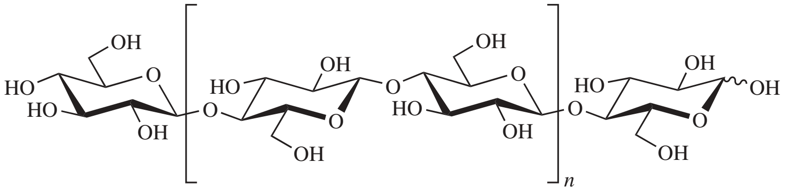
CELLULOSE ESTERS, INORGANIC ESTERS

1. Introduction

Cellulose plays an extremely important structural role in nature. Cellulose is a linear polysaccharide comprised of β-1,4-linked cellobiose repeat units (Fig. 1). The hydroxyl groups present on each anhydroglucose unit provide the biopolymer with the ability to form strong structures through hydrogen bonding. This vast network of hydrogen bonds that link the individual polymer chains into more complex structures greatly reduces the solubility of cellulose in conventional organic and aqueous solvents. Derivatization of cellulose as esters and/or ethers modifies the solubility profile of the cellulosic while maintaining many of the polymeric properties of the molecule. Cellulose esters have found numerous commercial applications, including plastics, coatings, and ion exchange applications. Esters of cellulose can be either inorganic or organic. The focus of this section is on inorganic esters of cellulose. This article covers both the synthesis and use of inorganic esters of cellulose.

The importance of the general structures in Figure 1 and the numbering scheme (the six carbons that make up the anhydroglucose backbone of a cellulosic are represented by a number between C1–C6) described in Figure 2 becomes clear to the reader throughout this article.

Inorganic esters of cellulose have been known for well over 100 years and are still commercially viable products. Cellulose nitrate, commonly called



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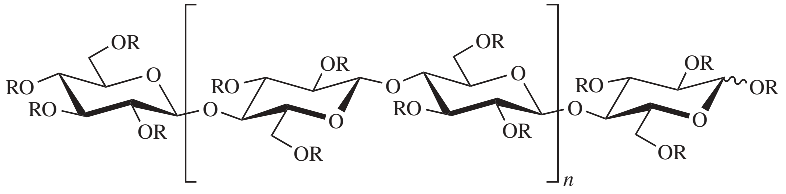

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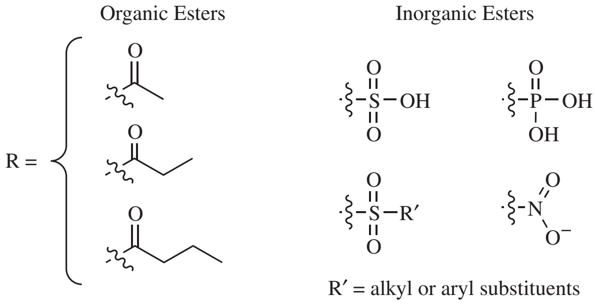


Fig. 1. General structures of cellulose and cellulose esters.

nitrocellulose, is the ester with the most significant historical importance. Cellulose nitrate led to the birth of the plastics industry, the film and motion picture industry, and major improvements in explosives and coatings applications. Additionally, cellulose nitrate played a prominent role in numerous biochemical discoveries, including elucidation of the genetic code.

Due to its historical importance cellulose, nitrate has traditionally dominated the content of articles devoted to inorganic esters of cellulose. While not understating the importance of cellulose nitrate, this report emphasizes the

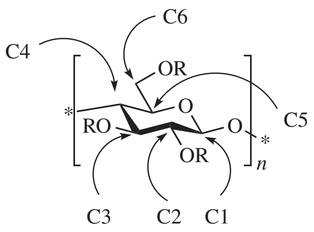


Fig. 2. Description of numbering of anhydroglucose carbons.

value of other inorganic esters of cellulose, including cellulose phosphate, cellulose sulfate, and cellulose sulfonates.

2. Preparation of Inorganic Esters of Cellulose

Inorganic esters of cellulose include all esters where the atoms linked directly to the cellulosic oxygens are non-carbon. The following cellulose derivatives will be discussed in this article, cellulose nitrate, cellulose sulfate, cellulose sulfonate, and cellulose phosphate.

2.1. Nitrogen-Containing Esters of Cellulose. *Cellulose Nitrate.* Cellulose nitrate, without question the most commercially important inorganic ester of cellulose, was first prepared in 1833 (1). Schonbein prepared the first stable form of cellulose nitrate in 1846 (2). The preparation of cellulose nitrate, most commonly called nitrocellulose, has been reviewed in the literature numerous times (3,4). Several nitration techniques have been reported for the preparation of cellulose nitrate, including $HNO_3/H_2SO_4/H_2O$, HNO_3 (>75%), N_2O_4 (g), HNO_3/H_3PO_4, $HNO_3/H_3PO_4/P_2O_5$, $HNO_3/Mg(NO_3)_2$, HNO_3/CH_2Cl_2, and $HNO_3/HOAc/Ac_2O$ (5–11). Cellulose nitrate is still manufactured using a mixture of nitric acid, sulfuric acid, and water.

