clump together under magnetic stirring that resulted in insoluble cellulose aggregates (Figure S8). Any amount of aggregation is detrimental toward proper synthesis of DHPC due to reduced accessibility of the hydroxy groups at the center of the cellulose clusters. Therefore, intermediate-polarity solvents with low reactivity for glycidol (e.g., acetone) should be used for cellulose etherification. The partitioning of glycidol and glycerol, which is the main product of glycidol hydrolysis, gave some insight into how the polarity of the organic solvent influences the course of the reaction. Figure 5 shows the partitioning of glycidol and glycerol between phases in three ketone solvents of varying polarity.

The most hydrophobic solvent in this series, MIBK, transferred most of the glycidol and nearly all glycerol into the aqueous phase. While glycidol transfer into the aqueous phase is necessary for reactivity, glycerol partitioning into the aqueous phase is detrimental to the reaction because its many reactive hydroxy groups will outcompete cellulose for glycidol.

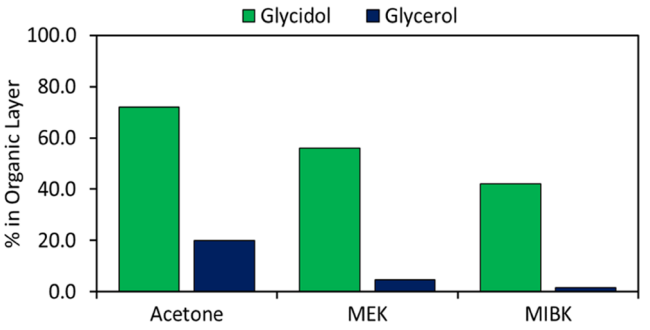

Figure 5. Partitioning of glycidol and glycerol into the organic phase (acetone, methyl ethyl ketone, methyl isobutyl ketone) versus a model aqueous phase containing 20 wt % NaOH, determined by ^{1}H NMR. See Section 2.3.10 for experimental details and Table S4 for raw data.

Spiking in just 0.5 equiv of glycerol into a model reaction (specifically the conditions in 1B of Table 1) stopped the production of any water-soluble DHPC, while spiking in extra glycidol or even up to 1.0 equiv of polyglycidol did not change the reaction significantly. Acetone and other polar solvents can draw some of the byproduct glycerol into the organic phase, which makes it more likely for glycidol to encounter cellulose upon transfer into the aqueous phase. We believe this is the main reason why moderately polar solvents tend to give better functionalization than hydrophobic solvents. We examined this further by performing a series of DHPC syntheses with ketone, secondary alcohol, and tertiary alcohol solvents with results shown in Table 2.

Among the ketone and tertiary alcohol solvents, the most polar option (acetone, 2A and *t*-BuOH, 2G) gave the highest MS. Decreasing the polarity by adding one methylene lowered the efficiency slightly (2B, 2H), and adding a second methylene group (2C, 2I) lowered MS significantly, particularly with the ketone solvent MIBK. All of the ketone solvents (particularly MEK and MIBK) led to visible aggregation in the reaction vessel, while the tertiary alcohols allowed for a free-flowing powder throughout the reaction. The trend is quite different in the secondary alcohol series, where the intermediate-polarity solvent (2-BuOH, 2E) led to much higher MS than either IPA (2D) or 2-PeOH (2F). Interestingly, there was a clear phase separation during mercerization in IPA but no phase separation after the introduction of glycidol. Glycidol was acting as a cosolvent in this system, which eliminated the phase boundary and allowed side reactions to dominate. These data highlight the importance of selecting a solvent with the right polarity for the reaction by maintaining a free-flowing three-phase system while facilitating the transfer of glycidol into the aqueous phase and drawing byproduct glycerol into the organic phase.

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Table 2. Summary of Physicochemical Properties of DHPC Prepared in Various Solvents

Sample[a]	Solvent[b]	Structure	LogP[c]	MS[d]	Turbidity (NTU)[e]	Viscosity (cP)[f]
2A	Acetone		0.2	1.3	41	36
2B	MEK		0.7	1.2	62	37
2C	MIBK		1.3	0.9	>1100	9
2D	IPA		0.4	1.1	112	34
2E	2-BuOH		0.9	1.7	15	19
2F	2-PeOH		1.5	1.3	108	21
2G	t-BuOH		0.9	1.4	48	37
2H	2-Me-2-BuOH		1.4	1.3	44	38
2I	2-Me-2-PeOH		1.9	1.1	97	25

