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Complete List of Authors:	Satari, Behzad; Isfahan University of Technology, Department of Chemical Engineering Karimi, Keikhosro; Isfahan University of Technology, Department of Chemical Engineering Kumar, Rajeev; University of California, Center for Environmental Research and Technology

Cellulose solvents-based pretreatment for enhanced second-generation biofuels production: A review

Behzad Satari,[1] Keikhosro Karimi,[1,2] and Rajeev Kumar[3,4,5,*]

[1]**Department of Chemical Engineering, Isfahan University of Technology, Isfahan 84156-83111, Iran**

[2]Industrial Biotechnology Group, Research Institute for Biotechnology and Bioengineering, Isfahan University of Technology, Isfahan 84156-83111, Iran

[3]Center for Environmental Research and Technology (CE-CERT), Bourns College of Engineering, University of California Riverside (UCR), Riverside, CA, 92507, USA

[4]BioEnergy Science Center (BESC), Oak Ridge National Laboratory (ORNL), Oak Ridge, TN, USA

[5]Center for Bioenergy Innovation (CBI), Oak Ridge National Laboratory (ORNL), Oak Ridge, TN, USA

*corresponding author

Abstract

Cellulose, in addition to hemicellulose and lignin, makes the major fraction of lignocellulosic biomass- the only sustainable feedstock to meet the long-term sustainable energy need of the world. Cellulose is soluble in a number of solvents, e.g., concentrated phosphoric acid (CPA), N-methylmorpholine-N-oxide (NMMO), and ionic liquids (ILs), and can be regenerated by an anti-solvent without major derivatization for various applications. For one, the regenerated and much less crystalline cellulose is highly reactive for its biological conversion to sugars, fuels, and chemicals mediated with enzymes and/or microbes. This ability can be used as a core pretreatment step for improved bioprocessing of lignocelluloses. In this comprehensive review, cellulose solvent-based lignocellulosic fractionation technologies for enhanced enzymatic hydrolysis to improve biofuels and renewable chemicals production are reviewed. The first part is focused on the background information of lignocellulosic biomass, lignocellulosic derived biogas, biohydrogen, and ethanol as well as acetone, butanol, and ethanol (ABE) production, and enzymatic hydrolysis. In the second part, the conditions for pretreatments applying CPA, NMMO, and ILs solvents, improvements in enzymatic hydrolysis rates and yields for solids resulting from application of these pretreatments, and the features of lignocellulosic structure affecting the improved bioprocessing have been thoroughly reviewed.

Keywords: Cellulose; solvent; pretreatment; enzymatic hydrolysis; biogas; ethanol; lignocellulose; ionic liquid

Abbreviation

Anaerobic digestion	AD
1-butyl-3-methylimidazolium chloride	[BMIM][Cl]
Cellulose binding module	CBM
Concentrated phosphoric acid	CPA
Consolidated bioprocessing	CBP
Cellulose accessibility to cellulase	CAC
Cellulose solvent- and organic solvent-based lignocellulosic fractionation	COSLIF
Crystallinity index	CrI
1-Ethyl-3-methylimidazolium acetate	[EMIM][OAc]
Greenhouse gas	GHG
Ionic liquid	IL
Lateral order index	LOI
National renewable energy laboratory	NREL
N-methyl-morpholine-N-oxide	NMMO or NMO
Room-temperature ionic liquid	RTIL
Single cell oil	SCO
Soaking in aqueous ammonia	SAA
Simons' Stain	SS
Specific surface area	SSA
Total crystallinity index	TCI
Total reducing sugar	TRS
Volatile fatty acid	VFA
Water retention value	WRV

Contents

1 Different generations and types of biofuels

Recent concerns about climate change due to greenhouse gas emissions and energy crisis have prompted the need for transition from unsustainable fossil-derived energies to sustainable and renewable energies.[1]

Development of sustainable and economically viable biorefinery process for biofuel production needs to use renewable carbon sources.[2] Biofuels produced from food-based crops like sugar- and starch-based substrates, e.g., sugarcane and corn, are considered as first-generation biofuels.[3,4] Nevertheless, there is a food-versus-fuel debate in using the feedstocks for first-generation fuels. Therefore, the next-generation biofuels were introduced and are considered as essential for meeting the world's energy demand in the transportation sector.[5-7]

Second-generation biofuels are produced from lignocellulosic biomass, which can reduce the carbon emission, increase energy efficiency, and reduce nations' energy dependency.[3,7-9] Non-food lignocellulosic substrates are abundant and potentially low-cost organic source for renewable chemicals and fuels production. Lignocellulosic wastes can be originated from industrial wastes (e.g., sawdust, paper mill discards, and food industry wastes), forestry wastes (i.e., hardwoods and softwoods), agricultural residues (e.g., straws, stover, and non-food seeds), domestic wastes (e.g., kitchen wastes, sewage, and waste papers), and municipal solid wastes.[10-12]

Third-generation biofuels are produced from algae.[13,14] Biofuels production from algal species, including *Botryococcus braunni*, *Chaetocero scalcitrans*, several *Chlorella* species, *Isochrysis galbana, Nanochloropsis, Schizochytrium limacinum,* and *Scenedesmus* species, is a promising technology since algae is fast growing, compared to many terrestrial plants, with no soil need,

while they have high capturing ability for CO_2 and other greenhouse gases.[15] Algae contain substantial amounts of carbohydrates and lipid (up to 70%), making them promising feedstocks for converting to biofuels, e.g., by simple hydrolysis followed by fermentation or consolidated bioprocessing.[16] A comprehensive overview on the composition, properties, and challenges of algae biomass for biofuel application was recently presented by Vassilev and Vassileva.[17] Biodiesel, bioethanol, biohydrogen, and biogas were reported to be produced from micro- and macro-algae via different technologies.[13,14]

Fourth-generation biofuels use engineered algae for biofuels production from oxygenic photosynthetic organisms.[18] Gaseous biofuels, algal ethanol, algal butanol, four carbon alcohols, and algal biodiesel were reported to be possible to produce by using this technology.[18]

Nonetheless, the production cost of biofuel is extremely sensitive to the feedstock cost.[19] Although algae do not need freshwater and can grow on wastewater streams (e.g., saline/brackish water/coastal seawater), harvesting and carbon supply are the major factors of algal biomass production cost.[20] Harvesting microalgae usually needs flocculation to aggregate small algal cells followed by filtration, centrifugation, and sedimentation to separate the algae from liquid medium. Besides, advanced and cheaper technologies are required for the extraction of algal oil. Although the land use is low for algal cultivation, infrastructure requirements, mixing, and separation costs are still high. Moreover, the high cost of edible crops and land requirements to meet the demand make them unsustainable. Therefore, lignocellulosic biomass is the only sustainable and low-cost feedstock to meet the near future growing energy needs and mitigate environmental problems.[20,21]

Regarding environmental impacts, all types of biofuel reduce greenhouse gas (GHG) emissions[22] (Figure 1). Life cycle assessment for biofuel production from different sources was performed

and the net GHG emission for different fuels, e.g., fossil fuel, soya oil biodiesel, palm biodiesel, sugarcane ethanol, wheat ethanol, corn ethanol, corn stover ethanol, and algal biodiesel, was compared.[21,23] It was shown that among them corn stover derived ethanol released the lowest net GHG emission.

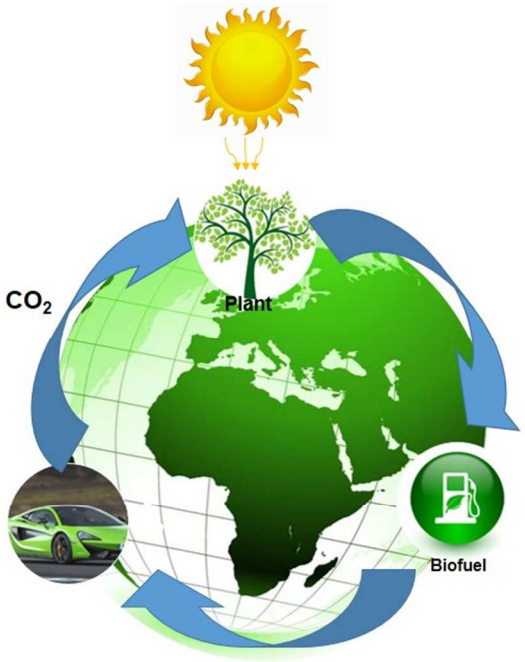


Figure 1. A simplified diagram showing a neutral carbon cycle for biofuels production from plants

Less (or negligible) competition to food, production of value-added byproducts, and energy security are among the advantages of second-generation biofuels. As shown schematically in Figure 2, the main steps for second-generation biofuels and chemicals production are usually substrate preparation, including size reduction and pretreatment, carbohydrate saccharification, fermentation, and product separation and purification.[24] The processing cost for second-generation ethanol is approximately two to three times higher than gasoline on an energy equivalent basis;[25] therefore, substantial attention has recently focused on the improvement of

process economy and technology development to make second-generation biofuels economically viable.

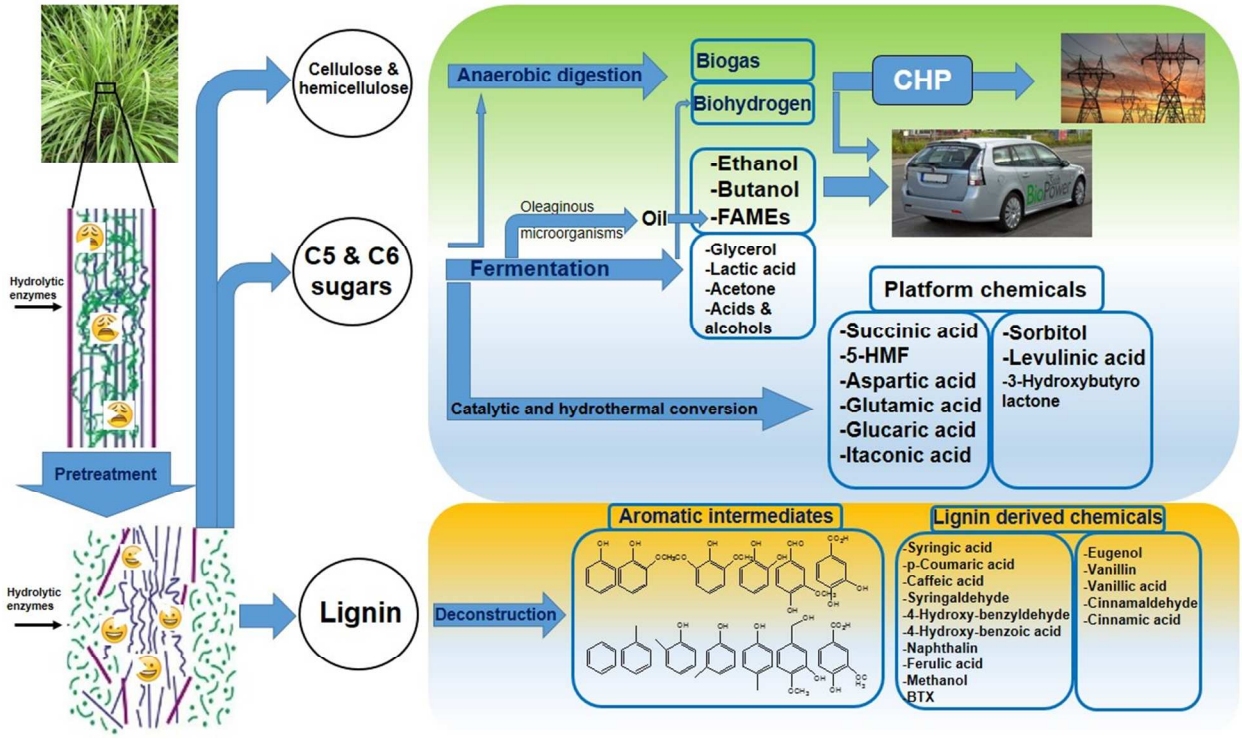


Figure 2. Schematic of various chemicals production from lignocellulosic feedstocks (second-generation biofuels and chemicals)

1.1 **Bioethanol**

Ethanol, blended with gasoline or as a neat fuel in vehicles, is an attractive transportation fuel, giving high octane number and heat of vaporization.[26] Currently, ethanol mainly produced by fermentation routes using sugar- and starch-based feedstocks, e.g., sugarcane and maize, is called first-generation ethanol[27] (Figure 3). Following fermentation, ethanol is separated and purified from the fermentation broth via distillation and molecular sieves, respectively.[28] The industrial technology for the fermentation of glucose to ethanol is quite robust and high concentrations of ethanol (12-15%) can be achieved.[29] In production of ethanol from starch, an extra step of

liquefaction and saccharification by α-amylases and glucoamylases, respectively, is necessary for converting starch to sugar[30] (Figure 3). Since the production capability of the first-generation ethanol is limited and is unsustainable at large scale, second-generation ethanol was then introduced, which utilizes variety of lignocelluloses as substrate.[27,31] (Figure 3).

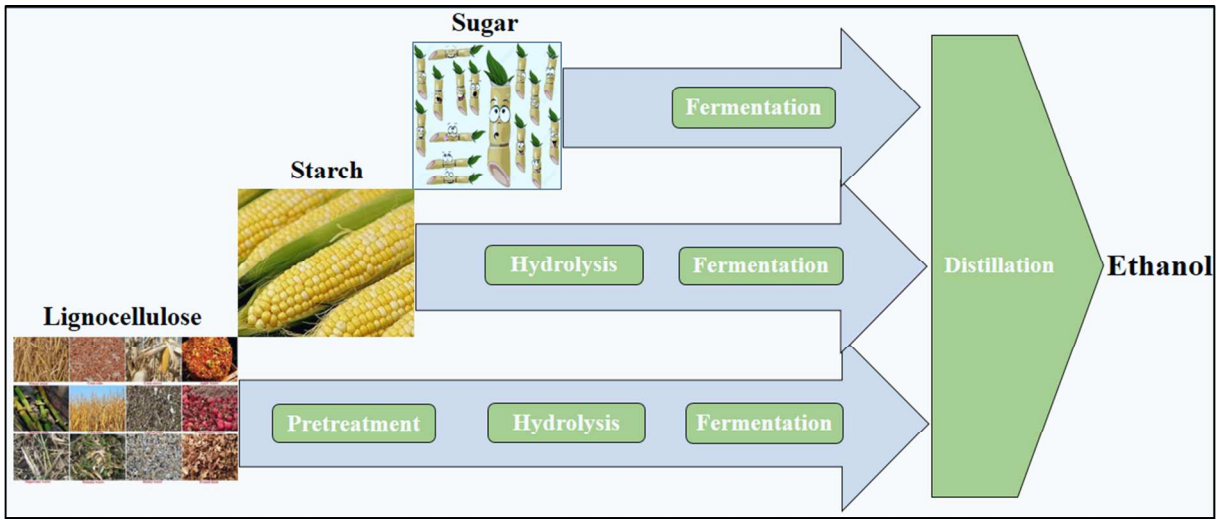


Figure 3. Conversion of different feedstocks to ethanol via fermentation route. The conversion from sugar- and starchy-based materials to ethanol is called first-generation and production from lignocelluloses is called second-generation.

1.2 Biobutanol

For gasoline blending, butanol, a four-carbon alcohol, is more desirable than ethanol due to higher energy density, lower hygroscopicity, lower Reid vapor pressure, better blending ability, and use in conventional combustion engines without modification.[32] Besides the fuel extender, biobutanol can be used as a feedstock for the synthesis of a variety of commercial products.[33,34] Fermentative route of production, e.g., by the microorganisms that belong to the genus *Clostridium*, is more sustainably and environmentally attractive than the petrochemical route.[35] These microorganisms typically produce a mixture of different solvents, mainly including acetone, ethanol, and butanol; thus, the process is referred to acetone-butanol-ethanol (ABE)

fermentation.[36,37] However, the major challenge in the microbial production of butanol is low butanol titer due to product inhibition.[38,39] Several strategies have been reported to address these issues[40] such as genetic and metabolic engineering of microorganisms[40] and promising integrated continuous culture technology with efficient product recovery techniques, e.g., using metal-organic frameworks,[41] liquid-liquid extraction,[42-44] pervaporation technique,[45] and gas stripping.[46]

Butanol can be synthesized via different metabolic and engineered pathways from different substrates. Starch/sugars can be converted to butanol via clostridial route that includes glycolysis, pyruvate:ferredoxin oxidoreductase, thiolase, 3-hydroxybutyryl-CoA dehydrogenase, crotonase, butyryl-CoA dehydrogenase, and butyraldehyde/butanol dehydrogenase. The conversion of lignocellulosic feedstocks to biobutanol also follows the same route after being converted to C_5 and C_6 sugars in the preceding pretreatment and/or enzymatic saccharification steps. Lignocellulosic biobutanol production has received a lot of attention, and it has recently been the focus of vast studies.[47,48] However, the low butanol titers and yields and requirement of extra pretreatment and enzymatic saccharification steps are some of the challenges in butanol production from lignocellulosic biomass. Moreover, syngas or CO_2/H_2 can also be fermented to butanol via clostridial pathway.[49] For starch and sugars, there is another non-fermentative pathway based on amino acid metabolism plus 2-keto acid decarboxylase and alcohol dehydrogenase.[36] Aerobic butane-utilizing bacteria use monooxygenase to oxidize butane to a butanol mixture (95% butanol, 5% iso-butanol).[36]

1.3 Biodiesel

Biodiesel, a mixture of fatty acid methyl esters (FAMEs), can be produced by transesterification of vegetable oil or animal fat. It recently received much attention as a renewable source of

energy.[50,51] However, these resources for biodiesel production do not meet the large-scale demands for transportation fuel and a sustainable renewable source is required.

Nonetheless, some microorganisms, called oleaginous microorganisms, can store intracellular lipids, usually referred to single cell oil (SCO), especially triacylglycerols (TAGs).[51] Microbial oil, as a raw feedstock for biodiesel production, is advantageous compared to vegetable oil because of short life cycle, less labor required, less affected by venue, season, and climate, and easier to scale up.[52] Different oleaginous microorganisms, including microalgae, yeasts, fungi, and bacteria, were reported to produce substantial amounts of SCO (e.g., 20–50% dry cell weight).[53-55] However, it is possible to increase the lipids accumulation in oleaginous microorganisms via metabolic engineering technology, involving the enhancement of fatty acid synthesis approach, enhancement of TAG synthesis approach, regulation of related TAG biosynthesis bypass approaches, blocking of competing pathways, and multigene approach.[56]

A variety of carbon sources from lignocellulose-based carbohydrates and other low-cost industrial wastes, e.g., glycerol, food processing waste, and even wastewater, have been reported to be assimilated by oleaginous microorganisms to produce lipid.[57-61] Auxiliary nutrients such as phosphorous and nitrogen are available from the waste streams. However, lipid accumulation in oleaginous microorganisms is usually triggered by a nutrient starvation, e.g., nitrogen or phosphorus, relative to the carbon source.[62]

Lipid production from lignocellulosic biomass has attracted substantial attention in the recent years and many researches have focused on its commercialization; however, substantial process improvements and reduction in the production cost are required.[63-66]

1.4 Biogas

Besides the liquid biofuels, the biomass with high organic content can be converted to another form of energy, biogas, via anaerobic digestion (AD). In this process, the organic matter is biologically decomposed by an assortment of microbes in an oxygen-free condition and produce biogas (about 50-75% CH_4 and 25-50% CO_2).[67,68] AD process can be divided into four steps: (i) hydrolysis of proteins and lipids to amino acids and long-chain fatty acids and carbohydrates into sugars, (ii) conversion of hydrolysis products and monomers to volatile fatty acids (VFAs) and other minor products such as alcohol by acidogenic bacteria, (iii) conversion of VFAs to acetate, carbon dioxide, and/or hydrogen by acetogenic bacteria, and (iv) methane formation from the other stage products by methanogenesis[69] (

Figure ***4***). Although methanogenesis is usually considered as the rate-limiting step in AD process for a number of substrates, the hydrolysis step is believed to be the limiting step for lignocelluloses. Sawatdeenarunat et al.[70] classified the current technologies in AD process of lignocellulosic biomass to anaerobic co-digestion, solid-state anaerobic digestion (SS-AD) (more than 15% TS) and using alternative biological pretreatment of feedstock for further biological conversion to sugars, e.g., by using rumen microorganisms.

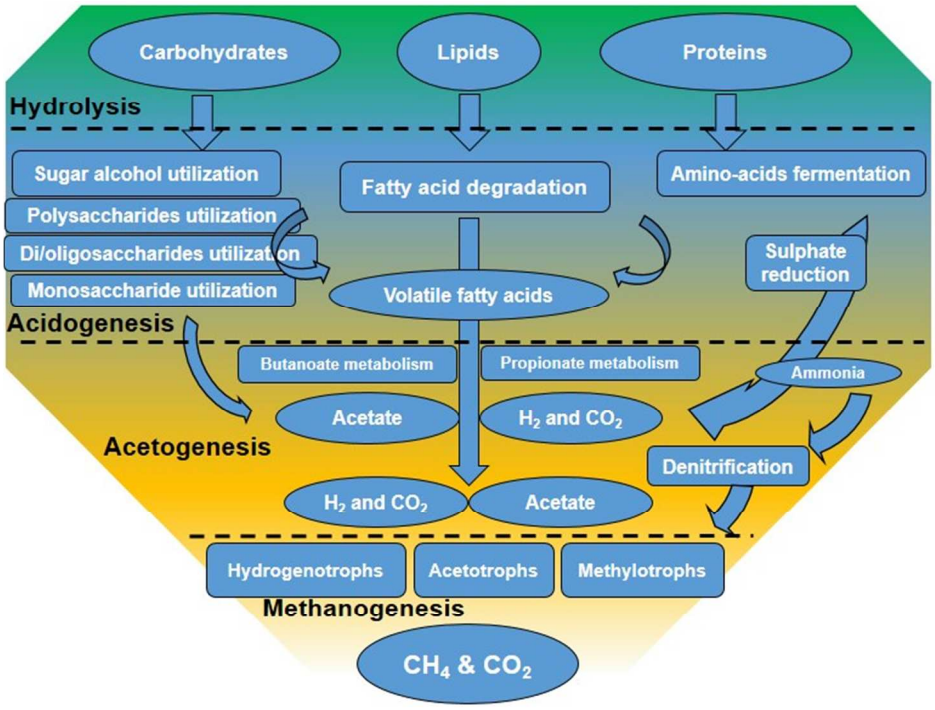


Figure 4. The main steps in degradation of organic matters through anaerobic digestion process[71]

1.5 Biohydrogen

Biologically produced hydrogen, biohydrogen, is recently becoming of great interest as a renewable energy carrier, because hydrogen utilization for combustion, in fuel cell, and/or electricity production produces no carbon byproducts.[72] Biological pathways for hydrogen production are primarily divided into photobiological processes and light independent methods.[73,74] Green algae from the genera *Chlamydomonas*, *Scenedesmus*, *Lobochlamys*, and *Chlorella* can reduce protons of water in the presence of light to produce mixed oxygen and hydrogen gases.[75] Some photosynthetic bacteria were also reported to produce hydrogen by the same mechanism of biophotolysis as that of by the green algae. Fermentative biohydrogen production, classified as photofermentation and dark fermentation, can be performed by a wide variety of microorganisms, e.g., strict anaerobes, facultative anaerobes, and aerobes kept under anoxic conditions.[73,76] Fermentative hydrogen production is more advantageous over

photosynthetic method since various organic feedstocks can be converted to hydrogen with high production rates and simple operations.[77] Several factors, including inoculum, i.e., mixed and pure cultures, substrate, reactor type, availability of nitrogen and phosphate micro-nutrients and metal ions, temperature, and pH, were reported to influence fermentative hydrogen production.[78,79] Because of higher hydrogen evolution rate, dark fermentation hydrogen production is more commercially feasible than photofermentation. In dark fermentation, organic substrates like glucose are converted by facultative and obligate anaerobes to hydrogen, volatile fatty acids, and carbon dioxide operated at mesophilic, thermophilic, or hyperthermophilic temperatures in the absence of light.[80] The knowledge in biological pathways for dark fermentation hydrogen production is quite mature and is comprehensively presented in the literature.[73,75,76,80-85] Here a brief discussion on the strategies to enhance biological hydrogen production and the feedstocks is presented.