A number of versions of cellulose nitrate are commercially available. Variations in nitrogen content and viscosity are the main differences between nitrocellulose product lines. The amount of water present during the preparation of cellulose nitrate directly influences the final nitrogen content of the product (Fig 3). The viscosity of the final product is determined by selecting a starting material with the appropriate degree of polymerization and/or by performing a viscosity reduction step following nitration. Cellulose trinitrate has a degree of substitution of 3 and a nitrogen content of 14.15%. Cellulose dinitrate (DS = 2) and cellulose mononitrate (DS = 1) have nitrogen contents of 11.11 and 6.76%, respectively (12). Degree of substitution is a term commonly used to describe

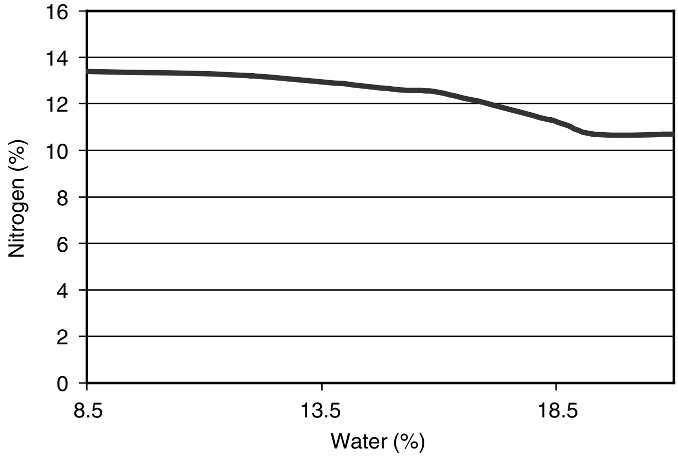


Fig. 3. Influence of water on degree of nitration of cellulose.

the amount of a substituent that is attached to a cellulosic backbone. Each anhydroglucose unit of a cellulosic backbone contains 3 hydroxyl groups and thus a fully esterified cellulose ester, commonly referred to as a triester, has a degree of substitution of 3 ($DS = 3$). Degree of substitution is used throughout this report to represent the extent of substitution on the cellulose ester. A subscript is often used to indicate the nature of the substituent, eg, DS_N means the degree of substitution of nitrogen-containing compounds. The terms DS_P and DS_S mean degree of substitution of phosphorus- and sulfur-containing compounds, respectively. The maximum DS_N of commercial nitrocellulose is ~2.9 (~13.8% N). The hydroxyl group at C6 is nitrated much faster than those at C2 and C3. Under equilibrium conditions (ie, commercial processes utilizing HNO_3, H_2SO_4, and H_2O), the relative rates of nitration of the hydroxyl groups on cellulose are as follows, C6 = 5.8, C2 = 1.8, C3 = 1.0 (13).

2.2. Sulfur-Containing Esters of Cellulose.

Cellulose sulfate and cellulose sulfonates are examples of sulfur-containing esters of cellulose. The sulfur is linked directly to an oxygen atom contained within an anhydroglucose unit of cellulose (see Fig. 1).

Cellulose Sulfate. Sulfation of cellulose has been accomplished via a number of procedures. Three forms of cellulose sulfate have been described in the literature; surface modified cotton fabric or fibers, water-swellable cellulose sulfate, and water-soluble cellulose sulfate. Sulfation of cellulose is commonly accomplished using sulfuric acid, chlorosulfonic acid, or sulfur trioxide/pyridine (eq. 1). Philipp and Wagenknecht (14) compiled a list of 50 sulfation strategies for the preparation of cellulose sulfate (Tables 1–5). The methods described in Tables 1–5 produce cellulose sulfate with various degrees of substitution. A common theme in the synthesis of cellulose esters (both inorganic and organic) is the trade-off between esterification and polymer degradation. Preparation of cellulose sulfate is no exception to this rule. Increasing the temperature during the sulfation reaction produces a more homogeneous mixture and thus more complete sulfation, but the rate of polysaccharide chain degradation is also rapidly

Table 1. **Preparation of Cellulose Sulfate Using H_2SO_4**

Sulfation system				DS
H_2SO_4				1.0–2
H_2SO_4	SO_2			0.9
H_2SO_4	chlorinated hydrocarbon			0.3
H_2SO_4	diethyl ether			0.2–0.4
H_2SO_4	low aliphatic alcohol			0.05–1
H_2SO_4	low aliphatic alcohol	inert solvent		0.35–0.7
H_2SO_4	chlorinated aliphatic alcohol			0.5
H_2SO_4	Ac_2O			0.6–2.8
H_2SO_4	Ac_2O	HOAc	salt	0.1–0.5
H_2SO_4	Ac_2O	HOAc	inert solvent	0.3–1.0
H_2SO_4	Ac_2O	pyridine	dioxane	2
H_2SO_4	aliphatic carboxylic acid C3-C4			NA[a]
H_2SO_4	HOAc	salt		0.3
H_2SO_4	HOAc	benzene		0.6

[a] Not available = NA.

Table 2. **Preparation of Cellulose Sulfate Using $ClSO_3H$**

Sulfation system			DS
$ClSO_3H$			NA[a]
$ClSO_3H$	SO_2		1.8
$ClSO_3H$	chlorinated hydrocarbon		NA[a]
$ClSO_3H$	pyridine		1.9–2.8
$ClSO_3H$	pyridine propanolamine		1.6
$ClSO_3H$	pyridine	toluene	2.8
$ClSO_3H$	formamide		2

[a] Not available = NA.

