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Synthesis of Cellulose Adipate Derivatives

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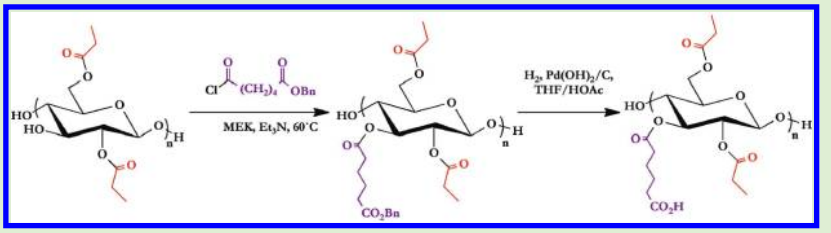
Supporting Information

ABSTRACT:



Cellulose esters containing adipates and other ester groups are synthesized by the reaction of commercially available cellulose esters in solution with the benzyl monoester of adipoyl chloride. The products, cellulose adipate esters in which the distal end of the adipate moiety is a benzyl ester, were easily converted to cellulose adipate derivatives by Pd-catalyzed hydrogenation. These cellulose adipate derivatives are promising biopolymers for drug delivery and other applications in which water-dispersion or swelling are desired.

INTRODUCTION

The synthesis of water-dispersible derivatives of cellulose has long been a difficult problem of significant scientific and commercial importance. Synthesis of water-soluble cellulose derivatives is relatively well-understood, for example, by acylation, followed by extensive back-hydrolysis,[1] or by reaction of cellulose with various alkylating agents under base catalysis to make derivatives like methylcellulose,[2,3] carboxymethylcellulose,[4] hydroxyethylcellulose,[5] or ethylcellulose.[6,7] These methods take advantage of the native hydrophilicity of cellulose and the fact that a low DS of nearly any substituent can render cellulose water-soluble by disrupting hydrogen bonding and crystallinity. For many applications, the ability to swell or disperse in water is far more desirable than water solubility. For example, in coatings applications, the low viscosity of aqueous dispersions permits the formulation of high-solids coatings, reducing drying time and transportation costs by minimizing the water content of the coating dispersion. One of the most straightforward ways to make an aqueous dispersion that can then coalesce into a film is to incorporate carboxyl groups into the molecule; these can be deprotonated by volatile amines, enhancing the dispersibility of the polymer.[8] Upon drying, the amine evaporates, promoting the formation of a continuous film. Polysaccharides that are fundamentally hydrophobic but contain carboxyl groups that enable swelling or dissolution at neutral pH are also highly useful for drug delivery applications.[9] Recent studies have shown that not only are such polysaccharide derivatives useful for traditional drug delivery applications such as pH-controlled release to avoid contact between drug and stomach,[9] but they also provide more valuable functional benefits. Recently, for example, hydroxypropylmethylcellulose acetate succinate (HPMCAS)[10] has proved to be a promising polymer for drug delivery formulations that significantly enhance drug solubility by entrapping the drug in metastable amorphous form dispersed in the polysaccharide matrix. Another pertinent example is carboxymethylcellulose acetate butyrate (CMCAB), which has been recently shown[11,12] to combine several desirable drug delivery functions; pH-controlled release, zero-order release (which is of great value since it can permit constant blood concentration of the drug over long time periods, minimizing side effects and reducing dosing frequency), and solubility enhancement by the amorphous dispersion method.[13−17] CMCAB and HPMCAS function by swelling in the neutral pH of the small intestine and colon because of ionization of the carboxyl groups; this swelling promotes drug release. The carboxyl groups of both cellulose derivatives and the hydrophobic substituents, particularly of CMCAB, promote miscibility of hydrophobic drugs in the polysaccharide matrix, helping to stabilize amorphous dispersions of otherwise poorly water-soluble drugs.[15] The kinetic stability of the thermodynamically metastable amorphous drug in the polymer matrix, for up to several years of storage at relatively high temperatures and humidity, is a critical performance feature of the amorphous dispersion formulations that are showing such promise for enhancing bioavailability of poorly water-soluble drugs. (There is at least one commercial amorphous formulation of the HIV drugs lopinavir and the CYP3A4 inhibitor ritonavir.[18]) Such kinetic stability should be enhanced both by the high T_g of cellulose derivatives and by the specific and hydrophobic interactions provided by hydrophobic cellulose derivatives that contain ionizable carboxyl groups.

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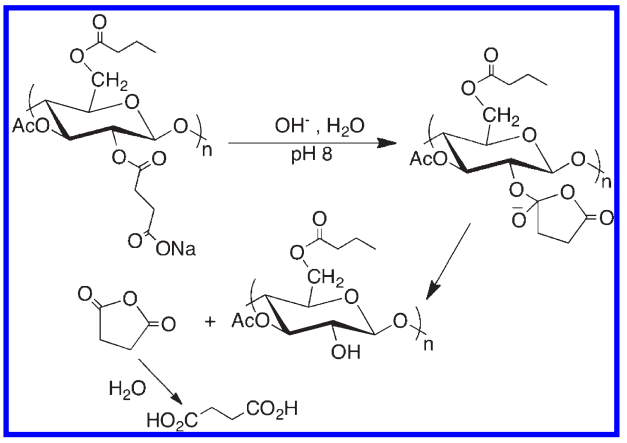
Scheme 1. Proposed CAB-Su Hydrolysis Mechanism

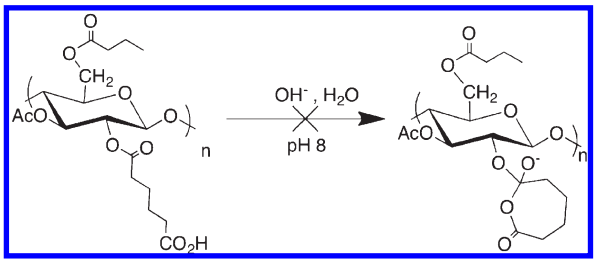


Unfortunately, there are a limited number of methods available for synthesis of carboxyl-containing polysaccharides and, in particular, carboxyl-containing cellulose derivatives. The most well-known synthesis of carboxyl-containing cellulose derivatives is that of the commercial aqueous thickener carboxymethylcellulose. Typically, cellulose is reacted with chloroacetic acid in water in the presence of sodium hydroxide as base. Conversion of carboxymethylcellulose into hydrophobic ester derivatives like acetate, propionate, and butyrate has been reported.[19,20] Whereas the resulting carboxymethylcellulose esters are very interesting materials for coatings and drug delivery applications,[21] there must be concern with acid-catalyzed esterification of a polymer that contains both carboxyl and hydroxyl groups; the potential for cross-linking by esterification must always be considered. Another method is the reaction of cellulose or a cellulose derivative with a cyclic anhydride, usually employing a basic catalyst such as pyridine or triethylamine. In this way, carboxyl-substituted derivatives of cellulose such as cellulose acetate phthalate[22] and cellulose acetate butyrate succinate[23] have been synthesized. The known carboxyl-substituted cellulose derivatives prepared by this cyclic anhydride ring-opening chemistry suffer from limited stability in aqueous systems, which is of course a drawback for polymers designed to work in aqueous media. The stability of cellulose acetate butyrate succinate in neutral to alkaline media, for example, is limited.[24] The authors of that study speculated that the particular instability of derivatives like succinate arises from their ability to catalyze their own hydrolysis (Scheme 1).

Cellulose adipate derivatives may be expected to possess superior properties to those of the cellulose phthalates and succinates synthesized in previous work. They are likely to be less prone to autocatalyzed hydrolysis because this would require an unfavorable . seven-membered ring transition state (Scheme 2). They will be more hydrophobic than the corresponding succinate or phthalate derivatives and thus would be expected to be more compatible with hydrophobic drugs. To date, there have been no reports of the synthesis of well-characterized cellulose adipates. Polysaccharide materials have been subjected to surface treatments with adipic acid to cross-link and strengthen those materials,[25−28] but the products were not fully characterized, and no discrete cellulose derivatives were described.