Different carbon sources, e.g., agricultural residues, industrial waste, organic fraction of municipal waste, and pure sugars, were reported as feedstock for biohydrogen production.[72,86,87] Lignocellulosic feedstocks are promising raw materials for biohydrogen production and recently have been the focus of a number of studies.[72] Different approaches for bioconversion of lignocellulosic biomass to H_2, i.e., separate hydrolysis and fermentation, simultaneous saccharification and fermentation, and consolidated bioprocessing of lignocellulosic biomass to H_2, have been discussed by Cheng et al.[72] and Ren et al.[88] Application of various pretreatment technologies for enhanced lignocellulosic bioconversion to biohydrogen have been also the topic of several studies.[89-93]

While theoretical hydrogen yield is 12 mole H_2 per mole of glucose, natural and genetically modified microorganisms can produce hydrogen at a maximum yield of 4 mole/mole glucose

when acetic acid is the only VFA product.[85] The strategies for biohydrogen production improvement include microbial culture immobilization, bioreactor modifications, optimization of operational parameters (i.e., temperature, pH, organic loading rate, hydrolytic retention time, and H_2 partial pressure), substrate type and inorganic nutrients, metabolic engineering of microbes, and cogeneration of biohydrogen and biomethane.[73,78,81,94,95]

The inoculum for dark fermentation biohydrogen production can be either pure cultures or anaerobic microbial consortia. Mixed culture is generally preferable because of the easiness to operate, no need for sterilization, and, especially for lignocelluloses, the presence of hydrolytic activities.[96] In such systems, methanogenesis activity can be easily eradicated by a heat shock or pH control, and the hydrogen-producing bacteria can sporulate.[74,97]

Another noteworthy approach based on cell-free hydrogen production was originally proposed by Dr. Jonathan Woodward at Oak Ridge National Laboratory,[98,99] and then has recently been revived by Ye et al.[100] and Zhang et al.[101]

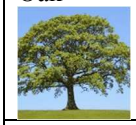
2 Lignocellulosic biomass structure

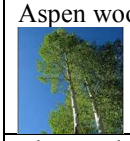
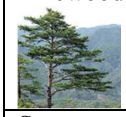
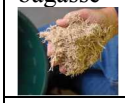
Lignocelluloses typically contain lignin, carbohydrate polymers (~75%; i.e., cellulose, hemicellulose, and pectin), acetate, proteins, salt, ash, and minerals.[102] Table 1 summarizes the major composition (carbohydrates and lignin) of some lignocelluloses used for second-generation biofuels production. Being the nature's most abundant organic substance after cellulose, lignin comprises 28-30% of woody gymnosperm stems and 20-24% of woody angiosperms.[103] Lignin composition varies between hardwoods and softwoods. Lignin has a heterogeneous three dimensional β-O-4, β-5, β-1, β-β, 5-5, and 4-O-5 linked structure of phenylpropane units, e.g., p-hydroxycinnamyl, p-coumaryl, coniferyl, guaiacyl, syringyl, and

sinapyl alcohol.[102,104] Lignin acts as a cement to hold the cell components together and provides the biomass integrity.[105]

Cellulose, with over 10^{11} metric tons production per year, is composed of linear chains of several hundreds to over ten thousand of β-D-glucopyranose residues linked by β-1,4 glycosidic bond with numerous inter- and intra-molecular hydrogen bonds.[106] It is a ubiquitous polysaccharide of plant cell wall (Figure 5), which makes it insoluble in water and common organic solvents.[104,107,108] Aggregation of cellulose chains forms nanofibrils and a 5–10 nm microfibril, hypothesized to be composed of 36 chains of cellulose, is used to define the next level of aggregation, which is observable via high magnification microscopy, e.g., electron microscopy, and atomic force microscopy[109-112] (Figure 5). Cellulose is the dominant component of primary cell wall (20–40% of cell wall dry matter).[113] The research on cellulose revealed that native celluloses are crystalline and are composites of two forms, I_α (with one-chain triclinic structure) and I_β (a two-chain monoclinic structure), which coexist in all native forms.[107]

Table 1. Composition (based on % dry weight) of some widely used lignocelluloses for second-generation biofuels production*

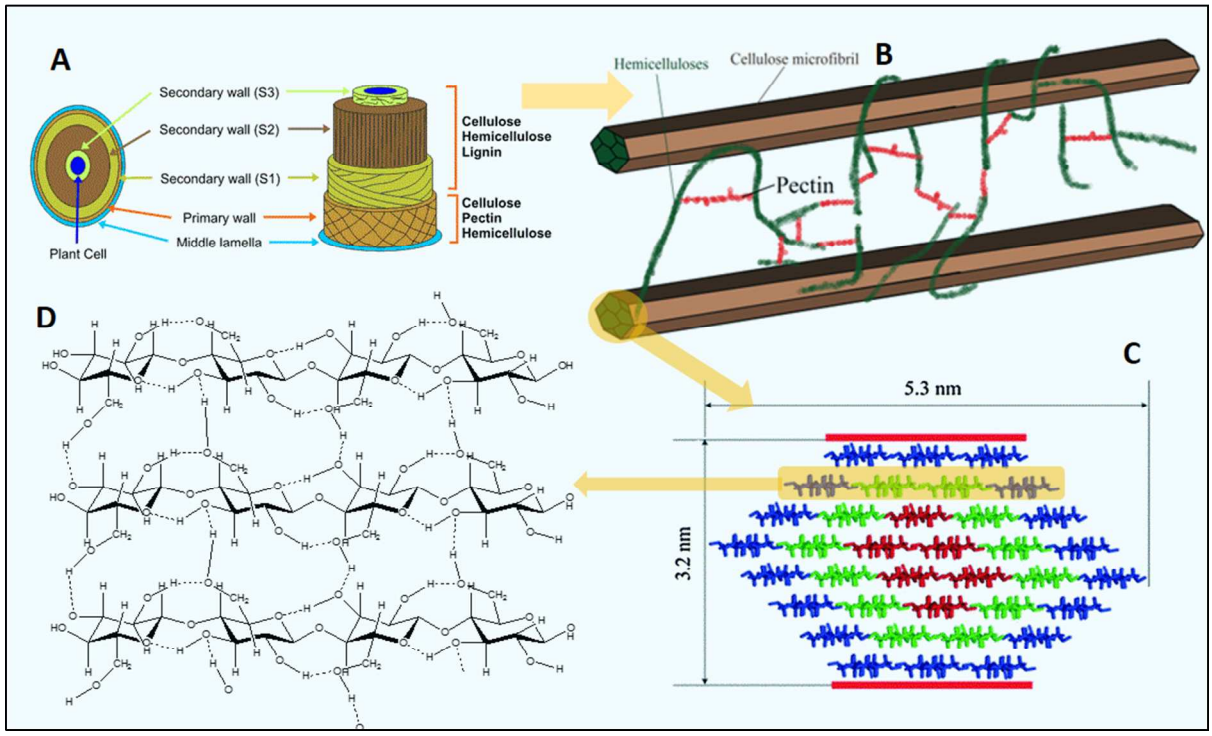
Biomass type	Substrate	Glucan	Xylan	Mannan	Galactan	Arabinan	Lignin			Ref.
							Total	Acid insoluble	Acid soluble	
Hardwood	Eucalyptus 	41.7	14.3	2.6	3.2	2.0	30.2			114
	Oak 	45.2	20.3	4.2	-	-		21.0	3.3	115
	Poplar 	39.2	13.1	1.8	0.9	-	14.7			116

	Birch 	40.3	16.9	1.7	0.6	0.3	20.3			117
	Aspen wood 	49.0	14.9	2.0	0.5	0.8		24.6	1.0	118
	Elmwood 	43.6	20.3	1.5	1.2	-	26.3			119
Softwood	Douglas-wood chips 	47.3	4.4	11.7	2.2	1.2		29.8	0.5	120
	Pinewood 	38.2	8.5	11.3	4.3	-		29.5	4.9	121
	Spruce (sawdust) 	38.5	5.0	11.7	1.9	1.3	28.5			117
Agricultural residues and grasses	Switchgrass 	32.0	17.9	-	1.73	1.78	21.4			122
	Rice straw 	37.4	22.4	-	0.51	6.2		13.2	1.9	123
	Wheat straw 	38.8	22.2	1.7	2.7	1.4	18.5			124
	Energy cane bagasse 	40.87	20.82	-	-	1.53	24.81			125
	Corn stover 	35.3	23.9	-	1.9	4		19.2	0.7	126
	Sweet sorghum bagasse 	41.33	17.96	0.85	1.26	1.96		16.4	1.78	127

*The carbohydrate contents were measured by analyzing the sugars released during a concentrated sulfuric acid (72%) hydrolysis at 30°C followed by a dilute acid treatment at 121°C to cleave the

carbohydrates to monomeric sugars. Acid-insoluble lignin was measured gravimetrically after subtraction the ash content of final acid insoluble materials.[128]

Hemicellulose, the stereo-irregular polysaccharides, is a heterogeneous plant cell wall polymer composed of linear β(1,4)-D-glycan backbones branched with one monosaccharide and/or small oligosaccharides, with an approximate degree of polymerization of 200.[129-131] Unlike cellulose, hemicellulose has an amorphous, random, and branched structure, which is more susceptible to thermal, biological, and acid hydrolysis.[132-135] Xylan, mainly in the form of heteroxylan, is usually substituted with acetate and arabinose residues. It is the most abundant hemicellulose in nature, which dominantly contains β-D-xylopyranosyl residues linked by 1,4 glycosidic bonds.[102,104] Xylan content of plant cell wall may vary depending on the biomass type, ranging between 15–35% of total dry weight.[102] Hemicellulose interacts with cellulose and lignin and build a rigid network structure which is a barrier to enzyme-catalyzed deconstruction of cellulose.[136]



290

291 **Figure 5.** (A) Pictorial illustration of lignocellulosic biomass framework (modified from Menon and
292 Rao[137] with permission), (B) A simplified model showing the interactin of carbohydrate polymers present
293 in cell wall, modified from Himmel et al.,[138] (C) Structure of 36-chain model for cellulose I_α or I_β
294 elementary fibril (the reds show six true crystalline chains; greens are 12 subcrystalline chains with a
295 small degree of disorder; the blues are 18 surface chains that are subcrystalline with a large degree of
296 disorder, taken from ref. 111), and (D) A model of inter- and intra-chain hydrogen-bonding patterns in
297 cellulose, taken from ref. 139 with permission.

298

299 Pectin (pectic polysaccharides) is a heterogeneous polysaccharide with dominantly methyl
300 esterified or de-esterified homogalacturonan (HG) backbone. Located in the cell wall and middle
301 lamella of plants, pectin is the major component of the primary walls of several non-woody plant
302 cells.[140,141] After cellulose, pectin acts as a major plant load-bearing component and plays a
303 "glue" role to hold cell-wall components together.[138,142-145]

3 Biomass recalcitrance and pretreatment

Lynd et al.[146] first defined the "biomass recalcitrance" as the natural resistance of lignocelluloses and their components to microbial and enzymatic deconstruction. Later, Himmel et al.[138] summarized the factors contributing to the biomass recalcitrance as "(i) epidermal tissue of plant body, especially cuticle and epicuticular waxes, (ii) the arrangement and density of the vascular bundles, (iii) the relative amount of sclerenchymatous (thick wall) tissue, (iv) the degree of lignification, (v) the structural heterogeneity and complexity of cell-wall constituents such as microfibrils and matrix polymers, (vi) the challenges for enzymes acting on an insoluble substrate, and (vii) the inhibitors to subsequent fermentations that exist naturally in cell walls or are generated during conversion processes". Due to the biomass inherent recalcitrance, the release of fermentable sugars via appropriate enzymatic hydrolysis as well as microbial hydrolysis is the bottleneck of the industrial lignocellulosic biorefineries.[147,148]

Therefore, an efficient pretreatment step is required to obtain the renewable chemicals and fuels from the lignocelluloses.[149] A suitable enzymatic or acid hydrolysis can then be applied to the pretreated substrates to convert them to fermentable sugars or AD process to obtain biogas. There are many reviews in the literature on pretreatment methods to enhance enzymatic digestibility of lignocellulosic feedstocks.[11,69,136,150-157] Pretreatment is a "physical", "chemical", "Physico-chemical", or "biological" process, which can open up the lignocellulosic recalcitrance structure and make it amenable for subsequent enzymatic/microbial degradation. Physical pretreatments are divided into mechanical comminution and pyrolysis, whereas physicochemical pretreatments are steam explosion, ammonia fiber expansion (AFEX), and carbon dioxide explosion, and chemical pretreatments can be categorized into ozonolysis, acid hydrolysis, alkaline hydrolysis, oxidative delignification, and organosolv process.[11,158] The two most

commonly used technologies for pretreatment of lignocelluloses are dilute acid and alkaline pretreatments.[159] Dilute acid and alkaline pretreatments mainly target hemicellulose and lignin fractions, respectively, in lignocellulosic biomass. Acids like HCl and H_2SO_4 and bases like sodium hydroxide and sodium carbonate are mostly employed, and the pretreatment temperature, time, and acid/base concentration are among the main factors determining the effectiveness of pretreatment. An additional process and/or chemicals is required for recovering and neutralizing the hydrolysates and removing the inhibitory compounds for downstream processes. Hydrothermal pretreatment with only hot water, which is performed by using saturated steam at temperature and pressure below water critical point (subcritical water) or supercritical water, has the advantages of low amount of biological inhibitors production, minimal chemical cost, and relatively low cost of reactors compared with using acid or alkali solutions. A technology used for hydrothermal pretreatment, called steam explosion, is a pretreatment in which the lignocellulosic biomass is heated up by high-pressure steam (160–240 °C and pressures 0.7-4.8 MPa) followed by an explosion decompression. Hemicelluloses are mostly hydrolyzed in this pretreatment via the reaction called "autohydrolysis".[160,161]

For an advanced and low-cost pretreatment, several key criteria should be considered. It should be effective for a variety of lignocellulosic types with different characteristics. Significant sugar degradation products, formation of inhibitory byproduct for subsequent sugar fermentation, and production of waste residues should not be occurred during the pretreatment. Moreover, the pretreatment should need minimum heat and power requirement and reasonable size and moderate cost reactors.[150,153,162]

An efficient biomass pretreatment strategy should, therefore, be capable of effectively disrupting and removing the linkages among cellulose, hemicellulose, and lignin present in the plant cell

350 walls. Furthermore, reordering or removing highly-ordered hydrogen bonds in cellulose fibers
351 and subsequently increasing the porosity and surface area, resulting in cellulose accessibility to
352 cellulase, are highly desirable traits of an effective pretreatment.[150,153,162]

353 Recently, a new pretreatment category based on cellulose solvent lignocellulosic fractionation,
354 meeting the desired criteria, was added to the traditional biomass pretreatments. A number of
355 low-toxic and mostly environmental friendly solvents, including N-methyl-morpholine-N-oxide
356 (NMMO), ionic liquids (ILs), LiCl/N,N-dimethylacetamide (LiCl/DMAc), aqueous NaOH
357 solution, alkali/urea and NaOH/thiourea aqueous solutions, tetra butyl ammonium
358 fluoride/dimethyl sulfoxide system, metal complex solutions, concentrated phosphoric acid, and
359 molten inorganic salt hydrates, have been introduced as cellulose solvents for regenerating
360 cellulosic materials.[163-165] The cellulose solvents can be classified into (i) derivatizing, (ii) non-
361 derivatizing, and (iii) aqueous and non-aqueous systems having the ability to eliminate the inter-
362 and intra-molecular hydrogen bonds among cellulose molecules.[166] The cellulose can then be
363 recovered using an anti-solvent such as water, ethanol, or acetone. The parallel arrangement of
364 cellulose I, in most regenerated celluloses, is irreversibly converted into an anti-parallel
365 orientation, cellulose II, which is much easier to hydrolyze using cellulases.[167] Cellulose II is
366 thermodynamically more stable and has a more dense packing structure than cellulose I.[168]
367 However, as examined by Wada et al.,[169] the hydrolysis of cellulose II (and especially its hydrate
368 form) proceeds faster than the hydrolysis of cellulose I. Changes in polarity, crystallinity, and
369 ultrastructure of cellulose I to cellulose II have been reported to be the factors responsible for
370 cellulose II faster hydrolysis.[167]

371

While some of the traditional pretreatments suffer from relatively low sugars yield, require severe reaction conditions (high temperature and/or high pressure), and result in the formation of fermentation inhibitory compounds, the cellulose solvent-based pretreatments can be performed under relatively mild conditions (100–160°C), resulting into insignificant amount of inhibitors from degradation of cellulose and hemicelluloses.[170,171] The cellulose solvent-based fractionations are regarded as a biomass-independent, or feedstock agnostics, pretreatments, which can break recalcitrant structure of biomass by increasing cellulose accessibility more than the traditional pretreatments.[172] The recovery of non-fermentable co-products, e.g., pure and unaltered lignin, in these methods, adds revenue streams to the fermentation products.[173,174] The use of cellulose solvents over traditional solvent systems, which are typically (e.g., ethanol) volatile, for biomass pretreatment is promising in the future of lignocellulosic biorefineries.

This review paper has mainly focused on the most promising cellulose solvent-based pretreatment, i.e., concentrated phosphoric acid (CPA), N-methyl-morpholine-N-oxide (NMMO, or NMO), and ionic liquids (ILs). Although a few other reviews are available in the literature,[172,175-186] this review is intended to be a comprehensive review, with focus on recent research on cellulose solvent-based pretreatment to improve the reactivity of lignocelluloses for biogas, ethanol, and renewable chemicals production. Furthermore, as the pretreatment is a preceding step to the microbial conversion mediated with enzymes, the basic concepts and the limiting factors in the enzymatic hydrolysis of lignocelluloses are also briefly reviewed.

4 Hydrolysis of pretreated lignocellulosic substrate

The hydrolysis of lignocelluloses has long been done by dilute and concentrated acids, e.g., sulfuric acid.[187,188] The main drawback of acid hydrolysis is degradation of sugars and formation

of byproducts that showed severe inhibition to the fermentation microorganisms. High investments and maintenance cost, high utility and disposal costs, high energy consumption for acid recovery, and environmental impacts are among the major disadvantages of acid hydrolysis.[189] Hydrolysis of lignocellulosic materials by "enzymatic" processes has emerged a prominent process for the production of monomeric sugars, e.g., for subsequent production of fuel ethanol.[190,191] Cellulases and hemicellulases are the two enzymes typically used for depolymerization of lignocellulosic carbohydrates to fermentable sugars for second-generation biofuel production. Although a lot of efforts have been made to reduce the production costs, the enzymes are still expensive.[192,193]

Cellulose can be hydrolyzed by three glycoside hydrolases: endo-1,4-β-D-glucanases (EG) (EC 3.2.1.4), which randomly hydrolyze internal β-1,4-glucosidic bonds in the cellulose microfibril; exo-1,4-β-D-glucanases or cellobiohydrolases I and II (CBH) (EC 3.2.1.91), which progressively convert cellulose into cellodextrins; and 1,4-β-D-glucosidases (EC 3.2.1.21), which hydrolyze cellobiose and cellodextrins to glucose.[139,194-196] In a synergistic mixture, cellulases have higher combined activities than the sum of their individual activities.[197] Cellulases typically have two separate domains: a catalytic domain (CD) and a cellulose binding module (CBM), comprised of approximately 35 amino acids, linked by a flexible linker region.[198] Over the years, several kinetics models for lignocellulosic biomass hydrolysis by cellulase have been proposed and developed[199-201] to understand the mechanisms. For example, recently a comprehensive model was developed by Bansal et al.[202] that included the following steps: (i) adsorption of cellulases onto the substrate via the binding domain, (ii) direction of cellulases to a bond (located on the chain end or cleavable bond) susceptible to hydrolysis on the substrate surface, (iii) formation of enzyme–substrate complex, (iv) hydrolysis of the β-glycosidic bond and simultaneous direction

417 of the enzyme to the cellulose chain, (v) desorption of cellulases from the substrate or repetition
418 of step iv or steps ii/iii if only the catalytic domain detaches from chain, and (vi) hydrolysis of
419 cellobiose to glucose by β-glucosidase (if available in the enzyme mixture). However, the exact
420 mechanism of cellulose hydrolysis mediated by fungal cellulases is still unknown as the binding
421 mechanism of binding module to cellulose, catalytic action of cellulase, and stimulation of
422 cellulose hydrolysis by CBMs are still not clearly understood.[203]

423 The catalytic domains in cellulase are connected to one or more CBMs by peptides linker of
424 varying length and structure.[139,204] CBMs, with high binding affinity, increase the interaction
425 between cellulase and cellulose surface and enhance enzyme penetration into the
426 substrates.[139,205,206] Several synergistic proteins, e.g., plant expansins and expansin-like proteins
427 such as swollenin,[207] and auxiliary activity family 9 (formerly GH61) proteins,[208,209] are able to
428 enhance the enzymatic hydrolysis of cellulose by cellulase in ways that are not yet clearly
429 understood.[210]

430 Hemicellulases refer to a diverse combination of enzymes that can synergistically hydrolyze
431 hemicellulose from mixed sources and are divided into two major categories: depolymerases and
432 debranching enzymes (accessory enzymes).[195,211] The former group is either endo-acting
433 enzymes, that attack polymer chains internally, or exo-acting enzymes that act processively[207]
434 from the reducing or non-reducing terminals.[213] Depolymerases mainly include xylanases,
435 mannanases, β-glucanases, and xyloglucanases, and debranching enzymes are α-glucuronidase,
436 α-arabinofuranosidase, α-D-galactosidase, acetyl xylan esterase, and ferulic acid esterase.[211,214]

437 Várnai et al.[215] reported that synergistic action of xylanase and mannanase can improve the total
438 hydrolysis of pretreated softwood. Synergism is defined as "the ratio of the rate or yield of
439 product released by enzymes when used together to the sum of the rate or yield of these products

when the enzymes are used separately in the same amounts as they were employed in the mixture".[216] It depends on both the ratio of the enzymes involved and characteristics of enzymes and substrate.[102] Synergism, as reviewed by Van Dyk and Pletschke,[102] can be grouped into cellulase components interaction, as mentioned earlier, hemicellulases interaction, and combined enzymes on complex substrates.

For degradation of lignocelluloses, many aerobic bacteria and fungi, e.g., *Acidothermus cellulolyticus*, *Trichoderma reesei*, and *Aspergillus niger*, produce free enzymes. Nonetheless, some anaerobic bacteria from genera of *Clostridium*, *Acetivibrio*, *Bacteriodes*, and *Ruminicoccus* are capable of producing multi-enzyme extracellular protein complexes, called cellulosomes, which can degrade cellulose, hemicellulose, and pectin.[102,139,198,205,217] The most important characteristic difference between cellulosomes and free enzyme is cohesion-containing scaffoldin(s) and the dockerin-containing enzymes (hemicellulases, cellulases, and pectinases).[218,219] Besides, free non-cellulosomal enzymes usually contain a CBM that attach to the substrate. The structure and function of cellulosomes and their differences with free enzymes have been reviewed by Bayer et al.[220]

The enzymatic hydrolysis and fermentation can be conventionally performed by separate enzymatic hydrolysis and fermentation (SHF) or via an integrated process, i.e., simultaneous saccharification and fermentation (SSF), non-isothermal simultaneous saccharification and fermentation (NSSF), simultaneous saccharification, filtration, and fermentation (SSFF), or simultaneous saccharification and co-fermentation (SSCF)[221] (Figure 6). Although a recent study reported higher ethanol yield by SHF over SSF at very high solids concentration by using newly preparations of a cellulolytic enzyme, Cellic® CTec2,[222] the integrated approaches were developed to enhance the overall ethanol yield by reducing the inhibitory effect of sugar released

during the hydrolysis process on enzymes.[223] Another approach, called consolidated bioprocessing (CBP), can convert biomass to biofuel by using anaerobic bacteria capable of producing cellulosome enzymes with high activity and ferment the resulting sugars to, e.g., ethanol, in a single step.[192,203,219] Although CBP is more effective process than the others; however, it is in the developing stage and further developments in metabolic and genetic engineering are required to meet the industrial requirements.