Table 3. **Preparation of Cellulose Sulfate Using SO_3**

Sulfation system				DS
SO_3				3
SO_3	SO_2			2.2
SO_3	CS_2			3
SO_3	chlorinated hydrocarbon			0.5–0.9
SO_3	diethyl ether			1.3–2.1
SO_3	DMSO[a]			1.3–2.0
SO_3	DMF[b]			1.5–2.6
SO_3	pyridine			NA[c]
SO_3	pyridine	various solvents		0.1–2.2
SO_3	aliphatic amine	DMF[b]		0.4–2.0
SO_3	aliphatic amine	pyridine		1.5
SO_3	triethylphosphate			3
SO_3	N_2O_4	DMF[b]		0.3–1.1
SO_3	N_2O_4	DMF[b]	various solvents	<2.0

[a] Dimethyl sulfoxide = DMSO.
[b] Dimethylformamide = DMF.
[c] Not available = NA.

increased. The rate of sulfation for the following sulfating agents is as follows: $H_2SO_4 < SO_3 < SO_2Cl_2 < HSO_3Cl$, with SO_2Cl_2 generating the most chain degradation during sulfation (14). Chlorosulfonic acid is generally considered the most effective sulfation agent with regard to both sulfation and retention of chain length. Excess sulfuric acid is typically used during sulfation reactions; however,

Table 4. **Preparation of Cellulose Sulfate Using SO_2Cl_2**

Sulfation system			DS
SO_2Cl_2	alkali cellulose		NA[a]
SO_2Cl_2	benzene	alkali cellulose	NA
SO_2Cl_2	$ClCH_2COOH$	alkali cellulose	NA
SO_2Cl_2	DMF, formamide		0.2–0.5
SO_2Cl_2	N_2O_4	DMF	0.4–0.8

[a] Not available = NA.

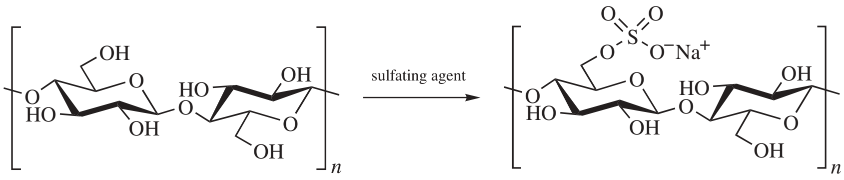
Table 5. **Preparation of Cellulose Sulfate Using Miscellaneous Reagents**

Sulfation system				DS
$NaSO_3Cl$	HOAc			NA[a]
$NaSO_3Cl$	Ac_2O	HOAc		NA[a]
$NaSO_3Cl$	pyridine			NA[a]
$C_2H_5SO_3H$	pyridine	nitrobenzene		2.8
NH_2SO_3H	urea			NA[a]
FSO_3H	pyridine			NA[a]
FSO_3Na	benzene	C_2H_5OH	alkali cellulose	NA[a]
FSO_3NH_4	benzene	C_2H_5OH	alkali cellulose	NA[a]
Na-acetylsulfate				NA[a]
$NOSO_4H$	DMF, DMSO, DMAc[b]			0.7–1.2
$NOSO_4H$	diethyl ether, various solvents			0.02–0.4

[a] Not available = NA.

[b] Dimethylacetamide = DMAC.

stoichiometric amounts of acetylsulfuric acid can be used to prepare cellulose sulfate (15).



(1) (3)

(1)

Cellulose sulfates with a wide range of degree of substitution can be water soluble, eg, cellulose sulfates with DS_S as low as 0.25 can be water soluble. The solubility of the final product is influenced by the method of preparation. The regioselectivity of sulfation can affect the properties and end uses of cellulose sulfate, eg, the ability of a cellulose sulfate to act as an anticoagulant is directly influenced by the distribution of the sulfates around the cellulosic backbone (16). A heterogeneous process, a homogeneous process, or a protection-deprotection strategy can be used to regioselectively derivatize cellulose (17). Generally, a bulky substituents is required to achieve reasonable regioselectivity in a heterogeneous process, so either a homogeneous process or a protection-deprotection strategy is preferred for the preparation of regioselectively substituted cellulose sulfate. Cellulose sulfates can be prepared under homogeneous conditions by first converting cellulose to the trimethylsilyl (TMS) ethers (18). Water-soluble cellulose sulfates were obtained by applying this strategy. The TMS ethers apparently act as reactive intermediates resulting in SO_3-induced sulfation only at sites previously silylated. The free hydroxyls present in the TMS cellulose (DS_{Si} 1.5–2.5) are unreactive during sulfation. When a similar sulfation strategy is applied to cellulose acetates (DS_{Ac} 1.8–2.5) the free hydroxyls are readily