Adipic anhydride would be the directly analogous reagent to consider for ring-opening reaction with cellulose to produce cellulose adipates. Adipic anhydride is highly reactive because of its relatively strained seven-membered ring structure. It is prone to

Scheme 2. Predicted CE-Adipate Hydrolytic Stability



homopolymerization and has most commonly been used to synthesize polyanhydrides[29] and polyesters.[30] Given its reactivity, we hoped that adipic anhydride[31] would react with the poorly nucleophilic cellulose in solution, providing that we could find an appropriate solvent and catalyst system. We report herein the unexpected difficulties we encountered in direct reaction of cellulose with adipic anhydride and how those were overcome by employing monofunctional adipate reagents to develop the first successful synthesis of cellulose adipate esters, which will permit the synthesis of a broad range of cellulose adipate alkanoates.

EXPERIMENTAL SECTION

Materials. The high-purity hardwood pulp used in these experiments was Sulfatate HJ from Rayonier. Cellulose acetate propionate (CAP-504-0.2), cellulose acetate butyrate (CAB-553-0.4), and cellulose acetate (CA-320S) were from Eastman Chemical. Methyl ethyl ketone (MEK) was dried by refluxing over potassium carbonate. Other purchased reagents were used as received. Adipic anhydride[31] was synthesized by following previously reported procedures. 10% Pd/C and 20% $Pd(OH)_2/C$ were purchased from Sigma Aldrich. Adipic acid, *p*-toluenesulfonic acid (PTSA), 1,3-dimethyl-2-imidazolidinone (DMI), oxalyl chloride, and triethylamine (Et_3N) were purchased from ACROS Organics. Benzyl alcohol, toluene, *N*,*N*-dimethylformamide (DMF), *N*, *N*-dimethylacetamide (DMAc), dichloromethane, lithium chloride, and glacial acetic acid were purchased from Fisher Scientific. DMAc and DMI were dried over 4 Å molecular sieves. Anhydrous tetrahydrofuran was purchased from Sigma Aldrich. All other reagents were synthesized by procedures described later in the Experimental Section.

Measurements. DSC analyses were obtained using a TA Instruments Q100 apparatus. Neat powders (1−3 mg) were loaded in aluminum hermetic pans. Dry N_2 was used as the purge gas at 50 mL/min. Samples were equilibrated at −40 °C and then ramped with a heat/cool/heat procedure between −40 and 160 °C at a heating rate of 10 °C/min and a cooling rate of 5 °C/min. All tests were performed in triplicate. T_g values were recorded as the step-change inflection point from second heat scans. IR spectra were obtained on a Nicolet 8700 instrument. Proton NMR spectra were acquired on an INOVA 400 spectrometer operating at 400 MHz. The sample tube size was 5 mm, and the sample concentrations were ca. 10 mg/mL in $CDCl_3$ or DMSO-d_6. CP/MAS ^{13}C NMR was carried out using a Bruker Avance II 300 instrument using 2048 scans at 27 °C. Elemental analyses were carried out by Micro-Analysis. Size exclusion chromatography (SEC) was used to determine the molecular weights of the polymers at 50 °C in DMF with 0.05 M LiBr at 1 mL min^{-1} flow rate. The DMF SEC system was equipped with a Waters 717 plus autosampler, a Waters 1525 HPLC pump, two Waters Styragel HR5E (DMF) columns, and a Waters 2414 differential refractive index detector. Number-average molecular weights relative to polystyrene standards are reported. Dynamic light scattering (DLS) was used to confirm the absence of polymer aggregates in solution. Solutions were prepared at a concentration of 1.0 mg/mL in

pure DMF and DMF with 0.01 M LiBr and analyzed in a quartz cuvette at 20.0 °C. DLS measurements were performed on a Malvern ZetaSizer Nano Series Nano-ZS instrument using Dispersion Technology Software (DTS) version 6.01 at a wavelength of 633 nm using a 4.0 mW, solid state He−Ne laser at a backscattering angle of 173°. The experiments were performed at a temperature of 20 °C in triplicate. Solubility testing on cellulose ester samples was performed by adding 10 mg of sample to a glass vial, then adding 2 mL of solvent. The mixture was subjected to vortex mixing for 5−10 min at room temperature; then, solubility was judged by visual examination.

Reaction of Cellulose in DMAc/LiCl Solution with Adipic Anhydride (Scheme 3). This procedure is typical for entries listed in Table 1. Cellulose (8.00 g, 49.3 mmol) was dissolved in DMAc (300 mL) and lithium chloride (15 g) by the procedure previously reported.[32] To this solution, at 80 °C under nitrogen (entry 1, Table 1) was added dropwise a solution of adipic anhydride (6.31 g, 49.3 mmol) in 20 mL of DMAc (entry 1, Table 1). After 45 min, it was observed that the solution gelled, and the gel broke up into small, translucent balls (ca. 1 to 2 cm in diameter) with mechanical stirring. The product was isolated by adding the reaction mixture to methanol, filtration of the gel-like product, and then extensive washing of the product with methanol, then with water. The product was insoluble in all solvents tried, including DMSO and chloroform. Analysis of the dried product by infrared spectroscopy and by solid-phase ^{13}C spectroscopy revealed that it was a cellulose adipate, which was cross-linked. Solid state ^{13}C NMR (Figure 1) showed adipate peaks, but the IR spectrum (Figure 2) showed no prominent COOH absorption, indicating the lack of pendant carboxylic acid groups and affirming the presence of ester cross-links. Solid-state CP/MAS ^{13}C (ppm): 173.5 (C═O), 104.6 (C-1), 83.1 (C-4), 74.8 (C-5, C-2, C-3), 62.7 (C-6), 33.8−38.5 ($COCH_2CH_2CH_2CH_2CO$ of adipate), 21.7−24.6 ($COCH_2CH_2CH_2CH_2CO$ of adipate). IR (cm^{-1}): 1812, 1742 (anhydride doublet).

Scheme 3. Reaction of Cellulose with Adipic Anhydride

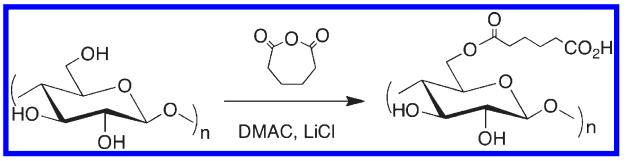


Table 1. Synthesis of Cellulose Adipate under Different Conditions Using Adipic Anhydride

entry	adipic anhydride (equiv)	temperature (°C)	remarks
1	1	80	cross-linked
2	1	40	no reaction
3	3.5	60	cross-linked

Synthesis of Monobenzyl Adipate (Scheme 5). Prepared by the procedure of English et al.,[32] as follows. Adipic acid (73 g, 0.5 mol), benzyl alcohol (81 g, 0.75 mol), PTSA (0.95 g, 5 mmol), and toluene (400 mL) were combined in a flask equipped with Dean−Stark trap and heated at reflux until the theoretical amount of H_2O (13.5 mL, 0.75 mol) was obtained. The solution was then cooled, 300 mL of H_2O was added, and the pH was adjusted to 8 with 6 N NaOH. The aqueous layer was separated and washed with ether (2 × 100 mL), 200 mL of fresh ether was added, and the pH was adjusted to 2.0 with 6 N HCl. The ether layer was separated, dried (Na_2SO_4), and concentrated to yield 47 g of monobenzyl adipate (40%) as a colorless oil: ^1H NMR ($CDCl_3$) 1.68 (m, 4 H), 2.36 (m, 4 H), 5.09 (s, 2 H), and 7.32 (m, 5 H).

