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A guide to lignin valorization in biorefineries: traditional, recent, and forthcoming approaches to convert raw lignocellulose into valuable materials and chemicals

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Lignin is the most abundant source of renewable aromatics on Earth, yet its enormous potential remains underexploited in current biorefinery and pulping processes. The extensive degree of condensation of the lignin fractions produced *via* the most widely adopted biomass pretreatments (*i.e.* "technical lignin") poses a prominent limitation to their subsequent conversion toward valuable products. In this work, a broad range of methods for biomass pretreatment are reviewed, illustrating the impact of each strategy on the properties of the isolated lignin and carbohydrate fractions. The main pathways for the valorization of the obtained lignin streams (*i.e.* toward polymeric materials or chemicals) are critically discussed, and the relationship existing between (i) native lignin structure, (ii) pretreatment conditions, and (iii) lignin processability is rationalized. A key aspect for producing lignin streams amenable to further upgrading is the prevention of condensation reactions between lignin fragments during biomass fractionation. In this respect, a class of so-called "lignin-first" pretreatments, targeting the prompt stabilization of reactive lignin intermediates to minimize lignin condensation, has recently gained momentum. Herein, lignin-first approaches are reviewed, discussing in detail the fate of lignin, cellulose, and hemicellulose for each strategy. The potential of lignin-first biorefineries to realize a more complete valorization of lignocellulose and the current limitations of each method are highlighted. Overall, this work provides a comprehensive overview of the technologies that are available or currently emerging for lignin isolation and subsequent valorization.

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Sustainability spotlight

Lignin is the most abundant source of renewable aromatics on Earth; yet its enormous potential remains largely underexploited in current biorefinery and pulping processes. Most large-scale industrial processes that use plant polysaccharides from lignocellulose used to burn lignin to generate power. With the advent of the integrated biorefinery concept, more lignin is being produced and therefore efforts are underway to transform it to value-added products: materials, fuels, and chemicals. This tutorial review provides a comprehensive overview of the technologies that are available or emerging for lignocellulose pretreatment, for lignin isolation and valorization, and for lignin depolymerization and valorization of the monomers. Research on lignocellulose and lignin valorization align with UN SDG number 9, 12, and 15.

1. Introduction

Driven by the growing environmental concerns related to massive exploitation of fossil resources and the consequent dramatic increase of CO_2 emissions (from about 6 billion tons in 1950 to over 36 billion tons in 2021),[1] the development of biorefineries for the conversion of biomass into energy, chemicals, and materials, is playing a pivotal role in the transition toward a more circular, sustainable economy.[2–4] From this point of view, lignocellulosic biomass, which comprises byproducts from the forestry and the wood industries, as well as agricultural residues and dedicated crops, represents the largest fraction of available terrestrial biomass and a promising candidate for the replacement of fossil resources.[5,6]

Lignocellulose is made of three main components: cellulose and hemicellulose, which are carbohydrate polymers, and lignin, which is an aromatic polymer.[7] On the one hand, the inherent heterogeneity of lignocellulose implies a large

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potential of this raw material for the manufacturing of a broad range of renewable, high-value products. On the other hand, it considerably complicates it processability.[8,9] For this reason, lignocellulose biorefineries commonly implement an initial pretreatment step, with the goal of separating the different components of lignocellulosic biomass prior to further upgrading.[10]

Traditionally, pretreatments have been almost exclusively focused on the valorization of the carbohydrate fraction of lignocellulose, while lignin was regarded as an obstacle, hindering (hemi)cellulose valorization (*e.g.* in the pulping industry, in second-generation bioethanol production, …).[9] Thus, the principal objective of many fractionation processes is the removal of lignin from biomass to yield a processable carbohydrate fraction, regardless of the properties of the isolated lignin stream.[11] As a result, the valorization of the lignin fractions obtained from conventional pretreatments (often referred to as "technical lignins") has been found to be particularly challenging.[12]

In spite of the difficulties related to its valorization, lignin represents the largest source of renewable aromatics available on Earth and, therefore, an alluring platform for the sustainable production of aromatic chemicals and polymers.[13] With this perspective, research on lignin valorization flourished in the last few years, and an increasing number of studies have been conducted, providing a better understanding of lignin chemistry and leading to the development of a wide range of strategies for lignin isolation and upgrading.[14] Recent notable reviews in this field include works by Rinaldi *et al.*,[15] Galkin and Samec,[11] Sun *et al.*,[16] Schutyser *et al.*,[14] Questell-Santiago *et al.*,[17] Luo *et al.*,[18] Abu-Omar *et al.*,.[19] and Zhang *et al.*[20] In this context, the conversion of lignin to chemicals and materials constitutes the focus of the present review. This work aims at providing a comprehensive overview of the strategies existing for the isolation and subsequent valorization of lignin in the landscape of lignocellulose biorefining. Rather than an exhaustive analysis of all the work being reported in the literature this field, the review is presented as a didactical guide, that we hope will be useful for newcomers and experts alike. We propose to cover the approaches that can be implemented to convert raw lignocellulose into valuable materials and chemicals, *via* a complete overview along the entire value chain and considering diverse methodologies; from the raw biomass to the valuable products.

After a brief introduction on the main compositional and structural properties of lignocellulose and its constituents (Section 2), the most largely adopted methods for biomass pretreatment are reviewed (Section 3), discussing in detail the impact of each strategy on the disassembly of lignocellulose and on the chemistry of lignin and (hemi)cellulose. We also discuss the pros and cons of the different technologies with respect to the subsequent processability of the isolated fractions. Thereafter, the main pathways existing for the valorization of the so-formed lignin streams (*i.e.* toward polymers or chemicals) are examined (Section 4), providing insight into the potential applications of lignin-derived products. The successful conversion of lignin toward chemicals and materials is strongly dependent on (i) native lignin properties, (ii) pretreatment methods and conditions, and (iii) lignin processing methods and conditions. The interrelation between these aspects is unraveled and critically discussed in Section 5. A key aspect for enhancing the processability of the lignin fractions isolated from biomass pretreatment is the suppression of recondensation reactions occurring between lignin fragments.[17] Centered on this objective, a new class of lignocellulose pretreatments, termed "lignin-first" biorefineries has recently gained momentum.[19] These lignin-first methods are reviewed in Section 6, wherein the advantages and disadvantages of each method and the current challenges for the upscaling of these strategies are illustrated.

2. Lignocellulosic biomass

Lignocellulose is generally recognized as the most abundant source of terrestrial organic matter on Earth.[21] It is the main component of plant biomass and it is principally found in the secondary cell wall of plant cells, the thick and robust layer that is formed toward the inside of the primary cell wall, once plant cells ceased to grow.[22] The main constituents of lignocellulose are cellulose, hemicellulose, and lignin, which are present in quantities that vary depending on the biomass source (plant species, tissue, environmental conditions, …).[23] In addition, minor constituents such as proteins, lipids, tannins, pectin, non-structural polysaccharides, waxes, and inorganic materials may also be present in lignocellulose.[23–25] Table 1 summarizes typical ranges for the composition of lignocellulose from hardwoods (angiosperms), softwoods (gymnosperms) and grasses.

From a structural point of view, lignocellulose possesses a complex tridimensional arrangement in which cellulose, hemicellulose, and lignin are deeply interconnected.[31] Cellulose strands are bundled together to form microfibrils, which are surrounded by hemicellulose and lignin.[31,32] In turn, microfibrils are arranged into larger clusters, termed macrofibrils.[33] Within these domains, cellulose is linked to hemicellulose and lignin principally by hydrogen bonding.[34] On the other hand, hemicellulose and lignin are coupled *via* covalent bonds (ether and ester linkages).[34] The structure of lignocellulose is schematically outlined in Fig. 1.