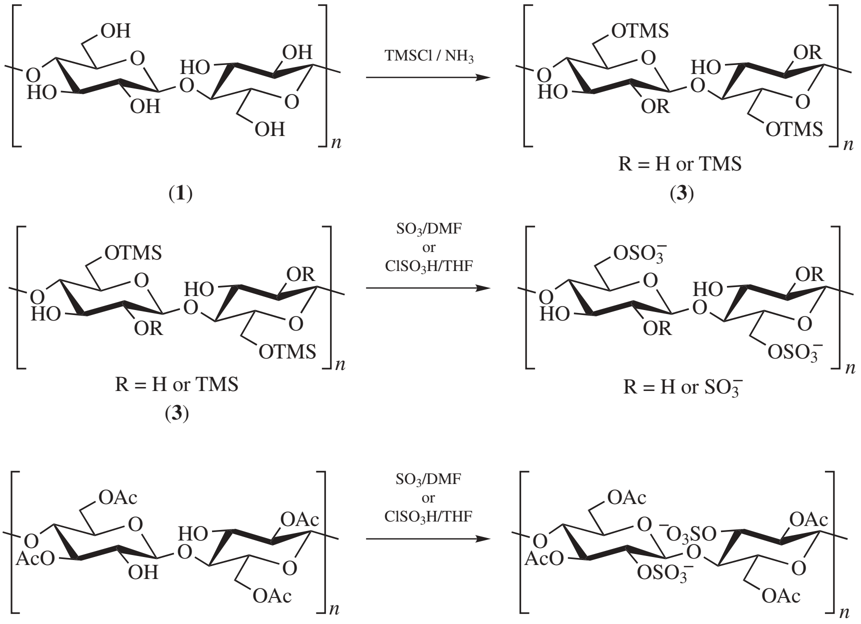


Fig. 4. Synthesis of cellulose sulfate from silylated and acetylated cellulose.

sulfated. It has been suggested that the TMS groups effectively shield the unreacted hydroxyl groups thus preventing sulfation (19). Sulfation of TMS cellulose derivatives with SO_3 or HSO_3Cl in DMF possibly occurs via insertion of SO_3 into the Si–O bond with the sulfate generated by subsequent hydrolysis and neutralization (16,18). Wagenknecht and co-workers (20) and Mischnick and co-workers (21) developed routes to evaluate the substitution pattern of cellulose sulfates.

There are numerous synthetic strategies available for preparing cellulose sulfates with a wide range of properties (see Fig. 4).

Cellulose Sulfonates. Cellulose sulfonates are inorganic esters of cellulose and sulfonic acids in which there is a sulfur–oxygen bond formed to link the cellulose and sulfonic acid moieties. Figure 5 depicts the three most common cellulose sulfonates described in the literature, cellulose toluenesulfonate (tosylate) (**8**), cellulose methanesulfonate (mesylate) (**7**), and cellulose dansylate (**9**) (22–25). Cellulose tosylate is the most commonly described cellulose sulfonate in the literature. Cellulose sulfonates are typically prepared in a homogeneous process by dissolving cellulose in a dimethylacetamide/lithium chloride (DMAc/LiCl) mixture and reacting the cellulose with sulfonylchloride in the presence of triethylamine (eq. 2) (25). Cellulose sulfonates can also be prepared *in situ* for use as reactive intermediates (26,27). The use of cellulose tosylate as a reactive intermediate will be discussed in more detail later in this article.

Cellulose deoxysulfonates have been described in the literature, but will not be discussed further in this report (28).

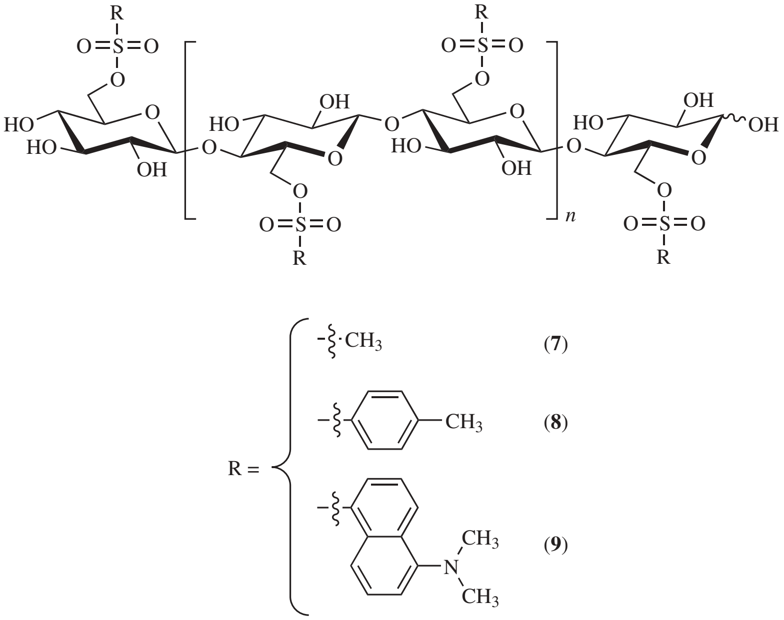
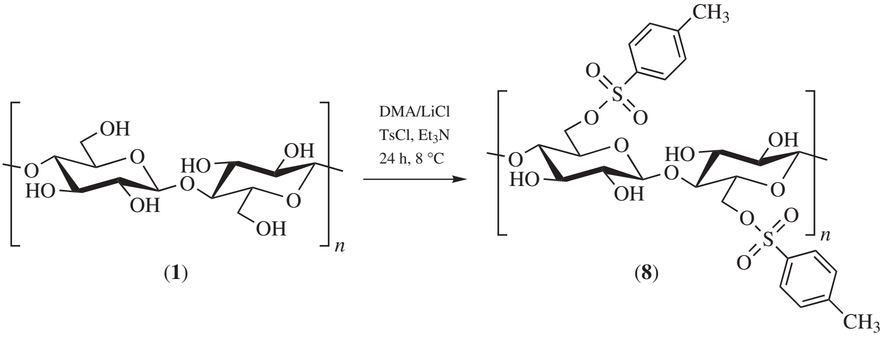


Fig. 5. Structures of cellulose sulfonates.