Synthesis of Monobenzyl Adipoyl Chloride (Scheme 5). Prepared by the procedure of Abell et al.,[33] as follows. A solution of monobenzyl adipate (20 g, 0.08 mol) and DMF (1 drop) in dichloromethane was cooled to 0 °C, and oxalyl chloride (57.15 g, 0.45 mols) was slowly added. After 30 min at 15 °C, the solvent was removed under

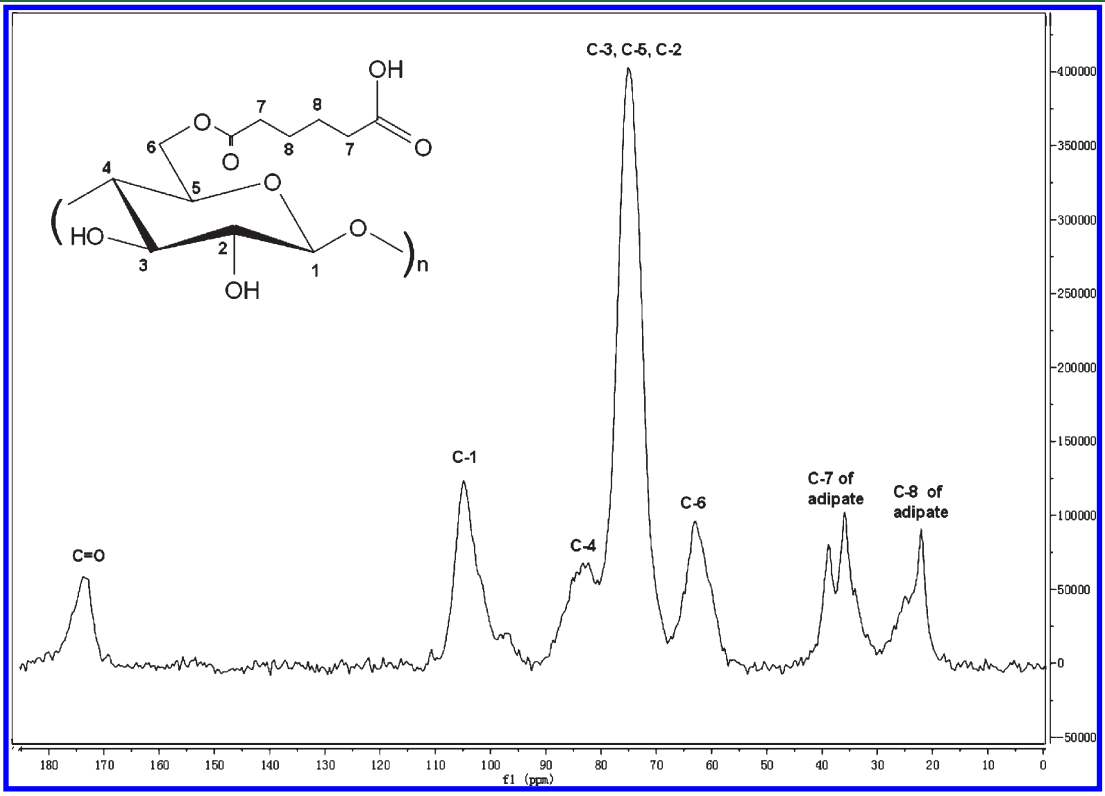


Figure 1. CP/MAS ^{13}C NMR spectrum of cross-linked cellulose adipate.

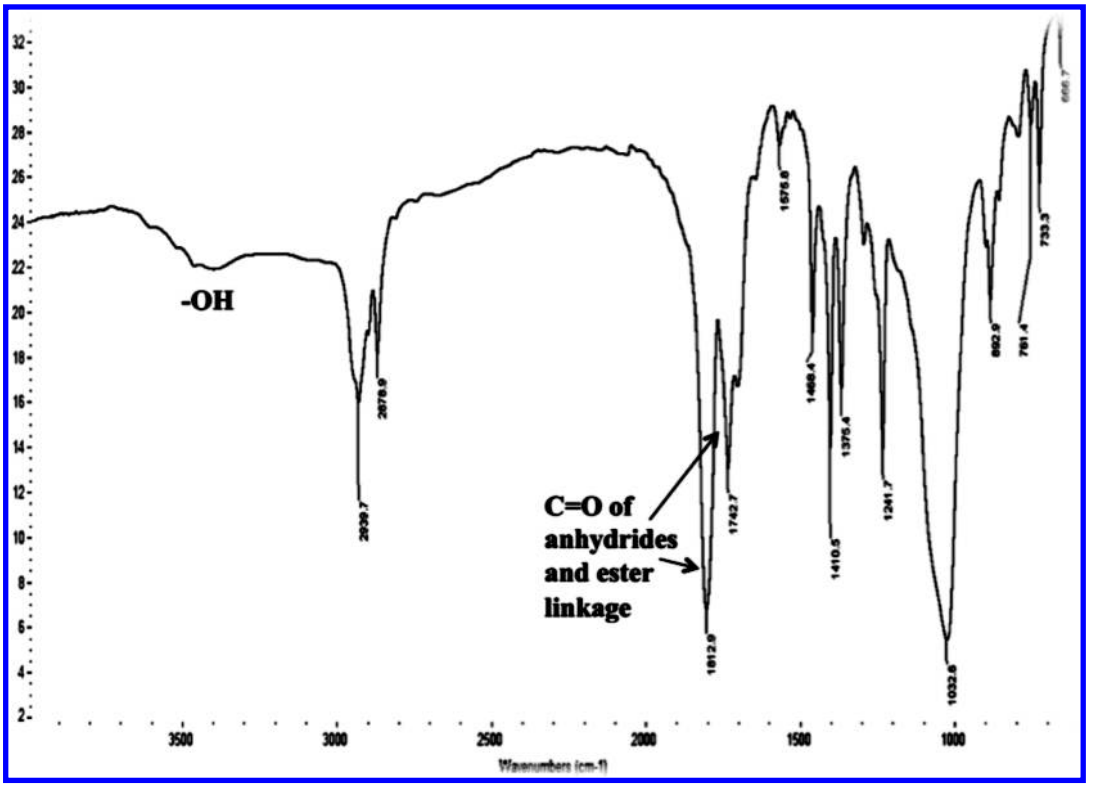


Figure 2. IR spectrum of cross-linked cellulose adipate.

reduced pressure. Toluene (200 mL) was added to the resultant oil and again the solvent was removed to yield the acid chloride as an oil that was not purified further. ^{1}H NMR ($CDCl_3$): 1.73 (m, 4 H), 2.39 (t, 2 H), 2.90 (t, 2 H), 5.12 (s, 2 H), 7.32 (m, 5 H).

Example Procedure for the Reaction of CAP with Monobenzyl Adipoyl Chloride (Scheme 6). CAP-504-0.2 (entry 1, Table 2) (1 g, 3.52 mmol) was dissolved in MEK (10 mL), and the solution was heated to 60 °C with stirring under nitrogen. Et_3N (0.53 mL, 3.87 mmol, 1.1 equiv) was added all at once; then, monobenzyl adipoyl chloride (0.89 g, 3.52 mmol, 1 equiv) was added. An immediate precipitate (presumed to be triethylammonium chloride) was observed. The solution was stirred at 60 °C for 20 h. The reaction mixture was filtered and then added dropwise to isopropyl alcohol at room temperature with stirring. The precipitate was collected by filtration and washed with water. It was redissolved in chloroform and precipitated with hexane. The product was washed with hexane and vacuum-dried at 50 °C.

A similar procedure was followed for the reaction of CAB with monobenzyl adipoyl chloride.