[a]DHPC Synthesis: 6.0 wt % cellulose in 90:10 organic/water with 1.5 equiv of NaOH and 4.0 equiv of glycidol; mercerization for 20 min at 20 °C, reaction for 4 h at 40 °C. [b]Full chemical names and the corresponding abbreviations are given in Section 2.1. [c]log *P* is the logarithm of the partitioning coefficient *P*, which shows the portioning of a molecule between octanol and water. Higher values are associated with more hydrophobic substances. log *P* values were calculated using the molecular properties calculator on molinspiration.com.[44] [d]MS determined by ^{1}H NMR in D_2O + 2% NaOD. [e]Turbidity of 3.0 wt % DHPC samples at room temperature. [f]Viscosity of 3.0 wt % DHPC samples at 25 °C.

3.4. Effect of Glycidol Concentration on DHPC Synthesis. Because IPA forms a single liquid phase upon introduction of glycidol, we hypothesized that gradual addition of glycidol could mitigate this cosolvent effect and allow the reaction to proceed to high MS. To our knowledge, there is no discussion in the literature on the impact of adding the electrophile gradually in heterogeneous cellulose etherification, although there is a report of DHPC synthesis in homogeneous conditions, which shows that stepwise addition of glycidol can improve the reaction efficiency.[45] Table 3 shows the results of a series of experiments designed to probe the importance of glycidol concentration in acetone or IPA. Four molar equivalents of glycidol were either added all at once (entries 3A and 3E) for a 4 h reaction or in a series of smaller additions evenly spaced throughout the reaction (i.e., 1 equiv every hour in 3C and 3G).

Table 3. Varying the Active Glycidol Concentration in DHPC Synthesis

sample[a]	solvent	glycidol additions	MS[b]	DS[c]	turbidity (NTU)[d]	viscosity (cP)[e]
3A	IPA	1	1.1	0.6	103	34
3B	IPA	2	1.3	0.7	33	34
3C	IPA	4	1.8	0.8	19	25
3D	IPA	8	2.1	0.8	17	23
3E	acetone	1	1.4	0.7	34	32
3F	acetone	2	1.5	0.8	33	23
3G	acetone	4	1.8	0.8	19	25
3H	acetone	8	2.1	0.8	17	23

[a]DHPC synthesis: 6.0 wt % cellulose in organic/water (90:10) with 1.5 equiv of NaOH and 4.0 equiv of glycidol. Mercerization for 20 min at 20 °C, reaction for 4 h at 40 °C. [b]MS determined by ^{1}H NMR in D_2O + 2 wt % NaOD. [c]DS determined by ^{13}C NMR in DMSO-d_6. [d]Turbidity of 3.0 wt % DHPC samples at room temperature. [e]Viscosity of 3.0 wt % DHPC samples at 25 °C.

When the active concentration of glycidol in the IPA system was too high (Entry 3A), there was no phase separation between the liquids, and side reactions dominated. When glycidol was added slowly to ensure clear phase separation throughout the reaction (3B−3D), side reactions were limited, and higher MS was achieved. The same reactions in acetone showed a clear phase separation at all glycidol concentrations so there was only a small difference between entries 3E and 3F. In every case, there was an increase in MS and decrease in turbidity when glycidol additions were spaced out during the reaction, which we attributed to decreased side reactions at lower active glycidol concentrations. Interestingly, slow addition of glycidol was detrimental to the viscosity of the product in water. Some of this effect can be explained by the increased mass of high MS polymers, which leads to fewer polymer chains in solution when viscosity is measured at a fixed weight percent. However, comparing viscosity on a molar basis still resulted in decreasing viscosity at high MS. One potential explanation for the reduced viscosity of highly functionalized DHPC is that significant glycidol branching from the cellulose backbone inhibits association between adjacent polymers in solution. One previous report of DHPC synthesis stated that the high viscosity of the dissolved polymer may be due to favorable interactions of under-functionalized regions of cellulose. This rationale was used to explain why the heterogeneous process led to better viscosity than a homogeneous method that gave a more uniform distribution of glycidol across the backbone.[28] In this work, DHPC samples with higher MS and DS have fewer under-functionalized pseudo-cross-linking loci leading to fewer and weaker interactions between adjacent cellulose chains.