Table 1 Composition of lignocellulose from different biomass sources[24,26,27]

	Composition[a] (wt%)		
	Cellulose	Hemicellulose	Lignin
Hardwoods	45–55	25–40	18–25
Softwoods	45–50	25–35	25–35
Grasses	25–40	25–50	10–30

[a] The compositional analysis of lignocellulose is commonly carried out as described in by Sluiter *et al.*[28] Lignin is quantified based on the so-called Klason lignin analysis. This method is generally recognized as reliable for woody biomass, but is known to be subject to errors when applied to other biomass types (grasses, bark, leaves, …). For a more exhaustive discussion on the subject, the reader is invited to examine the works by Bunzel *et al.*,[29,30] and the recent review by Abu-Omar *et al.*[19]

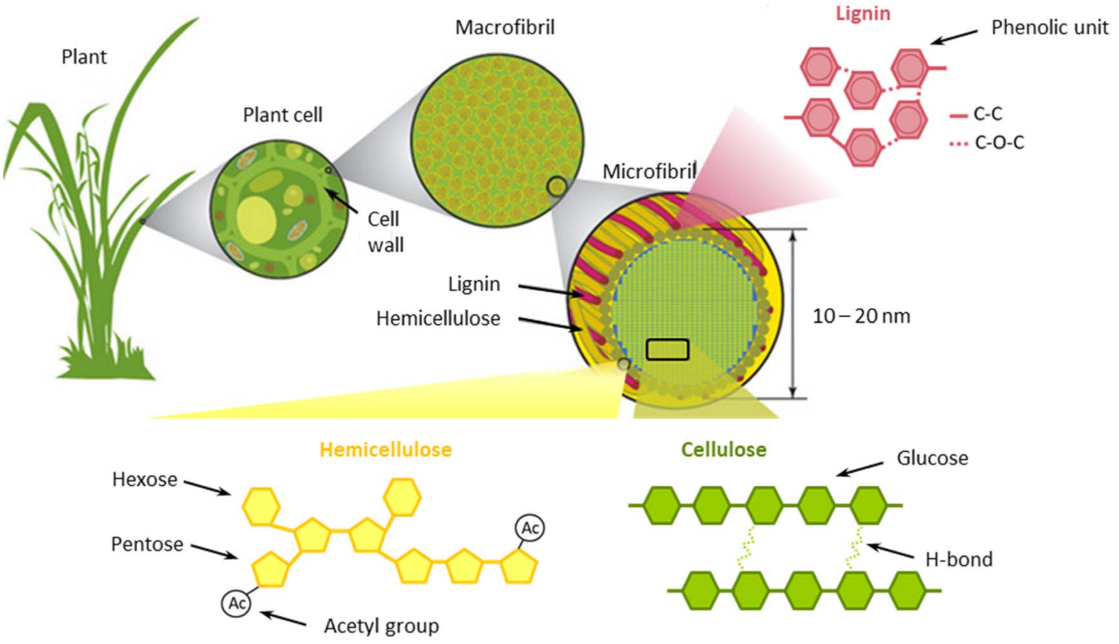


Fig. 1 Schematic structure of lignocellulose components. Modified from Potters *et al.*[33]

2.1. Cellulose

Cellulose is a linear syndiotactic polymer of glucose units, linked together by β-1,4 glycosidic bonds. The degree of polymerization may vary between few hundreds to tens of thousands, depending on plant species, tissue type, growth stage of the plant, and other environmental factors.[35,36] The glucose monomers in cellulose possess three free hydroxyl groups, which form both intramolecular and intermolecular hydrogen bonds, as schematized in Fig. 2. By virtue of this extensive hydrogen bonding, the polymer chains are strongly linked to one another and stack together to form microfibrils (Fig. 2), consisting of crystalline domains surrounded by paracrystalline or disordered domains.[37] The tight packing of cellulose chains within crystalline regions hinders both its solubility in most common solvents, as well as its enzymatic digestibility. Conversely, disordered domains are less densely packed, thus more accessible to solvents and hydrolytic enzymes.[38,39]

2.2. Hemicellulose

Hemicellulose comprises diverse linear and branched short polysaccharides that differ broadly in terms of composition based on plant species, tissue type, growth stage of the plant, and environmental factors.[40] Hemicellulose polymers consist of a backbone containing β-1,4-linked pentoses (mainly β-D-xylose) or hexoses (mainly β-D-mannose and β-D-glucose), branched with single or longer glycosyl residues (Fig. 3).[40,41] In addition, uronic acids such as α-D-glucuronic and α-D-galacturonic acids can be found in hemicellulose chains. Typically, xylans are the most abundant hemicellulose components in grasses and hardwoods, while mannans are the major hemicellulose components of softwoods (Fig. 3).[23] The degree of polymerization of hemicellulose is lower compared to that of cellulose, and is usually in the range of 100–200 units.[42]

Hemicellulose plays the role of a binding agent in the plant cell wall, linking cellulose bundles, lignin, cell wall proteins, pectin, and non-structural polysaccharides. Due to the high extent of branching, hemicellulose possesses an amorphous structure and is more easily subjected to depolymerization by the action of solvents or enzymes, compared to cellulose. Furthermore, hydroxyl groups in hemicellulose are acetylated to some extent and, during biomass pretreatment, the acetic acid formed upon cleavage of acetyl groups can further enhance hemicellulose decomposition.[23]

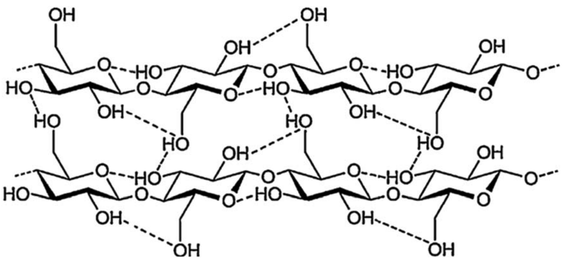


Fig. 2 Molecular structure of cellulose. Adapted from Liao *et al.*[39]

2.3. Lignin

Lignin is the most abundant non-carbohydrate component in the plant cell wall where it provides plant cells with rigidity, hydrophobicity, and resistance to microbial attack.[7] Owing to these properties, it is regarded as the principal contributor to lignocellulose recalcitrance.[9] It is an amorphous polymer of oxygenated *p*-propylphenol units and possesses a networked three-dimensional structure. The three main building blocks of lignin are *p*-coumaryl alcohol which forms *p*-hydroxyphenyl units (H-units), coniferyl alcohol which forms guaiacyl units (G-

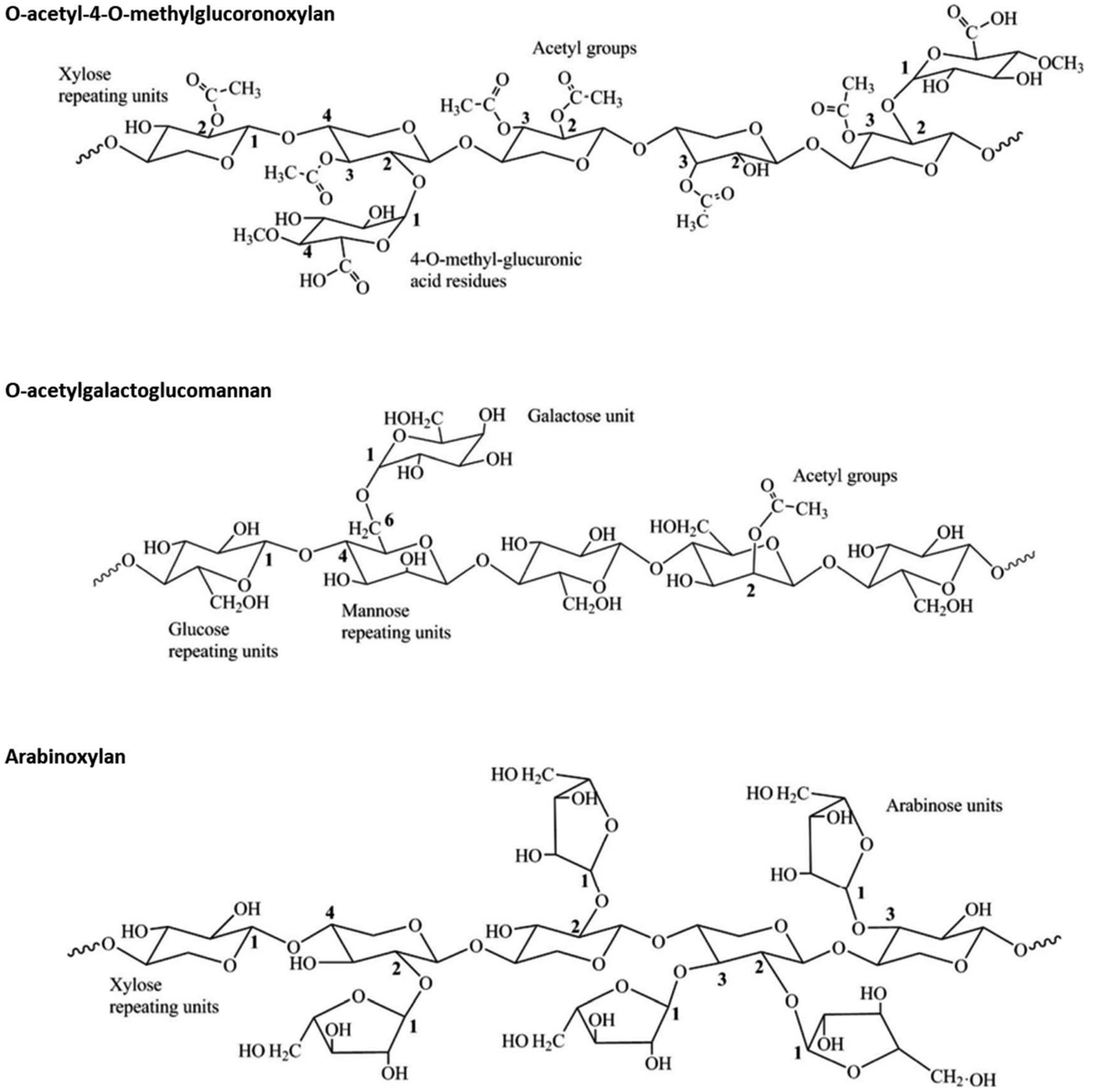


Fig. 3 Examples of hemicellulose structures typically found in hardwoods (*O*-acetyl-4-*O*-methylglucoronoxylan), softwoods (*O*-acetylgalactoglucomannan) and herbaceous crops (arabinoxylan). Adapted from Farhat *et al.*[43]

units), and sinapyl alcohol which forms syringyl units (S-units). These three types of units differ from one another based on the number of methoxy groups in the *ortho*-positions of aromatic rings: zero for H-units, one for G-units, and two for S-units (Fig. 4).