Benzyl Cellulose Acetate Adipate Propionate. ^{1}H NMR ($CDCl_3$): 1.02−1.20 (m, $COCH_2C\underline{H}_3$ of propionate), 1.66 (broad s, $COCH_2C\underline{H}_2C\underline{H}_2CH_2CO$ of adipate), 2.16−2.35 (m, $COC\underline{H}_2CH_3$ of propionate, $COC\underline{H}_3$ of acetate and $COC\underline{H}_2CH_2CH_2C\underline{H}_2CO$ of adipate), 3.25−5.24 (cellulose backbone), 5.10 ($C\underline{H}_2C_6H_5$), 7.33 ($CH_2C_6\underline{H}_5$). Degree of substitution (DS) by ^{1}H NMR: adipate 0.33, propionate 2.09, acetate 0.04. Yield: 58%.

Benzyl Cellulose Acetate Adipate Butyrate. ^{1}H NMR ($CDCl_3$): 0.89−0.98 (m, $COCH_2CH_2C\underline{H}_3$ of butyrate), 1.54−1.64 (m, $COCH_2C\underline{H}_2CH_3$ of butyrate, $COCH_2C\underline{H}_2CH_2CH_2CO$ of adipate), 2.14−2.31 (m, $COC\underline{H}_2CH_2CH_3$ of butyrate, $COC\underline{H}_3$ of acetate and $COC\underline{H}_2CH_2CH_2C\underline{H}_2CO$ of adipate), 3.25−5.31 (cellulose backbone), 5.10 ($C\underline{H}_2C_6H_5$), 7.33 ($CH_2C_6\underline{H}_5$). DS by ^{1}H NMR: adipate 0.5, butyrate 1.99, acetate 0.14. Yield: 60%.

Procedure for the Reaction of CA-320S with Monobenzyl Adipoyl Chloride. CA-320S (entry 4, Table 2) (1 g, 4.18 mmol) was dissolved in *N,N*- dimethylimidazolidinone (DMI, 10 mL), and the solution was heated to 100 °C with stirring under nitrogen. Triethylamine (0.63 mL, 4.59 mmol, 1.1 equiv) was added all at once; then, monobenzyl adipoyl chloride (2.12 g, 8.36 mmol, 2 equiv) was added. The solution was stirred at 100 °C for 20 h. The reaction mixture was filtered to remove the needle-shaped crystals of triethylammonium chloride. The filtrate was added dropwise to water at room temperature in a high shear mixer. The precipitate was redissolved in isopropanol and precipitated with water. The product, benzyl cellulose acetate adipate, was washed with water and vacuum-dried. ^{1}H NMR ($CDCl_3$): 1.66 (br s, $COCH_2C\underline{H}_2C\underline{H}_2CH_2CO$ of adipate), 1.94−2.09 (m, $COC\underline{H}_3$ of acetate), 2.37 (br s, $COC\underline{H}_2CH_2CH_2C\underline{H}_2CO$ of adipate), 3.25−5.31 (cellulose backbone), 5.10 ($C\underline{H}_2C_6H_5$), 7.33 ($CH_2C_6\underline{H}_5$). DS by ^{1}H NMR: adipate 0.7, acetate 1.8. Yield: 82%.

Procedure for the Reaction of Cellulose with Monobenzyl Adipoyl Chloride. Cellulose (0.63 g, 3.88 mmol) was dissolved in DMAC/LiCl by a previously reported procedure.[34] To this solution at 60 °C was added triethylamine (0.59 mL, 1.1 equiv). Then, the monobenzyl adipoyl chloride (3 g, 11.64 mmol, 3 equiv) was added dropwise at 60 °C. The reaction mixture was stirred for 20 h at that temperature and then cooled to room temperature. It was filtered and then added to isopropyl alcohol to precipitate the product. The product benzyl cellulose adipate was washed with water, and then was vacuum-dried at 40 °C to afford 1.83 g (78% yield) of white powder. ^{1}H NMR (DMSO-d_6): 1.47 (br s, $COCH_2C\underline{H}_2C\underline{H}_2CH_2CO$ of adipate), 2.37 (br s, $COC\underline{H}_2CH_2CH_2C\underline{H}_2CO$ of adipate), 3.25−5.31 (cellulose backbone), 5.10 ($C\underline{H}_2C_6H_5$), 7.33 ($CH_2C_6\underline{H}_5$). DS by ^{1}H NMR: adipate 2.0. Yield: 78%.

Example Procedure for the Pd/C Hydrogenation of the Benzyl Cellulose Ester. Benzyl cellulose acetate adipate propionate (200 mg) was dissolved in THF and to this solution was added 10% palladium on carbon (100 mg). A hydrogen balloon was attached to the flask, and the solution was stirred overnight under a hydrogen atmosphere

Table 2. Synthesis of Benzyl Cellulose Adipate Derivatives Using Monobenzyl Adipoyl Chloride (MAC)[a]

entry	substrate	MAC (equiv/AGU)	solvent	temp (°C)	DS			solubility
					Ad	other	total	
1	CAP-504-0.2	1	MEK	60	0.33	Pr 2.09 Ac 0.04	2.46	THF, $CHCl_3$, DMSO
2	CAP- 504-0.2	3	MEK	60	0.50	Pr 2.09 Ac 0.04	2.63	THF, $CHCl_3$, DMSO
3	CAB-553-0.4	1	MEK	60	0.25	Bu 1.99 Ac 0.14	2.38	THF, $CHCl_3$, DMSO
4	CA-320-S	2	DMI	100	0.70	Ac 1.80	2.50	THF, $CHCl_3$, DMSO
5	cellulose	3	DMAc/LiCl	60	2.00	none	2.00	sparingly soluble in DMSO

[a] Ac = acetate, Bu = butyrate, Pr = propionate. CAP-504-0.2 is commercial cellulose acetate propionate from Eastman (DS(Pr) = 2.09, DS(Ac) = 0.04). CAB-553-0.4 is commercial cellulose acetate butyrate from Eastman (DS(Bu) = 1.99, DS(Ac) = 0.14). CA-320S is commercial cellulose acetate from Eastman (DS(Ac) = 1.80).

at room temperature. The mixture was filtered through Celite and evaporated to afford the product. The product was dissolved in chloroform and reprecipitated into hexane. The product (150 mg, 82% yield) was soluble in DMSO and insoluble in water.

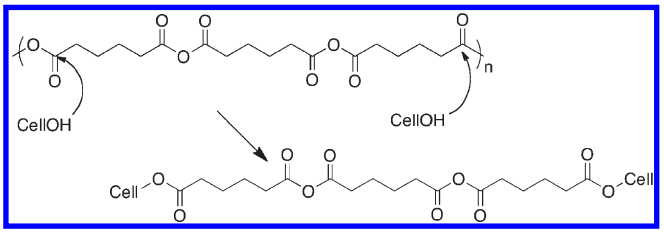
Cellulose Acetate Adipate Propionate. ^{1}H NMR ($CDCl_3$): 1.02−1.20 (m, $COCH_2\underline{CH_3}$ of propionate), 1.66 (broad s, $COCH_2\underline{CH_2}CH_2CH_2CO$ of adipate), 2.16−2.35 (m, $COCH_2\underline{CH_3}$ of propionate, $COCH_3$ of acetate and $COCH_2CH_2CH_2\underline{CH_2}CO$ of adipate), 3.25−5.24 (cellulose backbone). DS by ^{1}H NMR: adipate 0.33, propionate 2.09, acetate 0.04. ^{13}C NMR (DMSO-d_6): 172.0−175.0 (C═O), 99.6 (C-1), 75.1 (C-4), 72.8 (C-3), 72.1 (C-2, C-5), 62.8 (C-6), 33.2−34.0 ($CO\underline{CH_2}CH_2CH_2\underline{CH_2}CO$ of adipate), 26.8−27.6 ($COCH_2\underline{CH_3}$ of propionate), 24.0−24.8 ($COCH_2\underline{CH_2}CH_2CH_2CO$ of adipate), 23.1 ($COCH_3$ of acetate), 9.1 ($COCH_2\underline{CH_3}$ of propionate). Yield: 82%. Elemental analysis: Calculated C, 53.24%; H, 6.53%; O, 40.23%; Found C, 53.10%; H, 6.61%; O, 40.22%.