In addition to polymer−polymer interactions, there may be polymer−solvent effects that can help explain the low viscosity of highly functionalized DHPC. The absence of significant side branching at lower MS may lead to a more extended polymer chain with a higher effective volume fraction in solution.[46] In other words, more solvent can interact with a more extended

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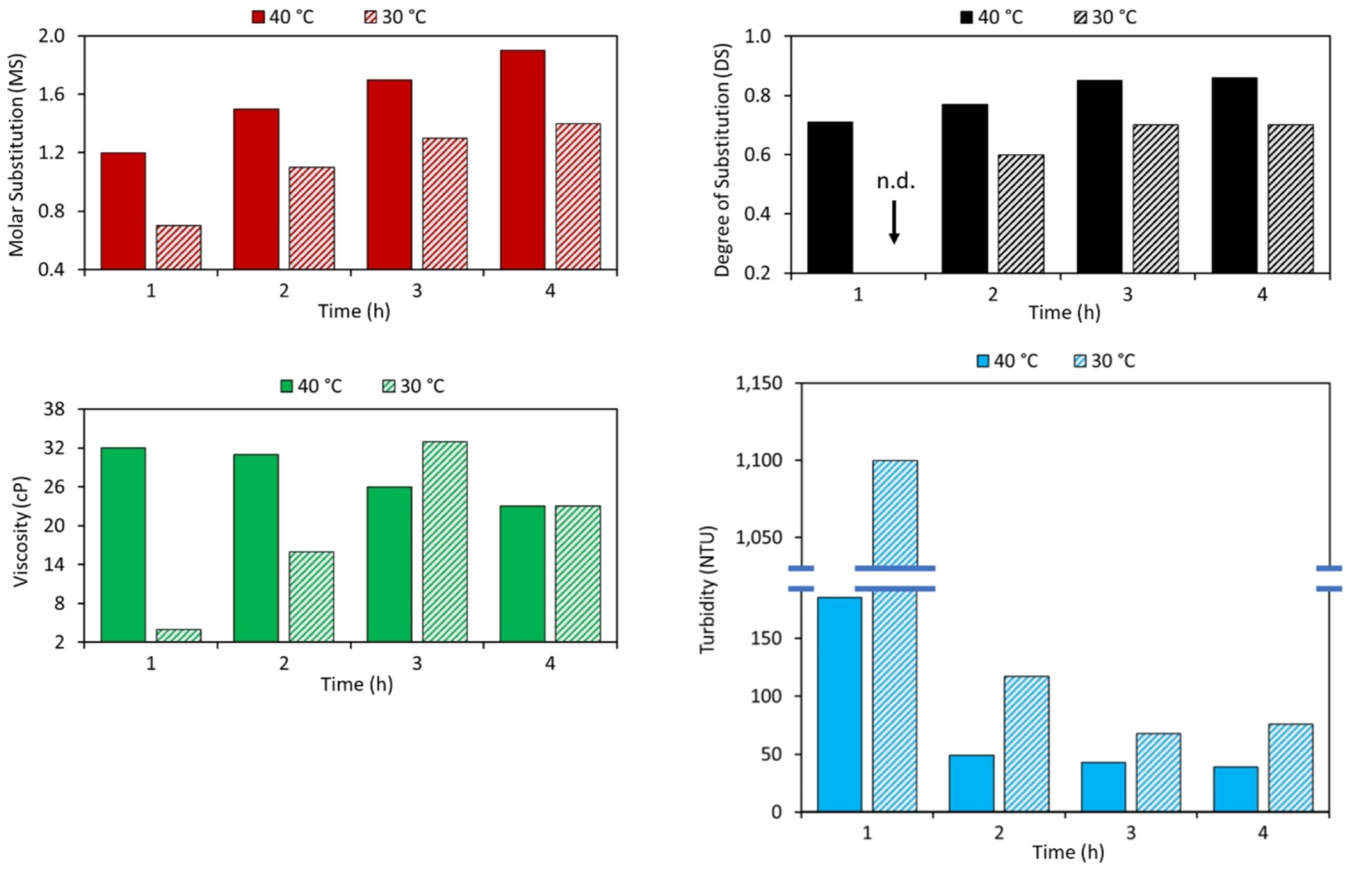

Figure 6. Kinetics of DHPC synthesis at 6.0 wt % in *t*-BuOH/water (90:10) with 1.2 equiv of NaOH and 3.0 equiv of glycidol. MS values from ^{1}H NMR in D_2O + 2 wt % NaOD, DS values from ^{13}C NMR in DMSO-d_6, viscosity, and turbidity values taken from DHPC samples at 3.0 wt % as described previously. Raw data can be found in Table S5.

polymer, so there is less free solvent available and the effective polymer volume fraction is higher. This effect, coupled with increased association and entanglement between polymer chains, may contribute to higher viscosity in solution for DHPC with moderate MS. Additional experiments are ongoing to further explore the relationship between levels of substitution and viscosity in water.