Following their synthesis in the cytosol *via* the phenylpropanoid pathway, monolignols are directed to the cell wall, where radical polymerization takes place, initiated by laccase and peroxidase enzymes, and the lignin polymer is formed.[15] An alternative view to the long-established model of random radical coupling of monolignols was proposed which postulates that so-called dirigent proteins catalyze a stereo-oriented biosynthesis of inter-unit lignin linkages.[44] The relative amount of H-, G- and S-units in the polymeric network varies substantially for different plant species and plant parts.[25] In general, softwood lignin is composed exclusively of G-units, whereas hardwood lignin contains both G- and S-units, and lignin from herbaceous biomass may comprise all three types of monolignols. In addition, other compounds may be incorporated in lignin structures, such as hydroxycinnamates (*p*-coumarate, *p*-ferulate), *p*-hydroxybenzoate, tricin and other minor components.[45–49] Lignin composition is also largely dependent on the specific plant part of origin and on environmental factors to which the plant has been exposed to during growth. For instance, compression wood, which is typically formed in the lower side of branches and stems of coniferous trees (softwoods) in response to mechanical stress, possesses a higher lignin content than normal softwood and a lignin structure that comprises significant amounts of H-units.[50] Another example is lignin from bark, which often displays a much higher degree of heterogeneity as compared to lignin in wood, comprising S-, G-, and H- units, as well as variable amounts of hydroxycinnamates, hydroxystilbenes, flavonoids, and other constituents.[51–53]

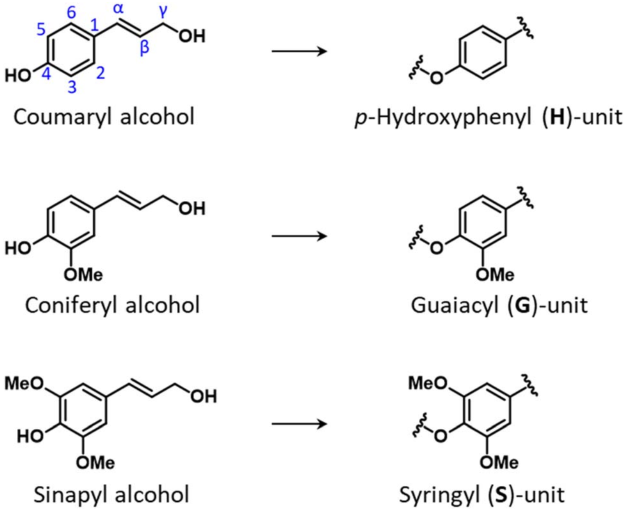
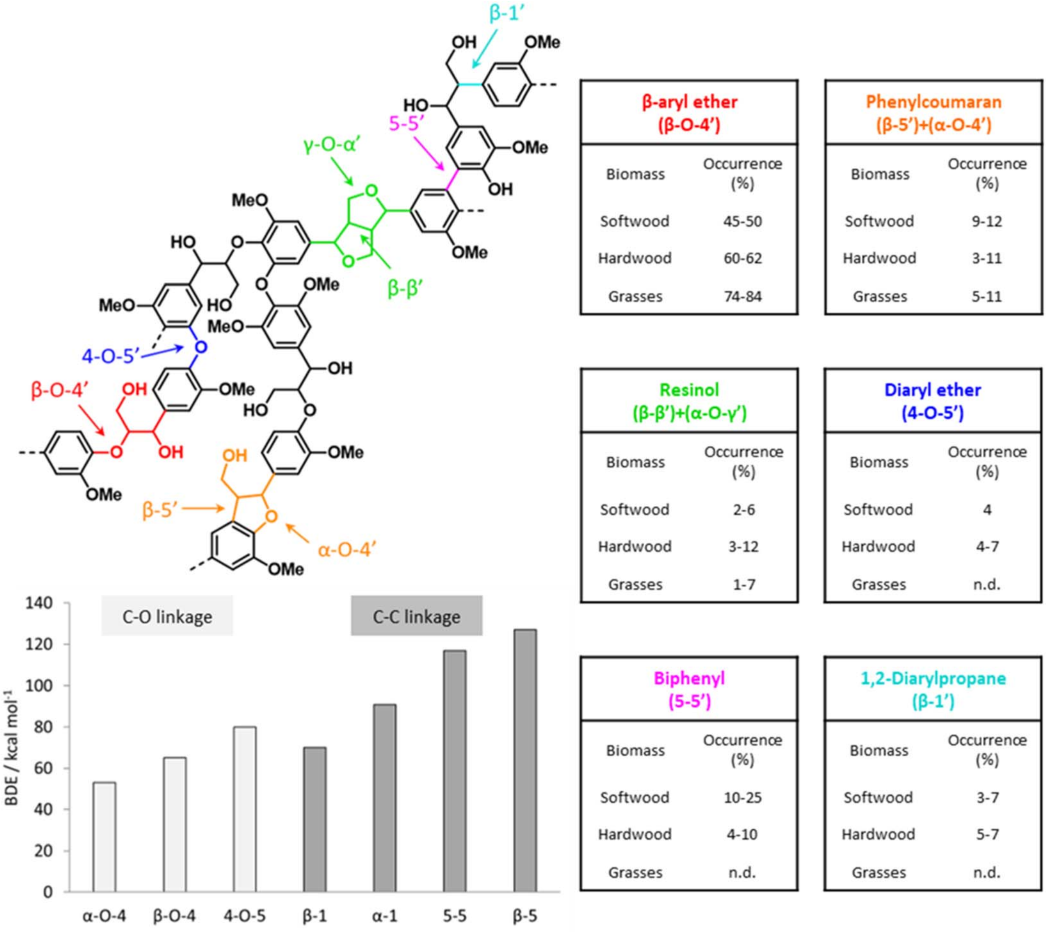


Fig. 4 Chemical structures of monolignols, and of the derived lignin units.

As illustrated in Fig. 5, various types of inter-unit linkages can be formed during the radical coupling of monolignols, including ether bonds, such as β-O-4′ (in β-aryl ether and dibenzodioxicin motifs), α-O-4′ (in phenylcoumaran and dibenzodioxicin motifs), 4-O-5′ (in diaryl ether motifs), γ-O-α′ (in resinol motifs), and α-O-α′ (in spirodienone motifs), as well as C–C bonds, such as β-5′ (in phenylcoumaran motifs), β-1′ (in 1,2-diarylpropane and spirodienone motifs), β-β′ (in resinol motifs), and 5-5′ (in biphenyl and dibenzodioxicin motifs). The content of inter-unit linkages also varies for different feedstocks.[15] A correlation has been proposed between lignin composition in terms of H-/G-/S-units and the content of C–C inter-unit bonds. Indeed, methoxy-substituted *ortho*-positions on aromatic rings of lignin units cannot participate in the formation of β-5′ and 5-5′ bonds during lignin polymerization, so the relative content of C–C bonds would be lower for lignin polymers richer in S-units.[14] However, besides the composition of lignin units, other factors, such as the transport of monolignols from the cytoplasm to the cell wall, have been suggested to affect the content of C–O and C–C inter-unit linkages in native lignin.[54] Feedstocks possessing lignin polymers with a low content of C–C bonds and a high amount of labile β-O-4′ linkages are the ideal target of processes that aim at depolymerizing lignin.[14]

Within the lignocellulose matrix, lignin is also linked to hemicellulose *via* ether and ester bonds to form hybrid



β-aryl ether (β-O-4′)

Biomass	Occurrence (%)
Softwood	45-50
Hardwood	60-62
Grasses	74-84

Phenylcoumaran (β-5′)+(α-O-4′)

Biomass	Occurrence (%)
Softwood	9-12
Hardwood	3-11
Grasses	5-11

Resinol (β-β′)+(α-O-γ′)

Biomass	Occurrence (%)
Softwood	2-6
Hardwood	3-12
Grasses	1-7

Diaryl ether (4-O-5′)

Biomass	Occurrence (%)
Softwood	4
Hardwood	4-7
Grasses	n.d.

Biphenyl (5-5′)

Biomass	Occurrence (%)
Softwood	10-25
Hardwood	4-10
Grasses	n.d.

1,2-Diarylpropane (β-1′)

Biomass	Occurrence (%)
Softwood	3-7
Hardwood	5-7
Grasses	n.d.