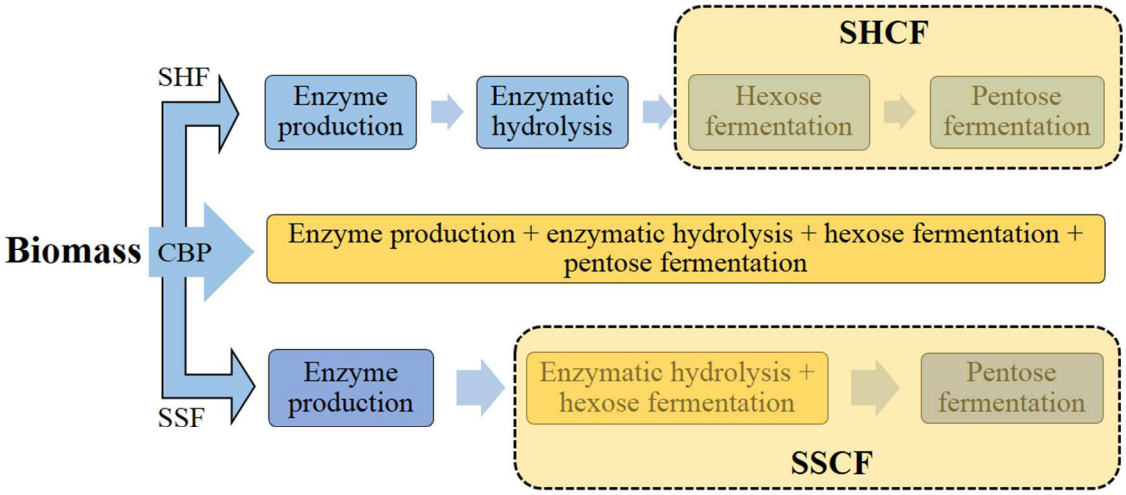


Figure 6. Different strategies for hydrolysis and fermentation of lignocellulosic substrates (SHF: separate hydrolysis and fermentation; SSF: simultaneous saccharification and fermentation; CBP: consolidated bioprocessing; SHCF: separate hydrolysis and co-fermentation; and SSCF: simultaneous saccharification and co-fermentation)

Commercial enzymes are usually a cellulase mixture derived from fungi such as *T. reesei* supplemented with β-glucosidase and contain more than 80 proteins.[195,224] Novozymes is one of the companies that provides enzymes for process optimization and commercialization of cellulosic ethanol. In this regard, the company started a dedicated work in 2000, under a national renewable energy laboratory (NREL) subcontract funded by the United States Department of Energy (DOE), to reduce the cost of cellulases.[203] In 2007, the company estimated 40-100 times

higher cost for the hydrolytic cellulase enzyme than the cost of enzymes for starch hydrolysis to glucose on a per gallon ethanol basis.[157] The outcome of the work was Cellic CTec & Cellic HTec enzymes cocktails in March 2009 followed by an improved and cost-effective product, Cellic® CTec2, in February 2010, and the company reported a 35% lower enzyme price. The company then developed a new generation of enzyme, called Cellic® CTec3, with 1.5 times better performance than the previous best product in the market. Cellic® CTec3 has been shown to work across a variety of feedstocks with consumption of approximately 50 kg of Cellic® CTec3 to produce 1 ton of ethanol (http://www.novozymes.com/). The cellulase assays usually measure the production of reducing sugars from high molecular weight cellulose,[225] like Whatman 1 filter paper, as first developed by Ghose[226] and later adopted and modified by NREL.[227] Protein content of the enzymes is also of great interests, which is usually measured by Bradford assay,[228] Pierce BCA assay,[229] and total crude protein by Kjeldahl nitrogen analysis.[230]

Equivalent glucose yield, proposed by the NREL, as % of theoretical yield (% cellulose or glucan digestibility) is usually calculated by using the equation 1:

$$Yield\ (\%) = \frac{[Glucose]+1.053[Cellobiose]}{1.111\ f\ [Biomass]} \times 100 \qquad (1)$$

where [Glucose] is the concentration of glucose (g/L), [Cellobiose], cellobiose concentration (g/L), [Biomass], biomass concentration dry basis at the beginning of the enzymatic hydrolysis (g/L), and f is cellulose fraction in the biomass on dry basis (g/g).[231]

5 Obstacles in the enzymatic hydrolysis of lignocelluloses and the role of pretreatment

The enzymatic hydrolysis performance of lignocelluloses is affected by not only cellulolytic enzyme-related factors (discussed in Section 4) but also by the physical, chemical, and

morphological characteristics of the lignocellulosic materials.[151,232-234] Cellulose crystallinity, structure, degree of polymerization (DP), accessibility, as well as hemicellulose and lignin contents are among the main structural and physicochemical features of cellulosic substrates that control the rate and extent of enzymatic hydrolysis.[113,235-238] Among all the factors that control cellulose hydrolysis mediated with fungal enzymes and to an extent, with cellulolytic such as *Clostridium thermocellum* and other microbes, cellulose accessibility to enzymes/microbes is believed to be the main factor affecting cellulose deconstruction.[113,172,239,240] However, tracking only one factor governing biological conversion is practically impossible because increase in cellulose accessibility in biomass is usually accompanied by hemicellulose and lignin removal and/or reduction in cellulose crystallinity.

5.1 Cellulose crystallinity and degree of polymerization (DP)

The cellulose microfibrils exist in different polymorphs, i.e., crystalline, paracrystalline (disordered), and amorphous structures. Amorphous cellulose is much easier to hydrolyze than crystalline cellulose.[241] One of the major obstacle for efficient hydrolysis of cellulose mediated with fungal enzymes is cellulose crystalline structure since lignin- and hemicellulose-free substrates, e.g., cotton fibers, still show resistance to enzymatic degradation.[242] However, based on findings in the literature, the correlation between cellulose crystallinity and enzymatic hydrolysis rate and yield is still debatable.[243-247]Although cellulose accessibility and enzyme adsorption can be affected by cellulose crystallinity; however, lignin/hemicellulose contents and distribution, biomass porosity, and biomass particle size can also affect the accessibility.[243] Besides, some reports have stated a constant crystallinity for cellulose during the course of hydrolysis;[244] while others reported a decrease in cellulose crystallinity during hydrolysis.[245]

Reported by Hall et al.,[246] at constant adsorbed enzyme concentration, crystallinity was found to be a more influencing factor for enzymatic hydrolysis rates than enzymes adsorption. Mittal et al.[247] have found a strong correlation between initial rate of digestion (up to 24 hours) and amorphous content for four cellulose samples with different degrees of polymerization and crystallinity indexes, which were subjected to aqueous sodium hydroxide and anhydrous liquid ammonia treatments. Besides, they reported a weak correlation of allomorph type with initial digestibility; however, a strong correlation with cellulose conversion was found at later hydrolysis times. Cui et al.[248] prepared four types of cellulose allomorphs from α-cellulose and concluded that the amorphous content had a strong positive influence on cellulose digestibility. The allomorphs digestibility was reported to be in the following order: cellulose III > cellulose II > cellulose I_α > cellulose I_β. In contrast, the crystalline polymorph of cellulose was reported to have a negligible influence on the conversion degree of non-dried and dried cellulose samples into glucose.[249] Finally, cellulose crystallinity can affect the synergism among cellulase components and the cellulase processivity, which has a notable effect on the hydrolysis.[241]

The crystallinity index measurements are highly dependent on the technique applied, i.e., Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), Nuclear Magnetic Resonance (NMR) Spectroscopy, and Raman spectroscopy, and also the methods used for calculating crystallinity index from the raw spectrographic data.[204,242] Cellulose crystallinity index (CrI) from XRD spectra has long been calculated by different calculation approaches.[243] The most frequent and simple calculation technique is based on peak height according to the empirical method of Segal et al.[250] for native cellulose:

$$CrI\ (\%) = [(I_{002}-I_{am})/I_{002}] \times 100 \qquad (2)$$

where I_{002} is the maximum intensity of the 002 lattice diffraction at $2\theta = 22.4°$ and I_{am} is the diffraction intensity at $2\theta = 18°$. However, the Segal's crystallinity method does not reflect the crystal sizes for a given polymorph, e.g., the two cellulose polymorphs, I_β and II, were calculated to have different CrIs despite having the same crystal sizes.[251]

Degree of polymerization (DP) of cellulose is the number of glucose units in the cellulose molecule chain and varies between 6,000 in primary cell wall and up to 14,000 in secondary cell wall.[252] The DP of cellulose is believed to contribute to the enzymatic hydrolysis of lignocelluloses since long cellulose chain has more hydrogen bonds, while shorter chains has more cellulose ends available to the exoglucanases.[253]

However, tracking changes in DP of cellulose, especially for complex lignocelluloses, during the course of pretreatment cannot be easily assayed. A method developed by Zhang and Lynd[254] is only applicable for pure cellulosic substrates. Besides, DP is not typically an independent factor influencing cellulose digestibility because altering DP is always accompanied by crystallinity changes.[148,255]

5.2 Cellulose accessibility to cellulases

One of the primary barriers for cellulase enzymes in the hydrolysis of lignocellulose is their limited access to much of the cellulose confined in a highly packed structure.[256] The presence of lignin significantly decreases the swelling/accessibility of cellulose resulting in low sugar yields at commercially viable low enzyme loading.[120] Arantes and Saddler[257] found that the required protein loading to achieve efficient hydrolysis of lignocellulosic substrates, regardless of their source, structure, and type of pretreatment, had a strong linear dependency on the cellulose accessibility for each substrate. Biomass porosity is considered as lignocellulosic interior surface

568 area and exterior surface area that is largely determined by particle size.[258] The accessible pore
569 sizes required for anaerobes and cellulase and hemicellulases enzymes were reported to be at
570 least 0.2-20 μm and 40-60 nm width, respectively, to allow sufficient penetration.[253] Wiman et
571 al.[259] correlated the higher rate of enzymatic hydrolysis, in spite of the negative effect of lignin
572 accumulation on the particle surface, to the increase in specific surface area. Rollin et al.[240] also
573 showed that increasing cellulose accessibility is more important than removing lignin in the
574 enzymatic hydrolysis of pretreated substrates, while removing lignin increases the accessibility
575 of hemicelluloses which in turn affects cellulose accessibility.[260] Similar to cellulose
576 crystallinity, a strong relationship was observed between accessible cellulose surface and degree
577 of synergistic action of cellulase components, which is crucial to enhance hydrolysis
578 efficiency.[261]

579 5.2.1 Cellulase adsorption

580 The rate-limiting step in enzymatic saccharification is the amount of protein adsorbed on the
581 substrate during enzymatic hydrolysis. The rate of saccharification increases with increasing
582 enzyme concentration up to a plateau, typically corresponding to the maximum capacity of
583 substrate to adsorb enzyme.[262,263] Decrease in hydrolysis rates with reaction is believed to be
584 mainly due to reduced enzyme adsorption and accessibility to the substrate.[264] The adsorption
585 parameters (maximum adsorption capacity [σ] and equilibrium constant [K_d]) are usually
586 determined by fitting the cellulase adsorption data to Langmuir equation by non-linear
587 regression:

588 $$[CE] = \frac{\sigma[E_f]}{K_d + [E_f]} \quad (3)$$

where [CE] is the amount of adsorbed enzyme in mg/g substrate, [E_f] is the free enzyme concentration in mg/mL, σ is the maximum adsorption capacity in mg/mg substrate, and K_d is the equilibrium constant in mg enzyme/mL.[260]

The concentration of free enzymes is measured either directly by analyzing adsorbed protein on substrate or calculated as the difference between the total amount of protein initially added and the amount left in aqueous solution at any time.[262,265-267] The enzymes were reported to adsorb quickly in the initial stage and remain attached throughout hydrolysis.[268] For instance, equilibrium time for cellulase on pretreated sugarcane bagasse was approximately 120 min and was even shorter for Avicel (10 min), while β-glucosidase (from *A. niger*) was not significantly adsorbed.[269]

5.3 Hemicellulose content

Hemicelluloses, a physical barrier around cellulose, can retard the enzymatic hydrolysis by precluding the access of enzymes to cellulose (Section 5.2) and inhibiting the endoglucanase and cellobiohydrolase activity.[270,271] The presence of xylan is believed to limit the cellulose hydrolysability, as evident by slow digestion of delignified substrates compared to pure cellulose.[272,273] Although it is commonly found in pulp and paper industry that xylan and other hemicelluloses adsorb on cellulose and enhance pulp strength, Kumar et al.[274] recently showed that hemicelluloses adsorption and their strong association with cellulose during pretreatments can retard cellulose digestion significantly; however, supplementation of xylanase to cellulase was shown to relieve the inhibition. In other report, Wang et al.[275] also reported that the re-adsorption of dissolved xylan, produced during the pretreatment, on cellulose can inhibit the cellulose hydrolysis by cellulases. The supplementation of cellulases by xylanase was suggested to hydrolyze the xylan adsorbed on cellulose and potentially improved the hydrolysis efficiency

612 of lignocelluloses. As discussed earlier (Section 4), the supplementation of xylanase has been
613 also reported to synergistically improve the performance of cellulases in the hydrolysis of
614 lignocelluloses.[216,276-278] Nonetheless, hemicellulases supplementation to cellulase not only
615 enhances cellulose accessibility to cellulase by simultaneously removing structural/non-structural
616 hemicelluloses but also depolymerize shorter hemicellulose oligomers in the solution that have
617 been shown to be strongly inhibitory to cellulases by Kumar and Wyman and others.[279-284] On
618 the other hand, negative effect of xylose accumulation on cellulase cocktails was also
619 observed.[285] Partial removal of hemicelluloses by concentrated NaOH was reported to be more
620 effective than complete removal for poplar, and a maximum enzymatic hydrolysis of 94.6 % was
621 achieved.[285] More information on the inhibitory effects of sugars and oligomers on the enzymatic
622 hydrolysis is provided in Section 5.5.

623 **5.4 Lignin content**

624 In general, lignin plays a negative role in the biochemical processes for producing lignocellulosic
625 biofuels.[286,287,288,289] Nonetheless, Nakagame et al.[290] concluded that an increase in the carboxylic
626 content of lignin resulted in a decrease in non-productive binding of cellulase and consequently
627 an increase in hydrolysis yield. A slight enhancement in enzymatic hydrolysis was also reported
628 by Wang et al.[291] by adding Kraft lignin to the enzymatic hydrolysates. Lai et al.[292] reported
629 contrasting results for the effect of ethanol organosolv lignin on enzymatic hydrolysis. They
630 found that the addition of 8 g/L hardwood organosolv lignin significantly improved the
631 enzymatic yield of organosolv pretreated sweetgum and loblolly pine, while addition of
632 softwood organosolv lignin was shown to decrease the yields.

633 Lignin can retard enzymatic hydrolysis of lignocelluloses via three mechanisms: 1) enzymes can
634 be adsorbed on lignin through hydrophobic interactions, electrostatic interactions, and/or

635 hydrogen-bonding interactions, 2) lignin in lignocellulosic materials acts as a surface barrier to
636 block the accessible surface of carbohydrates through physical blockage on the surface and
637 chemical blockage through lignin-carbohydrate complex, and 3) enzymes deactivation by soluble
638 lignin.[293,294]

639 Öhgren et al.[278] evaluated the effects of partial delignification of corn stover by acid-catalyzed or
640 autocatalysis pretreatment to increase the enzymatic hydrolysis yield. Due to the delignification,
641 a slight increase in glucose yield and a decrease in xylose yield due to hemicellulose loss were
642 observed. Várnai et al.[272] concluded that the limitation in the enzymatic hydrolysis of spruce was
643 mainly due to the presence of lignin, since the removal of lignin with chlorite delignification
644 doubled the hydrolysis yield with near theoretical yield within 2 days. Nlewem et al.[295]
645 performed alkali, dilute acid, and hot water pretreatments on switchgrass and compared its
646 enzymatic hydrolysability. Although it was not only due to delignification, the alkali
647 pretreatment generally produced glucose in higher concentrations than the others, since it caused
648 higher reduction in lignin content and lots of pores were formed by the pretreatment. In another
649 study, fungal delignification of wet milled rice straw by *Trichoderma viride* in the presence of a
650 surfactant for 30 days resulted in 74% of lignin removal and 56% of enzymatic
651 saccharification.[296]

652 5.4.1 Adsorption of cellulases on lignin

653 The non-productive cellulase adsorption onto lignin is believed to associate with the inhibitory
654 effect of lignin on the enzymatic hydrolysis of lignocellulosic feedstocks.[297-299] Both raw
655 softwood lignin and isolated lignin from steam pretreated softwood were reported to adsorb
656 major commercial *T. reesei* cellulases (Celluclast) and inhibit the hydrolysis of Avicel.[300]
657 Composition and functional groups of lignin, e.g., syringyl/guaiacyl lignin ratio, carboxylic acid,

aliphatic hydroxyl, and phenolic hydroxyl, were reported to affect the enzyme adsorption.[301] Lignin adsorbed the enzymes in the following order: cellobiohydrolases (CBHs) and xylanase > endoglucanase (EG) > β-glucosidase (BG). In contrast, Ko et al.[302] reported that β-glucosidase from *T. reesei* had the strongest adsorption onto lignin and only 2–18% of the initial β-glucosidase activity remained in the supernatant, while 50–60% of cellobiohydrolase and endoglucanase activities were recovered after incubation with lignin. However, they stated that β-glucosidase from *A. niger* exhibits less adsorption than that from *T. reesei*. Rahikainen et al.[303] prepared lignin films from steam explosion pretreated and untreated spruce and wheat straw and compared their capacity to adsorb cellulases. The pretreated biomass film showed higher capacity to adsorb the major cellulase Cel7A of *T. reesei* than the untreated biomass. Yu et al.[293] also showed that the lignin obtained from pretreated woods resulted in two to six times more cellulase adsorption than untreated woods. The degree of lignin condensation after pretreatment, which significantly increased especially for softwoods, has a critical impact on cellulase adsorption and enzymatic hydrolysis.[293]

5.4.2 Lignin-derived phenolic compounds

Lignin-derived phenolic compounds, e.g., vanillin, syringaldehyde, trans-cinnamic acid, and hydroxybenzoic acid, generally produced during pretreatment inhibit cellulase (endo- and exo-cellulases and β-glucosidase) as well as fermentative microorganisms.[304-307] The enzymes deactivate and precipitate with vanillin, where a 10 mg/mL vanillin concentration was reported to decrease cellulose conversion from 53% to 26%.[304] Structure of the phenolic compounds, e.g., presence of hydroxyl, carbonyl, and methoxy groups, can affect the inhibition. Li et al.[308] reported that aldehyde and phenolic hydroxyl groups of vanillin have inhibitory effects on cellulase. However, β-glucosidases from *T. reesei* and *A. niger* are less susceptible to inhibition

and correspondingly require approximately 10 and 100 times higher concentrations of phenols for the same levels of inhibition as cellulase components.[305] Oliva-Taravilla et al.[309] showed that the addition of laccases was able to remove the phenolic compounds from steam-pretreated lignocellulosic materials; however, application of laccases reduced glucose yield during hydrolysis. They concluded that the proportion of lignin besides the composition of phenols are key factors in the cellulase inhibition when the enzymatic hydrolysis is combined with laccases detoxification.

5.5 Formation of inhibitory byproducts

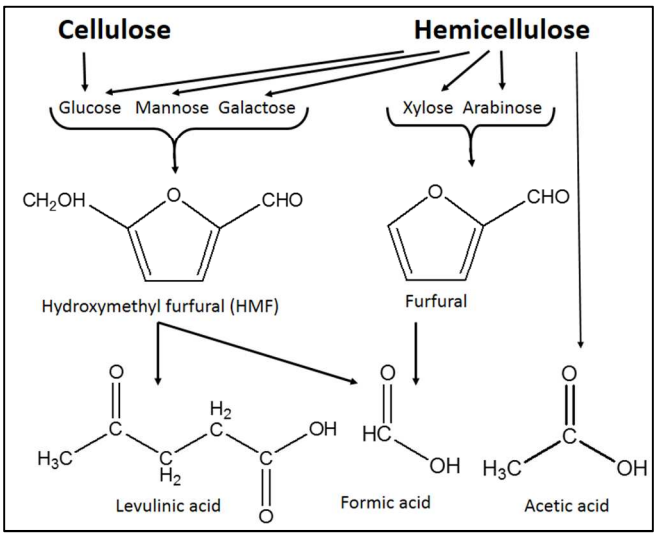
Besides hemicellulose and lignin-derived compounds, some inhibitory byproducts produced during pretreatment, e.g., furan aldehydes, weak acids, and hydrolysis-derived substances like soluble mono/oligomeric sugars (Section 5.3), hamper the performance of cellulases and fermentable organisms.[307,310,311] Furan aldehydes, i.e., furfural and 5-hydroxymethylfurfural (HMF), are formed by dehydration of pentose and hexose sugars, respectively[312,313] (Figure 7). By the release of acetic acid during pretreatment, mainly by hydrolysis of acetyl group, or by re-hydrolysis, furan aldehydes can be converted to weak acids such as levulinic acid and formic acid (Eq. 4).[314-316]

$$Cellulose \xrightarrow{H^+} Glucose \xrightarrow{H^+} HMF \xrightarrow{H^+} Levulinic\ acid + Formic\ acid \quad (4)$$

Formation of inhibitory byproducts during pretreatment is strongly dependent on feedstock and pretreatment type applied. For example, agricultural residues and hardwoods with higher amounts of acetylated xylan generate higher concentration of acetic acid during pretreatment. Most of the pretreatments under severe conditions, such as long reaction time and high temperature, result in the formation of inhibitory by-products. In acid-catalyzed thermochemical

703 pretreatment process, dehydration of pentose sugars and uronic acid result in inhibitory
704 byproducts (Figure 7). In addition, the splitting of lignin's β-O-4 ether and other acid labile
705 linkages forms phenolic and non-phenolic aromatic inhibitory compounds. However, formation
706 of carboxylic acid by peeling-off reaction takes place in alkaline conditions[307,311].

707



708

709 **Figure 7.** Formation of major inhibitory by-products from main carbohydrates present in lignocelluloses
710 (modified from Reginatto et al.[317]).

711

712 Jing et al.[318] compared the inhibitory effect of the major lignocellulose degradation products on
713 Spezyme®CP cellulase with the following order: lignin derivatives > furan derivatives > organic
714 acids > ethanol. Arora et al.[319] reported a severe inhibition by formic acid (5 or 10 mg/mL) on
715 enzymatic hydrolysis of cellulose powder as well as dilute acid-pretreated poplar.

716 Xiao et al.[320] quantitatively calculated the inhibitory effect of sugars on cellulase and β-
717 glucosidase during enzymatic hydrolysis of softwood substrates and showed a dramatic increase
718 in both enzymes inhibition by increasing glucose concentration. They also reported the

719 significant inhibitory effect of mannose, xylose, and galactose during the hydrolysis on cellulase
720 activity but not on β-glucosidase activity. Xylooligomers (XOs), especially at high
721 concentrations, were reported to have more inhibitory effect than xylan and xylose in decreasing
722 the initial hydrolysis rate and final glucose yield of Avicel.[280,284] Addition of xylanase and β-
723 xylosidase was recommended to reduce xylooligomers and xylan inhibition of enzymatic
724 hydrolysis of pretreated corn stover.[321] In a recent study, Kumar and Wyman[279] revealed that
725 mannan polysaccharides and their enzymatically derived oligomers were more inhibitory to
726 cellulase than XOs and cellobiose. They also showed that cellulase inhibition dramatically
727 increased with mannan backbone substitution with galactose. However, the amount of mannan
728 re-adsorption on cellulose after pretreatment was reported to be higher than that of glucomannan
729 and galactomannan at the same concentrations.[322] In a recent study, Cellic® CTec3 enzyme
730 mixture was reported to be more resistant than Celluclast 1.5L cellulase to the inhibitory
731 compounds produced during steam pretreatment of poplar and lodgepole pine.[323] Furthermore,
732 monomeric sugars were shown to have more inhibitory effects than phenolics, depending upon
733 their types, and oligomeric sugars.

734 It is notable that the discussed byproducts also have inhibitory effects on the bioconversion
735 routes leading to biofuels and renewable chemicals production. For example, the concentration
736 of furfural and HMF in the range of 0.5-1 g/L and formic and acetic acids at more than 4 g/L
737 were reported to be toxic in batch lactic acid fermentation by *Rhizopus oryzae*.[324] For a
738 recombinant *S. cerevisiae* strain, initial furfural concentrations below 5 g/L was reported to have
739 negligible effect on ethanolic fermentation in a xylose and glucose containing medium, while
740 xylose consumption rates were affected at initial furfural concentrations of 10–15 g/L.[325]

6 Concentrated phosphoric acid pretreatment

Phosphoric acid (85%) was first recognized as a swelling agent to produce reactive cellulose from air dried cellulose by Walseth[326] in 1950s. Since then, phosphoric acid swollen cellulose (PASC) has been the subject of vast studies as cellulose substrate for cellulase activity assays and preparation of microcrystalline cellulose.[327-329] Bellamy and Holub[330] patented a process using CPA (80–85%) for decrystallization of cellulose to improve its hydrolysis. The process included formation of a gel by mixing cotton and wood pulp with CPA at room temperature followed by acid removal from the cellulosic substrate by water washing. Zhang et al.,[331] however, observed cellulose dissolution behavior when the phosphoric acid concentration reached greater than 80.5%, critical concentration value for dissolution of Avicel. During the first stage of the dissolution, an esterification reaction between hydroxyl group of cellulose and phosphoric acid occurs and cellulose phosphate (Cellulose–O–PO_3H_2) is formed. In the second stage, a competitive hydrogen-bond reaction between the cellulose hydroxyl groups and the solvent molecules or hydrogen ions happens and regenerated cellulose and phosphoric acid without major substitution are recovered.[332,333] Meanwhile, cellulose hydrolysis remains minimum since the reaction temperature is kept low enough (30-70°C) to retard the depolymerization and side reactions.[334]

Conte et al.[335] by applying high- and low-field NMR confirmed that a direct bonding between phosphoric acid and cellulose is formed. Zhang et al.[333] particularly investigated the structural changes of microcrystalline cellulose (MCC) dissolution in 83% phosphoric acid (at temperatures of 30-70°C) with X-ray diffraction, solid-state cross-polarization magic angle spinning ^{13}C-NMR, and X-ray photoelectron spectroscopy (XPS). The XRD pattern

763 demonstrated a decrease in χ_c (crystallinity index) with increasing temperature (from 30 to 70°C)
764 or time (from 2 to 6 h). χ_c was calculated according to the following,

765 $$\chi_c = F_c/(F_a + F_c) \times 100\ \% \quad (5)$$

766 where F_c and F_a are the area of the crystal (peak of cellulose I at $2\theta = 22.8°$) and non-crystal
767 regions (peak at $2\theta = 19.8°$), respectively.