(2)

2.3. Phosphorus-Containing Esters of Cellulose. *Cellulose Phosphates.* There are a number of strategies for preparing cellulose phosphate. Reaction of cellulose with tetrapolyphosphoric acid in the presence of triethylamine produced cellulose phosphate with $DS_P \leq 1.75$ (29). Treatment of cellulose with $POCl_3$ resulted in cellulose phosphate with low DS_P, but also resulted in introduction of chlorine to the cellulosic backbone (Table 6) (30). Phosphorylations of cellulose with *N*-phosphoryl-*N*′-methylimidazole and a mixture of phosphorus pentoxide, triethyl phosphate, and phosphoric acid have been reported (Fig. 6) (31,32).

Table 6. **Phosphorylation and Chlorination of Cellulose with $POCl_3$**

Reaction temp	$POCl_3$ (%)	DS_P	DS_{Cl}
50	2	0.09	0.02
	4	0.08	0.03
	8	0.03	0.03
75	2	0.19	0.04
	4	0.08	0.08
	8	0.06	0.47
	10	0.08	0.52
	12	0.07	0.55
100	2	0.22	0.04
	4	0.18	0.12
	8	0.20	0.37

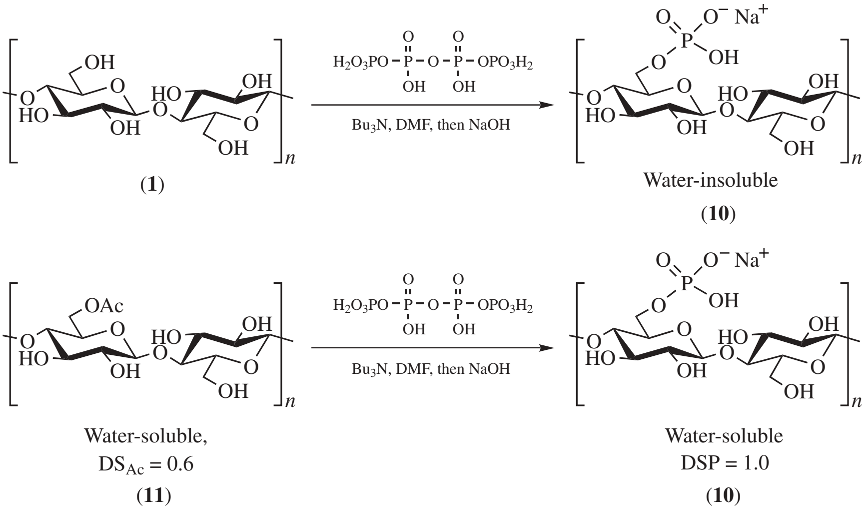


Fig. 6. Synthesis of water-insoluble and water-soluble cellulose phosphate.

3. Properties of Inorganic Esters of Cellulose

In general, inorganic esters of cellulose have significantly different solubility profiles than native cellulose. Cellulose has poor solubility in most organic or aqueous systems, while inorganic esters of cellulose are typically more soluble. Inorganic esters of cellulose that are soluble in organic or aqueous solvents are available. The solubility of inorganic esters of cellulose is dependent on the identity and degree of substitution of the substituents, the number of unreacted free hydroxyls, and the degree of polymerization of the cellulose backbone.

3.1. Solubility. Cellulose sulfate and cellulose phosphate can be either water-soluble or water-swellable depending on the conditions used during preparation (see above). Cellulose nitrate and some cellulose sulfonates are generally more hydrophobic and are typically soluble in organic solvents. In general, the level of esterification of cellulose directly impacts the solubility of the product in various solvents and solvent blends.

3.2. Film Formation and Rheology. The ability to form films is the most important property of inorganic cellulose esters. When cellulose nitrate is dissolved in an organic solvent and then applied to a substrate (eg, wood, metal, glass) a clear film is formed on the substrate once the solvent evaporates. Coatings of this nature are referred to as lacquers. Coatings applications are the largest commercial applications for cellulose nitrate and will be discussed further in the applications section of this article. Clear films of cellulose sulfate (33) and cellulose phosphate (34) have also been reported.

The rheological behavior of cellulose esters, both inorganic and organic, is an important property that contributes to the utility of these cellulosics, particularly in coatings applications. Rheological profiles of cellulose nitrate are well documented (35–38). The semirigid cellulose nitrate displays a flow behavior similar to that of linear flexible polymers (38). Marx-Figini and Gonzalez (35) suggested that the transition from Newtonian to non-Newtonian behavior is likely due to entanglement of molecules above a critical concentration. The higher the degree of polymerization of the cellulose nitrate, the lower the critical concentration at a given shear rate and the lower the critical shear rate at a given concentration. The critical concentrations are much lower for cellulose nitrate than for other synthetic polymers, such as polystyrene or polyacrylamide, with comparable molecular weights (35).

4. Applications of Inorganic Esters of Cellulose

Nitrocellulose is the most commercially important inorganic ester of cellulose. The use of nitrocellulose led to development of the plastics industry, the motion picture industry, and powder-less ammunition. In most cases, nitrocellulose has been replaced over the years by less expensive or less flammable materials. Though considerable market share for nitrocellulose has been lost to alternate products, nitrocellulose remains a commercially viable product and should be for many years.