Fig. 5 Main lignin inter-unit linkage motifs with relative occurrence in different types of lignocellulose feedstocks and their bond dissociation energy (BDE). Based on Rinaldi *et al.*,[15] Wang and Wang,[55] and Parthasarathi *et al.*[56]

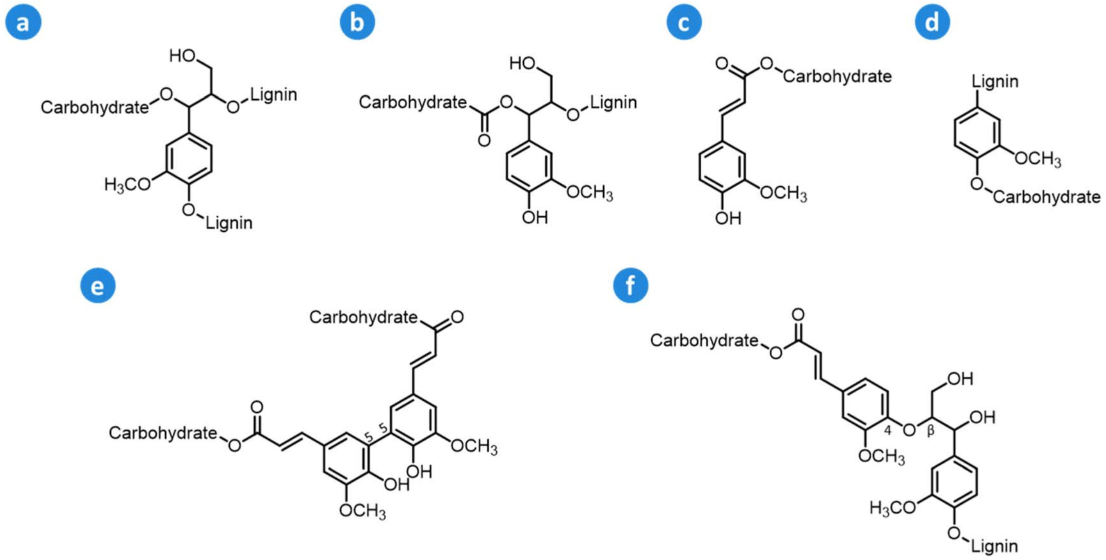


Fig. 6 Main types of LCC linkages: (a) benzyl ether, (b) benzyl ester, (c) ferulate ester, (d) phenyl glycosidic, (e) diferulate ester (5-5′), and (f) diferulate ester (β-O-4′). Based on Zhao *et al.*[57] and Tarasov *et al.*[58]

structural motifs known as lignin–carbohydrate complexes (LCCs).[57–60] The main types of linkages that are typically found in LCCs include benzyl ether, benzyl ester, ferulate ester, phenyl glycosidic, and diferulate ester (Fig. 6). Benzyl ether and phenyl glycosidic linkages connect glycosyl or mannosyl units of carbohydrates to phenolic or hydroxyl groups in lignin, whereas benzyl ester bonds link sugar uronic acids in hemicellulose to hydroxyl groups in lignin structures.[58] The abundance of the different LCC motifs in lignocellulose varies depending on the feedstock: hardwood LCCs are characterized by a high content of phenyl glycosidic linkages,[61,62] whereas softwood LCCs feature a high amount of benzyl ether structures,[61,63] and herbaceous LCCs possess high contents of (di)ferulate and phenyl glycosidic bonds.[64] As a general trend, herbaceous biomass possesses higher amounts of LCCs compared to woody biomass.[58,65] Even though the influence of LCCs on lignocellulose pretreatment has not been fully elucidated yet, it has been shown that a high presence of LCCs may hamper biomass delignification during pretreatment and the enzymatic hydrolysis of the isolated (hemi)cellulose.[57,58]

Due to the strong bonds existing between lignin and hemicellulose, which complicate the isolation of pure native lignin, the molecular weight (MW) of lignin polymers is difficult to assess. However, close-to-native lignin fractions have been reported to possess MWs in the range: 2500–10 000 g mol^{-1}.[14]

3. Lignocellulose pretreatment as a source of lignin

One of the major obstacles to lignocellulose valorization in a biorefinery is its recalcitrance toward enzymatic hydrolysis. Several factors affect lignocellulose recalcitrance, including both physical and chemical factors. Cellulose crystallinity correlates negatively with enzymatic hydrolysis, due to the tight packing of cellulose chains in crystalline regions, and a consequently reduced enzymatic accessibility.[9] The biomass particle size exerts as well an impact on cellulose hydrolysis potential; smaller biomass particles have an enhanced enzymatic digestibility.[66] Similarly, substrates with a higher porosity and with larger pore sizes possess a better processability, in view of a larger surface area of cellulose available for enzymatic attack.[67] On the contrary, the presence of hemicellulose and lignin hinders the enzymatic digestion of cellulose, since they both constitute a physical barrier that limits enzymatic accessibility, and they can also interfere with enzyme recognition or irreversibly adsorb enzymes.[9]

Thus, producing energy, chemicals and materials from renewable lignocellulose requires the development of effective pretreatment strategies that could reduce its inherent recalcitrance toward further processing. In general, such biomass pretreatments are aimed at the disruption of lignocellulose structure by the partial removal of lignin and hemicellulose and by a partial amorphization of cellulose crystalline domains.[68,69]

Lignocellulose pretreatments have long been employed in the pulping industry to convert woody biomass into pulp for papermaking. In this case, the pretreatment typically aims at removing lignin and hemicellulose from the biomass to yield a pulp with a high cellulose purity. The amorphization and the depolymerization of cellulose are undesirable, as they negatively affect the mechanical resistance of the pulps. In the context of "integrated biorefining", in view of the various applications envisaged for lignocellulosic biomass, several pretreatment approaches have been developed, including physical, physicochemical, chemical, and biological methods.[39,68–70] A common feature of many of them is the isolation of a solid carbohydrate fraction, amenable to further processing (saccharification or papermaking), and a lignin fraction, possibly comprising hemicellulose as well. The following sections explore the main aspects of the pretreatment strategies that are most widely adopted in biorefineries and in the pulping industry, with a focus on the properties of the isolated lignin fractions.

3.1. Physical pretreatment methods

Physical pretreatments include mechanical comminution, extrusion, and irradiation. In contrast to chemical and physicochemical pretreatments, physical pretreatments do not target the removal of lignin and hemicellulose from the produced pulp, thus they do not realize an actual fractionation of biomass. Instead, physical pretreatments aim at the partial disruption of the lignocellulose structure to enhance its subsequent processability.

3.1.1. Mechanical pretreatment. Mechanical pretreatment is the oldest method applied in wood pulping. It has been adopted since the 1840s and, nowadays, about 35 million tons of mechanical pulp are produced annually worldwide.[39] In view of the residual presence of lignin and hemicellulose in the pulp, mechanical pulping results in higher pulp yields compared to chemical or physicochemical pulping methods.[71] However, a partial damaging of cellulose fibers cannot be avoided during the grinding process, and the obtained pulps possess a lower strength, as well as a higher tendency to gain a yellow color with time (due to the presence of lignin).[71,72]

In biorefineries, the main goal of mechanical pretreatments is the reduction of the particle size and crystallinity of lignocellulosic biomass, to enhance the enzymatic accessibility of cellulose, thus more intense milling can be applied compared to what is done for pulping. Previous works reported a substantial increase of (hemi)cellulose digestibility (yields of monosaccharides up to 80–90%) upon the application of ball milling to herbaceous and woody biomass.[73–75] The most critical shortcomings related to the adoption of ball milling for lignocellulose pretreatment are the high energy demand of this method, and the large equipment cost.[69,76,77] Moreover, even though cellulose is made more accessible through milling, the residual presence of lignin may still hinder further processing.[39,75]

On the other hand, the use of milling as a pretreatment is of paramount importance for research efforts aimed at investigating lignocellulose structural properties. For instance, mechanical pretreatment at room temperature coupled with lignin extraction in an organic solvent constitute the basis for the isolation of native-like lignin (termed "milled wood lignin").[78,79]

3.1.2. Extrusion pretreatment. Extrusion is one of the most widely adopted physical pretreatments.[69] It consists of a thermomechanical process relying on the action of one or two screws that spin inside a tight barrel through which the lignocellulosic biomass is passed. The extrusion process is usually performed at a temperature comprised between 40 and 200 °C.[80] During the extrusion, the lignocellulosic biomass is subjected to shear and thermal stresses that disrupt the lignocellulose structure. The temperature applied and the screw configuration (design, turning speed) are key parameters that determine the properties of the obtained pulp.[81]

Extrusion pretreatment is often coupled with other chemical pretreatments.[82–84] For instance, an extrusion in hot water, or in the presence of an acid or basic catalyst can result in a partial removal of amorphous components (in acidic environment: hemicellulose hydrolysis; in alkaline environment: lignin solubilization), and consequently in a higher enzymatic digestibility of the cellulosic pulp.[80,84]