768 Besides, the crystallinity characteristic peaks for both cellulose I and II diminished or greatly
769 decreased after cellulose regeneration from concentrated phosphoric acid (CPA). In the spectra
770 of CP/MAS and ^{13}C solid-state NMR, distinct peaks of C_4 verified transition from crystalline to
771 an amorphous cellulose after CPA treatment.[333] The XRD patterns of MCC treated with 85%
772 CPA at 323 K also demonstrated that more cellulose I was converted to cellulose II by increasing
773 reaction time from 0 to 6 h.[336] Jia et al.[337] chemically modified MCC with phosphoric acid in
774 order to enhance its processing for applications in gelling material and emulsion stabilizers.
775 Regenerated cellulose at some angles corresponding to crystallographic planes of cellulose II
776 exhibited less crystallinity compared to intact MCC. Besides, the crystallinity index was reduced
777 by 48% after regeneration.

778 The dissolution was also capable of fractionating lignocellulose components at the modest
779 reaction conditions, and the cellulose can be regenerated by an organic solvent, e.g., ethanol and
780 acetone, or water.[240,334] Addition of an antisolvent, e.g., acetone, makes the dissolved cellulose
781 and hemicellulose to precipitate and partial dissolution of lignin in acetone also takes place.
782 Besides, hemicellulose oligomers are fractionated from cellulose due to higher solubility in water
783 and poor solubility in water/acetone mixture.[334] The regenerated amorphous cellulose,
784 precipitated from the dissolved cellulose, demonstrated extremely high reactivity for enzymatic

digestibility, suggesting the dissolution technique as a new approach for the pretreatment of lignocelluloses.[331] Recently, a new cellulose solvent- and organic solvent-based lignocellulosic fractionation (COSLIF) using concentrated phosphoric acid, as a cellulose solvent, and an organic solvent (e.g., acetone or ethanol) for the solute precipitation, at modest reaction conditions was developed.[334] This novel pretreatment was able to effectively disrupt lignocellulosic structure of switchgrass,[340] bamboo,[338] common Reed,[339] and miscanthus and hybrid poplar.[340] Table 2 summarizes the results of glucan digestibility improvement after COSLIF, as well as the applied conditions, for different lignocelluloses. As can be seen in Table 2, COSLIF pretreatment is performed at mild conditions, e.g., temperatures of ca. 50-60 °C, atmospheric pressure, and short pretreatment time (~1 h), using acetone, ethanol, and water as anti-solvent. Compared with other most commonly used pretreatment methods, such as dilute acid, alkali, and hydrothermal, the sugar yields for CPA pretreatment for a variety of hardwoods and agricultural residues are very high. For an instance, over 90% glucan digestibility was achieved after 72 h hydrolysis even at low enzyme loadings. Moreover, some studies reported ethanol yield enhancement by the CPA pretreatment (Table 3).

COSLIF was observed to follow a different mechanism than alkali or acid pretreatment with respect to changes in lignocellulosic components. Zhu et al.[341] compared glucan, hemicellulose, and lignin contents of the COSLIF and dilute acid (DA) pretreated corn stover. They reported that COSLIF removed more lignin compared to DA pretreatment. Siripong et al.[342] reported removals of all xylan and ca. half of acid-insoluble lignin from two wood species as a result of CPA (80%) pretreatment. Similarly, Rollin et al.[240] reported a 67% and 34% hemicellulose and lignin removals , respectively, from switchgrass by CPA pretreatment. They reported more increase in cellulose susceptibility to hydrolysis in COSLIF pretreatment than soaking in

808 aqueous ammonia (SAA, 10% w/w ammonia, 140°C, 20:1 liquid/solid ratio, 14 h) for Alamo
809 switchgrass (Figure 8). However, cellulose content was remained almost constant after the both
810 pretreatments. Another action of CPA pretreatment is to hydrolyze hemicellulose acetyl groups
811 to acetic acid.[334,339] The remaining hemicellulose can be enzymatically depolymerized and used
812 as a co-substrate for fermentation.[342,343]

813 There are few studies in the literature that showed biogas production improvement by CPA
814 pretreatment. A study showed 40% improvement in the methane yield obtained after CPA
815 pretreatment (85.7% CPA at 50°C for 30 min) compared with that of the untreated oil palm
816 empty fruit bunches.[344] Conversely, CPA pretreatment did not improve methane yield for berry
817 and poplar woods.[345] This is persumably due to the repelling interaction of anaerobic bacteria
818 and biomass surface after CPA pretreatment. In addition, the pores generated following CPA
819 pretreatment may not be large enough for anaerobic bacteria to penetrate into the biomass
820 structure.

821

822 **Table 2.** Glucan digestibility of various substrates prepared by cellulose solvent- (phosphoric acid) and organic solvent-based lignocellulosic
823 fractionation (COSLIF) pretreatment

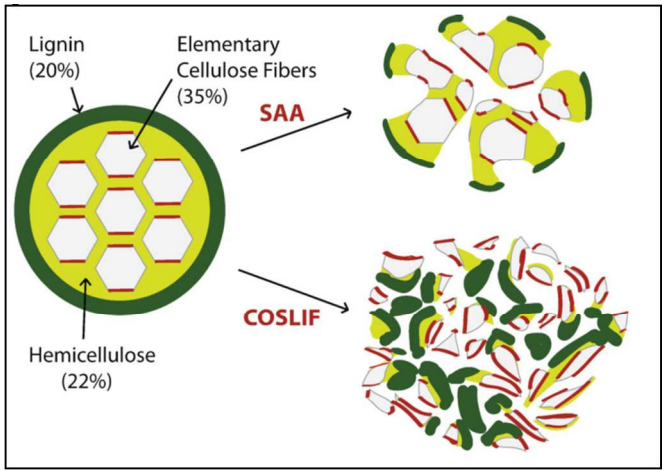
Substrate	COSLIF condition	Enzymatic hydrolysis	Glucan digestibility	Ref.
Sesbania grandiflora (L.) Pers.	H_3PO_4 (85%), 50°C for 45 min, 95% (v/v) ethanol as an organic solvent	1 FPU cellulase from Sigma	86% glucose in 72 h	346
Achyranthes aspera and *Sida acuta* weed	70%, 75%, and 80% phosphoric acid (1.0 g/8.0 mL), and 60°C for 1h, and acetone as an organic solvent	30 FPU/g dry biomass Celluclast 1.5 L and 60 U/g dry biomass β-glucosidase	Up to 86.2% and 82.2% glucan conversion yields, respectively	342
Alamo switchgrass (*Panicum virgatum*)	85% H_3PO_4, 60°C, 1 atm, for 45 min, 95% (v/v) ethanol as an organic solvent	Novozymes 50013, 15 and 3 FPU/g glucan, supplemented with 10 IU/g β-glucosidase	90% and 85%, respectively, in 72 h	240
Moso bamboo	85% H_3PO_4, 50°C, 1 atm, for 60 min, 95% (v/v) ethanol as an organic solvent	Novozymes 50013 and β -glucosidase (Novozymes 50010) 1, 2, 5, and 15 FPU of cellulase per g glucan supplemented with 10 β-glucosidase IU/g	88.2%, 89.8%, 93.3%, and 94.9%, respectively, in 72 h	338
Common Reed *(Phragmites australis)*	85% H_3PO_4, 50°C, 1 atm, and 60 min, 95% (v/v) ethanol as an organic solvent	15, 10, and 5 FPU and 30 units of β-glucosidase per gram of glucan (Novozymes 50013 and Novozyme 50010)	94%, 93%, and 90%, respectively, 24 h	339
Miscanthus and poplar	85% H_3PO_4, 50°C, 1 atm, and 60 min, 95% (v/v) ethanol as an organic solvent	5 FPU of cellulase and 10 units of β-glucosidase per gram of glucan (Novozymes 50013 and Novozyme 50010)	~93% in 72 h	340
Microcrystalline cellulose	83% H_3PO_4 and ice-cold distilled water as an anti-solvent	15 FPU/g cellulose and 60 IU β-glucosidase/g cellulose	100% cellulose conversion after 3 h	331
Avicel and α-cellulose	81.7% phosphoric acid at room temperature for half-hour, and acetone as an organic solvent	15 FPU/g glucan of Genencor Spezyme®CP cellulase and 60 IU/g glucan of Novozymes 188 β-glucosidase	100% conversion within 3 h	334
Corn stover and switchgrass	84% phosphoric acid at 50°C for 45 min, and acetone as an organic solvent	15 FPU/g glucan of Genencor Spezyme®CP cellulase and 60 IU/g glucan of Novozymes 188 β-glucosidase	~96 – 97% in 24 h	334, 341
Hybrid poplar and douglas fir	85% phosphoric acid at 50°C for 60 min, and acetone as an organic solvent	15 FPU/g glucan of Genencor Spezyme®CP cellulase and 60 IU/g glucan of Novozymes 188 β-glucosidase	~97% and ~75% in 24 h for hybrid poplar and douglas fir, respectively	334
Oriented strand board, chipboard, plywood, and	85.9% phosphoric acid at 50°C for 30 min, and acetone as an organic solvent	20 FPU cellulase (Sigma, C2730) and 50 IU β-glucosidase (Sigma, G0395) per gram of substrate	87.0 – 93.5% in 96 h	348

wallpaper				
Hybrid poplar (*P. tormentosa* Carr.)	85% phosphoric acid and room temperature until complete dissolution, and water as solvent	50 FPU 1:1 blend of Celluclast 1.5 L and Novozyme 188/g substrate	92%, 72 h	349
Industrial hemp stalks	85.9% H_3PO_4 at 50°C for 1 h, and organic solvent, acetone	15 FPU cellulase (Spezyme CP), and 60 IU β-glucosidase per gram of glucan	95.9%, 24 h	350
Bermudagrass, reed, and rapeseed	85% phosphoric acid at 50°C for 60 min, and acetone as an organic solvent	25 FPU of Celluclast® 1.5 L per gram of cellulose	97.5 – 99.4% (24 h)	351
Eastern gamagrass (*Trypsacum dactyloides*) and switchgrass	The pretreatment method reported by Zhang et al.[334] and modified by Ge et al.[352]	100 μL of Novozymes 188, or 600 μL of cellulase and 200 μL of Novozymes 1800 for high solid-loading	80.5 – 99.8% and 73.5 – 87.1%, for eastern gamagrass and switchgrass, respectively, 36 h	353
Giant reed, elephantgrass, and sugarcane clone	85% phosphoric acid at 50°C for 60 min, and organic solvent, acetone	300 μL of cellulase (Sigma C2730) and 100μL of Novozymes 188 (Sigma C6105)	Glucose yields from biomass: 0.306, 0.309, 0.331, 0.317, and 0.290 g/g for giant *miscanthus*, giant reed, giant *miscanthus* (Q42641), elephantgrass, and sugarcane, respectively	352
Corn stover and Avicel	85 %(w/w) phosphoric acid, 2 % (w/v) solid loading, described by Zhang et al.331	5 FPU/g of glucan (Novozymes 50013) and 10 units of *β*-glucosidase (Novozymes 50010) per gram of glucan	~90% (72 h) for corn stover and 100% (6 h) for Avicel	354

824 **Table 3.** Ethanol production from pretreated lignocelluloses prepared by COSLIF pretreatment.

Substrate	CPA pretreatment condition	Method and microorganism	Ethanol yield	Ref.
Dedicated energy crops and crop residues	Same as reported by Zhang et al.[331]	SHF, three self-Flocculating *Saccharomyces cerevisiae* strains: SPSC01, ATCC24859, ATCC4126	0.375 to 0.396 g/g (SPSC01), 0.380 to 0.394 g/g (ATCC24859), and 0.384 to 0.405 g ethanol/g (ATCC4126) glucose	352
Oil palm empty fruit bunches (OPEFB)	Same as reported by Zhang et al.[334]	SSF, *S. cerevisiae*	89.4% of theoretical maximum ethanol yield	355
Aspen wood (*Populus tremula*)	Phosphoric acid (85%), 12.5% solid loading, 50°C, 90 rpm, 30 min, and acetone as an organic solvent	NSSF, *Mucor hiemalis*	72.4% of theoretical maximum ethanol yield	356
Rice straw, elmwood, and pinewood	Same as of Rollin et al.[240]	SHF, *Mucor indicus*	Over 78-92% ethanol yield based on glucose consumed	342
Trypsacum dactyloides	Same as of Zhang et al.[334]	SHF, a self-flocculating yeast strain SPSC01	Up to 0.496 g ethanol/g glucose	353
SHF: separate enzymatic hydrolysis and fermentation; SSF: simultaneous saccharification and fermentation; NSSF: non-isothermal simultaneous saccharification and fermentation				

825



826

827 **Figure 8.** Conceptual image of alteration in lignocellulose structure as a result of cellulose solvent-
828 (concentrated phosphoric acid) and organic solvent-based lignocellulose fractionation (COSLIF) and
829 soaking in aqueous ammonia (SAA) pretreatments (taken from ref. 235 with permission)

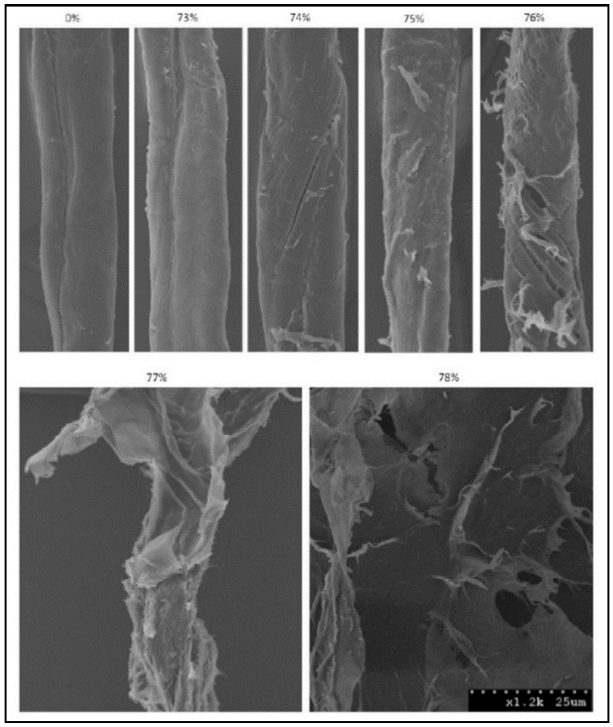
830

6.1 Criteria for efficient phosphoric acid pretreatment

A narrow range of phosphoric acid concentration is required for cellulose phase transition from swelling to dissolution to occur. Only phosphoric acid above its critical concentration is able to disrupt lignocellulose recalcitrant structure.[331] Critical phosphoric acid concentration is 77–83 wt.%, depending on substrate type and its moisture content. Figure 9 shows SEM images of pretreated cotton fibers with a range of o-phosphoric acid concentrations.[357] As this figure shows, amorphogenesis begins to develop at the surface of the cotton fibers when the acid concentration was increased to near its critical values of cellulose dissolution. At 74% acid concentration, splitting, roughening, fibrillation, and peeling/delamination were observed, indicating that amorphogenesis started at the surface of the cotton fibers and developed by increasing acid concentration to 76%, and 78%, caused to destroy fiber structure and diminishing, respectively.[351] Moxley et al.[350] have also found that a minimum phosphoric acid concentration of 81% is required to obtain a very rapid hydrolysis rate and high digestibility of hemp stalks. Jia et al.[337] discovered minimum 77.8 wt.% CPA for significant solubilization of MCC powder. Zhang et al.[331] showed that 77 wt.% of CPA caused only cellulose swelling while ice-cold phosphoric acid (≥83%) completely dissolved MCC.

The dissolution of (ligno)celluloses in CPA also depends on the reaction temperature and time. Cellulose dissolution by CPA usually occurs at modest reaction temperatures.[334] Moxley et al.[350] investigated the effect of 84.0% H_3PO_4 pretreatment at different reaction time (from 30 to 120 min) at 50°C and pretreatment temperature (from 40 to 60°C) for 60 min on the enzymatic glucan digestibility of hemp stalks. Higher reaction temperatures and time resulted in faster fiber dissolution; however, significant hydrolysis of cellulose and hemicellulose or sugar degradation occurred at this condition. In terms of enhanced MCC processing ability by CPA, however, a

854 decreasing trend in solubility was observed by increasing the temperature from 5 to 75°C.[337]
855 Sathitsuksanoh et al.[339] optimized the COSLIF conditions for enhanced saccharification at
856 decreased cellulase loadings by response surface methodology (RSM). The optimal conditions
857 were 85% (w/v) CPA, 50°C, and 60 min, regardless of the biomass moisture contents from 5–
858 15% (w/w). These modest reaction conditions can minimize sugar degradation, inhibitors
859 formation, and capital investment of industrial plant.



860

861 **Figure 9.** SEM images of cotton linter pretreated with different concentrations of O-phosphoric acid (0–
862 78% w/w). Pretreatment conditions were: ice-cold temperature, one hour with occasional mixing, and
863 water as an antisolvent (taken from ref. 357).

864

865 Addition of the volatile organic solvents is used for regenerating amorphous cellulose and
866 hemicellulose, dissolving organic solvent lignin soluble fraction, and recycling and re-
867 concentration of PA.[358] Recently, replacement of acetone by ethanol was presented and widely
868 used in a modified version of the COSLIF. This modification is advantageous because ethanol is

more chemically stable than acetone for solid/liquid separation and less corrosive. Besides, very high yield of acetone recovery (e.g., >99.99%) is required for having an economically viable COSLIF implementation, whereas lower ethanol recycling/recovery after pretreatment (e.g., 98–99%) is acceptable,[338-340] since the remaining ethanol can be separated in ethanol distillation process. Moreover, a 40% decrease in organic solvent consumption was achieved in the replacement of acetone by ethanol.[339]

6.2 Why is phosphoric acid so effective in enhancing enzymatic hydrolysis?

Many studies reported that substrate accessibility to cellulase determines the susceptibility of lignocellulosic substrates to enzymatic hydrolysis.[257,260,261,297,359-361] Cellulose accessibility to cellulase (CAC) is usually quantified by cellulase adsorption Langmuir kinetics, as discussed in Section 5.2.[261,362] Recently, a quantitative assay for CAC, based on adsorption of a nonhydrolytic fusion protein containing CBM and GFP, was developed by Hong et al.[363] and applied for pretreated substrate characterization. CAC (m^2/g of cellulose) was calculated by multiplying a constant to maximum cellulase adsorption capacity obtained from Langmuir equation (Eq. 3).[363] For pretreated lignocellulosic biomass, total substrate accessibility to cellulase (TSAC) represented the cellulase adsorption capacity for the whole biomass and was calculated by adding CAC and non-cellulose accessibility to cellulase (NCAC).[341] TSAC was equal to CAC for protein thioredoxin-GFP-CBM (TGC) adsorption to biomass. Similarly, CAC and TSAC (m^2/g biomass) can be calculated by TGC adsorption after BSA blocking of the lignin fraction. Therefore, NCAC (m^2/g biomass) can be calculated as the difference between TSAC and CAC.[341] TSAC, CAC, and NCAC (m^2/g biomass) measurements of intact lignocelluloses were reported to be approximately 1 m^2/g biomass.[240,339-341] Untreated Alamo switchgrass (*Panicum virgatum*), for example, had 1.27, 0.49, and 0.77 m^2/g-biomass TSAC, CAC, and NCAC,

892 respectively.[364] SAA slightly improved all the accessibilities, while COSLIF resulted in
893 considerable increase of 9.6 and 8.0 for TSAC and CAC (m^2/g biomass), respectively.[240]
894 Similarly, almost 2-fold increase in the accessibilities was observed for COSLIF-treated corn
895 stover compared to DA pretreatment.[341] TSAC (m^2/g-biomass) of miscanthus and poplar also
896 increased after COSLIF pretreatment but more radically from 0.18 to 20.7 and 0.23 to 18.2,
897 respectively.[340] Common reed followed the same pattern as miscanthus and poplar after the
898 pretreatment.[339]

899 Breaking or even restructuring highly ordered intra- and inter-molecular hydrogen-bond network
900 of crystalline cellulose is believed to enhance its depolymerization rate.[106,337,365] The evidence of
901 breaking hydrogen-bonding networks in cellulose fibers of switchgrass after COSLIF was
902 confirmed by CP/MAS ^{13}C-NMR and FTIR.[365] Other analytical techniques, e.g., microscopy and
903 X-ray diffraction, also showed the disruption of hydrogen-bond network of cellulose for MCC
904 regenerated from CPA.[337] John et al.[366] investigated the structures of native and regenerated
905 celluloses by X-ray methods and proposed the same lattice plane location of the inter-molecular
906 hydrogen bonds between adjacent cellulose molecules. The empty space between adjacent
907 cellulose chains could be occupied by the hydrogen ion from phosphoric acid; therefore, inter-
908 molecular hydrogen bonds formation is destroyed during the regeneration process.[349]

909 Recently, computer simulations have been employed to study the biomass recalcitrance at
910 molecular level that otherwise cannot be analyzed with available experimental techniques.[367,368]
911 Molecular dynamics simulation (MDS) and quantum chemical calculations, e.g., density
912 functional theory (DFT) methods, are the tools of molecular simulation. These techniques have
913 been used for the simulations of lignin biosynthesis and degradation,[369,370] cellulose
914 insolubility,[371] and recently for the simulation of the effect of ammonia pretreatment on cellulose

I_{β}.[106] Although models of secondary plant cell walls incorporating cellulose, xylan, water, and lignin by MD simulations were carried out,[372] the molecular simulation studies on lignocelluloses are scarce. This is due to the complex lignocellulose biomass structure and also the intricate relationship between enzymes, chemicals, and biomass. Molecular simulation for lignocelluloses is still in its early stage of development and needs further investigation to fill the gap of advancing analytical methods in pretreatment.

6.3 Summary and future perspectives of phosphoric acid pretreatment

Taking all into consideration, COSLIF was successful with a number of agricultural residues and hardwoods[342,373] and demonstrated the advantages of high glucan digestibility even at low cellulase loadings, high hydrolysis rates, modest reaction conditions, higher revenues from co-products (acetic acid, lignin, and hemicelluloses), and less inhibitor formation. Besides, the remaining CPA on treated biomass did not show inhibitory effects for enzymatic hydrolysis or fermentation processes. However, it is still in its early stage of development and its commercialization is a far promising priority that needs pervasive consideration. Although there are only a few studies in the literature, CPA pretreatment does not seem to be very effective for improving biogas production from lignocelluloses. Substantial reduction in the use of chemicals (both CPA and organic solvent) is required in order to have an economically competitive process. Improvement of ethanol production process economy was suggested by the production of two major value-added byproducts, i.e., unaltered and purified lignins by the COSLIF and byproducts from fermentation.[342] Although CPA pretreatment seems to be very promising given the high end-product and by-products yields; however, a detailed techno-economic analysis of CPA pretreatment is required in order to study the feasibility of this pretreatment for a large-scale operation.

7 N-methylmorpholine-N-oxide (NMMO) pretreatment

N-methylmorpholine-N-oxide (NMMO or NMO) is categorized as a family of cyclic, aliphatic, tertiary amine oxides.[374,375] Tertiary amine oxide systems were first patented by Graenacher and Sallmann[376] in 1939 to dissolve cellulose for enhanced chemical processing. However, Johnson,[377] for the first time in 1969, introduced a cyclic mono(N-methylamine-N-oxide) compound to interact with inter-molecular hydrogen bonding networks and can dissolve cellulose, wool, silk, hair, and feather, which are insoluble in commonly used solvents. Since the late 1970s, the research on the dissolution of cellulose in NMMO was initiated when McCorsley and Varga[378] produced a highly concentrated, yet economical, cellulose solution by dissolving cellulose in a NMMO-water system. At that time, research on NMMO-cellulose tertiary systems was mainly focused on producing regenerated cellulose fiber that has applications in textiles and nonwovens, lyocell process, strengthening paper films, and paper coatings.[374,377,379-381] However, this technology has been recently introduced as a pretreatment method of lignocelluloses, e.g., for the improvement of either second-generation bioethanol[115,382-388] or biogas production.[388-397] Having a strong N-O dipole, which acts as either ionic or donative and single bond, NMMO is capable of disrupting the hydrogen-bond networks of cellulose and building new hydrogen bonds between the polymer and the solvent[375,379,398] (Figure 10). Cellulose dissolution in NMMO leads to a tertiary phase of cellulose-NMMO-water system.[379,399] Hydration with 1–1.2 water molecules per NMMO (water content 13.3–17 wt.%) significantly improves its interaction with a solute and boosts its solvation ability, while increasing water content to 19–24% and 25–30% results into heterogeneous swelling by forming balloons and ballooning, respectively.[400] Higher water contents (above 35%) make fibers swell homogeneously and precipitate, because in the tertiary system water is further preferred to form hydrogen bond with NMMO than

cellulose.[375,379,400] Ballooning and swelling modes of cellulose dissolution is more efficient for biogas production, while for ethanol production pretreatment with 85% NMMO leads to a better lignocellulose bioprocessing.[384] Figure 11 shows a microscopic image of wood fiber swollen by ballooning in NMMO solution, where three zones of the membrane of the balloons, the inside of the balloons, and the nonswollen crystalline regions are easily identical.