4.1. Coatings, Adhesives, and Inks. The largest market for cellulose nitrate is in the coatings industry. Relatively clear and workable (ie, sandable or removable) lacquers are generated when cellulose nitrate is used in a coatings application. Cellulose nitrate lacquers dry rapidly, have excellent flow properties and the final coating has excellent appearance, with reasonable strength and durability. Cellulose nitrate became a commercially viable product in the 1920s and rapidly replaced slower drying varnishes that were used in both automotive and wood coatings (39). Cellulose nitrate has played such a significant role in lacquer coatings applications that cellulose nitrate-based lacquers are simply referred to as "lacquers" and it is assumed that a lacquer is cellulose nitrate-based unless stated otherwise. Over time, cellulose nitrate was replaced in automotive topcoats by more durable acrylic lacquers. Cellulose nitrate maintained much of its market share in applications where high temperature curing is not acceptable, for example in wood coatings (39). Cellulose nitrate is still used in some automotive primer refinish applications, but currently its primary use is in wood coatings. Cellulose nitrate provides enhanced wood grain appearance, rapid drying, and easy damage repair to wood coatings. Cellulose nitrate has also been used as an additive to improve the performance, appearance, and drying time of coatings based on other resins, such as acrylics, vinyls, polyamides, epoxies, and polyesters (40). Cellulose nitrate aids in pigment dispersion and acts as a binder following solvent evaporation.

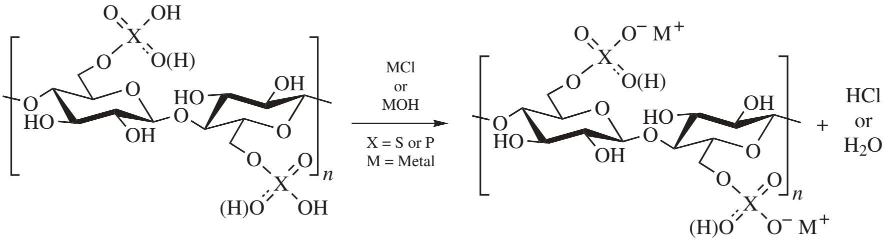
Cellulose nitrate used in coatings applications is commercially available in three general forms based on nitrogen content: SS (10.7–11.3% N), AS (11.3–11.7% N), and RS (11.7–12.2% N) (39). Additionally, each product type is available in low, medium, and high viscosity grades. According to product literature from ICI Nobel Enterprises (Scotland, U.K.) low and medium nitrogen grades are typically used in ink applications. Medium nitrogen content is used for film coatings. High nitrogen content cellulose nitrate is commonly used in wood coatings, general purpose lacquers, and automotive refinish applications. Cellulose nitrate-based lacquers have many advantages over other coatings. They are easily applied, have good adhesion, good solvent release properties and excellent pigment dispersion. The problems with nitrocellulose lacquers include yellowing, flammability, and that they must be sprayed at low solids levels. Nitrocellulose-based lacquers found use in cloth book bindings (40). Nitrocellulose is also used in adhesives and inks (40,41).

4.2. Explosives. Cellulose nitrate with a nitrogen content of 12.3–13.5% N (degree of substitution, $DS_N = 2.25–2.5$) is used in explosive and propellant applications. Cellulose nitrate was initially developed for use in explosives and propellants and this remains one of the largest markets for cellulose nitrate today.

4.3. Plastics. In 1847, it was discovered that cellulose nitrate could be dissolved in a mixture of ether and alcohol to produce a solution called Collodion. Collodion is still in use today in pharmaceutical applications. Combination of nitrocellulose with castor oil and eventually camphor by Parkes (1862) and Hyatt (1870) led to the production of Celluloid and ultimately the birth of the plastics industry.

4.4. Flame Retardants. Flame retardant cotton fibers are prepared by surface modification of cotton cellulose via phosphorylation or phosphorylation–halogenation producing cellulose phosphate and deoxychlorocellulose phosphate, respectively. Surface modification of cotton fibers generates flame retardant fabrics by increasing the char content of the fiber, which in turn produces a lower percentage of flammable volatiles. Since the phosphorylated–halogenated fibers break down to produce acidic products, the overall thermal stability of the fabric is greatly reduced, and the material breaks down at a lower temperature and ultimately reduces the potential of the fabric bursting into flames (42).

4.5. Separations Applications. *Ion Exchange.* Inorganic esters of cellulose have been used in ion exchange applications and as chromatographic adsorbents since the late 1950s (43). Cellulose sulfate and cellulose phosphate are excellent ion exchangers. Exposure of the ester to a salt of a metal ion (eg, NaCl, KCl) or neutralization of the acid with a base (eg, NaOH, KOH) will result in exchange of the metal ion from the salt or base onto the sulfate or phosphate attached to the cellulose backbone (eq. 3).



(3)

Cellulose phosphate is the most widely used cellulose inorganic ester for ion exchange. Cellulose phosphate is an effective cation exchanger used in the bioprocessing industry (44). Cellulose phosphate and cellulose polyphosphate effectively remove Al^{3+} contamination from adenosine triphosphate (ATP) (45). A number of products are commercially available, most notably from Whatman, for use as stationary phases in column chromatography and filtration applications. Whatman P1, P11, and P81 are examples of commercially available cellulose phosphate-based ion exchangers.

The ion exchange nature of cellulose sulfate resulted in its use to concentrate viruses (46).

Molecular Weight Determination. Since there are nitration methods available that have minimal impact on the chain length of cellulose, conversion from cellulose to cellulose nitrate is an established method of molecular weight determination of cellulose. This is another situation where the improved solubility of cellulose nitrate is advantageous over the relative insolubility of cellulose. Cellulose nitrate molecular weight can be successfully determined using size-exclusion–gel permeation chromatography due to its improved solubility over cellulose (47–53).