3.1.3. Irradiation pretreatment. Irradiation pretreatments include the treatment of lignocellulosic biomass with electromagnetic radiation (high energy: gamma ray, electron beam; low energy: microwave), as well as acoustic radiation (ultrasounds).[39] The use of high-energy irradiation causes the removal of electrons and ionizes atoms, resulting in profound chemical changes. Gamma ray and electron beam irradiation have been reported to induce lignocellulose decomposition and depolymerization, thus enhancing cellulose enzymatic processability.[85–90] However, these techniques are energy intensive and slow, so they are not currently employed at a commercial scale.[68]

Low-energy microwave radiation excites molecular vibrational and rotational modes, thereby providing thermal energy which, ultimately contributes to the disruption of lignocellulose structure.[87,91–93] Microwave pretreatment induces a rapid heating,[69] and is often used to assist other pretreatment strategies.[39,94–97] However, the treatment of heterogeneous substrates may result in a non-uniform temperature profile in the biomass.[98] This can lead to the creation of hot spots, where lignocellulose degradation may occur, together with the formation of enzyme inhibitors. The high energy consumption also represents a limitation to the industrial application of microwave irradiation.[68,91,98]

Ultrasound irradiation creates pressure differences in the reaction medium and cavitation phenomena, resulting in shear forces that break down the lignocellulose structure and enhance mass transfer and mixing processes.[87,99] Additionally, the cavitation of microbubbles generates radicals that contribute to the cleavage of intermolecular bonds between lignin, hemicellulose, and cellulose.[87,99] Ultrasonication is often used in combination with chemical or physicochemical pretreatments to improve the extraction of desired lignocellulose components in the reaction medium.[100–104] Similarly to other irradiation pretreatments, ultrasonication is energy intensive and difficult to implement at large scale.[69]

3.2. Physicochemical pretreatment methods

In physicochemical pretreatments, the lignocellulose structure is decomposed either by the hydrolytic action of water or by pressure shocks ("explosions").

3.2.1. Liquid hot water pretreatment. Liquid hot water (LHW) pretreatment relies on the use of hot water to enhance the disassembly of lignocellulose. At the applied temperature (typically between 150 and 240 °C) water undergoes partial autoionization liberating protons with a concomitant reduction of the pH of the medium.[82,105–107] This process initiates the hydrolysis and the solubilization of hemicellulose and the cleavage of acetyl groups to form acetic acid, which further catalyzes the hydrolysis.[108]

Generally, the severity of LHW pretreatments is described by means of a severity factor $\log(R_0)$ (eqn (1)).[39,108–110]

$$\log(R_0) = \log\left[t\exp\left(\frac{T(t)-100}{14.75}\right)\right] + |\mathrm{pH}-7| \tag{1}$$

wherein, t is the time in minutes, and $T(t)$ is the temperature in °C. Long durations, high temperatures and harsh pH conditions cause more extensive modifications of the lignocellulose structure. For maximizing the enzymatic digestibility of the isolated pulp, the severity factor should be comprised between 3 and 4.5.[108] During LHW pretreatment, LCCs are hydrolyzed, contributing to an enhanced accessibility of cellulose fibers. Concomitantly, the surface area of cellulose is greatly increased by non-chemical swelling, thereby facilitating subsequent enzymatic digestion.[108] By virtue of its good performance in terms of enhancing cellulose digestibility and its economic effectiveness, LHW pretreatment is considered an industrially attractive method for processing lignocellulosic biomass in biorefineries.[39,82] Remarkably, this method was reported to give excellent cellulose to ethanol conversion yields of ~95% for wheat straw, and was proven effective at industrial scale.[111,112] Recently, a LHW process was successfully applied to softwood biomass and scaled up to industrial scale in the Sweetwood plant by Fibenol in Estonia, representing the first of its kind industrial scale biorefinery aiming at producing high quality lignin and sugar hydrolysates.[113]

Although LHW pretreatment solubilizes only a limited amount of lignin, it causes considerable modifications of the lignin chemical structure. Most prominently, β-O-4′ ether linkages undergo acid-catalyzed cleavage, as illustrated in Fig. 7.[39] The first step of the reaction pathway involves the cleavage of the hydroxyl group in the α-position with the formation of an intermediate benzylic carbenium ion (**1**).[114–117] The latter can then transform into two enol–ether structures (**2** and **3** in pathways A and B, respectively), prone to undergo hydrolysis to yield C_3-ketone-substituted phenolics (**4**, known as Hibbert's ketones) or C_2-aldehyde-substituted phenolics (**5**).[115–117] Hibbert's ketones, together with C_2-aldehyde-substituted phenolics and carbenium ions (pathway C) participate in repolymerization reactions, ultimately leading to the formation of condensed recalcitrant lignin structures.[39,118] Furthermore, lignin can undergo melting at high temperature, followed by redeposition on the surface of cellulose fibers in the form of lignin droplets upon cooling, potentially reducing the accessibility of cellulose.[119]

Carbohydrate polymers are also affected by the acidic environment of LHW pretreatment, particularly hemicellulose, which is more exposed to the action of solvents. Glycosidic bonds undergo hydrolysis to yield oligo- and monosaccharides,[108,109,120] according to the mechanism shown in Fig. 8a. The released sugar fragments are subject to further acid-catalyzed degradation reactions (Fig. 8b), resulting in the formation of short aldehydes (furfural (**6**), 5-hydroxymethylfurfural (**7**)) and organic acids (levulinic (**8**), formic acid (**9**)).[108,109,120] These products inhibit the subsequent fermentation of the pulp (post-enzymatic saccharification).[39,108] Additionally, products from carbohydrate degradation may generate so-called pseudolignin (also termed humins),[121,122] which deposits on the pulp surface, limiting the accessibility of cellulose fibers.[108,123]

3.2.2. Steam explosion pretreatment.

Steam explosion (SE) pretreatment is a particular type of hydrothermal pretreatment and one of the most common and effective pretreatment methods adopted for reducing the recalcitrance of lignocellulosic biomass toward enzymatic digestion.[124–126] In SE pretreatment, the biomass is initially contacted with saturated steam under elevated pressure and at high temperature (typically between 160 and 260 °C) for a short contact time (usually

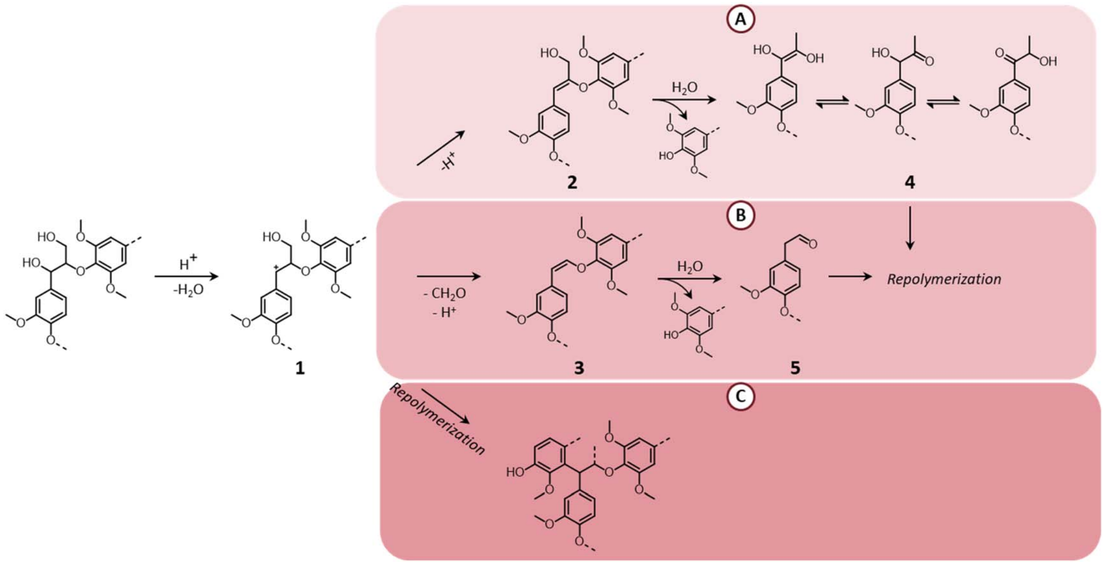


Fig. 7 Lignin chemistry in acidic conditions. Pathway A: formation of Hibbert's ketones; pathway B: formation of C_2-aldehyde substituted phenolics; pathway C: repolymerization. Based on Liao *et al.*[39]

between 5 and 30 minutes) resulting in an initial swelling of lignocellulose structure.[125–130] Then a sudden decompression is realized, which causes the expansion of water inside biomass and the disruption of lignocellulose, with the creation of a porous structure.[39,69,125,127,128] An important feature of this process is that the explosion causes a reduction of the biomass particle size with a much lower energy expenditure compared to mechanical pretreatments.[131]