3.5. Effect of Reaction Temperature on DHPC Synthesis. Understanding the kinetics of DHPC synthesis is central to controlling the distribution of glycidol along the cellulose backbone (DS) and the overall level of functionalization (MS). Figure 6 shows the results of a kinetic study that revealed the functionalization is quite fast at 40 °C, yielding highly soluble and viscous DHPC in just 2 h. The reaction was slower at 30 °C but still yielded soluble and viscous DHPC in just 3 h. Interestingly, there only appears to be a distinct difference in reaction rate between the two temperatures during the first hour. Between 2 and 4 h, the reactions appear to progress at roughly the same rate that suggests there may be two kinetic regimes with different levels of temperature dependence. The kinetic study was performed in *t*-BuOH/water mixtures due to the good performance of *t*-BuOH in the solvent screen (Section 3.3).

The reaction conducted at 40 °C showed a gradual decrease in turbidity throughout the reaction as more polymer was driven into solution. The reaction conducted at 30 °C showed an even more pronounced drop in turbidity, which was due to the relative insolubility of the sample at 1 h. The sample run for 1 h was only mildly soluble in the NMR solvents and thus prohibited a reliable ^{13}C NMR for DS. In the 40 °C data, viscosity decreased continuously as the reaction progressed. At 30 °C, viscosity increased in every sample for the first 3 h before finally decreasing between 3 and 4 h. In each case, the MS increased faster than DS as the reaction progressed, possibly due to easier accessibility of the more flexible and less sterically hindered side chains. If the viscosity of DHPC comes primarily from the cellulose backbone, any additional modifications that do not help drive the polymer into solution may be counterproductive toward achieving high viscosity. These data corroborate the trend of high-MS DHPC samples giving lower viscosity in water than their moderate MS counterparts.

3.6. Optimized DHPC Synthesis Using the Principles of Green Chemistry. According to the principles of green chemistry, sustainable synthesis of DHPC should use a benign and abundant organic solvent, have a short reaction time and low temperature, use minimal loadings of NaOH and glycidol, and limit the amount of solvent used during purification.[29] We have found that using a 90:10 mixture (by weight) of *t*-BuOH and IPA provides the organic solvent the right polarity and lack of reactivity toward glycidol. IPA and *t*-BuOH are both preferred solvents according to the CHEM21 solvent selection guide, and when used together they are able to maintain the three-phase system and draw glycerol away from the reactive aqueous layer.[47] This solvent system is a liquid at room temperature (in contrast to pure *t*-BuOH) and allows the translation of this procedure to cellulose of higher molecular

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Table 4. Optimized Synthesis of DHPC in Heterogeneous Slurry Conditions

sample[a]	source	DP (η)[b]	DP (M_n)[c]	DP (M_w)[c]	MS[d]	DS[e]	turbidity (NTU)[f]	viscosity (cP)[g]	% yield[h]
4A	MCC	646	283	720	1.3	0.8	31	37	88
4B	GP	773	600	992	1.7	0.8	21	400	84

[a]DHPC synthesis 4A: 8.0 wt % cellulose in *tert*-butanol/IPA/water 80:10:10 with 1.2 equiv of NaOH and 2.0 equiv of glycidol for 3 h at 40 °C. DHPC synthesis 5B: 6.0 wt % cellulose in *t*-BuOH/IPA/water 80:10:10 with 1.2 equiv of NaOH and 3.0 equiv of glycidol for 3 h at 40 °C. [b]DP estimated by intrinsic viscosity in 50:50 DMSO/1-butyl-3-methylimidazolium acetate (BMIMAc) mixture (Figure S9). [c]DP estimated by averaging M_n or M_w of three representative samples by aqueous SEC (Figure S10). [d]MS determined by ^{1}H NMR in D_2O + 2 wt % NaOD. [e]DS determined by ^{13}C NMR in DMSO-d_6. [f]Turbidity of 3.0 wt % DHPC samples at room temperature. [g]Viscosity of 3.0 wt % DHPC samples at 25 °C. [h]Percent yield calculated by mass gain assuming the MS indicated by ^{1}H NMR.

weight, which tends to aggregate significantly in less hydrophilic solvents.