Chiral Chromatography. Cellulose trinitrate-impregnated silica beads was used as a chiral stationary phase for the separation of several racemic aromatic compounds (54).

4.6. Membrane Applications. Cellulose esters are effective in membrane applications. Ultrafiltration membranes based on cellulose nitrate were first described by Collander in 1924 (55). Cellulose nitrate films cast from mixtures of methyl acetate or acetone with glycerine and mixtures of ether and ethanol produce microfiltration and ultrafiltration membranes, respectively (56). Cellulose nitrate microfiltration membranes typically have 0.02–10-μm diameter pores and 4×10^{-3}–15 cm/s · atm permeability. Cellulose nitrate ultrafiltration membranes typically have 0.003–0.03 μm diameter pores and $1–100 \times 10^{-4}$ cm/s · atm permeability (56). Nitrocellulose membranes are used in numerous biochemical and diagnostic applications and will be discussed later.

Cellulose sulfate, in particular C6 sulfates, can be used for preparing polyanion–polycation complexes for pervaporation membranes (57–59).

4.7. Synthetic Intermediates. Cellulose sulfonates have been evaluated as synthetic intermediates (27,60–63). Cellulose tosylate activates the C6 hydroxyl for substitution with various nucleophiles (eq. 4). Additionally, cellulose sulfonates can also function as a protecting group to prevent reaction of the C6 hydroxyl during esterification reactions (Fig. 7). Cellulose tosylates with degrees of substitution from 0.38 to 2.30 have been reported. Though an effective synthetic tool, the expense of organic solvents utilized and the cost and corrosive

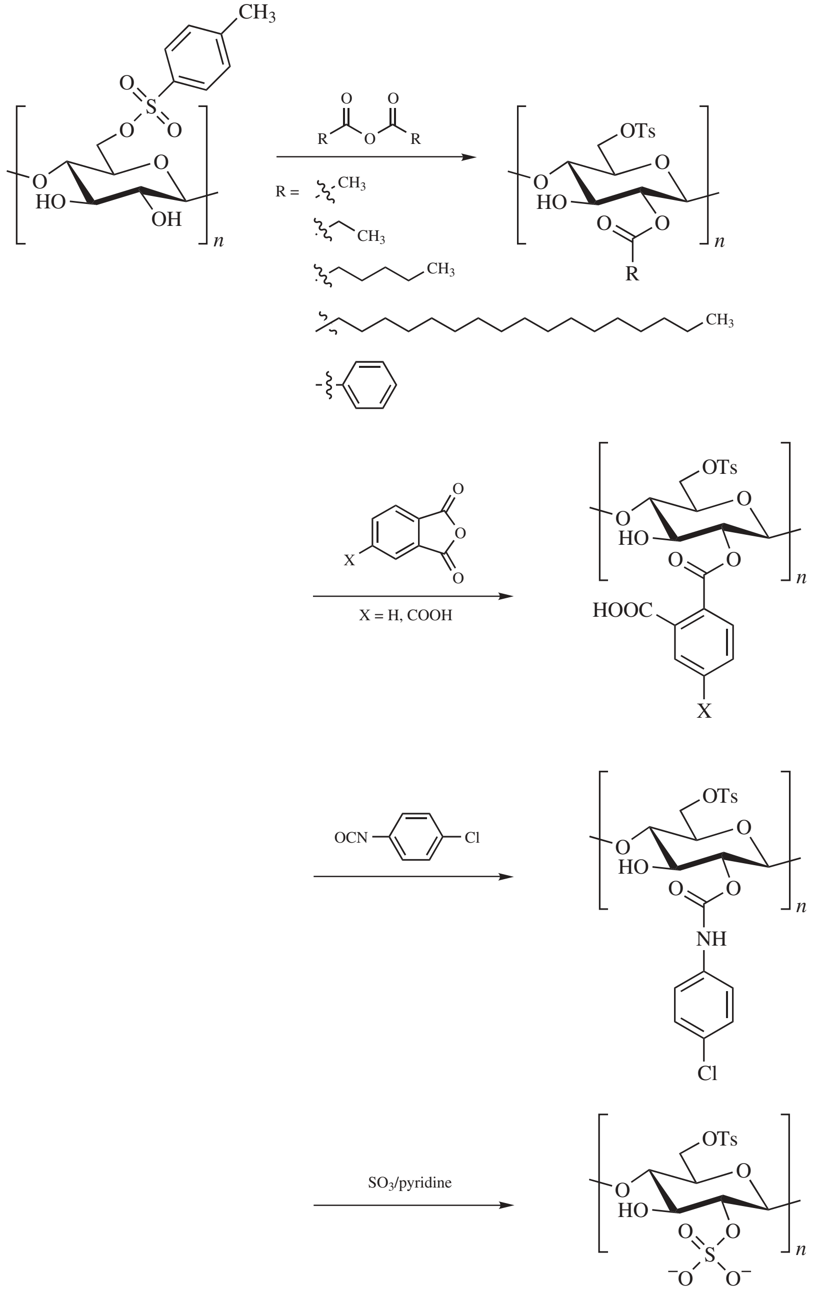
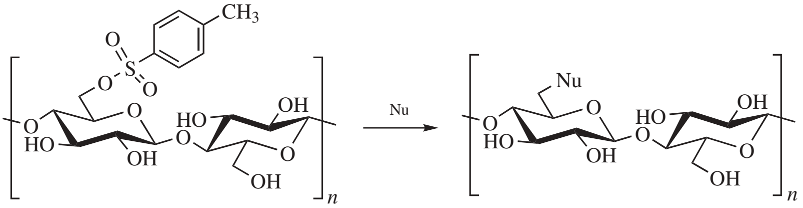


Fig. 7. Subsequent chemical modification of cellulose tosylate.

nature of tosyl chloride have limited the use of this methodology on a commercial scale.