Cellulose Acetate Adipate Butyrate. ^{1}H NMR ($CDCl_3$): 0.89−0.98 (m, $COCH_2CH_2\underline{CH_3}$ of butyrate), 1.54−1.64 (m, $COCH_2\underline{CH_2}CH_3$ of butyrate, $COCH_2\underline{CH_2}CH_2CH_2CO$ of adipate), 2.14−2.31 (m, $COCH_2\underline{CH_2}CH_3$ of butyrate, $COCH_3$ of acetate and $COCH_2CH_2CH_2\underline{CH_2}CO$ of adipate), 3.25−5.31 (cellulose backbone). DS by ^{1}H NMR: adipate 0.5, butyrate 1.99, acetate 0.14. ^{13}C NMR (DMSO-d_6): 171.2−175.0 (C═O), 99.9 (C-1), 76.5 (C-4), 72.0−73.0 (C-2, C-3, C-5), 63.1 (C-6), 35.9 ($COCH_2\underline{CH_2}CH_3$ of butyrate), 34.1 ($CO\underline{CH_2}CH_2CH_2\underline{CH_2}CO$ of adipate), 24.8 ($COCH_2\underline{CH_2}CH_2CH_2CH_2CO$ of adipate), 21.0 ($COCH_3$ of acetate), 18.2−18.6 ($COCH_2\underline{CH_2}CH_3$ of butyrate), 13.9 ($COCH_2CH_2\underline{CH_3}$ of butyrate). Yield: 85%. Elemental analysis: Calculated C, 55.69%; H, 7.14%; O, 37.17%; Found C, 55.59%; H, 7.11%; O, 36.89%.

Cellulose Acetate Adipate. ^{1}H NMR (DMSO-d_6): 1.47 (s, $COCH_2\underline{CH_2}CH_2CH_2CO$ of adipate), 1.84−2.05 (m, $COCH_3$ of acetate), 2.18 (s, $COCH_2CH_2CH_2\underline{CH_2}CO$ of adipate), 2.95−5.15 (cellulose backbone). DS by ^{1}H NMR: adipate 0.7, acetate 1.8. ^{13}C NMR (DMSO-d_6): 168.0−175.0 (C═O), 99.5 (C-1), 76.4 (C-4), 70.3−73.7 (C-2, C-3, C-5), 62.8 (C-6), 33.2−34.0 ($CO\underline{CH_2}CH_2CH_2\underline{CH_2}CO$ of adipate), 24.0−24.5 ($COCH_2\underline{CH_2}CH_2CH_2CO$ of adipate), 20.3-21.3 ($COCH_3$ of acetate). Yield: 88%. Elemental analysis: Calculated C, 50.61%; H, 5.87%; O, 43.52%; Found C, 46.73%; H, 6.07%; O, 45.66%.

Example Procedure for the $Pd(OH)_2$/C Hydrogenation of the Benzyl Cellulose Ester. To a solution of 200 mg benzyl cellulose acetate adipate propionate dissolved in 30 mL of anhydrous THF/acetic acid (1:1, v/v), 100 mg palladium hydroxide, 20 wt % Pd (dry basis) on carbon was added. A hydrogen balloon was attached to the flask, and the solution was stirred overnight under hydrogen atmosphere at room temperature. The mixture was filtered through Celite and concentrated. The product was dissolved in dichloromethane and precipitated into hexane. The precipitate was collected and dried under vacuum. Yield: 130 mg (71%).

Scheme 4. Reaction of Cellulose with Poly(adipic anhydride)

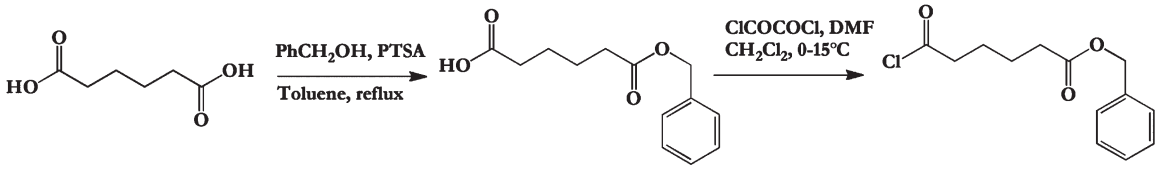


RESULTS AND DISCUSSION

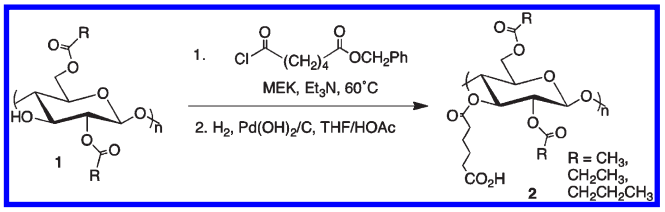
We initially explored the solution phase reaction of cellulose with adipic anhydride in DMAc/LiCl (Scheme 3), which is one of the best understood and most broadly useful solvent systems for reactions in which cellulose is a nucleophile.[35,36] We found in previous studies[34] that cellulose reacts smoothly in DMAC/LiCl with carboxylic anhydrides (cyclic or otherwise) at 80 °C or higher without the need for added catalyst. Therefore, we added adipic anhydride dropwise to cellulose in DMAC/LiCl solution at 80 °C (entry 1, Table 1). We were surprised to observe that the solution gelled almost immediately upon commencement of adipic anhydride addition. The gelled product was insoluble in all solvents tried, including DMSO and chloroform. Whereas it is possible that the observed gelation could have been caused by inherent poor solubility of cellulose adipate, this would not be predicted from previous observations of carboxyalkyl cellulose ester solubility[37] and was not supported by subsequent observations of the solubility of cellulose adipates prepared in other ways (vide infra). Analysis of the dried product by infrared spectroscopy and solid-phase ^{13}C spectroscopy revealed that it was a cellulose adipate, which was cross-linked. Solid-state ^{13}C NMR (Figure 1) showed adipate peaks at δ 21.7−24.6 and 33.8−38.5, and the IR (Figure 2) spectrum showed no prominent COOH absorption, indicating the lack of pendant carboxylic acid groups. Interestingly, a doublet characteristic of anhydrides (in this case due to poly(adipic anhydride))[36] was seen at 1812 and 1742 cm^{-1} in the infrared spectrum.

The cross-linking observed is extraordinarily rapid; furthermore, no such cross-linking is observed when employing succinic anhydride as the electrophile under otherwise identical conditions.[37] Therefore, it seems extremely unlikely that the rapid gelation observed could be caused by condensation between the pendant carboxyl group of adipate groups attached to cellulose and free hydroxyl groups on cellulose (nor would such ester

Scheme 5. Monobenzyl Adipoyl Chloride Synthesis



Scheme 6. Synthesis of Cellulose Adipates via Acid Chloride



cross-links be consistent with the IR and ^{13}C analyses of the product). Rather, we postulate that the cross-linking is being caused by reaction between cellulose and poly(adipic anhydride) (Scheme 4) in which each poly(adipic anhydride) chain reacts on average with more than one cellulose molecule. We have observed that even freshly prepared adipic anhydride contains a measurable amount of poly(adipic anhydride) by ^{1}H NMR spectroscopy (poly(adipic anhydride) gave signals at 1.75 and 2.5 ppm due to $-CH_2CH_2-$ and $CH_2-CO-O-CO-CH_2$ protons, respectively, and adipic anhydride signals appeared at 2.8 and 2.0 ppm), and that this amount grows over the course of days as the adipic anhydride is stored, even if refrigerated. This postulate is consistent with the observed anhydride carbonyl absorbances in the IR spectrum (1812, 1742 cm^{-1}). These poly(anhydride) cross-links would not be expected to hydrolyze rapidly (even though thermodynamically labile) because of the hydrophobicity of the adipate group and the poor solubility of these high-molecular-weight cross-linked species.[38,39]

We made several attempts to circumvent the apparent cross-linking problem by adjusting reaction conditions. Table 1 shows the results of several of these attempts. Lower temperature (40 °C, entry 2) condensation was attempted in an effort to enhance reaction selectivity and minimize cross-linking, but at that low temperature, no desired esterification was observed. We thought that by increasing the number of equivalents of adipic anhydride (entry 3) and employing rapid anhydride addition, we might block all of the hydroxyls as adipate esters, preventing cross-linking. This approach also was unsuccessful; gelation of the reaction mixture occurred even before adipic anhydride addition was complete.