We performed optimized syntheses of DHPC in the *t*-BuOH/IPA mixture using MCC and a higher-molecular-weight cellulose from GP Cellulose. The degree of polymerization (DP) of each starting material was estimated by an intrinsic viscosity method and an aqueous SEC method, which were both adapted from the literature.[48,49] The discrepancy in DP values is due to the inaccuracies inherent in each method. The intrinsic viscosity method estimates DP of the cellulose feedstock prior to the reaction but does not account for the molecular-weight distribution (dispersity, $Đ$). The SEC method measures M_w directly through light scattering and calculates M_n indirectly, allowing for dispersity estimation but with the caveat that the molecular-weight distribution may change during the reaction and purification. The higher-molecular-weight cellulose led to highly turbid mixtures under most of the conditions described previously, but the optimized conditions in Table 4 led to a soluble and viscous product with just 3.0 equiv of glycidol and 3 h of reaction at 40 °C. Under the same conditions, the lower-molecular-weight MCC required only 2.0 equiv of glycidol to achieve good solubility and viscosity.

While controlling the MS and DS was vital in ensuring maximum solubility and viscosity for MCC, the data in Table 4 showed that the primary factor determining aqueous viscosity was the starting material molecular weight. With both cellulose feedstocks, the optimized conditions led to high yields (>80%) of a viscous, water-soluble polymer with efficient use of glycidol. These reactions showed that DHPC synthesis can be significantly more efficient than the published homogeneous methods, which required higher temperatures, longer reaction times, and/or higher reactant loadings to achieve good solubility in water (see Table S6).[9,50−52] In addition, the heterogeneous method employed in this work did not require operationally costly and wasteful procedures such as precipitation or dialysis for purification. For certain applications, including in pharmaceuticals and food, further purification may be required for DHPC prepared by this method. However, for less rigorous applications such as in personal care products, our products have similar purity to samples of the commercially available cellulose ether HEC.

4. CONCLUSIONS

In this work, the functionalization of cellulose with glycidol under heterogeneous conditions was optimized in accordance with the principles of green chemistry to form 2,3-dihydroxypropylcellulose (DHPC), a water-soluble cellulose ether capable of significant aqueous viscosity enhancement. Our studies showed the importance of reaction conditions including time, temperature, solvent composition, reagent loading, and reagent concentration on the physicochemical properties of the product. The physical properties of DHPC were probed by turbidimetry and rheology, and clear relationships were found between the reaction conditions, the extent of functionalization, and the performance of the polymer. Mercerization with at least 1.0 mol equiv of NaOH per anhydroglucose unit was necessary to ensure full swelling prior to the reaction, while more than 1.5 equiv of NaOH lowered the reaction efficiency without any benefit to the solubility and viscosity in water. Using at least 12 equiv of water was also necessary to ensure proper swelling, while adding more than 18 equiv of water caused increased side reactions and aggregation of reaction intermediates. Moderately polar organic solvents that can maintain the three-phase mixture resulted in the most efficient functionalization, which is likely due to the transfer of byproduct glycerol out of the reactive aqueous phase and into the organic phase. This research is the first to display the importance of solvent selection on heterogeneous slurry reaction dynamics for cellulose etherification. The step-by-step optimization led to DHPC with improved balance of solubility and viscosity in water. Notably, both under-functionalized and over-functionalized DHPC did not contribute significant viscosity to water at 3 wt %. Therefore, the reaction parameters should be precisely controlled so the product is optimized in MS, DS, viscosity, and solubility.

Another important outcome was the development of facile methods for studying structure−property relationships in DHPC. Adding just 2 wt % NaOD to D_2O allowed for simple determination of MS by ^{1}H NMR, and increasing the temperature and concentration of ^{13}C NMR samples in DMSO-d_6 reduced the time required for DS determination from more than 20 h to less than 4 h per sample. This streamlined characterization provided a foundation for future research in this area, particularly for comparison of data between institutions since different characterization techniques yielded different results. In addition, the relationships between process, structure, and performance can be generalized to other water-soluble cellulose derivatives. This work further advances the development of renewable materials with greener syntheses and enhanced properties that can contribute to the growth of a sustainable economy based on biomass valorization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsapm.4c01002.

NMR spectra, FTIR spectra, SEC chromatograms, rheology data, images of dried DHPC and DHPC in solution, PXRD spectra, TGA, data tables, and statistical analysis (PDF)

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Author Contributions

[⊥]The manuscript was written by J.K. and N.B.R. with equal contributions. Experiments were performed by J.K., N.B.R., and T.J.W. T.M.R. and P.J.D. provided mentorship, advice, and editing. All authors have given approval to the final version of the manuscript.

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Notes

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