(4)

Nu- = Cl^-, N_3^-, $NH_2\text{-}(CH_2)_m\text{-}NH_2$, or other nucleophiles

4.8. Medical Applications.

Inorganic esters of cellulose have been evaluated in a number of medical–pharmaceutical applications. A few examples include treatment of hypercalciura, use as antiviral agents, reduction of cholesterol levels, orthopedic applications, and blood stabilization.

Sodium cellulose phosphate is used in the treatment of adsorptive hypercalciura and nephrocalcinosis (both a common cause of kidney stones). The ability of inorganic esters of cellulose to function as ion exchangers, described previously in this report, is the key to the use of sodium cellulose phosphate in the treatment of adsorptive hypercalciuria. Hypercalciuria is an increased level of calcium in a patient's urine. This disorder commonly results in painful kidney stones. Sodium cellulose phosphate has been used to complex the calcium ions and thus remove them from the patient and minimize the risk of stone formation (64–68).

It is well established that sulfated polysaccharides play important biological roles (69–77). Cellulose sulfate displays heparin-like activity and to a lesser extent antiviral activity (78). More specifically, cellulose sulfates with a medium to high degree of sulfation at the C2 and C6 positions of the anhydroglucose units are the most active forms of the ester. High molecular weight cellulose sulfate lowers cholesterol levels in humans by inhibiting pancreatic cholesterol esterase (79,80). Contamination of high molecular weight cellulose sulfate with its low molecular weight counterpart results in a toxic, unusable product. A method to prepare and isolate high molecular weight cellulose sulfate without contamination with low molecular weight cellulose sulfate has been developed (79). Ushercell (a commercial form of sodium cellulose sulfate marketed by Polydex Pharmaceuticals) has been evaluated in the treatment of papilloma virus infection (81). Usher and co-workers (82) also investigated the use of sodium cellulose sulfate as an antimicrobial agent and a contraceptive. Cellulose sulfate with a DS > 1.0 and sodium cellulose sulfate when complexed with (β-hydroxy-γ-trimethylaminopropyl) hydroxyethyl cellulose chloride show excellent anticoagulative property (83,84).

Encapsulation of microorganisms, enzymes, plant cells, and animal cells (including mammalian cells) has been accomplished using a mixture of sodium cellulose sulfate with polydiallyldimethyl ammonium chloride (85,86). Encapsulation of hydridoma cells with cellulose sulfate has provided a means of subcutaneous delivery of monoclonal antibodies. The implant vascularized as early as

15 days after implantation and the "neoorgan" remained an active source of antibodies in mice for several months (87).

Cellulose phosphate has been evaluated in femoral implants to improve the mineralization of biomaterials used in orthopedic applications (88). Cellulose phosphate (with or without bound antimicrobial agents) and cellulose phosphate borate effectively stabilize blood for over four years (89).

4.9. Biochemical Applications.

Cellulose phosphate paper (P81), also called phosphocellulose paper, has been used for enzyme assay applications (90). As with many other applications of cellulose phosphate, the ability of the material to act as an ion exchanger is the key property that leads to its use in enzyme assays. Cellulose phosphate paper quantitatively binds small peptides that contain at least two basic residues and a free amino terminus, which allows for protein kinase assays to be performed and ^{32}P-labeled cofactors [γ-^{32}P]ATP and non-peptidic by-products [^{32}P]Pi to be washed away (91).

Even though a number of applications have been demonstrated for cellulose phosphate in the biotechnology laboratory, the use of cellulose nitrate dominates the field. Cellulose nitrate filters and membranes have played key roles in numerous biochemistry and molecular biology discoveries and still play important roles in these laboratories today. Protein and glycoprotein immobilization, absorption of single-stranded DNA (Southern blotting), absorption of single-stranded RNA (Northern blotting), binding of transfer RNA linked to ribosomes, tissue printing, and dialysis are common practices accomplished through the use of nitrocellulose membranes or filters (92–97). The binding of ribosomes and tRNAs to nitrocellulose was used to elucidate the genetic code. Cellulose nitrate is an efficient binder of antibodies and can be used as a solid support for immunoaffinity chromatography (98).

4.10. Diagnostic Applications.

The binding characteristics of cellulose nitrate membranes have led to their use in numerous biosensor applications, such as in an electrochemical microbial biosensor for EtOH (99), and in glucose oxidase-based glucose sensors (100). Cellulose nitrate continues to play an important role in the development of new biosensors as both a solid support and a method for removal of unbound reagents (101–107).

Additionally, cellulose nitrate has been utilized in nonbiological detectors including an indoor radon gas detector. The cellulose nitrate portion of the film-based detector is the active portion for the detection of α-particles (108).

5. Conclusions

Inorganic esters of cellulose have a valuable place in history, from the birth of the plastics industry to elucidation of the genetic code. It is important not to forget the large number of applications in which these materials have played a role: coatings, explosives, pharmaceuticals, membranes, and synthetic intermediates. Though inorganic esters of cellulose have been around for >100 years, these materials remain important tools for coatings scientists, explosives experts, and biochemists.

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