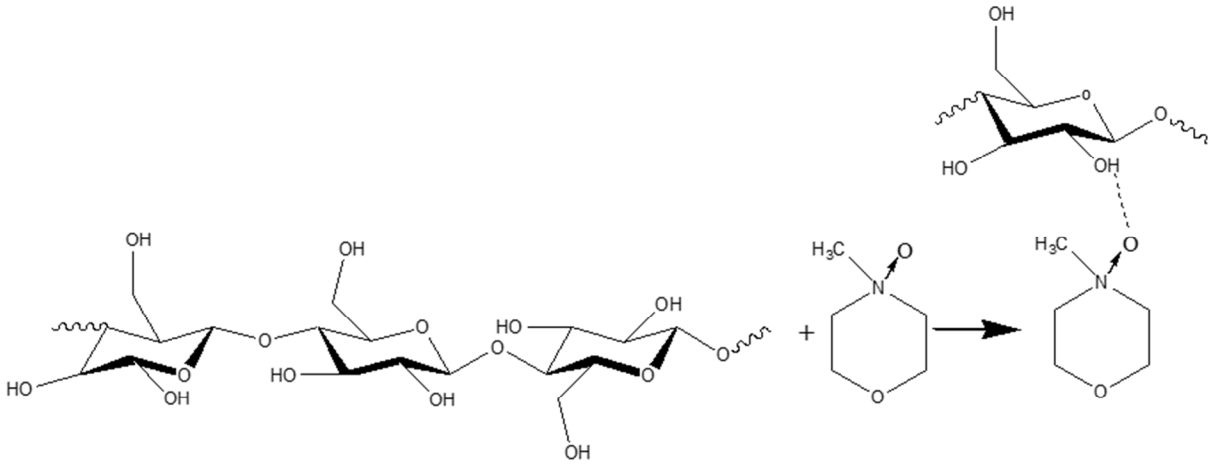


Figure 10. The mechanism of cellulose dissolution in NMMO, adapted from Wang et al.[163] with permission.

Lignocelluloses are directly dissolved in the solvent at moderate temperatures (90–130°C) under atmospheric pressure for 20 min to 5 h with negligible derivatization. Cellulose is subsequently regenerated by adding water as an anti-solvent to the slurry. The regenerated cellulose (cellulose precipitated from NMMO solution) is converted from cellulose I to cellulose II structure, which is much more reactive for cellulase adsorption and subsequently hydrolysis.[401,402] The solvent is washed away from the regenerated solids by distilled boiling water, and the excess water can be easily vaporized due to the low vapor pressure of NMMO, allowing approximately 99% of NMMO recycling.[403]

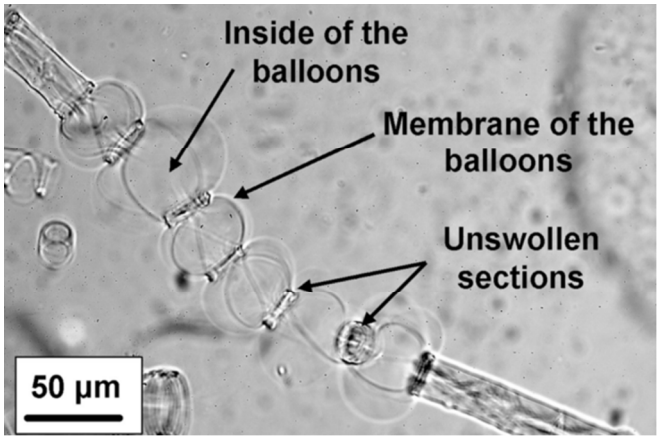


Figure 11. Wood fiber swollen by ballooning in a 78 wt.% NMMO solution in water, taken from ref. 404.

7.1 Effect of NMMO pretreatment on the superstructure of lignocelluloses

The enhancement in digestibility of regenerated lignocellulosic biomass by NMMO pretreatment is mainly due to reduced cellulose crystallinity. The crystalline structure of regenerated lignocellulose from NMMO solution as well as the untreated one are usually expressed by Total Crystallinity Index (TCI) and Lateral Order Index (LOI) using FTIR.[405] FTIR spectra of lignocelluloses can also give some valuable information of the structure and the variation in characteristic bands by the pretreatment. Table 4 summarizes the characteristics of bands, their corresponding functional groups, and assignments to the major biomass constituents.

Table 4. Characteristics of bands from FTIR spectra of lignocelluloses, from ref. 121.

Wavenumber (cm^{-1})	Functional group	Assignment
3175	–OH stretching (inter-molecular hydrogen-bonds)	Cellulose II
2900	C–H stretching	Cellulose
1740	C=O stretching (acetyl or carboxylic acid)	Hemicellulose and lignin
1510, 1610	C=C stretching (aromatic ring)	Lignin
1465	$C–H_3$ (bending)	Lignin
1420, 1430	$C–H_2$ (bending)	Cellulose
1375	C–H (bending)	Cellulose
1335	–OH (bending)	Cellulose
1315	$C–H_2$ (wagging)	Cellulose
1158	C–O–C (stretching)	Cellulose

Purwandari et al.[396] reported that TCI (the absorbance ratio A1427/A898 calculated from FTIR spectra) of oil palm empty fruit bunch (OPEFB) reduced by up to 78% following the pretreatment in 85% NMMO at 120°C for 3 h. In addition, ballooning and swelling modes of NMMO result in lower TCI at 120°C than at 90°C. This finding is in contrast with ballooning and swelling modes of NMMO pretreated cotton that result in lower crystallinity indexes at 90°C than 120°C.[384] However, compared to the untreated cotton, crystallinity indexes decrease slightly for different modes of dissolution, ballooning, and swelling.[121] Besides, the intra-molecular hydrogen-bonding OH stretching at about 3,350 cm^{-1} (FTIR spectra) in pretreated cotton is broadened and shifted to a higher wave number,[384] which is an indication of transforming cellulose I to cellulose II.[406,407] This finding is in accordance with another report on NMMO pretreatment of straw[389] and also confirms that the pretreatment reduced the structural lignin content. NMMO pretreatment of bagasse at 130°C for 1 h transformed crystalline structure into amorphous form, since the TCI and LOI decreased from 1.39 and 1.44 to 1.18 and 1.10, respectively.[385] LOI, a criterion for the estimation of amorphous to crystalline portion of the structure, was considerably decreased from 2.68 to 0.88 when straw fraction of manure was pretreated for 5 h at 120°C using 85% NMMO and decreased more with increase in pretreatment time to 15 h.[389] Moreover, LOI and TCI of rice straw pretreated with 85 wt.% NMMO for 5 h at 120°C were decreased from 0.46 to 0.40 and 1.69 to 1.62, respectively.[387] Likewise, Khodaverdi et al.[408] reported that NMMO (85%) treatment of cotton linter at 120°C for 2 h resulted in TCI and LOI decrease from 7.1 and 2.7 for untreated cotton to 3.3 and 1.1, respectively.

The FTIR analysis also indicated that lignin and acetyl groups from the hemicellulose backbone were partially removed by the pretreatment, while cellulose content was increased. Liu et al.[362] qualitatively studied the abundance and distribution of lignin and cellulose in NMMO-pretreated

pine flour using FTIR technique. Diminishing of the absorbance peaks at 1270 cm^{-1} and 1596 cm^{-1}, referring to lignin,[409] indicated a reduction in lignin content on the surface of pine flour after NMMO pretreatment.[362] Furthermore, crystallinity measurement of the biomass by X-ray diffraction confirmed a linear correlation (R^2 = 0.91) between cellulose crystallinity and initial hydrolysis rates of the pine flour samples. Virtanen and Maunu[410] investigated the dissolution process of softwood pulp fibers in NMMO at 110°C for 15, 30, and 90 min by employing different NMR spectroscopic methods: solid state cross polarization magic angle spinning (CP-MAS), ^{13}C and ^{15}N spectroscopies, and ^{1}H high resolution MAS NMR spectroscopy. Cellulose crystallinity of NMMO pretreatment sample for 90 min was decreased by 15%, and the C_4 signal appeared different from the untreated pulp, while it remained almost constant for the first 30 min of treatment with broadening C_4 signal.

7.2 Changes in composition and microstructure during NMMO pretreatment

In general, carbohydrate contents of lignocelluloses do not undergo significant changes and high solid recoveries are achieved after NMMO pretreatments.[115,394,396,397,411] This is an advantage of NMMO pretreatment over conventional pretreatment methods, since carbohydrate loss is a major problem in most chemical, physicochemical, and biological pretreatments.[136,187] However, longer pretreatment time and/or temperature lead to partial removal of acid-insoluble lignin and xylan (or mannan in softwoods) and enrichment of glucan constituent.[382,383,386,387,389,393,411] Furthermore, structural studies confirmed liberation of acetic acid from acetyl groups of biomass during NMMO pretreatment, especially at longer pretreatment times and higher temperatures.[115] Ash content was also reported to decrease from 5.4% up to 1.3% as a result of NMMO pretreatment of OPEFB,[396] while no considerable change was reported for rice straw.[387]

7.2.1 Cellulose accessibility to cellulases

Porosity or specific surface area (SSA) of exposed cellulose is considered as another key feature of pretreated lignocellulosic substrates that influence the hydrolysis of cellulose by cellulases. In other words, cellulose accessibility is directly associated with the rates and extents of enzymatic deconstruction of lignocelluloses.[411] Simons' Stain (SS) is a potentially useful semi-quantitative technique for specific surface area measurement of lignocellulosic substrates,[413] which was first introduced in 1950 to evaluate mechanical damage of pulp fibers during beating.[414] SS method is based on dying substrates with direct blue 1 (DB) and then direct orange 15 (DO) to quantify smaller and larger pore sizes, respectively.[413] It has advantages of measurement of interior and exterior surface area at even wet state and being relatively fast and simple over other accessible surface area measurement techniques.[415] The total adsorbed dye amount, which represents the number of overall pores, considerably increased up to 1.5- and 2.2-fold for barley straw and forest residues, respectively, after NMMO pretreatment at 90°C for 3–30 h.[394] Moreover, the more the pretreatment time, the more the overall dye adsorbed. This finding was also confirmed by Teghammar et al.[416] for rice and triticale straw. Over 74% and 86% increase in total dye adsorption was observed for rice and triticale straw, respectively, after 15 h NMMO pretreatment at 130°C. The biomass displays the same pattern in dye adsorption as in enzymes adsorption,[416] which is directly related to the enzyme accessibility of substrate.[263] An increase in enzymes adsorption by 100, 140, and 290% for triticale straw and 11, 50, and 240% for rice straw was observed after 1, 3, and 15 h of NMMO pretreatment, respectively.[416]

Cellulose accessibility for NMMO-treated substrates was then evaluated by comparing maximum adsorption capacity (by Langmuir adsorption isotherm) of pretreated samples and enzyme lignin (EnzL),[362] prepared by complete hydrolysis of carbohydrates in the pretreated

biomass with excessive cellulase loadings.[261] Maximum adsorption capacity of cellulase onto pine flour samples as well as cellulose accessibility considerably increased with increasing NMMO pretreatment time from 30 to 120 min at 120°C. Moreover, a nearly good linear correlation between cellulose accessibility and overall glucan conversion rate was also reported for pine flour.[362]

The other rapid specific surface area assessment technique is water retention value (WRV) or water swelling capacity, which has been used to quantify swelling potential of paper pulps.[417] WRV is the ability of water adsorption or the swelling capacity of substrate and reflects the accessibility of the substrate to subsequent hydrolysis by enzymes.[412] Besides, since substrate swelling and water adsorption occur mainly in the amorphous regions, the WRV can be used as a criterion to assess changes in crystalline structure after pretreatment.[418] Water swelling capacity of birch hardwood after pretreatment with 85% NMMO at 130°C for 3 h substantially increased by 46.6-119.9% depending on the applied drying method.[383] The WRV of triticale straw also slightly increased by 10%, 10%, and 20% at NMMO pretreatment time of 1, 3, and 15 hours, respectively, and smaller increase of 10% for rice straw was realized.[416] However, significant reduction in the WRV of cellulose was reported by NMMO pretreatment in dissolution mode at either 90 or 120°C.[384] This behavior was observed less at lower concentrations of NMMO (than 85%), but it still had lower WRV values compared to untreated one.[384]

7.3 Advantages and disadvantages of NMMO pretreatment

NMMO is able to dissolve up to 15 wt.% of cellulose[419] with no/less chemical modification at relatively mild conditions (low/moderate temperatures and atmospheric pressures). High bioprocess efficiency, high solvent recovery, and formation of low carbohydrates degradation and inhibitory products are also among the favorable characteristics of NMMO pretreatment.

Table 5 and Table 6 summarize an overview of treatment conditions along with improvements in saccharification/fermentation and biogas production from different lignocelluloses after NMMO pretreatment. These tables show that NMMO pretreatment is conducted under relatively mild conditions, i.e., temperature 90-130°C for a few hours, using ~85% NMMO. As can be seen in these tables, NMMO pretreatment causes significant improvement in ethanol, biogas, and enzymatic hydrolysis yields for different types of lignocelluloses including hardwoods, softwoods, agricultural residues, and other cellulosic substrates. By applying NMMO pretreatment, ethanol can be produced by *S. cerevisiae*, *M. indicus*, and *Z. mobilis* via different strategies, e.g., SSF, SHF, and NSSF (Table 5). The pretreatment resulted in up to 100% conversion of cellulose in enzymatic hydrolysis and 93.3% ethanol yields of theoretical maximum for rice straw (Table 5). An improvement of about 100% in the methane yield was also reported after NMMO pretreatment of cotton linter.[392] At pilot scale, maximum hydrolysis sugar yields of 195 and 175 mg sugar/g wood for spruce and birch wood chips, respectively, in NSSF with *Mucor indicus* was also achieved.[386]

Table 5. Improvement in glucan conversion/ethanol production yield from different lignocelluloses pretreated by NMMO

Substrate	NMMO condition	Method and fermentation microorganism	Glucan conversion and/or ethanol yield	Ref.
Spruce and oak	90, 110, and 130°C , 1–3 h	NSSF[1], *Saccharomyces cerevisiae*	Up to 85.4% and 89% improvement in ethanol yield for spruce and oak, respectively	115
Rice straw	85 wt.% NMMO, 120°C, 1, 3, and 5 h, 5% loading	SSF, *S. cerevisiae*	Hydrolysis yield of glucan 96%, 93.3% of theoretical maximum ethanol yield	387
Cotton linter	90 and 120°C, 0.5-15 h using 85%, 79%, and 73% NMO	SSF, *S. cerevisiae*	Improvement of up to 100% yield in enzymatic hydrolysis and 83.75% ethanol yield	384
Spruce and birch	85% NMMO, 130°C, 1–5 h	Bench-scale and airlift cultivations, *Mucor indicus*	Maximum ethanol yields of 195 and 175 mg/g wood for spruce and birch, respectively	386

Birch	85% NMMO, 130°C, 3 h	SHF, *S. cerevisiae,*	Maximum 76.8% ethanol of theoretical yield, 9-fold increase in ethanol yield compared to untreated	383
Wheat straw	85% NMMO 120°C for 1–5 h	Anaerobic cultivations, *M. indicus*	Up to 92.1% of theoretical maximum ethanol yield	382
Sugarcane bagasse	NMMO monohydrate, 130°C, 1 h	SSF, *Zymomonas mobilis*	Approximately 0.15 g ethanol/g bagasse (86% of the theoretical maximum ethanol yield)	385

[1]Non-isothermal simultaneous saccharification and fermentation

Table 6. Improvement in biogas production from different lignocelluloses pretreated by NMMO

Substrate	Pretreatment condition	(Improvement in) methane yield	Ref.
Oil palm empty fruit bunch (OPEFB)	90 and 120°C, 1, 3, and 5 h, 85%, 79%, and 73% NMMO	Methane yield up to 0.408 Nm^3/kg-VS, improvement by 167% compared to untreated	396
	73, 79, and 85% NNMO, 90 and 120°C, 1, 3, and 7 h	Maximum 0.408 Nm^3 CH_4/kg-VS	395
Softwood spruce, rice straw, and triticale straw	130°C, 1-15 h, 85% NMMO	Up to 245, 157, and 203 Nml CH_4/g raw material, respectively, 400-1200% improvement compared to the raw materials	397
Forest residues	120°C, 3, 7, and 15 h, 75% and 85% NMMO	Up to 0.17 Nm^3/kg-VS[1] methane yield (83% of theoretical maximum yield)	393
Straw fraction of cattle and horse manure	5 h and 15 h, 120°C, 85% NMMO	Maximum methane yield increase by 53% and 51% for cattle and horse manure, respectively, after 15 h pretreatment	389
Barley straw and forest residues	85% NMMO, 3–30 h, 90°C	0.23 and 0.15 Nm^3 CH_4/kg-VS from barley straw and forest residues, respectively; corresponding to 88% and 83% of the theoretical maximum yields	394
Blended-fibers waste textiles	85% w/w NMMO, 120°C, 2 h	Up to 62.18% of theoretical maximum methane yield (after 6 days)	391
Forest residues	NMMO concentrations of 75% and 85%, 120 and 90°C, 3 and 15 h	Maximum 141% increase in methane production (75% NMMO at 120°C for 15 h)	388
Jeans textiles	85% NMMO, 120°C, 3 h	Two-stage semi-continuous process, 400 mL methane/g-VS/day	390
Cotton linter	85% NMMO, 5% w/w solid loading, 120°C, 3 h	Approximately 100% methane yield (% of maximum theoretical) for 5 g/L cellulose concentration after 30 days	392

[1]Volatile solid

The solvent is recycled by treating the solution with ion-exchange resins to remove contaminants and subsequent dewatering the solvent.[420] Due to low vapor pressure of NMMO, excess water can be easily vaporized from the recycled solvent and leave the monohydrate form of NMMO.[403] However, the water evaporation unit demands high-energy input which has considerably negative effects on the economy of the whole process.[421,422] Besides, in order to have an economical feasible process of bioethanol and biogas production by NMMO pretreatment of lignocelluloses, more than 99 percent of NMMO recovery is required.[421,422] Some side reactions and/or NMMO ring cleavage can occur in cellulose-NMMO solutions, especially at the elevated process temperatures,[423,424] which hamper efficient solvent recovery. A study showed that a smaller amount of reducing sugars was liberated from NMMO-pretreated sugarcane bagasse at

130°C rather than 100°C, possibly due to NMMO or cellulose degradation.[385] In some studies, recycled NMMO showed the same performance in hydrolysis improvement and biogas production of pretreated sugarcane bagasse and barley straw, respectively,[385,394] as compared with fresh NMMO. However, in contrast, forest residues with high lignin and bark content resulted in 55% reduction in methane yield after pretreatment with recycled NMMO in comparison with those pretreated with the fresh NMMO.[394]

The remaining NMMO in the regenerated solids may prove to have inhibitory effects on fermenting organisms and/or hydrolytic enzymes. NMMO concentration of 5 and 100 g/L has been shown to reduce the enzymatic hydrolysis yields by 12% and 76%, respectively, after 12 h of hydrolysis for cotton linter.[384] Although NMMO decreased the glucose uptake rate by *S. cerevisiae* a little, it had negligible impact on the final ethanol yield even at concentration of 100 g/L.[115,384] However, ethanol yield and productivity were decreased at concentrations above 2% NMMO for *M. indicus*, while total production of metabolites was not significantly changed.[386] This was because some glucose shunted from the ethanol to the glycerol pathway as the glycerol yield and production increased in proportion to NMMO concentration. Recently, He et al.[425] introduced a NMMO-tolerant cellulase-producing strain from a newly isolated *Galactomyces* sp. CCZU11-1. The results showed that up to 25% (w/v) NMMO had no significant effect on the saccharification of NMMO-pretreated sugarcane bagasse prepared at 130°C for 1 h or fermentation by *S. cerevisiae.* On the other hand, NMMO remaining in the pretreated substrate at concentrations higher than 0.002% was reported to considerably decrease the methane yield.[393]

Once the solvent was washed away from the substrate, NMMO leaving the process ends up in the wastewater stream. Nevertheless, it is not of great concern, since NMMO is an environmentally friendly solvent.[426,427]

Techno-economic analysis of NMMO pretreatment of spruce for bioethanol and biogas[421] and forest residues for biogas production elucidated high process energy efficiency.[422] In the case of bioethanol production, a biogas plant in parallel to valorize pentoses can improve the process economy.[421] This is because most ethanol-producing organisms cannot assimilate pentoses efficiently.[343] When forest residues were co-digested with two-thirds of organic fraction of municipal solid waste in order to avoid nitrogen deficiency, the process of biogas production was evaluated to be financially feasible at 15% internal rate of return or higher for minimum plant capacity of 50,000 tons per year.[422] Generally, large amounts of water need to be vaporized in order to efficiently recover NMMO, and this is among the barriers for its commercialization.[421]

8 Ionic liquid pretreatment

8.1 Ionic liquids: historical evolution and general properties

Ionic liquids (ILs) are usually defined as large organic salts, composed entirely of an organic cation and an organic or inorganic anion, which exist in liquid form at or below 100°C.[428] The field of ILs was first discovered in 1914 by Walden,[429] who synthesized and characterized ethyl-ammonium nitrate ($[EtNH_3][NO_3]$) by neutralizing of ethylamine with concentrated nitric acid. Organic based chloroaluminates ILs were first developed by Hurley et al.[430] in 1951. A new class of ILs with melting point lower than ambient temperature based on 1-alkyl-3-methylimidazolium cation, called room-temperature ionic liquids (RTILs) and considered as the first generation ILs, has emerged since 1982 after the study by Wilkes et al.[431] The replacement of the moisture-sensitive anion in the first generation ILs by the tetrafluoroborate ion ($[BF_4]^-$) and other anions resulted in more water-stable ILs in 1992, known as second-generation ILs.[432] Third generation

ILs, known as "task-specific" ionic liquids (TSIL), which covalently incorporate either anions or cations or both as functional groups, were introduced by Davis[433] in 2004.

ILs have negligible vapor pressures, high viscosity, and reasonable thermal and chemical stability, compared with typical organic solvents.[434,435] These properties can be changed and controlled by selection of cations and anions developed for a special application. This is why ILs are usually defined by the term "designer solvents".[436] ILs, due to their unique properties, have received significant attention for vast applications in chemical and biochemical industries.[428,435,437-441]

8.2 Solvation in ILs

A simulation and vibration spectroscopy study of water-IL suggested the concentration dependence solubility of water in IL. At low concentrations, the dissolution mechanism of water is molecular dispersion, while water aggregation takes place at higher concentrations. Dissolution of benzene in [DMIM](1,3-dimethylimidazolium)[PF_6], however, makes an expansion in the IL structure, while the long-range charge ordering pattern in the IL still exists.[442] One of the promising solvation features of ILs is their ability to dissolve monosaccharides, which are barely soluble in common solvents, except water.[443,444] Like benzene, a simulation understanding of glucose dissolution in the ionic liquid [DMIM][Cl] has been established.[445,446] The nature of the solute-solvent interaction in the system is mainly hydrogen bond with high chloride content of the IL. Youngs et al.[446] suggested that the dominant coordinate of glucose dissolution in excess IL is formation of three hydrogen-bond between OH groups of glucose and three anions, and a OH···Cl···HO bridge between the last two OH groups and the forth chloride. The RTILs that contain dicyanamide anion were also reported to dissolve significant amounts of glucose, sucrose, lactose, and cyclodextrin.[447] Other monosaccharides,

including arabinose, fructose, mannose, and xylose, seem to have partial to high solubility in different ILs.[448] Surprisingly, not only monosaccharides but also oligosaccharides and even polysaccharides are soluble in ILs. α-cyclodextrin and starch, for example, were shown to have 30% and 10% solubility, respectively, in [BMIM](1-butyl-3-methylimidazolium)[Cl].[448] Unlike dissolving saccharides in classic solvents, e.g., DMF and DMSO, the derivatization of native carbohydrates in ILs is of great importance since it is a green process.[443] However, the aim of most studies on carbohydrate ILs interaction is to produce non-derivatized cellulose, which has demonstrated vast applications in fibers and composite fibers production,[449] as monoliths and films,[443] and more recently, lignocellulosic biomass pretreatment.[173]

8.2.1 Dissolution of cellulose in ILs

The first attempt to dissolve cellulose in ILs is dated back to 1934 when Graenacher[450] first utilized heated N-ethylpyridinium chloride in the presence of N-containing bases. Although many studies consider Graenacher's patent as the pioneer in IL dissolution of cellulose; however, recently, Sun et al.[451] claimed that the dissolution was stipulated by the addition of nitrogen-containing bases and not by IL alone. Besides, the co-solvents used were volatile and the IL itself had a relatively high melting point (T_m; 120°C) over conventional ILs. More recently, Swatloski et al.[452] investigated cellulose dissolution in ILs based on 1-butyl-3-methylimidazolium cations by publishing a highly cited paper in 2002. They further analyzed cellulose and cellulose oligomers in 1-butyl-3-methyl-imidazolium chloride IL solution using high-resolution ^{13}C NMR.[453] The ^{13}C NMR data indicated that β-(1→4)-linked glucose oligomers were disordered, with conformational behavior parallels the one observed in water.