If ester cross-linking by condensation of carboxyls on one cellulose chain with hydroxyls on another cellulose chain was the problem, then bases like triethylamine and pyridine might be useful to convert the initial product cellulose adipate carboxylic acid into a carboxylate anion, making condensation with a cellulosic hydroxyl to form an ester linkage far less favorable. However, the use of organic bases was not pursued, because of our evidence that reaction with poly(adipic anhydride) was in fact the issue and because of reports[40] that triethylamine can initiate ring-opening polymerization of adipic anhydride to polyadipic anhydride at room temperature.

If our conclusions about the mechanism for the cross-linking observed with adipic anhydride were sound, then a sure-fire way to avoid cross-linking would be to replace adipic anhydride with a monofunctional equivalent. Fortunately for us, there were reports in the literature of the monobenzyl ester of adipic acid,[32] and the conversion of that ester to the monobenzyl ester monoacid chloride[33] (benzyl 6-chloro-6-oxohexanoate, Scheme 5). We knew from prior reports[3,41,42] that the removal of benzyl ether groups from cellulose by hydrogenation was feasible and were hopeful that our adipate benzyl ester groups would be at least as easily removed by hydrogenation. We first examined the reaction of monobenzyl adipoyl chloride with commercial cellulose esters of relatively low degree of substitution; this permitted us to work in solvents of moderate polarity. Reaction of monobenzyl adipoyl chloride with CAP-504-0.2 (DS (propionyl) 2.09, DS(acetyl) 0.04) (entry 1, Table 2) in MEK at 60 °C for 20 h cleanly afforded benzyl cellulose acetate adipate propionate, with no evidence of gelation or cross-linking. The benzyl adipate substituent was then hydrogenated to remove the benzyl groups and deprotect the adipate groups; again, the reaction went smoothly and no cross-linking was observed, affording cellulose acetate adipate propionate (Scheme 6; note that no regiospecificity is implied by the structures in Scheme 6; we have no conclusive information at this time about the regiospecificity of the reaction). We found that hydrogenation using Pd/C was always successful but sluggish on larger scale (multigram) reactions. The use of $Pd(OH)_2/C$ gave more rapid hydrogenations on the gram scale and eliminated the occasional necessity for multiple hydrogenations to attain complete debenzylation.

The formation of these products was confirmed by proton NMR studies. Figure 3 shows the ^{1}H NMR spectrum of benzyl cellulose acetate adipate propionate. One of the adipate peaks ($COCH_2\underline{CH_2}\underline{CH_2}CH_2CO$) appears as a broad singlet at δ 1.66. The other adipate peak ($COC\underline{H_2}CH_2CH_2C\underline{H_2}CO$) merges with the $COC\underline{H_3}$ and $COC\underline{H_2}CH_3$ peaks from CAP at δ 2.16−2.35. The benzyl protons appear at 5.1 ($C\underline{H_2}$) and 7.33 (Ph). Figure 4 shows the ^{1}H NMR spectrum of the hydrogenation product, cellulose acetate adipate propionate. The success of the hydrogenation is confirmed by the disappearance of the benzyl aromatic signals, and the spectrum clearly indicates that cellulose acetate adipate propionate has been formed. The ^{13}C NMR spectrum (Figure 5) also clearly indicates the nearly complete absence of benzyl signals (aromatic signals 110−130 ppm) and the presence of the adipate groups. Therefore, the use of the monofunctional reagent has indeed resulted in smooth preparation of an un-cross-linked cellulose adipate product, as predicted.

Table 2 shows the results of several attempts to apply this chemistry to other cellulose derivatives, expanding the range of adipate derivatives available. MEK was used as a solvent for reaction of monobenzyl adipoyl chloride with cellulose acetate propionate (CAP-504-0.2; entry 1, Table 2) and cellulose acetate butyrate (CAB-553-0.4; entry 2, Table 2). The cellulose acetate we

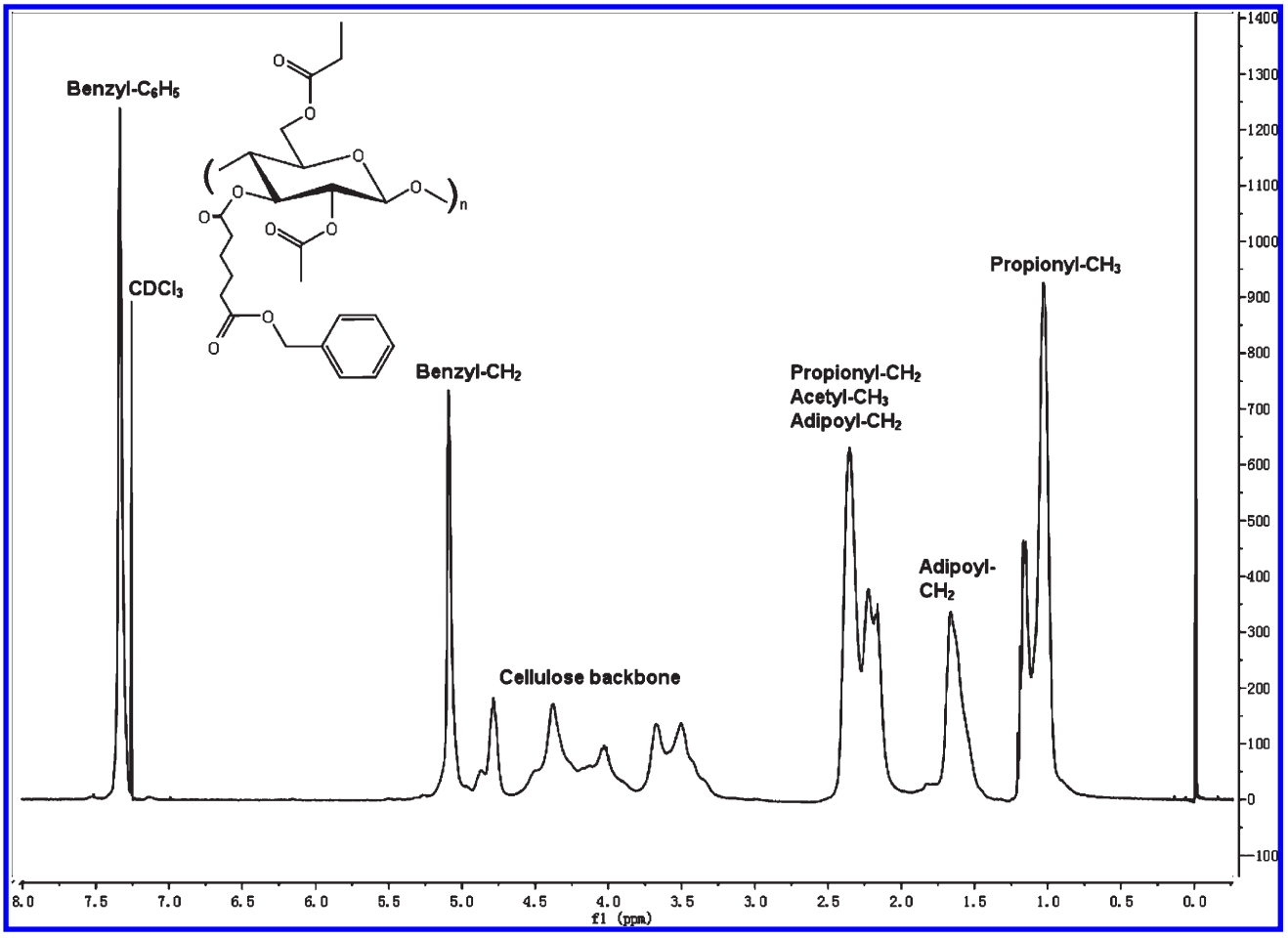


Figure 3. ^{1}H NMR spectrum of benzyl cellulose acetate adipate propionate in $CDCl_3$.