During SE pretreatment, the linkages between cellulose and hemicellulose, and between hemicellulose and lignin are broken down by the action of temperature and pressure, resulting in a partial solubilization of hemicellulose and (to a minor extent) lignin.[124,126,132] The extracted lignin possesses features analogous to the lignin obtained from LHW pretreatment, since it undergoes similar acid-catalyzed depolymerization and repolymerization reactions.[130] Thus, depending on the treatment severity, lignin can be subject to moderate or extensive chemical modifications.[126,133]

The hydrolysis of hemicellulose and the degradation of the released sugars to form aldehydes and organic acids occur, which can cause inhibition of fermentative microorganisms during the downstream processing of the isolated pulp.[82,127,133] Despite this, the low energy requirements, the absence of the use of expensive chemicals (with the associated recycling/disposal cost), and the effective deconstruction of lignocellulose structure make SE pretreatment an attractive method for biorefineries.[124,125,134,135]

3.2.3. Ammonia fiber expansion pretreatment.

Ammonia fiber expansion (AFEX) pretreatment relies on the treatment of lignocellulosic biomass in liquid ammonia at mild temperature (between 60 and 100 °C) under elevated pressure.[69,136,137] These conditions are applied for a short time (usually between 5 and 30 minutes), after which the pressure is suddenly released causing the rapid expansion of ammonia and the mechanical disruption of lignocellulose fibrous structure.[69,136,137] This results in an increased porosity and a reduced size of biomass particles, which improve cellulose enzymatic accessibility.[138]

During AFEX, ammonolytic and hydrolytic cleavage of LCCs occurs, with the partial solubilization of hemicellulose and lignin, which, upon the release of the applied pressure, are redistributed in the pretreated solids.[14,39] Even though AFEX does not delignify biomass, it facilitates downstream lignin extraction, for example with an organic or alkaline solution.[14,139] In contrast to the lignin obtained from LHW or SE processes, the structure of AFEX lignin is usually composed of oligomeric fragments, with well-preserved β-O-4′ bonds, thus amenable to further upgrading.[14]

Another advantage of AFEX lies in the minor degradation of hemicellulose and lignin, with a negligible formation of fermentation inhibitory compounds (*e.g.* furans, organic acids, phenols).[69,82] On the other hand, the need to recycle ammonia increases the operating cost. Also, the method is unsuitable for the pretreatment of biomasses possessing high lignin contents (*e.g.* softwood or hardwood).[39,140] Nevertheless, when applied to herbaceous plants with low lignin contents, AFEX showed better results compared to other pretreatments, yielding a pulp with enhanced digestibility.[69,140,141] Thus, it is regarded as a promising method for overcoming the high enzyme cost of many current biorefinery processes.[142]

3.2.4. CO_2 explosion pretreatment.

In CO_2 explosion pretreatments, supercritical CO_2 is used to impregnate lignocellulosic biomass, promoting the hydrolysis of hemicellulose

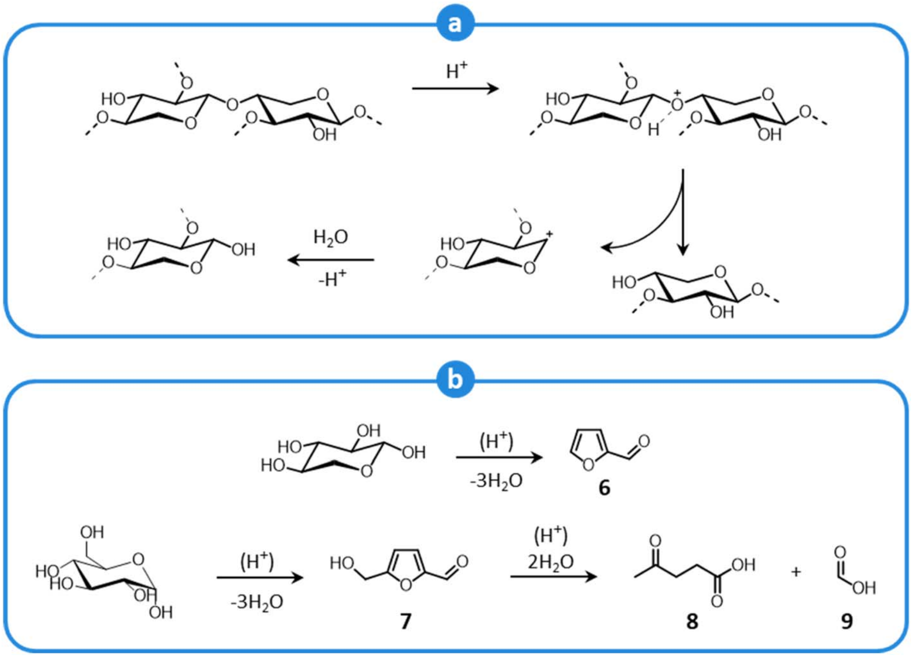


Fig. 8 Acid-catalyzed cleavage of glycosidic bonds (a) and possible decomposition reactions of the released sugar fragments (b). Based on Cybulska *et al.*,[108] and Xiao *et al.*[109]

and LCCs.[69,143,144] The presence of moisture favors the dissolution of CO_2 to form carbonic acid and further enhances hemicellulose hydrolysis and degradation reactions.[39,69,144,145] Upon release of the pressure, the explosion breaks down the lignocellulose matrix, improving the enzymatic accessibility of cellulose fibers.[143–147] During the process lignin undergoes acid-catalyzed depolymerization and recondensation reactions (see Fig. 7), but is not solubilized. Delignification can be achieved in a subsequent step, or simultaneously by the use of an additional organic solvent, such as ethanol or acetic acid.[39,82,143]

Compared to SE and AFEX pretreatments, the principal advantages offered by CO_2 explosion are the lower energy requirements, and the non-flammability, non-toxicity and low cost of CO_2.[69,144,148] Despite this, the high cost of the equipment necessary to withstand the elevated pressure constitutes an obstacle for industrial implementation.[148]

3.3. Chemical pretreatment methods

In chemical pretreatments lignocellulosic biomass is processed in the presence of an exogenous chemical agent. These treatments include common pulping methods such as kraft, sulfite, and soda pulping, as well as acid, oxidative, organosolv, ionic liquid and deep-eutectic solvent pretreatments.

3.3.1. Kraft pulping. Kraft pulping is the pulping process that is most widely adopted worldwide, accounting for about 70% of the global pulp production,[149] and about 85% of the global production of lignin.[11] It was invented at the end of the 19th century and soon became the dominant pulping process, in view of the superior mechanical properties of the produced pulps, of the excellent recovery of pulping chemicals, and of the high efficiency in terms of energy usage.[149–151]

Lignocellulosic biomass is treated in an aqueous solution of sodium hydroxide (NaOH) and sodium sulfide (Na_2S) termed white liquor (pH ~14), at a temperature comprised between 150 and 170 °C.[149] Under such conditions, lignin and part of the hemicellulose are solubilized, leaving behind a cellulosic pulp. Delignification takes place by the action of the OH^- and HS^- ions, present in the white liquor, that cause the cleavage of LCCs and the depolymerization of lignin into fragments, which are soluble in the alkaline medium. Ester bonds between hemicellulose and lignin are cleaved by saponification reactions.[39,69] On the other hand, lignin depolymerization involves mainly the cleavage of β-O-4′ inter-unit linkages, with a mechanism that follows different pathways for phenolic units (possessing free phenolic OH-groups) and non-phenolic lignin units (possessing etherified phenolic OH-groups).[149,150,152–155]

As schematized in Fig. 9, under the harsh alkaline conditions applied during kraft pulping, a phenolic unit (**10**) that possess a suitable leaving group on the α-position (*e.g.* –OH, –OR) is transformed into a quinone methide (**11**).[149,150,153] In the