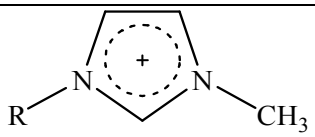
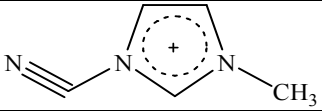
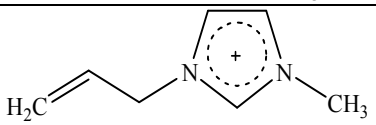
The selection of cations and specially anions in ILs plays a crucial role in cellulose dissolution.[108] Since the cellulose-IL bond, in nature, is hydrogen-bond,[446] it seems that anions

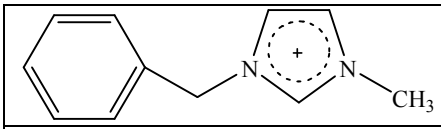
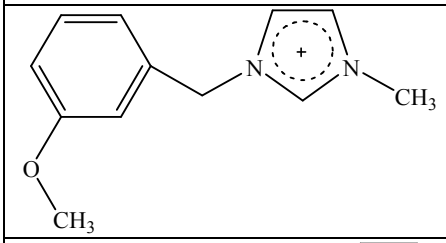
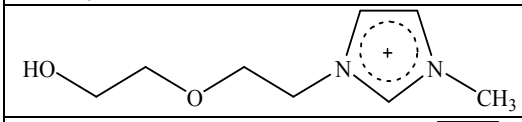
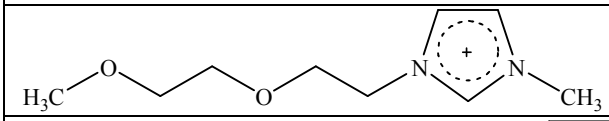
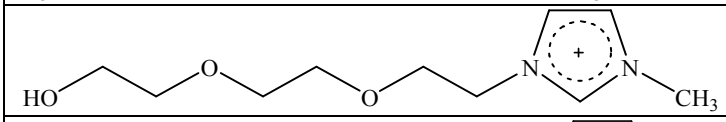
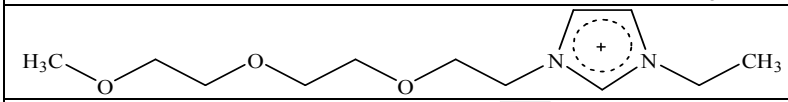
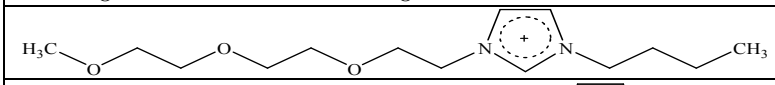
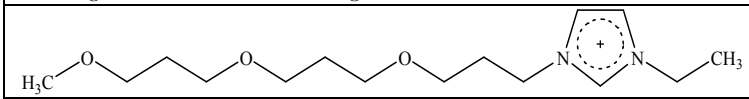
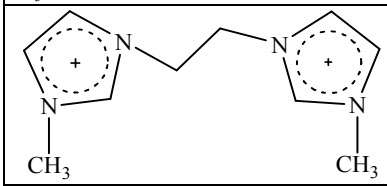
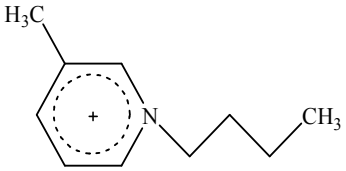
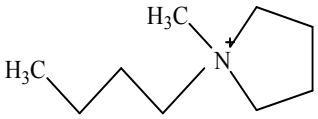
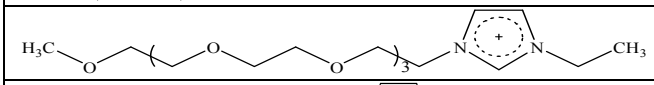
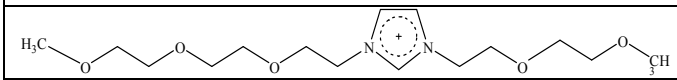
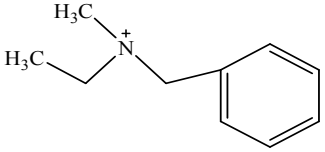
with more hydrogen-bond-acceptor capability, e.g., OAc^-, $HCOO^-$, $(MeO)_2PO_2^-$, and Cl^-, are the suitable candidates for the solubility, while ILs with low-basicity anions, such as dicyanamide-based ILs, are not that efficient in dissolving cellulose.[108] ILs containing 'noncoordinating' anions, including $[BF_4]^-$ or $[PF_6]^-$, on the other hand, display no cellulose solubility.[452] Unlike anions, cations in ILs play an unclear, but effective role, in the cellulose dissolution.[108] Table 7 listed the structure of some well-known ILs' cation for cellulose dissolution. Li et al.[454] performed a simulation study and concluded that ILs with unsaturated heterocyclic cations can dissolve cellulose, whereas ILs with saturated ring cations can hardly dissolve cellulose. The reason for that was reported to be related to the structure factor and dynamic effect of the cations. Zhang et al.[455] synthesized and used 1-allyl-3-methylimidazolium chloride as a non-derivatizing solvent for molecular dissolution of cellulose at room temperature. Although intra- and inter-molecular hydrogen-bond disruption were mainly due to the formation of chloride hydrogen-bond network, it was suggested that small polarized cation, $[AMIM]^+$, also helped the attack on oxygen atoms of cellulose hydroxyl in this case.[455,456] The ^{13}C NMR spectrum of MCC dissolved in [AMIM][Cl] clearly resolved the six signals of carbon atoms of unmodified anhydroglucose similar to cellulose dissolved in sodium hydroxide solution or [BMIM][Cl].[455] However, the dissolution mechanism was not dominated by hydrogen bond formation between cellulose and chloride. Thus, first, it is important to compare cellulose solubility in chloride alkali metal salts. Chloride in LiCl, for example, perfectly interacts with cellulose hydroxyl groups and dissolve cellulose in the presence of N,N-dimethylacetamide (DMAc).[455] Nevertheless, other chloride salts, e.g., sodium, potassium, barium, and calcium chloride, are unable in dissolving cellulose.[455] Although concentrated zinc chloride is able to dissolve cellulose, its solvation behavior is due to the formation of zinc-cellulose complex.[457] Second, a unique anion with

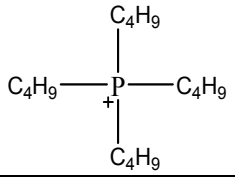
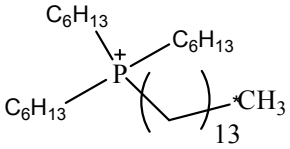
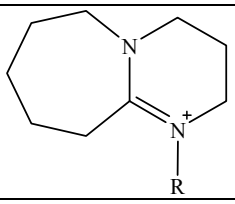
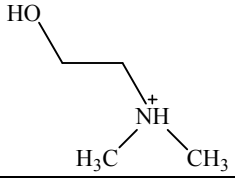
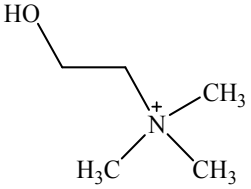
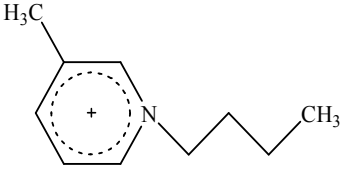
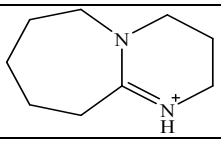
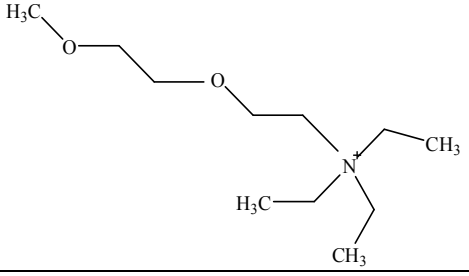
solubility potential, when combining with all range of cations, was not found. Vitz et al.[458] conducted a thorough study on cellulose dissolution in imidazolium-based ILs with particularly bromide and chloride anions. An odd-even effect for imidazolium chloride ILs with more cellulose solubility in even-numbered alkyl chains of cation compared to the odd-numbered was observed. Whereas, this pattern was not generalized for imidazolium-based ILs containing bromide anion. 1-Ethyl-3-methylimidazolium diethyl phosphate, however, demonstrated the maximum solubility of cellulose among the all imidazolium-based ILs. Although the role of cation is not yet well-clarified, it was reported that the size and polarizability and attached functional groups of the cation, e.g., hydroxyl end-group, or basic oxygen atoms affected its solubility.[108]

Sets of TSILs, or so-called tailor-made ILs, were also designated and characterized for dissolution and depolymerization of cellulose under mild conditions.[459] Thermal heating especially by microwave or sonication, degree of polymerization of cellulose, and the IL viscosity are among the non-IL-intrinsic effective factors in cellulose dissolution.[108,460-463]

Table 7. Structure of cations of well-known ILs used in dissolution of lignocellulosic feedstocks

Cation structure	Name
	R=CH_3: 1,3-dimethylimidazolium R=C_2H_5: 1-ethyl-3-methylimidazolium R=C_3H_7: 1-propyl-3-methylimidazolium R=C_4H_9: 1-butyl-3-methylimidazolium R=C_5H_{11}: 1-pentyl-3-methylimidazolium R=C_6H_{13}: 1-hexyl-3-methylimidazolium R=C_7H_{15}: 1-octyl-3-methylimidazolium R=C_8H_{17}: 1-nonyl-3-methylimidazolium R=C_9H_{19}: 1-decyl-3-methylimidazolium
	1-cyano-3-methylimidazolium
	1-allyl-3-methylimidazolium

	1-benzyl-3-methylimidazolium
	1-(3-methoxybenzyl)-3-methylimidazolium
	1-(3,6-dioxahexyl)-3-methylimidazolium
	1-ethyl-3-(3,6-dioxaheptyl)imidazolium
	1-(3,6,9-trioxanonyl)-3-methylimidazolium
	1-ethyl-3-(3,6,9-trioxadecyl)-imidazolium
	1-butyl-3-(3,6,9-trioxadecyl)-imidazolium
	1-ethyl-3-(4,8,12-trioxatridecyl)-imidazolium
	3,3-ethane-1,2-diylbis(1-methyl-1 H-imidazol-3-ium)
	1-butyl-3-methylpyridinium
	1-butyl-1-methylpyrrolidinium
	1-ehyl-3-(3,6,9,12,15,18,21-heptaoxadococyl)-imidazolium
	1-(3,6-dioxaheptyl)-3-(3,6,9-trioxadecyl)-imidazolium
	N-benzyl-N,N-dimethylammonium

	tetrabutylphosphonium
	trihexyltetradecylphosphonium
	R=CH_3: 8-metyl-1,8-diazabicyclo[5.4.0]undec-7-enium R=C_4H_9: 8-butyl-1,8-diazabicyclo[5.4.0]undec-7-enium R=C_8H_{17}: 8-octyl-1,8-diazabicyclo[5.4.0]undec-7-enium
	N,N-dimethylathanolammonium
	Choline bis[(trifluoromethane)sulfonyl]imide
	1-butyl-3-methylpyridinium
	1,8-diazabicyclo[5.4.0]undec-7-enium
	N,N,N-triethyl-3,6,9-trioxadecylammonium

1241 8.2.2 Dissolution and regeneration of lignocellulosic biomass in ILs

1242 Kilpeläinen et al.[464] demonstrated the capability of imidazolium-based ILs in dissolving
1243 hardwoods and softwoods under mild conditions. Xie et al.[465] also reported the preparation of

wool keratin/cellulose blended materials by dissolution and regeneration using [BMIM][Cl]. Fort et al.[466] processed and analyzed the dissolution of woods of different hardness in [BMIM][Cl]. They reported the partial dissolution of untreated wood and celluloses with purities, physical properties, and processing characteristics comparable to those of pure cellulose samples subjected to similar treatment, which can be easily recovered from the resulting solutions by the addition of a variety of precipitating solvents. Li et al.[467] investigated the factors affecting dissolution of three wood species and regeneration in [AMIM][Cl]. Wood density, pulverization intensity, and the nature of the regeneration anti-solvents were reported as the main factors affecting the overall process. Generally, the ILs' anion and cation (cf. Section 8.2.1 for cellulose), viscosity, solvation properties, melting point and thermal decomposition, biomass particle size and type and loading, temperature and time of treatment, and microwave heating and sonication are among the important factors governing the dissolution of lignocellulosic biomass in ILs, which were recently reviewed by Badgujar and Bhanage.[468] Freire et al.[469] determined a set of thermophysical properties, i.e., density, viscosity, and refractive index, and isobaric thermal expansivity and heat capacities, for eight imidazolium-based ILs, as the important intrinsic IL parameters in the lignocellulose dissolution, and also the impact of anion type was investigated. Among the studied ILs, [EMIM][CH_3CO_2] was reported as the best candidate for lignocellulose dissolution, since it has shown to have a low viscosity and density. As the solvent properties of ILs, Doherty et al.[470] concluded, by comparison of Kamlet–Taft α, β, and π* solvent polarity parameters of three RTILs, (i.e., [EMIM][OAc], [BMIM][OAc], and [BMIM][$MeSO_4$]) that the β parameter is an excellent predictor of pretreatment efficacy. Regarding the properties of lignin, Li et al.[471] achieved rapid dissolution of bagasse and southern

yellow pine in [EMIM][OAc] by using a dissolution temperature above the glass transition of lignin.

8.2.2.1 Role of solvent in regeneration of cellulose from IL solution

Hauru et al.[472] characterized the Kamlet−Taft (KT) values of [EMIM][OAc], [TMGH][$EtCO_2$], and [TMGH][OAc], and NMMO at several water contents and temperatures to investigate the role of the solvent in cellulose regeneration from the ILs solution. The regeneration of cellulose was reported to start at thresholds values of approximately $\beta < 0.8$ ($\beta-\alpha < 0.35$). Shi et al.[473] investigated pretreatment of switchgrass with different [EMIM][OAc] and water concentration (50-80%) at 160°C and concluded a strong dependency of the chemical composition and crystallinity of the pretreated biomass as well as the corresponding lignin dissolution and depolymerization on the IL concentration. They found the hydrogen-bond basicity of the [EMIM][OAc]–water as a suitable indicator of predicting the cellulose dissolution, lignin depolymerization, and sugar yields. Besides, their molecular simulation indicated that water acts as a co- and anti-solvent in cellulose dissolution at below and above 50% [EMIM][OAc] concentration, respectively. The role of anti-solvent, e.g., ethanol, water, and acetone, in cellulose regeneration from a cellulose/[BMIM][OAc] mixture was studied by molecular simulation.[474] Structural analysis based on radial distribution function revealed that among the three studied solvents, water was the most effective solvent at breaking the cellulose–$[Ac]^-$ H-bonds, lead to the subsequent formation of cellulose–cellulose H-bonds, and demonstrated the best solvent for cellulose regeneration. Another molecular dynamics study was conducted to investigate the interaction of [EMIM][OAc], a cellulose oligomer, and water as an antisolvent.[475] Figure 12 shows the proposed intermediate formed during the regeneration of a cellulose oligomer from IL solution by using water, based on the simulation.

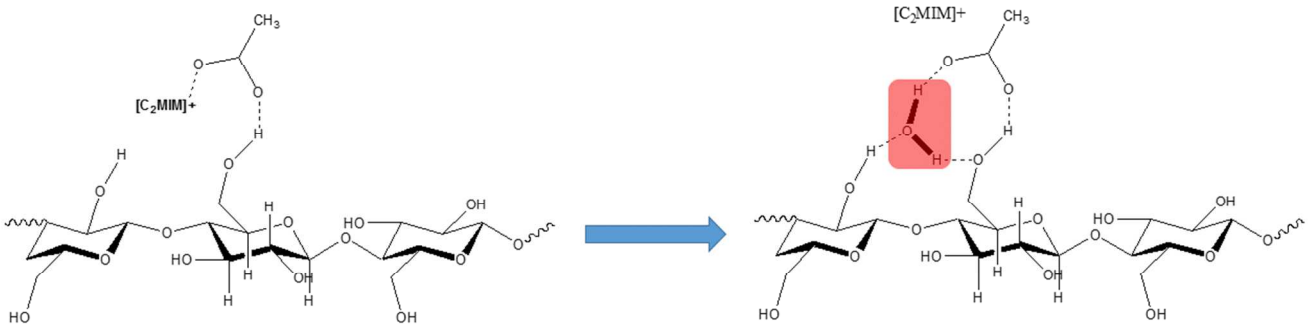


Figure 12. Intermediate structure of celluloses regenerated from an IL in the presence of water as an anti-solvent proposed by Liu et al.[475] using MD simulation, picture adapted from Liu et al.[475]

8.2.2.2 Biomass loading

Some studies on IL pretreatment have focused on high biomass loading in the pretreatment, instead of typical approximate 5.0 wt.%, since it is a crucial factor for process economy. Besides, a minimum amount of consumed IL and waste generation happen at high biomass loading.[476] Cruz et al.[477] investigated the effects of switchgrass loading on [EMIM][OAc] pretreatment in terms of viscosity, cellulose crystallinity, chemical composition, saccharification kinetics, and sugar yield. The IL pretreatment caused reduction in biomass recalcitrance for 3, 10, 20, 30, 40, and 50 wt.% biomass loading and a "solid" like behavior was observed when the biomass loading increased. Moreover, the IL pretreatment caused transformation of cellulose crystalline structure from I to II for 3, 10, 20 and 30 wt.% samples, while a mostly amorphous structure was found for 40 and 50 wt.% samples. Likewise, Wu et al.[478] reported the feasibility of [EMIM][OAc] pretreatment of corn stover at 125°C for 1 h at 50 wt.% biomass loadings in dramatic reducing the recalcitrance of the biomass. In another study, da Silva et al.[479] used a twin-screw extruder with high shear force to pretreat sugarcane bagasse at high solids loading in [AMIM][Cl]. They obtained the maximum glucan digestibility of 90% after 24 h of enzymatic

saccharification of pretreated substrate at a loading as high as 25 wt.% at 140°C for 8 min. The pretreatment decreased the crystallinity significantly and increased specific surface area (SSA) by more than 100-fold. At higher biomass loading of 50 wt.%, still 76.4% glucose yield was obtained. Li et al.[480] obtained 99.8% fermentable sugars from switchgrass by [EMIM][OAc] pretreatment at 15% (w/w) biomass loading during a 600- and 60-fold process scale-up for the pretreatment and enzymatic hydrolysis, respectively. Ninomiya et al.[481] investigated the cholinum IL pretreatment as a function of IL/biomass weight ratio of bamboo. They obtained a critical IL/biomass ratio of 3 g/g to obtain a cellulose saccharification of 80%, in a solid-state pretreatment.

8.2.3 Dissolution of lignin in IL

The mechanism of lignin dissolution and regeneration in [AMIM][Cl] has been investigated by density functional theory (DFT), atoms in molecules (AIM) theory, natural bond orbital (NBO) analysis, and Wiberg bond index (WBI) by Ji et al.[482] The theoretical results showed that lignin mainly reacted with [AMIM][Cl] via H bonds, and it can be precipitated by adding water, since the absolute value of the interaction energy of AmimCl−nH_2O (n = 1, 2, and 3) is greater than that of AmimCl−LigOH. Further analyses of the regenerated lignin by FTIR, TG, and SEM, revealed that no chemical reaction occurred for lignin during the dissolution and regeneration process. Wang et al.[483] investigated the lignin dissolution in dialkylimidazolium-based IL–water mixtures at 60°C. They found the maximum lignin solubility at 70 wt.% IL, which was consistent with the Hansen theory, in which the IL type is important in the solubility. Accordingly, 1-butyl-3-methylimidazolium and methanesulfonate showed the maximum solubility of lignin among the examined ILs with the same anions and cations, respectively. Diop

et al.[484] invented new ILs for dissolution of lignin and concluded that lignin solubility decreased with increasing the length of the grafted carbon chain.

The capability of ILs in dissolving lignin can be employed in delignification of lignocelluloses. Fu et al.[485] chose [EMIM][OAc] amongst six ILs as the best candidate for the selective extraction of lignin to improve enzymatic hydrolysis of triticale and wheat straw at various temperatures (70–150°C) and time intervals (0.5–24 h). Lee et al.[486] also reported the enhancement in cellulose digestibility caused by partial delignification of wood flour by [EMIM][CH_3COO]. They reported the maximum digestibility of cellulose to be 95% for triticale straw pretreated at 150°C for 90 min. Wen et al.[487] used [EMIM][OAc] under varying IL pretreatment conditions (i.e., 110–170°C and 1–16 h) to isolate poplar alkaline lignin. Chemical transformation monitoring of the isolated lignin via elemental analysis, 2D-HSQC spectra, quantitative ^{13}C-NMR spectra, ^{31}P NMR, and GPC analyses revealed a decrease of aliphatic OH, mainly as a result of cleavage of β-O-4' linkage happened at high temperatures, and an increase in phenolic hydroxyl groups in lignin, attributed to the dehydration reaction during the pretreatment. The same study confirmed the β-O-4′ linkage broken with the dehydration and demethoxylation reactions during kraft lignin dissolution.[488] 2D NMR bond abundance data and size exclusion chromatography (SEC) results also revealed that lignin was depolymerized during [EMIM][OAc] pretreatment at 120 and 160°C of wheat straw, miscanthus, and Loblolly pine,[489] and lignin with different molecular mass was released in different stages of the pretreatment. Brandt et al.[490] obtained the same result in lignin characteristics isolated from miscanthus after extraction with the protic ionic liquid 1-butylimidazolium hydrogen sulfate ([HC_4im][HSO_4]). Their ^{13}C-NMR, ^{1}H–^{13}C HSQC NMR, ^{31}P-NMR, Py-GC-MS, GPC, and elemental analyses showed that the lignin-hemicellulose linkages break and more than 80% depolymerization of

lignin through the cleavage of glycosidic, ester, and β-O-4 ether bonds occurs during the early stage of the pretreatment. As the pretreatment proceeded, repolymerization of lignin happened, which was evidenced by increased lignin molecular weight determined by GPC, increased phenolic hydroxyl groups content and C/H ratio in the lignin prepared at the later stage. In another study, Varanasi et al.[491] pretreated *Panicum virgatum* and *Eucalyptus globulus* with [EMIM][OAc] at different temperatures and studied compositional changes in lignin. Preferential breakdown of S-lignin in both eucalyptus and switchgrass at high pretreatment temperature (160°C) and breakdown of G-lignin for eucalyptus and no preferential breakdown of either S- or G-lignin in switchgrass were observed at lower pretreatment temperatures (120°C), which may be linked to its hydrogen-bond accepting capacities at these temperatures. Accordingly, they suggested the mechanism similarity of the IL pretreatment to alkali pretreatment at lower temperature and to acid pretreatment at higher temperatures. S-G-H type lignin was obtained from bamboo by [AMIM][Cl] treatment, where partial degradation of lignin and hemicellulose was observed.[492]

Thermochemical analysis is also used for characterization of lignin extracted by ILs. The depolymerization and breakdown of lignin pretreated by [EMIM][OAc] at 120°C and 160°C for 1, 3, 6, and 12 h on model biomass compounds and bioenergy feedstocks, by thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) was reported.[493] Lignin dissolution in cholinium ILs resulted in a higher maximal decomposition temperature (T_m) and a higher glass transition temperature (T_g) of kraft lignin.[488] Moghaddam et al.[494] compared the physicochemical properties of lignin isolated from sugarcane bagasse pretreated by acidified aqueous ethylene glycol (EG) and ILs, and soda lignin from NaOH pretreatment of bagasse. Accordingly, depolymerization of thermally stable IL and EG lignins occurred at higher

temperatures compared to soda lignin. Moreover, unlike soda lignin, IL and EG lignins contained less/no carbohydrates, with slightly lower hydrogen and higher oxygen contents.[494]

George et al.[495] investigated the effects of imidazolium-based IL cation and anion combinations on the macromolecular structure of three lignins, i.e., organosolv, alkali, and alkali low sulphonate. The results showed a significant reduction in molecular mass and remarkable structural change of the lignins, primarily influenced by the anion, with anion influence in the reduction in order sulfates > lactate > acetate > chlorides > phosphates, meanwhile cleavage of different linkages within the lignins caused by different anions. However, at least 40% of the original large-lignin molecules, from each of the lignins studied, were observed to remain intact. On the other hand, extraction of lignin, with relatively uniform molecular weight without significant structural changes, from bagasse using an ionic liquid mixture [EMIM][ABS] at atmospheric pressure and elevated temperatures (170–190°C) with maximum yield of 93% was reported by Tan et al.[496] They also concluded that the ILs with the better phase separation properties would be desirable for higher lignin extraction.