used (CA-320S) was not soluble in MEK, so reaction of CA was carried out in the polar aprotic solvent DMI. In each case, rather low DS commercial cellulose esters were used as starting materials to provide a higher DS of available OH groups for reaction with the adipate derivative. Triethylamine was employed as catalyst and acid scavenger. The product benzyl adipate derivatives of CAP, CAB, and CA were each soluble in THF. Hydrogenation of each of these three products at room temperature using a hydrogen balloon proceeded smoothly, resulting in benzyl deprotection to afford the respective cellulose adipate derivatives (**2**, Scheme 6).

However, hydrogenation of benzyl cellulose adipate (DS (adipate) = 2.00, entry 5, Table 2) could not be carried out because of limited solubility of the product in common organic solvents. Synthesis of cellulose adipate alkanoates from cellulose in solution in solvents like DMAc/LiCl and ionic liquids should overcome this product solubility problem. Our results on the synthesis of cellulose adipates in ionic liquids will be discussed in a forthcoming paper.

The degrees of substitution (DS) of the products were assigned from the proton NMR spectra using the ratios of appropriate acyl proton integrations to the backbone proton integration. For example, DS (adipate) 0.33 was achieved by reaction between CAP-504-0.2 and 1 equiv of monobenzyl adipoyl chloride (entry 1, Table 2). The level of carboxyalkanoyl substituent achieved is promising for the use of this cellulose adipate derivative for oral dosage forms in drug delivery or for water-borne dispersions. For comparison,[11] carboxymethylcellulose acetate butyrate (Eastman CMCAB-641-0.2, DS of carboxymethyl = 0.33) can be readily dispersed in aqueous media and swells at near-neutral pH. CMCAB with that DS carboxyl-containing substituent was also found to provide an excellent matrix for pH-controlled drug release, zero-order drug release, and solubility enhancement. Therefore, we anticipate that cellulose adipate alkanoates may be valuable biopolymers for pharmaceutical formulations. Higher DS (adipate) can be achieved, although with some reduction in efficiency; using 3 equiv of monobenzyl adipoyl chloride (entry 2, Table 2) afforded CAP adipate of DS (adipate) 0.5. Reaction of cellulose acetate butyrate with 1 equiv of monobenzyl adipoyl chloride afforded the anticipated cellulose acetate adipate butyrate with adipate DS 0.25. Reaction of monobenzyl adipoyl chloride with CA-320S, which has less bulky substituents and a higher DS(OH) than the other starting esters, afforded the expected product with a higher adipate DS of 0.7. The benzyl ester products and their characteristics are summarized in Table 2; deprotected cellulose ester adipate properties are summarized in Table 3.

For amorphous dispersion formulations of drugs in polymer matrices, high polymer glass-transition temperature (T_g) is an advantage.[43] If the polymer remains in the glassy state, even at high ambient temperatures and at high humidity, then the mobility of the drug molecules is restricted and their crystallization is suppressed. Therefore, it was of interest to investigate the thermal properties of our cellulose adipate esters. Table 3

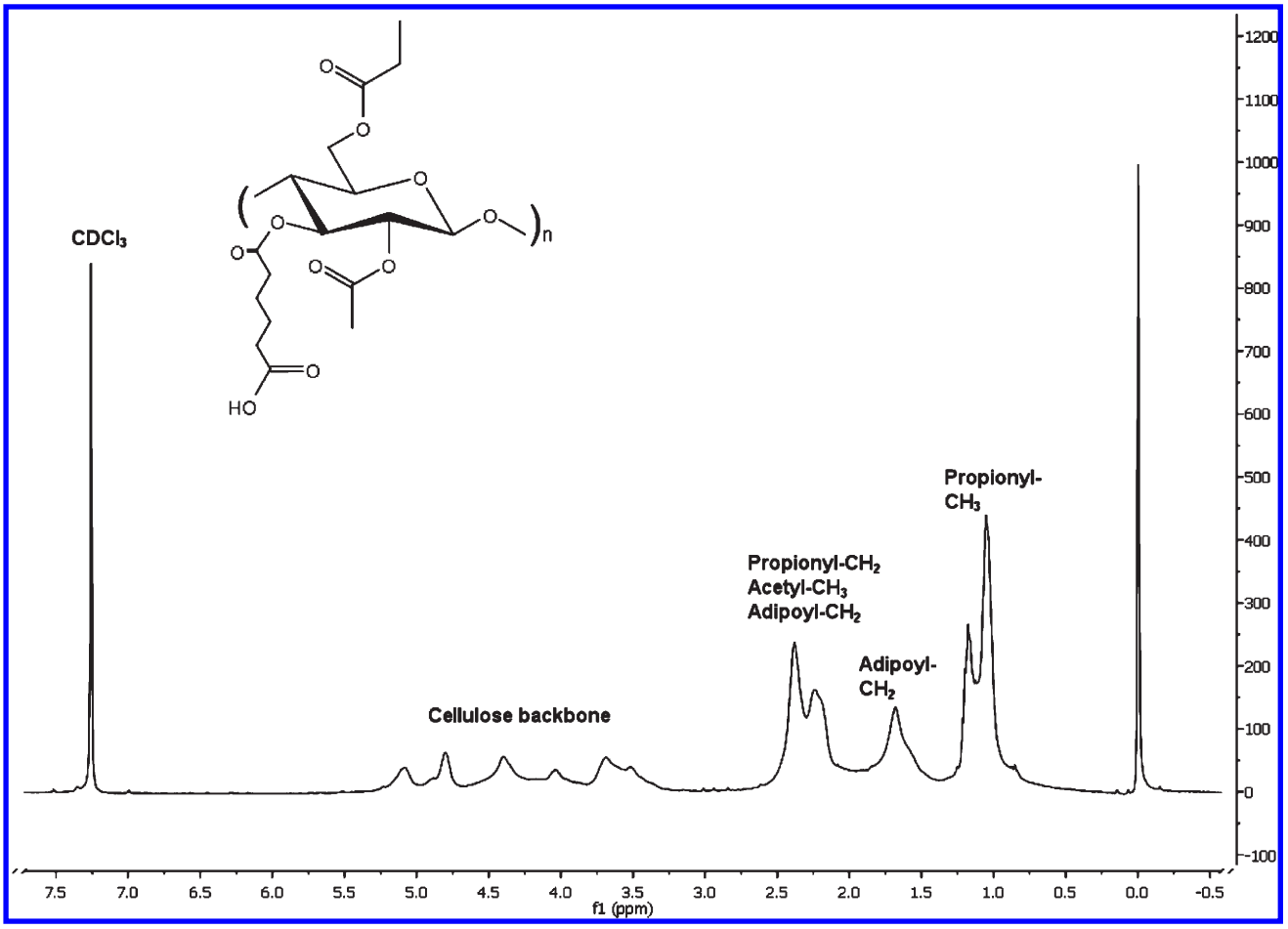


Figure 4. ^{1}H NMR spectrum of cellulose acetate adipate propionate in $CDCl_3$.