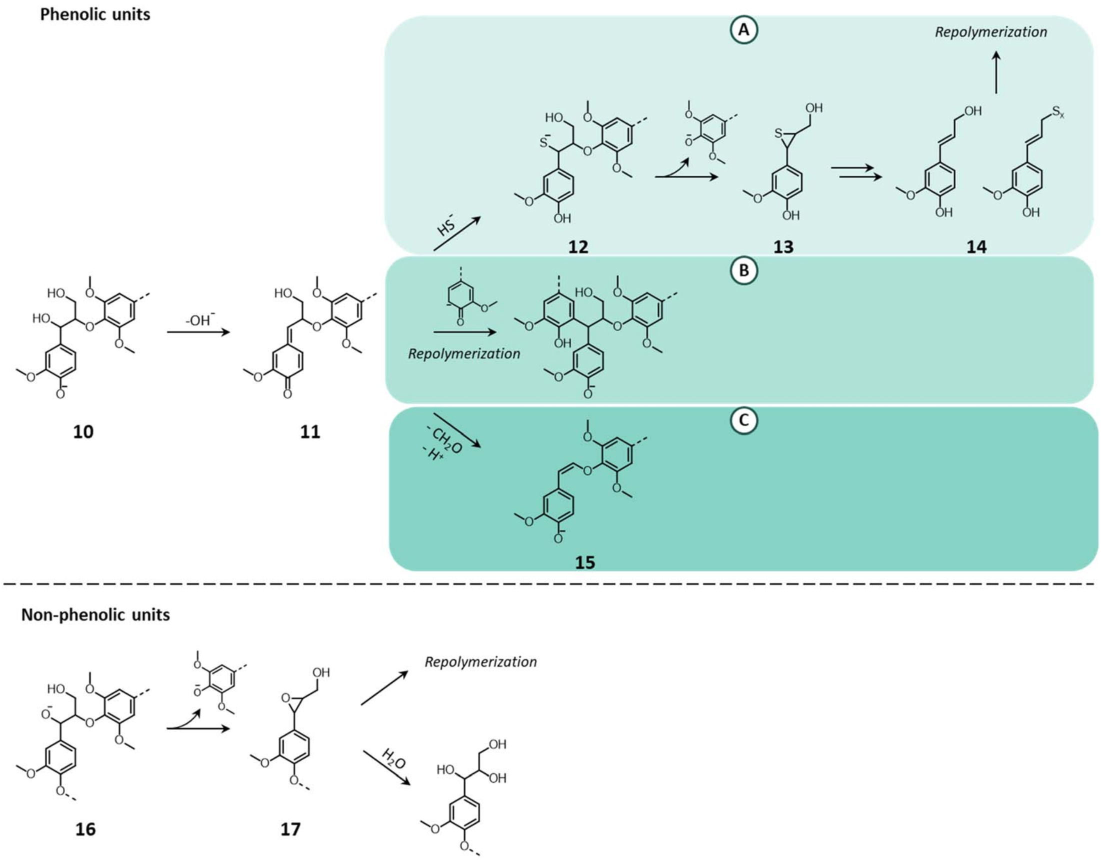


Fig. 9 Lignin chemistry in alkaline conditions. Pathway A: nucleophilic attack by HS^-; pathway B: repolymerization; pathway C: loss of formaldehyde and enol ether formation. Based on Lachenal[149] and Rinaldi *et al.*[15]

presence of HS^-, the quinone methide undergoes nucleophilic attack to restore the aromaticity (pathway A), forming a benzyl mercaptide (**12**). The ionized form of the thiol attacks the β-carbon breaking the β-O-4′ bond and leading to the formation of an episulfide (**13**).[149,150,153] The latter may undergo a variety of reactions, ultimately leading to the formation of compounds with unsaturated (thio)/(hydroxy)alkenyl side chains (**14**) that are prone to undergo repolymerization.[15,149,153] Alternatively, the quinone methide can also react with a lignin nucleophile (phenolate), leading to the recondensation of lignin (pathway B).[150,154,155] Hence, for kraft pulping, the addition of HS^- to quinone methides is in competition with lignin condensation. Indeed, the presence of HS^- contributes to prevent excessive lignin repolymerization, thereby ensuring the solubility of lignin fragments and the successful biomass delignification.[149,154] Finally, the quinone methide can restore the aromaticity *via* retro-aldol reaction and the loss of the γ–CH_2–OH in the form of formaldehyde to yield an alkali-stable enol ether (**15**) (pathway C).[153,154] However, this reaction pathway is more likely to occur in the absence of a strong nucleophile (as is HS^-).[15] For non-phenolic units (**16**), the cleavage of β-O-4′ bonds is due to the partial dissociation of the –OH groups at the α- or γ-positions (predominantly at the α-position, which possesses a higher acidity).[149,150,153] The ionization of these groups causes a nucleophilic attack on the β-carbon and the cleavage of the β-O-4′ bond to generate an epoxide (**17**), which quickly opens by reaction with water or with another lignin unit.[149,150,153]

Cellulose and, most prominently, hemicellulose are also affected by the alkaline environment of kraft pulping. Carbohydrate polymers undergo extensive depolymerization and a substantial amount of hemicellulose is solubilized during pulping. Carbohydrate degradation occurs *via* a so-called peeling reaction, which causes the removal of sugar units one by one from the reducing ends of the polymer chains (cellulose and hemicelluloses), as shown in Fig. 10a. The peeling mechanisms is initiated by the reaction of OH^- with the H-atom at the α-carbon of an aldehyde group, which is slightly acidic (Step I).[149,150] This causes an alkaline-induced isomerization of an aldose to a ketose (Step II). The latter is then transformed into an enediol (Step III), which can go through β-alkoxy elimination, leading to the cleavage of the glycosidic bond (Step IV).[149,150] The cleaved end-unit ultimately rearranges into a carboxylic acid and is solubilized, causing the concomitant undesired neutralization of the alkaline pulping medium (Fig. 10b).[149] The peeling process goes on until competing reactions that convert the reducing end groups into stable carboxylic acid groups become preponderant.[149,156]

Alkaline hydrolysis of polysaccharides also contributes to polysaccharides decomposition. Under kraft pulping conditions, the hydroxyl groups of carbohydrate molecules may partially dissociate to give alkoxide anions, which can perform an intramolecular nucleophilic attack leading to the cleavage of glycosidic bonds and to the formation of oxirane structures (Fig. 11).[149,156,157] Ultimately, the hydrolysis of such oxiranes gives new reducing end groups, which can undergo peeling reaction (this process is termed secondary peeling).[149]

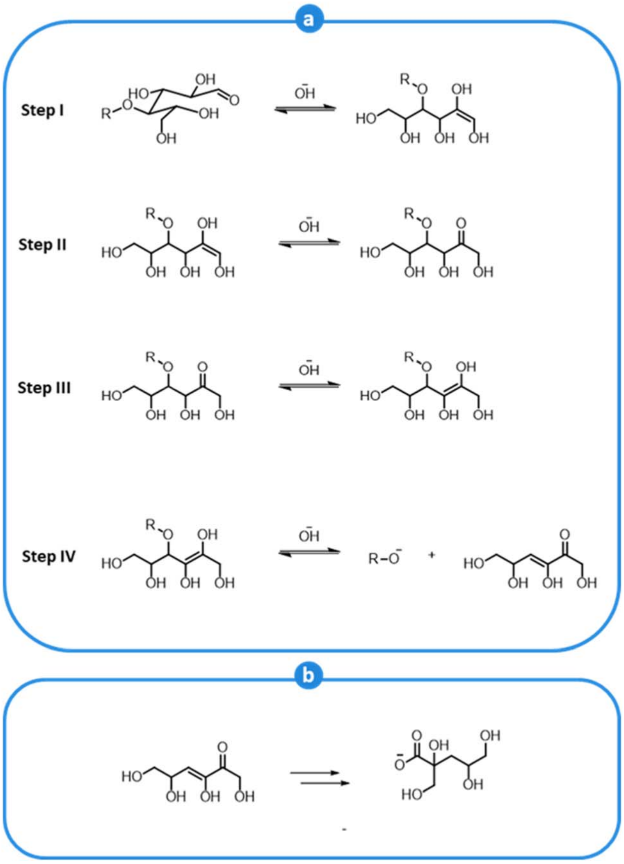


Fig. 10 Peeling reaction of carbohydrates in alkaline conditions (a), and fate of the eliminated units (b). Based on Lachenal[149] and Fearon *et al.*[156]

As a result of the considerable lignin and carbohydrate degradation occurring during kraft pulping, the spent process liquor, termed black liquor, contains partially condensed lignin structures, heavily contaminated with carbohydrate and sulfur derivatives.[11,15] Black liquor is commonly combusted to recover thermal energy and to fuel the pulping process.[149,150] Alternatively, lignin can be precipitated from the liquor by acidification.[11,14] However, the low content of residual β-O-4′ linkages, the high degree of condensation and the presence of contaminants (*e.g.* 1–3% of sulfur)[11] make kraft lignin particularly recalcitrant toward further upgrading.[11,14,15] Despite the excellent quality of kraft pulps and the near-complete recovery of chemicals and energy in modern kraft mills,[158] the limited possibilities for the valorization of the lignin and hemicellulose fractions of biomass represent critical shortcomings for an effective valorization of lignocellulose during the kraft process. Recently, research efforts were spent with the goal of better elucidating the structural motifs in kraft lignin.[159,160] Arguably, such work will serve as a means for the development of improved valorization strategies for kraft lignin.