8.3 Effects of ILs pretreatment on the cellulose structure

A majority of studies on characterization of IL-treated lignocelluloses have focused on the transition of cellulose crystalline structure and surface morphology of biomass (e.g., Figure 13 for macroscopic morphological changes). Zhang et al.[497] studied the changes in cellulose crystalline structure of three different feedstocks, switchgrass, corn stover, and rice husk, pretreated by [BMIM][OAc] at temperatures of 50–130°C for 6 h by XRD. Increasing the treatment time led to a drop in biomass CrI, which was due to the swelling of crystalline cellulose and transition of cellulose I to cellulose II. Cheng et al.[498,499] pretreated Avicel cellulose, switchgrass, pine, and eucalyptus with [EMIM][OAc] at 120°C and 160°C for 1, 3, 6,

and 12 h, and investigated the structural transformation and crystalline structure of cellulose. Although for Avicel the transformation to cellulose II occurred for all processing conditions, higher temperatures and times were required for the same transformation process for the other feedstocks, and only expanded cellulose I lattice was observed at the mild conditions applied. Comparable with these results, XRD analysis showed a decrease in CrI from 39.2% to ~0.09% and 28.6% to ~0.03% for switchgrass and agave bagasse, respectively, after [EMIM][OAc] pretreatment at 120°C for 3 h.[500] The regenerated cellulose from rice husk resulted from [EMIM][DEP] pretreatment at 100°C for 10 h (1.5% (w/v) loading) showed the highest decrease in crystallinity index from 46.0 to 32.0, amongst the different ILs used.[501]

The morphological characterizations of wood cell wall treated with 1-ethylpyridinium bromide ([EtPy][Br]) and [EMIM][Cl] was studied by Kanbayashi and Miyafuji.[502,503] The analyses of three hardwood by light microscopy and SEM revealed that treatment with [EMIM][Cl] at 120°C for 72 h caused significant swelling of all the woods. However, depending on the wood species, various behavior and different morphological changes in pits have been occurred mainly due to their chemical component and the microfibril angle.[504] Similarly, treatment of Japanese cedar with [EtPy][Br] caused the cell wall swelling and elimination of warts, while it did not change pit membranes and the cellulose crystalline structure.[503] Additionally, Raman microscopic analysis showed that chemical changes in the cell walls were different for different cell wall layers in that lignin in the compound middle lamella and the cell corner resisted to interact with [EtPy][Br]. Singh et al.[504] used auto-fluorescent mapping to visualize cellulose and lignin in switchgrass stems for determining the mechanism of biomass dissolution during 1-n-ethyl-3-methylimidazolium acetate pretreatment. Swelling of the secondary cell wall followed by complete dissolution of biomass within 3 h at 120°C, and subsequent lignin removal by adding

an anti-solvent was observed. The surface roughness of switchgrass, pine, and eucalyptus samples pretreated by [EMIM][OAc] at 120°C for 1, 3, 6, and 12 h showed that switchgrass possessed much rougher internal surfaces than eucalyptus and pine.[499] Zhang et al.[505] monitored the swelling and dissolution behavior of poplar during [EMIM][OAc] pretreatment by employing confocal Raman microscopy. They concluded the dissolution of the biomass was divided into two parts: slow penetration of IL, which determined the process reaction rate, and rapid dissolution of lignin and carbohydrates. Therefore, enhancement of the penetration capacity of IL, which was suggested to depend upon the properties of the IL, was crucial for improving the pretreatment efficiency. Confocal Raman microscopy and confocal fluorescence microscopy were also used to analyze the changes in different cell types including tracheids, sclerenchyma cells, and parenchyma cells of corn stover during [EMIM][OAc] pretreatment.[506] A direct correlation was then observed between changes in the morphologies and chemical composition and swelling occurred mainly in the secondary plant cell walls.

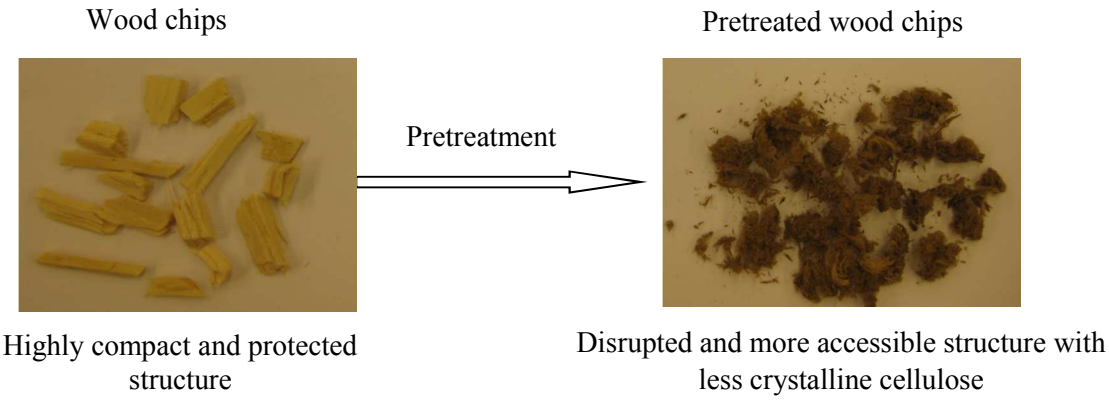


Figure 13. The macroscopic effects of [EMIM][OAC] pretreatment on spruce softwood (picture taken from Shafiei et al.[507])

8.4 Acid-catalyzed hydrolysis in ionic liquids

Different acids, e.g., mineral acids, Brönsted acids,[508,509] solid protic-acid resin,[510] and even amino acids,[511] have been functionalized or co-utilized to enhance the effect of the IL pretreatment on enzymatic hydrolysis. The research conducted on using acidic ionic liquid solution for the pretreatment of lignocelluloses can be divided into three parts. The use of acid for direct depolymerization of polymeric carbohydrates in the presence of IL,[512-514] the use of acid in ILs as a boosting pretreatment agent which can enhance the effectiveness of pretreatment on enzymatic hydrolysis,[510,515,516] and using acid-functionalized IL for either direct hydrolysis or enhanced enzymatic hydrolysis of lignocelluloses.[508,517-521] Although the use of homogeneous acid catalysts has its drawbacks, acid catalyst is currently used in ILs pretreatment. One of the main reasons is the economic viability of the IL used for pretreatment. For example, even though [BMIM][Cl] costs ca. $1/60^{th}$ of [EMIM][OAc], it is not highly efficient solvent for pretreatment; however, the addition of acid catalyst can boost the performance of the cheaper ILs for pretreatment.[510] Another reason is that acid hydrolysis of carbohydrates in such systems occurs at lower temperatures than in aqueous phase.[513] Besides, because of the presence of lignin in solid phase, sugar-lignin fractionation is easily achieved in such systems compared with aqueous phase reactions.[513]

Development in the acidic IL pretreatment was first focused on the direct conversion of lignocelluloses into monomeric sugars. Li et al.[512] developed a method for direct hydrolysis of cellulose in [BMIM][Cl] at 100°C under atmospheric pressure catalyzed by mineral acids. The maximum glucose and total reducing sugar (TRS) yield of 43% and 77%, respectively, was obtained at 0.11 sulfuric acid/cellulose mass ratio for 540 min reaction time. Likewise, a maximum TRS yield of 65% was obtained from corn stover pretreated by [AMIM][Cl] at 100°C

for 90 min in the presence of 2.0 mmol HCl per gram lignocellulosic substrate.[514] Pretreatment of three wood species including eucalyptus, pine, and spruce thermomechanical pulp was performed at 120°C for 3 h in [AMIM][Cl] followed by dilute hydrochloric acid hydrolysis for 5 h.[513] This IL-based acid pretreatment resulted in near-complete conversion of the woods' cellulose and hemicellulose at acid concentration of 1.4-1.5 mole of HCl/g wood. However, at higher acid concentrations, the presence of several degradation compounds, such as 5-hydroxymethylfurfural (HMF), furan-2-carboxylic acid, catechol, methylcatechol, methylguaiacol, acetoguaiacone, and acetol, were detected in recycled IL.

Although the dissolution step was conducted in low-water content, the hydrolysis step required much more water. Consequently, high processing cost for sugar separation is a major barrier for industrialization of this process. da Costa Lopes and Bogel-Łukasik[522] comprehensively reviewed the challenges and possibilities of direct IL acid-catalyzed conversion of cellulose and lignocellulosic biomass.

A majority of studies on acidic ILs pretreatment, however, has recently focused on acid co-solvent IL pretreatment for enhanced enzymatic hydrolysis. Partial saccharification of carbohydrates is inevitable in such systems; however, 2- to 12-fold higher glucose conversion rate was reported from combined acid-IL pretreatment of pine than the single pretreatment of acid or IL.[523] Besides, the sole use of IL in the pretreatment usually requires high temperature and longer reaction time.[515] Moreover, using an IL solution containing significant amount of water and acid solution can reduce the expensive IL usage, in spite of significantly reducing the solubility of lignocelluloses in most ILs at above 1% water concentration. The action of acid in IL is a catalytic role in the hydrolysis of ether linkages between adjacent glucose in cellulose chain and, consequently, reducing the length of the cellulose chain[510] (Figure 14). Zhang et al.[515]

developed an optimized sugarcane bagasse pretreatment process using aqueous [BMIM][Cl] containing 1.2% HCl in the presence of 10–30% water at 130°C for 30 min. Accordingly, a glucan digestibility of 94–100% was obtained after 72 h of enzymatic hydrolysis using HCl, in the pretreatment medium, as a more effective catalyst than H_2SO_4 and $FeCl_3$. Hydrochloric acid was also reported the most effective catalyst, amongst seven other inorganic acid studied, with [MMIM][DMP] in the pretreatment of corn stover at 110°C for 2 h.[524] Under these conditions, the maximum TRS yield of 92.7% was obtained after 96 h enzymatic hydrolysis.

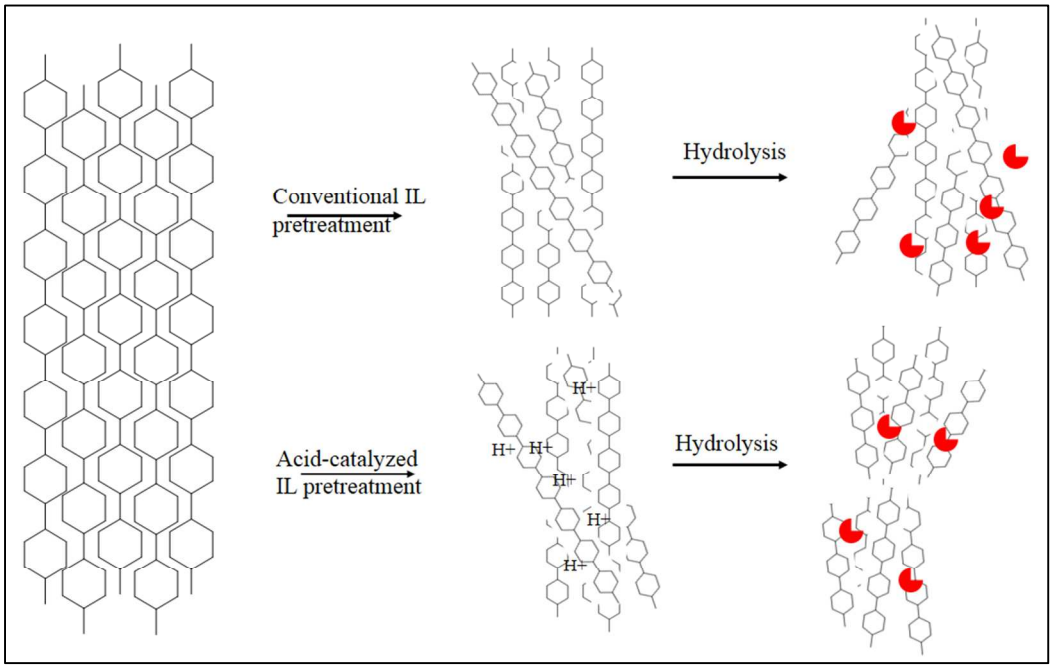


Figure 14. A comparison between lignocellulosic biomass pretreatment with conventional IL and acid-based IL (modified from ref. 510 with permission)

The first attempt for dissolution and hydrolysis of cellulose (DP ≈ 450) in Brönsted acidic ionic liquids 1-(1-propylsulfonic)-3-methylimidazolium chloride and 1-(1-butylsulfonic)-3-methylimidazolium chloride at moderate reaction temperatures was reported by Amarasekara and Owereh[525] in 2009. The maximum TRS yield of 62% was obtained after 1 h of preheating at

70°C followed by 30 min heating after adding 2.0 moles equivalent of water per glucose unit. Then, they discovered a more effective dilute aqueous solution of 1-(1-propylsulfonic)-3-methylimidazolium chloride and p-toluenesulfonic acid to be a better catalyst than aqueous sulfuric acid with the same H^+ ion concentration for the degradation of cellulose at moderate temperatures and pressures.[526] Amarasekara and Shanbhag[527] dissolved switchgrass biomass in 1-(alkylsulfonic)-3-methylimidazolium Brönsted acidic ILs by heating at 70°C for 2 h (0.22 g water/g switchgrass) and obtained maximum 58.1% and 15.3% TRS and glucose yields, respectively. Li et al.[517] used six kinds of SO_3H-functionalized IL based on 1-methylimidazole, 1-vinylimidazole, and triethylamine to promote the hydrolysis of MCC in [BMIM][Cl]. The acidic ILs resulted in over 83% TRS yield at 100°C with the maximum yield of 99% for Triethyl-(3-sulfo-propyl)-ammonium hydrogen sulfate. Zhuo et al.[519] synthesized and used six acidic ILs based on 2-phenyl-2-imidazoline for the hydrolysis of cellulose in [BMIM][Cl]. The maximum TRS yield of 85.1% was obtained by using 1-propyl sulfonic acid-2-phenyl imidazoline hydrogen sulfate, functionalized by HSO_4^- and Cl^- instead of $H_2PO_4^-$, at 100°C for 60 min and dosage of 0.2 g water/g cellulose. The hydrolysis activity was reported to directly relate to the activity of catalyst and also the possibility of further degradation of the resulting carbohydrates in acidic IL to HMF.[528] Tao et al.[529] investigated the acidity and structure of fifteen SO_3H-functionalized ILs on the MCC hydrolysis and selectivity for HMF, furfural, levulinic acid (LA), and TRS yields. A maximum MCC conversion of 91.2% and selectivities for HMF, furfural, and LA of 45.7%, 26.2%, and 10.5%, respectively, were achieved in $MnCl_2$-containing ILs. The efficiency of Brönsted acidic ILs for the conversion of hardwood hemicellulose to pentose sugars at 160°C was reported to be related to acid strength in the following order: $[C_3SO_3HMIM][HSO_4]$ > $[C_3SO_3HMIM][PTS]$ > $[C_3SO_3HMIM][Cl]$ >

[BMIM][Cl].[509] Besides the activity of catalyst, solution pH is also another factor, which was investigated by Zhang et al.[520] using different acid-catalyzed imidazolium IL solutions (80% in water) at 130°C for 30 min for sugarcane bagasse. The pretreatment effectiveness was reported to be similar by using [BMIM][CH_3SO_3], [BMIM][CH_3SO_4], and [EMIM][Cl], at the same solution pH. Besides, by decreasing solution pH from 6.0 to 0.4, an increase in bagasse delignification, xylan removal, and consequently glucan digestibility was reported. Apart from Brönsted acidic ionic liquids, Muhammad et al.[518] synthesized and used an amino acid-based ionic liquid, namely 1-ethyl-3-methylimidazolium glycinate, which was capable of effectively dissolving bamboo and changed its cellulose from type I to type II.

8.5 Enhancement in enzymatic digestibility of IL-pretreated lignocelluloses

The key and widely studied role of the IL pretreatment is to enhance enzymatic digestibility of lignocelluloses.[530-534] Table 8 reviewed some reports on improving enzymatic hydrolysis of different lignocelluloses due to IL pretreatment. ILs with [BMIM] and [EMIM] cations and [Cl], [OAc], and [CH_3COO] anions have been vastly used for pretreatment of different lignocellulosic substrates. The pretreatment conditions applied were temperature 90-160°C, reaction times ranging from several minutes to few hours, and biomass loading of ca. 2-15% depending on the biomass and IL types. As reviewed in the table, enzymatic hydrolysis of different (ligno)celluloses improved significantly as a result of IL pretreatment. From the reported data, maximum 100% digestibility was reported for MCC by using [BMIM][Cl] at 90°C for 20 min. For lignocelluloses, TRS yield was sometimes reported and in these cases the xylose yield was also significantly improved due to IL pretreatment. For *Typha capensis*, for instance, maximum reducing sugar yield of 82.4 g/100 g biomass was obtained by [BMIM][OAc] pretreatment. A

high xylose yield of 87% was also obtained from switchgrass pretreated by [EMIM][Lys] at 140°C for 1 h.

8.6 Challenges with in-situ enzymatic hydrolysis of lignocelluloses in aqueous-IL media

Unlike water and buffers, which are capable of dissolving the enzymes without unfolding their active structure, the biocatalysis activity in organic solvents may be hampered by a variety of factors. Most cellulases and other hydrolytic enzymes are deactivated in the presence of ILs, even low concentration.[535,536] A comprehensive review on enzymatic hydrolysis of lignocelluloses in the presence of ionic liquids, or the so-called in-situ or one-pot pretreatment and hydrolysis, has been recently published by Wahlström and Suurnäkki.[537] This review was mainly focused on the ways to keep cellulase enzyme active for enzymatic hydrolysis in the presence of IL. The hydrolytic enzymes stabilization techniques include enzyme immobilization, e.g., by encapsulation[538] or thermostabilization.[539] Besides, the discovery and development of IL-tolerant enzymes,[540,541] e.g., enzymes isolated from thermophilic and halophilic microbes,[542,543] are of great importance in this regard. A review on various cellulase stabilization techniques for the single-step process and the design of enzyme compatible biomass-dissolving ILs was recently published by Elgharbawy et al.[544] The recent trends in IL-tolerant enzymes and microorganisms was also critically reviewed by Portillo and Saadeddin[545] and Xu et al.[546]

It is notable here to mention that the residual ILs in the enzymatic hydrolysates inhibit the growth and productivity of microorganisms in downstream and fermentation processes.[547,548] The residual [EMIM][OAc] in the hydrolysates (higher than 0.1%) was reported to inhibit the growth and ethanol production by *S. cerevisiae,* suggested due to a potential synergistic effect between this particular combination of anion and cation.[549] Water-wash step results in a significant sugars lost and generation of large amounts of wastewater. To address this issue, Xu et al.[550] recently

developed a one-pot conversion process via using dilute bio-based ILs to produce high-titer cellulosic ethanol. Moreover, a novel CBP process was developed for ethanol production using IL pretreatment by cellulase-displaying yeast and approximately 90% ethanol yield was reported.[551]

1574 **Table 8.** Improvement in enzymatic digestibility of different lignocelluloses pretreated by ionic liquids (ILs)

Ionic liquid	Substrate	Pretreatment conditions	Enzymatic digestibility	Ref.
[BMIM][Cl]	Avicel	130, 140, or 150°C for 10, 30, 60, 120, or 180 min, 5% biomass (w/w) loading	Maximum ~80% cellulose conversion to glucose after 24 h of enzymatic hydrolysis	551
[EMIM][CH_3COO]	α-Cellulose	110°C for 40 min, 2% (w/v) cellulose loading	61% yield of glucose at 76 h	553
	Medium fibers of cellulose		69% yield of glucose at 76 h	
	Long fibers of cellulose		75% yield of glucose at 76 h	
	Microcrystalline cellulose		71% yield of glucose at 76 h	
[EMIM][$MeO(H)PO_2$]	α-Cellulose		67% yield of glucose at 76 h	
	Medium fibers of cellulose		86% yield of glucose at 76 h	
	Long fibers of cellulose		88% yield of glucose at 76 h	
	Microcrystalline cellulose		75% yield of glucose at 76 h	
[BMIM][OAc]	*Typha capensis* (TC)	110°C for 6 h, 5.0 g IL per 0.26 g TC	Maximum reducing sugar yield of 82.4 g/100 g	554
[EMIM][OAc]	Cellulose isolated from sugarcane bagasse	90°C for 6 h, 33.3 g IL per g cellulose	95.2% glucose yield	555
Cholinium amino acids ILs	Rice straw	90°C for 5 h	Maximum glucose and xylose yields of 84.0% and 42.1%, respectively	556
Cholinium lysine IL ([Ch][Lys] IL)-water mixtures	Rice straw	20% [Ch][Lys]-water mixture at 90°C for 1 h	Maximum sugar yields of 81% for glucose and 48% for xylose	557
[EMIM][OAc]	Sugarcane bagasse	150°C, 90 min and 5% bagasse in IL	83% and 21% glucan and xylan digestibility, respectively	558
[EMIM][OAc]	Energy cane bagasse	120°C for 30 min, 5% (w/w) biomass loading	87.0% and 64.3% glucan and xylan digestibility, respectively	125
[EMIM][OAc]	*Pinus radiate* compression wood	120°C for 3 h	93% glucan digestibility, 65% xylan digestibility, and 39% mannan digestibility after 24 h	559
1-hexylpyridinium chloride	Avicel and bagasse	80°C or 100°C, 5% (w/w) loading	Over 95% conversion to glucose after 24 h for Avicel, and 1–3-fold higher conversion than untreated biomass for bagasse	560
1-butylimidazolium hydrogen sulfate	*Miscanthus giganteus*	120°C for 15 min up to 24 h, 10% (w/v) biomass loading	Recovery of up to 90% of the glucan as fermentable glucose and up to 39% saccharification yield for hemicellulose	561
[EMIM][OAc]–DMSO solutions	Eucalyptus	Ratios of 4:1, 3:2, 2:3 and 1:4 (v/v) [EMIM][OAc]-to-DMSO, 15% (w/v) biomass loading, at temperatures ranging from 80 to	95% of glucose theoretical maximum yield and up to 65% xylose yield	562

		140°C		
Chloride, acetate, and formate based IL	MCC	90°C for 20 min	100% digestibility by using [BMIM][Cl]	563
[EMIM][OAc]	Rice husk	100°C for 10 h, 1.5% (w/v) biomass loading	42.1% reducing sugar yield	501
[EMIM][OAc]	Agave bagasse (AGB) and switchgrass (SWG)	120 and 160°C for 3 h and 15% biomass loading	Increase in TRS by 100% for SWG and by 183% for AGB	500
[EMIM][OAc]	Bagasse	Optimum condition: 145°C, 15 min and 14 wt.% solid loading	69.7% of RS yield	564
[EMIM][OAc]	Sugarcane bagasse	8 min at 140°C, 25 wt.% biomass loading	Glucose yields of more than 90% after 24 h of enzymatic saccharification and maximum xylose yield of ca. 85%	479
[EMIM][OAc]	Switchgrass	160°C and 3 h, 15% biomass loading	Glucose and xylose yields of 94.8% and 62.2%, respectively	480
1-Butyl-3-methylimidazolium methyl sulfate and 1-butyl-3-methylimidazolium hydrogen sulfate	*Miscanthus giganteus*, pine (*Pinus sylvestris*), and willow (*Salix viminalis*)	120°C and 2 h, 10% (w/v) biomass loading	Up to 90% of the glucose and 25% of the hemicellulose by the combined ionic liquid pretreatment and the enzymatic hydrolysis	565
[EMIM][OAc]	*Eucalyptus globulus*	120°C for 3 h, 9.7 g IL and 0.3 g biomass	37 and 30% glucose and xylose yields, respectively, after 4 h enzymatic hydrolysis	566
1-Ethyl-3-methylimidazolium acetate	Wheat straw	Temperature (130–170°C), time (0.5–5.5 h) and ionic liquid concentration (0–100%), biomass loading 5% (w/w)	71.4% sugars recovery at optimum conditions of 158°C, IL concentration, 49.5% (w/w), and 3.6 h	567
[EMIM][OAc]	Triticale straw	150°C for 90 min, 1.5 g straw to 48.5 g of water-IL mixture	81% fermentable sugar yield	568
[EMIM][OAc] and [BMIM][Cl]	Cotton cellulose	Microwave irradiation or 110°C for 30 min, 2% (w/v) biomass loading	At least 12-fold and by 50-fold enhancement in enzymatic hydrolysis at 110°C and microwave irradiation, respectively	569
[BMIM][Cl]	Sugarcane bagasse	Temperatures (110–160°C) and times (30–180 min); 0.25 g bagasse in 5 g IL (≤5% impurities and 2% moisture)	Optimum condition: 150°C for 90 min complete (100%) and rapid (3 h) glucan saccharification Up to 70% xylan solubilization	570
[BMIM][Cl]	Cotton	130°C for 20 min, 5% w/w	At least 4-fold enhancement on cellulose saccharification conversion	571
[EMIM][CH_3COO]	Wood flour	Various temperatures, 5% w/w biomass loading	>90% conversion of cellulose	486