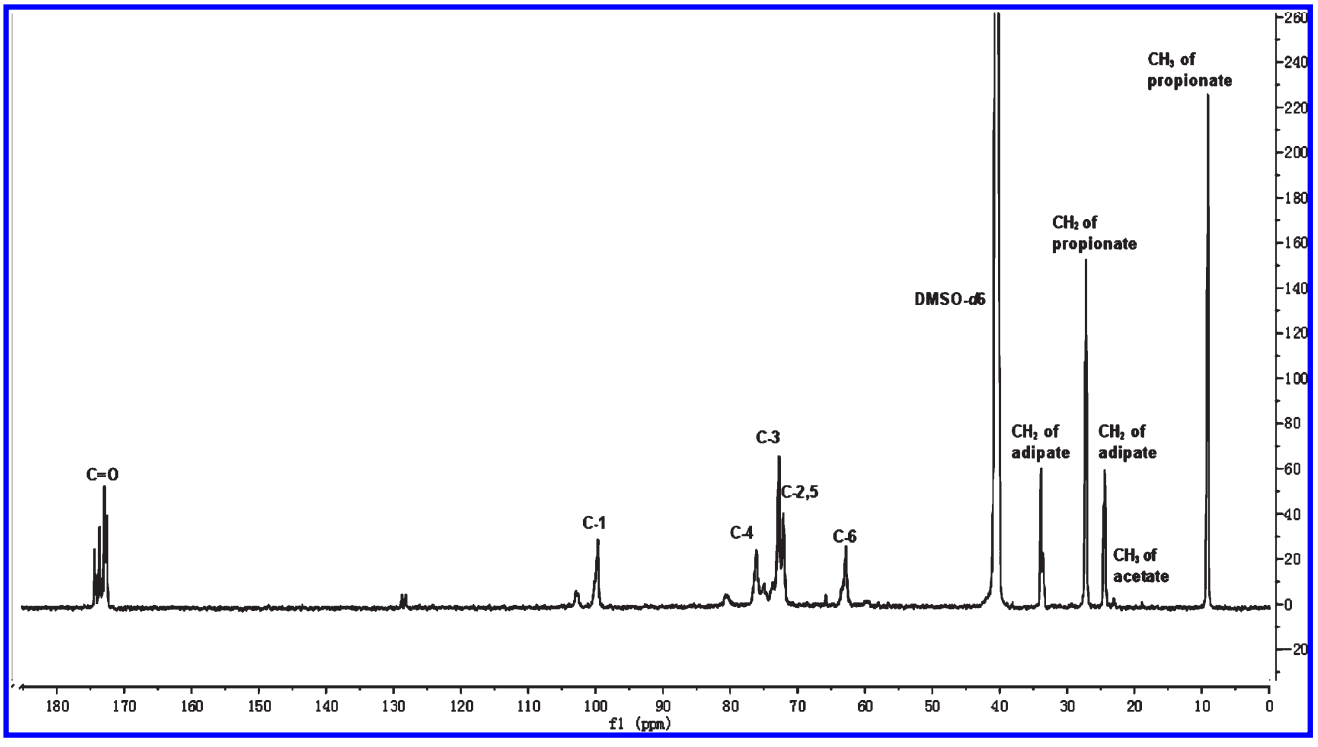


Figure 5. ^{13}C NMR spectrum of cellulose acetate adipate propionate in DMSO-d_6.

Table 3. Properties of Starting Materials and Deprotected Cellulose Ester Adipates

	starting material data				product data			
entry	starting material	T_g 2nd heat(°C)	T_m (°C)	$M_n/10^3$ (SEC)[a]	product	T_g 2nd heat (°C)	$M_n/10^3$ (SEC)	solubility
1	CAP-504-0.2	158	188	15.0	CAP adipate	−14, 125	10.8	$CHCl_3$, NMP, DMSO
2	CAB-553-0.4	100	155	20.0	CAB adipate	−18, 94	61.0	$CHCl_3$, NMP, DMSO
3	CA-320S	180	230−250	38.0	CA adipate	−18, 131	[b]	NMP, DMSO

[a] Reported by supplier, versus polystyrene standards. [b] M_n could not be measured by SEC.

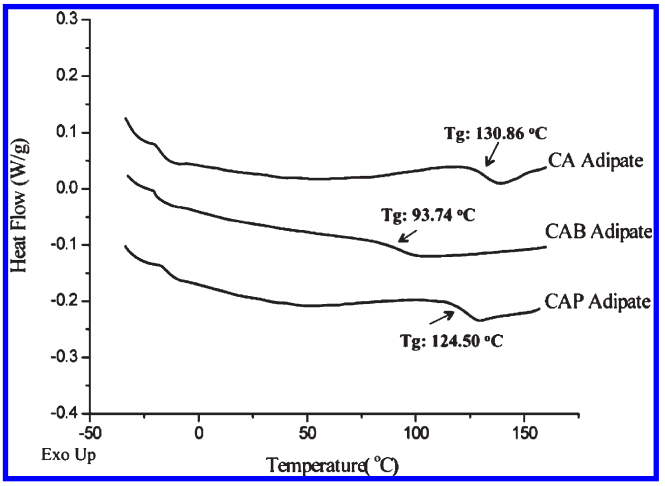


Figure 6. DSC curves of cellulose adipate derivatives at heating rate 10 °C/min (2nd heat).

summarizes the results of differential scanning calorimetry (DSC) studies of the respective adipates, and Figure 6 displays the DSC traces. All cellulose ester adipates prepared had glass-transition temperatures in excess of 90 °C, and the CA and CAP adipates had T_g well in excess of 120 °C, indicating promise for amorphous dispersion formulations. We also observed low-temperature transitions for these cellulose ester adipates, well below ambient temperature, which were not evident in the starting materials. We speculate that these transitions may be due to cooperative motions of the relatively long adipate side chains, similar to those observed by Glasser and coworkers for cellulose long-chain esters.[44]

Molecular weight characterization of these cellulose adipate materials was challenging. We first explored size-exclusion chromatography (SEC) in an NMP/LiCl solvent system but did not observe polymer signals in the column eluant. Some samples showed aggregation by laser light scattering studies in DMF solvent, whereas other samples did not. Apparently these cellulose adipates are somewhat prone to aggregation and have high affinity for the polystyrene beads of the SEC column. Finally, we found that SEC in DMF containing 0.05 M LiBr was successful for the CAP and CAB adipates; the less-soluble CA was still problematic in this system. In general, the M_n results (Table 3) obtained indicate no more than moderate chain degradation during the adipate ester preparation, consistent with the relatively mild conditions used.

CONCLUSIONS

We have developed a general process for the synthesis of cellulose adipates, with or without other ester groups, by reaction of cellulose in DMAC/LiCl solution or cellulose esters in MEK solution with a monofunctional adipate reagent, monobenzyl adipoyl chloride, followed by removal of the benzyl group by mild hydrogenation. We have observed no limitation on the type of alkanoate group that may be present. In some cases, we have achieved high DS of adipate, so there is no apparent limitation on achievable adipate DS. Suitable starting materials include cellulose and esters of cellulose; ethers and other cellulose derivatives are also likely to be suitable. This process circumvents the cross-linking problems seen when using adipic anhydride and leads to soluble cellulose (ester) adipate derivatives. We anticipate that these new cellulose derivatives will be useful in aqueous coatings systems and for controlled release of drugs and other active molecules. Studies of the utility of these cellulose adipate esters in drug delivery are under way.

ASSOCIATED CONTENT

Supporting Information. Complete infrared, ^{13}C NMR, and ^{1}H NMR spectra for the new cellulose derivatives synthesized in this work, other than those included in the body of the manuscript, the DSC spectrum of cellulose acetate adipate propionate, and ^{1}H NMR spectra of the monofunctional adipate reagents prepared for this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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