Choline acetate (ChOAc)	Bagasse	IL/ultrasound-assisted pretreatment (60 min at 24 kHz and a power of 35W), 0.25 g bagasse in 5 g IL	Cellulose and hemicellulose saccharification percentages 80% and 72%, respectively, *in situ* saccharification for 48 h	572
Choline formate (ChFor), choline acetate (ChOAc), and choline propionate (ChPro)	Kenaf powders	Microwave heating or 110°C for 20 min, 5% w/w biomass loading	20% cellulose conversion for regular heating and 60-90% for microwave heating	573
[BMIM][Cl]	Sweet sorghum bagasse	110°C for 1 h, 10% w/w biomass loading	Approximately 40% conversion of cellulose after 60 h enzymatic hydrolysis	574
[BMIM][Cl]	*Populus tomentosa* Carr.	130°C, 0.5 g of the substrate and 9.5 g of the IL	92% glucose yield after 72 h enzymatic hydrolysis	349
[EMIM][Cl] and [EMIM][OAc]	Pine wood	80, 100, or 120°C for 3 h with stirring, 0.35 g wood and 7.0 g IL	Glucan conversions ranging from 23% to 84% with [EMIM][OAc] being more effective than [EMIM][Cl]	575
[BMIM][Cl]	Oil palm frond (OPF)	Temperatures less than 100°C and times less than 1 h, and maximum loadings of 10%	100% glucose recovery with pretreatment condition: 80°C, 15 min, and 10% solid loading	576
[EMIM][OAc]	*Panicum virgatum* (switchgrass)	90°C for 5 h, 10% (w/w) biomass loading	Glucose yield: 31%; Xylose yield: 29%	577
[EMIM][Lys]			Glucose yield: 70%; Xylose yield: 68%	
[Ch] [Lys]			Glucose yield: 42%; Xylose yield: 58%	
[Ch][OAc]			Glucose yield: 27%; Xylose yield: 23%	
[EMIM][OAc]		140°C for 1 h, 10% (w/w) biomass loading	Glucose yield: 65%; Xylose yield: 86%	
[EMIM][Lys]			Glucose yield:59% ;Xylose yield: 87%	
[Ch] [Lys]			Glucose yield: 61%; Xylose yield: 82%	
[Ch][OAc]			Glucose yield: 55%; Xylose yield: 79%	
[EMIM][OAc]	Poplar and switchgrass	120°C for 30 min, 5% (w/w) biomass loading	~70% and 46% glucan conversion after 24 h enzymatic hydrolysis for poplar and switchgrass, respectively	578
[EMIM][$MeO(H)PO_2$] and [EMIM][CH_3COO]	Cotton cellulose	45 and 25°C for 20 min, 2%, w/v biomass loading	Glucose yield after 24 h of enzymatic hydrolysis: 58.5% and 45.4%	579
[EMIM][OAc]	Spruce and oak sawdust	110°C for 40 min, 2% w/v biomass loading	Up to 7 times increase in enzymatic saccharification compare with the untreated substrate	580
[AMIM][Cl]	Cotton-based waste textiles were	90, 110 , and 130°C until 2% (w/w) biomass was dissolved	7 times higher yield of fermentable sugars than untreated fabrics	581
[EMIM][OAc]	Oil palm empty fruit bunch (OPEFB)	130°C, 2 h, 5% (w/w) biomass loading	95.5% enzymatic digestibility of glucan	582
[BMIM][Cl]			54.8% enzymatic digestibility of glucan	
MTBS			22.0% enzymatic digestibility of glucan	
[EMIM][DEP]			48.9% enzymatic digestibility of glucan	

[EMIM][DEP]	Wheat straw	130°C for 30 min, 4% (w/w) biomass loading	54.8% reducing sugar yield after being enzymatically hydrolyzed for 12 h	583
ChOAc	Bamboo powder	110°C for 60 min, and ultrasonic pretreatment in the same IL at 25°C for 60 min, 0.5 g bamboo in 5 g IL	55% and 92% cellulose saccharification for regular heating and ultrasonic pretreatment, respectively	584
[EMIM][OAc]	Beechwood chips	115°C for 1.5 h, 500 mg or 1 g of the wood in IL to obtain a mass of 10 g	Cellulose conversion of 90.2 wt.% for hydrolysis times of 72 h	585

1575

Another challenge in enzymatic in-situ saccharification of lignocelluloses is the recovery of sugars produced during the hydrolysis in IL media. Chromatographic techniques[586] and membrane-based methods[587] have been suggested for the separation and recovery of sugars and IL from biomass hydrolysates. This challenge also applies in the case of acid-catalyzed hydrolysis in IL,[588] and it is considered a major challenge and a drawback in using IL as a pretreatment agent. However, in most cases, the recovery of sugars and the recycle of IL occur simultaneously in a single process.

8.7 Recovery and reuse of ionic liquids

Due to the current high price of ILs for an economically viable pretreatment process, efficient recovery and recycling of ILs is vital.[589-592] Besides, the wastage of ILs can cause environmental issues associated with slow degradation and toxicity to downstream processes[589,590] Mai et al.[593] reviewed the different methods for recovery of ILs in detail. Here, we discuss briefly the methods of ILs recovery with application in the IL pretreatment of lignocelluloses.

The most widely used method for recovery and recycling of ILs from IL-anti-solvent-lignocellulose systems is distillation.[580,590,594-596] The method consists of evaporating anti-solvent (e.g., water and alcohol) after removing precipitated lignocellulose from the pretreatment media. Since a large quantity of precipitating solvent is required to prevent gel phase formation, the evaporation step needs a lot of energy and often presents environmental problems. When water is used for the precipitation, the situation is even worse, because of its high specific heat capacity and high solubility of produced biomass compounds, e.g., monomeric and small oligomeric carbohydrates.[590,596] Approximately, 85–90% recovery of [EMIM][OAc] was reported in a IL-water system via distillation by Qui et al.[594]

The ability of ILs to form aqueous biphasic systems with a kosmotropic anion, e.g., phosphate, carbonate, or sulfate, was first reported by Gutowski et al.,[597] which can be utilized to recycle hydrophilic ILs from aqueous solution. The upper IL-rich phase can be easily recovered by simple decantation or a magnetic field. However, further separation is required in order to extract water and remaining monosaccharide hydrolysates from IL solution.[598] The recovery of ILs in these systems depends on the salt type and concentration as well as the IL cation and anion type.[599] A recovery of over 95.0% for [BMIM][OAc] in K_3PO_4-containing systems (pH 12-13) was reported.[599]

Apart from these traditional separation methods, recently, the so-called green processes were developed based on chromatography (resin and alumina column chromatography)[598,600] and electrodialysis[601-603] for the ILs recovery.

Unfortunately, the recovered ILs do not sometimes show the same performance in the pretreatment as their virgin forms.[594,604] Qiu et al.[594] reported a decrease in recycled [EMIM][OAc], by evaporation, performance in pretreatment of energy cane bagasse. This phenomenon could be attributed to the accumulation of IL's degradation products in the pretreatment process which affect the recycling efficiency and properties of IL. Besides, the recycled ILs may contain carbohydrate monomers and oligomers and biomass decomposition products. It is most likely for recycled IL that have the both of mentioned impurities that negatively affect its performance in pretreatment.[175] On the other hand, Auxenfans et al.[580] reported the same ability and similar efficiency of recycled [EMIM][OAc], via distillation by rotary evaporator, as fresh in enzymatic saccharification performance for pretreatment of industrial wood sawdust. In another study, they again reported the similar performance of two recycled imidazolium-based ILs in maintaining their efficiency to pretreat cellulose.[579]

8.8 IL pretreatment of lignocelluloses for enhanced biogas and renewable chemicals production

Different pretreatment methods for enhanced biogas production from lignocelluloses have been comprehensively reviewed by Zheng et al.[69] Mancini et al.[605] also reviewed the solvent pretreatments of lignocellulosic materials to enhance biogas production. Nonetheless, there are few studies in the literature on the enhancement of biogas production from lignocelluloses by using IL pretreatment. Gao et al.[606] pretreated water hyacinth, rice straw, mango leaves, and spruce by [C_nMIM][Cl] (n = 2, 4, and 6) at different conditions and evaluated the effect of the pretreatment on biogas production. The maximum enhancement of biogas production was obtained by pretreatment with [BMIM][Cl] at 120°C for 2 h for water hyacinth followed by spruce, while maximum methane production from rice straw and mango leaves, i.e., 233 and 125 mL/g carbohydrates, was obtained for pretreatment at 140°C for 2 h and 140°C for 8 h, respectively. They also obtained an increase in biogas yield and methane concentration by 16.3–97.6% and 13.2–28.3%, respectively, from water hyacinth by [BMIM][Cl] and DMSO co-solvent pretreatment at 120°C for 120 min.[607] Li and Xu[608] reported severe toxicity of imidazolium-based ILs in anaerobic digestion of grass (1:10 ratio). However, they reported a low toxicity and high recyclability potential for [BMIM][OAc] in the methane production of 221 mL/g-VS from grass.

Most of studies on using IL pretreatment for the production of renewable products from lignocelluloses have focused on the hydrolysis of pretreated biomass into sugar-rich hydrolysates (cf. Section 8.5), which are then used by microorganisms for carbon and energy sources, e.g., for microbial lipid production. For example, Gong et al.[609] prepared corn stover solids by [EMIM][OAc]–N-methylpyrrolidone (NMP) pretreatment at 140°C and converted the pretreated

solids to microbial lipids by *Cryptococcus curvatus* via a simultaneous saccharification and enhanced lipid production process. They obtained maximum 112 mg/g pretreated biomass lipid yield with efficient co-utilization of cellulose and hemicellulose. Xie et al.[610] also used 20% (mole fraction) [EMIM][OAc] in NMP at 140°C for 60 min to pretreat corn stover followed by enzymatic hydrolysis for the cultivation of *Rhodosporidium toruloides* Y4 for lipid production. The oleaginous microorganism utilized both C_6 and C_5 sugars in the hydrolyzates and produced a moderate 15.2 $g.L^{-1}$ biomass yield and 36.4% lipid yield. Bokinsky et al.[611] reported the synthesis of biofuels, i.e., fatty acid ethyl esters, butanol, and pinene, from [EMIM][OAc] pretreated switchgrass using engineered *Escherichia coli* which can express cellulase, xylanase, β-glucosidase, and xylobiosidase enzymes. They reported that the IL pretreatment made the biomass completely susceptible to hydrolysis.

On the using of ILs for renewable chemicals production from lignocelluloses, Huang et al.[612] evaluated the effects of residual [EMIM][Cl], [EMIM][DEP], and [EMIM][OAc] on the lipid production by oleaginous yeast *Rhodosporidium toruloides* AS 2.1389. By adjusting pH to 6.0 in the presence of 30 mM ILs, minor inhibition effects were reported, while the presence of 60 mM ILs caused a significant inhibition on the yeast. Liu et al.[613] also reported that the residual ILs in the hydrolysate of rice straw inhibited the growth and lipid accumulation by *Geotrichum fermentans*. The inhibition was induced by both anion and cation of the ILs used, and the side chain of cation showed a clear inhibition.

Varanasi et al.[614] focused on the production of lignin-based renewable chemicals from different lignocelluloses by selective breakdown of lignin using [EMIIM][OAc] pretreatment at 120 and 160°C for 6 h. The generated chemicals, (i.e., phenols, guaiacols, syringols, eugenol, and catechols), their oxidized products (i.e., vanillin, vanillic acid, and syringaldehyde), and their

easily derivatized hydrocarbons (i.e., benzene, toluene, xylene, styrene, biphenyls, and cyclohexane) were produced from lignin by tuning the process conditions. The production of levulinic acid directly during the IL pretreatment was reported in some studies.[615,616] Muranaka et al.[616] successfully converted 60.7 % (72.9 mol%) of cellulose into levulinic acid by using [EMIM][Br] and [EMIM][P] at 80-120°C for 1-6 h under stirring. Sun et al.[615] used a series of heteropolyacid (HPA) ILs to catalyze one-pot depolymerization of cellulose into glucose and subsequence levulinic acid (up to a 60% yield) in a water–methyl isobutyl ketone (MIBK) biphasic system. Xiao et al.[617] optimized the catalytic conversion of cellulose into HMF by $AlCl_3$ in DMSO–[BMIM][Cl] mixtures. They obtained a maximum HMF yield of 54.9% from cellulose at 150°C after 9 h in a mixed solvent of DMSO–[BMIM][Cl] (10 wt.%).

8.9 Techno-economic analysis of ionic liquid pretreatment

For economic evaluation of IL pretreatment of lignocelluloses, Sen et al.[618] identified the IL cost as the major cost driver in IL pretreatment. They suggested the lower IL consumption and/or effective separation strategies to improve the economy of IL pretreatment. Konda et al.[619] compared the cost drivers and economic potential of two variants of IL pretreatment for ethanol production: first based on complete removal of the IL prior to hydrolysis and second based on one-pot process. At a high biomass loading of 50%, both routes were reported to be economically viable with a minimum ethanol selling price of $6.3/gal. With more reduced water and acid/base consumption in the first and second routes, respectively, improved pretreatment efficiency, and by lignin valorization, the minimum ethanol selling price could be reduced to $3.2 for the former route and $2.8 for the later route. Baral and Shah[620] conducted a techno-economic comparison study on [EMIM][OAc] and sulfuric acid pretreatment of corn stover, poplar, and switchgrass, and estimated sugar production cost of 2.7, 3.2, and 3.0 $/kg,

respectively. They further reported that optimistic considerations of at least 97% IL recovery, less than \$1/kg IL cost, and >90% heat recovery are required to have an economically competitive IL pretreatment. To improve the process economy, George et al.[621] attempted to lower the cost of IL, which is one of the main impediments to IL utilization in the pretreatment step, by designing a number of low-cost and stable protic ILs based upon the [HSO_4] anion with promising potential in the pretreatment. The most effective solvent, triethylammonium hydrogen sulfate IL, demonstrated approximately 75% as effective as [C_2C_1IM][OAc] for switchgrass. A set of new low-cost RTILs based on butylammonium prepared by reacting carboxylic acids with aliphatic amines cation under ambient conditions was also synthesized and characterized by de Andrade Neto et al.[622] for lignocellulose hydrolysis applications. Among them, n-butylammonium acetate favored the subsequent acid hydrolysis of corn fiber. Oleskowicz-Popiel et al.[623] also reported the acidolysis of IL pretreated lignocelluloses as a more economically viable route than using costly enzymes for saccharification. They further calculated that the minimum ethanol selling price could be reduced to \$4.00/gal, when the performance of the hydrolysis, extraction, and sugar recovery is improved. Socha et al.[624] synthesized some tertiary amine-based ILs from aromatic aldehydes derived from vanillin, p-anisaldehyde, and furfural, and confirmed their effectiveness in switchgrass pretreatment. Their approach of producing renewable ILs from lignocelluloses in a so-called "closed-loop" can be a solution for the drawback of expensive IL in the pretreatment.

8.10 Present status and future prospects of IL pretreatment

Taking all these points into consideration, ILs, as powerful non-derivatizing cellulose solvents, have been recently subjected to vast studies for lignocellulose dissolution and regeneration. The promising features of using ILs for biomass pretreatment are negligible vapor pressure, thermal

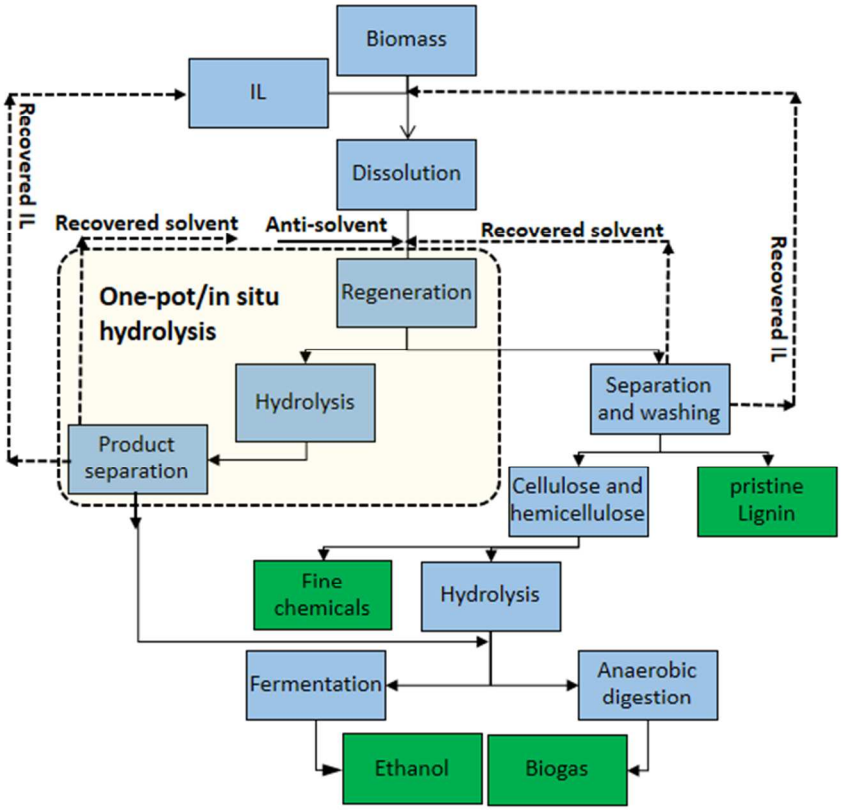
stability, non-flammability, and high polarity, and being "green" solvent in many cases.[625-627] They are capable of fractionating variety of lignocelluloses, reordering or restructuring the hydrogen bonds in cellulose network, decreasing cellulose crystallinity, and increasing cellulose accessibility to cellulases. The pretreatment requires low equipment costs with low energy consumption. The regenerated materials are more susceptible to enzymatic hydrolysis than the untreated form, with comparable or even superior yields of fermentable sugars, than the conventional pretreatments.[628,629] By adjusting ILs' anion and cation, different ILs are synthesized to tune their properties. Mora-Pale et al.[630] stated that lignin released during RTIL pretreatment of lignocelluloses is likely to be far more "pristine" than Kraft lignin, which have general applications in phenol-formaldehyde replacements, conversion into liquid fuels following hydrogenative depolymerization, or possibly into specific low molecular weight chemicals.

A process diagram for bioconversion of lignocelluloses to ethanol and biogas using IL pretreatment was proposed in Figure 15. The process can be applied for production of other fermentative chemicals via sugar platform as well. Besides, this process is advantageous in production of other byproducts, which can improve the overall process economy.

However, IL pretreatment of lignocelluloses is facing several technological and economic challenges. Although some efforts have been made to design low-cost ILs[621,631] (as discussed in Section 8.9), still a major obstacle in implication of many ILs at large scale is their high price. Efficient recovery and recycling of ILs are crucial in order to reduce the inhibitory effects of ILs on subsequent enzymatic hydrolysis and fermentation. Besides, the residual ILs on waste stream can cause environmental problems depending on their degradability.[632] Although research is underway using amino acids to synthesize biodegradable ILs, most ILs for biomass processing

1736 are not easily biodegradable. However, a cost-effective technology, despite the ease of recycling
1737 via distillation, is needed to make the process competitive to conventional pretreatment
1738 strategies. This problem is not only for ILs recovery, but also for the anti-solvent used in the
1739 regeneration process. Although many ILs, e.g., [EMIM][OAc] and [AMIM][Cl], were reported
1740 to be excellent solvents for cellulose dissolution,[632] the selection of ILs for biomass pretreatment
1741 should compromise between solubilizing power and compatibility with enzymes and/or
1742 organisms. In case of acidic ILs, the rate of formation of degradation products should be
1743 manipulated by the side chains of the cation. Not all, but some ILs are corrosive, toxic, and
1744 hygroscopic, which should be utilized with care.

1745



1746

1747 **Figure 15.** A process diagram for IL pretreatment of lignocelluloses for ethanol or biogas production
1748 applying two routes: 1) one-pot/in-situ hydrolysis and 2) separated enzymatic hydrolysis and
1749 fermentation, with IL and solvent recycling.

9 Comparison of ILs, CPA, and NMMO pretreatment

A few studies compared the effectiveness of the IL, CPA, and NMMO pretreatment on improving enzymatic hydrolysis yield and fuels/chemicals production.[165, 386, 571, 633-637] Wheat straw was pretreated with CPA (85%, 50°C for 1.5 h), NMMO (130 °C for 2 h), and IL ([AMIM][Cl], 110 °C for 1 h) and the results showed that the most prominent difference in chemical composition of wheat straw was >90% solubilization of xylan due to CPA pretreatment, while for the other two treatments, xylan was solubilized <10%.[633] Phosphoric acid acts as a Brønsted acid catalyst and generally promotes the hydrolysis of glycosidic bonds in cellulose\hemicellulose, which leads to considerably higher solubilization of xylan. Moreover, cellulose hydrolysis followed the order of CPA > NMMO > [AMIM][Cl]. Similarly, CPA was more successful in pretreatment of corn stover than IL, whereas, compared to 96% glucan digestibility of corn stover pretreated with CPA, a 55% glucan digestibility was obtained after pretreatment with [BMIM][Cl]. A tradeoff between cellulose disruption and the inhibitory effects of the presence of residual lignin and residual cellulose solvent in the pretreated biomass were reported as the main reasons for incomplete hydrolysis for IL pretreatment. However, cellulose digestibilities of 100% and 92% were obtained with CPA and [BMIM][Cl], respectively, for Avicel cellulose as a susbtrate.[634]

In a study, high glucose yields were obtained for rice straw following pretreatment with NMMO and [BMIM][OAc], and the obtained yields were comparable for both pretreatments.[381] Crystallinity index and total crystallinity of the substrate were quite similar for both pretreatments. Similarly, the glucan conversion (after 72 h) for *Populus tomentosa* pretreated with IL ([BMIM][Cl] at 130°C), NMMO (130°C for 30 min), and CPA (85% at room temperature) were reported 80%, 82%, and 92%, respectively.[635] The results also

showed that the hydrolysis rate for IL pretreated sample was higher than that of the CPA pretreated sample. These results were possibly due to transformation of cellulose I to amorphous cellulose and cellulose II in IL and CPA pretreatments, respectively. CPA was reported as a better cellulose solvent than NMMO and [BMIM][Cl] in improving the saccharification rate and yield of cotton cellulose due to the high specific surface area and low DP for CPA pretreated cellulose.[636]

On the other hand, IL pretreatment ([EMIM][Br] and [EMIM][P]) was reported to be more effective than CPA pretreatment in converting cellulosic substrates to levulinic acid.[637] Decrease in cellulose crystallinity, solubilization of cellulose, and IL interaction with cellulose were the determinant factors for higher yields.

In summary, the effectiveness of different cellulose solvents on the pretreatment of lignocelluloses is strongly dependent on biomass type and final chemicals produced. In contrast with phosphoric acid, residual ILs and NMMO cause inhibitory effects on biotechnological downstream processes.

10 Concluding remarks

Regarding the high worldwide fuel demand and the significant potential for biomass conversion to offset fossil fuel usage, a high number of studies and efforts have been made in the past several decades in the cellulosic fuel area. The cellulosic fuels production process involves four major steps of biomass preparation, pretreatment, hydrolysis, and fermentation, with the pretreatment step being one of the most cost contributing and the rate and yield limiting step. Giving the significant ability to fractionating lignocellulosic structure, the cellulose solvents are excellent starting points for industrial biorefinery applications. Although this category of

pretreatment has several advantages over other conventional pretreatments, which was the focus of this review, several issues should be addressed to make the process economically and environmentally viable. One of the promising features of cellulose solvents for the pretreatment of lignocelluloses is associated with their properties as "green" solvent. They should have negligible vapor pressure to help their recyclability, and should be easily biodegradable. Using cellulose solvents for the pretreatment of lignocelluloses is advantageous due to their application at high solid loadings and relatively low pressure/temperatures with no/less chemical modification and inhibitory byproducts formation. The solvents can be oriented towards different purposes for the pretreatment of lignocelluloses. They can be selected for (1) separation of mainly cellulose, (2) separation of mainly hemicellulose, (3) separation of mainly lignin, (4) opening the compact structure, (5) regeneration and structural modification, (6) cellulose crystallinity reduction; although more than one of these actions typically take place. Organic cellulose solvents, e.g., concentrated phosphoric acid and concentrated NaOH, are capable of removing and/or reorganizing the hydrogen bond network structure of cellulose, decreasing cellulose crystallinity, and enhancing cellulose accessibility to cellulases, and consequently enhancing glucan digestibility even at low cellulase loadings that is vital to reduce overall process cost. There are some cellulose solvents, e.g., NMMO, that modify the structure of lignocelluloses by dissolution and regeneration of the whole biomass, without significant lignin/hemicellulose removal. Meanwhile, ILs are target-oriented solvents that can be designed to separate specific part of lignocelluloses. The high revenues from co-products (acetic acid, lignin, and hemicelluloses) of the pretreatment can drastically improve the economy of the cellulosic fuels. However, the cellulose solvent-based pretreatment of lignocelluloses is still in its early stage of development, mainly in the laboratory scale, and facing several technological and

economic challenges. The efficient recovery of the solvents, which is usually a high energy intensive process, is necessary because of not only the solvents' high price, but also because of inhibitory effects of the solvents on subsequent processes. Furthermore, substantial reduction in the use of chemicals (both the cellulose solvents and organic solvents) is required in order to have an economically competitive process.

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