3.3.2. Sulfite pulping. Sulfite pulping was developed between the 1850 and the 1860 and was the first widely industrially implemented pulping method.[161] After the advent of kraft

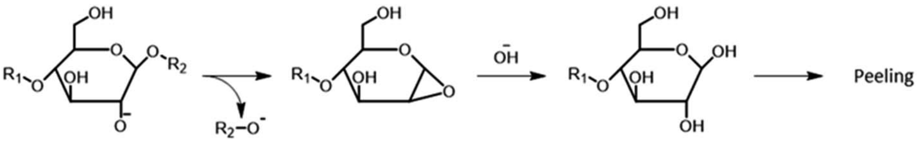


Fig. 11 Alkaline hydrolysis of carbohydrates in alkaline conditions. Based on Lachenal[149] and Gierer.[157]

pulping in the 1940s, the market of sulfite pulps has seen a continuous decrease.[150,161,162]

Sulfite pulping relies on the treatment of lignocellulosic biomass in an aqueous solution of salts of sulfurous acid, at a temperature in a range between 130 and 180 °C.[161] The salts employed in the process can be formed by different cations, such as calcium, magnesium, sodium and ammonium, and the choice of the cation ultimately affects the pH of the pulping medium (typically comprised between 2 and 12).[11,150,161] In turn, the pH of the medium determines the active sulfur species (H_2SO_3, HSO_3^-, or SO_3^{2-}).[161]

During sulfite pulping biomass delignification is achieved by two mechanisms: sulfonation and hydrolysis. Sulfonation introduces polar sulfonate groups in lignin structures, thereby increasing lignin solubility in the aqueous medium, while hydrolysis breaks LCCs and intermolecular ether linkages between lignin units (*i.e.* β-O-4′ and α-O-4′ bonds).[150,161,163]

Lignin sulfonation follows different pathways under acidic and neutral/alkaline conditions. In an acidic medium, benzylic carbenium ions are formed according to a mechanism illustrated in Fig. 7, which implies a nucleophilic attack by bisulfite ions (Fig. 12a), ultimately yielding α-sulfonic acid structures (**18**).[150,161,163,164] On the other hand, under neutral or basic conditions, sulfonation involves only phenolic units, which generate quinone methides (Fig. 9). In the presence of sulfite ions, quinone methides (**11**) are subjected to nucleophilic attack (Fig. 12b), and α-sulfonic acids are formed (**19**).[150,161,163,164] Moreover, other inter-unit linkages can undergo sulfonation, and β- and γ-sulfonic groups are introduced as well in lignin units, both under acid and alkaline conditions.[150,161,163,165–167]

The cleavage of lignin inter-unit bonds and the recondensation of lignin fragments principally follow the previously discussed acid-catalyzed or a base-catalyzed chemistry depending on the pH of the pulping medium (Fig. 7 and 9, respectively).[161,163] Additionally, in neutral/alkaline sulfite pulping the cleavage of β-O-4′ linkages through the displacement of the β-substituent by a sulfite ion can also occur, in a mechanism known as "sulfitolysis" (Fig. 13), ultimately leading to the formation of lignin units with β-sulfonated, unsaturated side chains, prone to undergo repolymerization (**20**).[150,161,163,164]

Hemicellulose and cellulose are impacted as well by sulfite pulping and undergo acid-catalyzed hydrolysis and degradation (Fig. 8), or alkaline hydrolysis and peeling reactions (Fig. 10 and 11) in acid and basic medium, respectively.[150,161]

Overall, sulfite pulping has become gradually less popular as a pulping method due to the low strength of the produced pulps.[150,162] Other shortcomings include the extensive

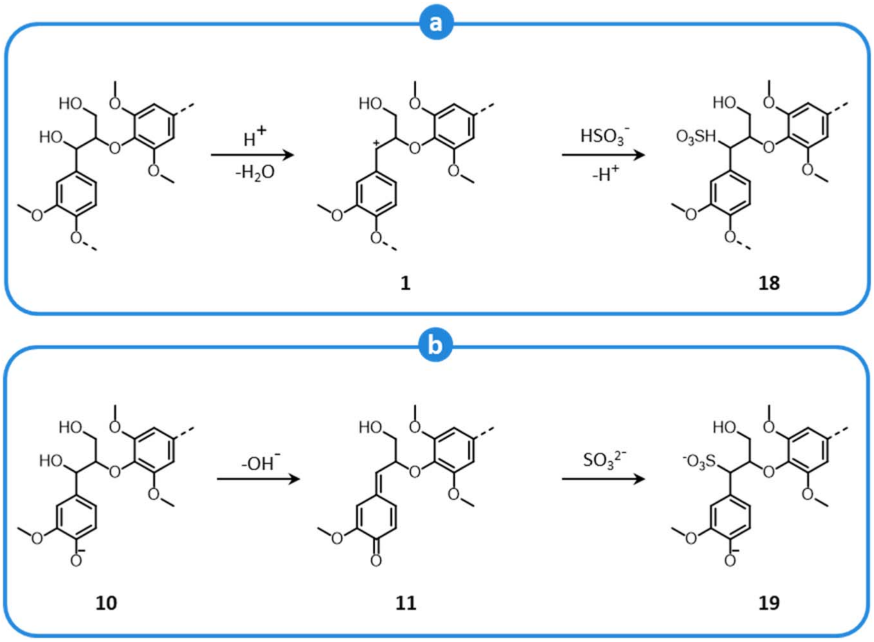


Fig. 12 Sulfonation of β-O-4′ lignin motifs during sulfite pulping at acid conditions (a), and neutral/basic conditions (b). Based on Sjöström,[150] and Evtuguin.[161]

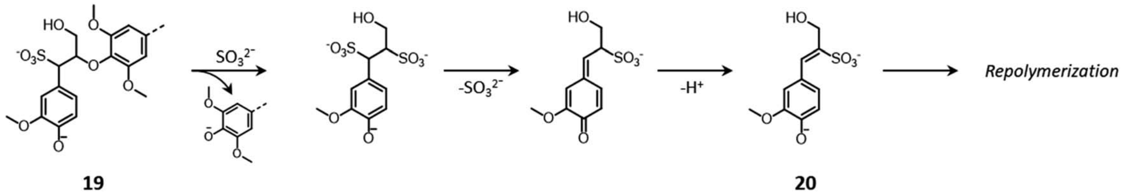


Fig. 13 Sulfitolysis of β-O-4′ linkages during neutral/alkaline sulfite pulping. Based on Sjöström,[150] and Evtuguin.[161]

degradation of hemicellulose and the low quality of the produced lignin streams (lignosulfonates), which are heavily condensed and contaminated by sulfur (3–8%),[11] carbohydrates, and other impurities (*e.g.* minerals, extractives, …).[11,149] Importantly, while the high degree of condensation and the presence of impurities hinder the upgrading of lignosulfonates toward high-value aromatics, the unique properties of these lignin products (chiefly the molecular weight and the degree of sulfonation) make them effective materials for the manufacturing of composites, dispersants, or flocculants.[168] Currently, lignosulfonates account for nearly 90% of the total market of commercial lignin,[169] and represent a prominent example of lignin valorization at the industrial scale.

3.3.3. Soda pulping. Soda pulping is the first chemical pulping process that was developed and dates back to 1851.[170] It is similar to kraft pulping, with the major difference being the absence of a strong nucleophile in soda pulping.[150] This feature makes the delignification process slower and less efficient compared to kraft pulping.[150] For this reason, soda pulping is more often employed for the treatment of non-woody biomass, which typically possess a lower lignin content, and a larger portion of alkali-labile LCCs.[171–173]

In some configurations, soda pulping implements the use of anthraquinone that simultaneously stabilizes polysaccharides against peeling reactions and catalyzes the cleavage of β-O-4′ bonds in lignin.[150,174,175] Anthraquinone (**21**) acts as a redox shuttle between carbohydrates and lignin (Fig. 14). On the one hand, it oxidizes the reducing ends of polysaccharides (**23**) toward alkali-stable aldonic acid groups (**24**), with the concomitant formation of anthrahydroquinone (**22**).[150,174] On the other hand, the latter performs a nucleophilic attack on quinone methides (**11**), ultimately causing the reductive cleavage of β-O-4′ bonds and the regeneration of anthraquinone.[150,174]

Despite the improvement deriving from the introduction of anthraquinone, soda pulps possess lower mechanical resistance compared to kraft pulps.[150] A major advantage of soda pulping is the production of sulfur-free lignin, which can be recovered by precipitation.[11,171] This makes soda lignin more attractive as a raw material, compared to kraft lignin or lignosulfonates. Nonetheless, the high degree of condensation still represents an obstacle for the upgrading of soda lignin.[11]

3.3.4. Acid pretreatment. Acid pretreatment allows removing hemicellulose and part of the lignin from lignocellulose, thereby increasing the accessibility of cellulose fibers for subsequent enzymatic hydrolysis.[39,68,69,176,177] A wide range of acids can be employed for the pretreatment of lignocellulosic biomass, including inorganic (*e.g.* H_2SO_4, HCl, H_3PO_4, HNO_3, …) and organic acids (formic, acetic, oxalic, …).[39,69,176] The treatment can be performed either in a dilute acid solution (0.1–10%) at high temperature (100–250 °C) or in a concentrated solution (30–70%) at low temperature (<100 °C),[69] and the severity of the pretreatment can be expressed using a severity factor, as defined above.

Concentrated acid pretreatment targets the complete conversion of polysaccharides in the biomass to fermentable sugars, circumventing the need of an enzymatic hydrolysis of the pulp.[176] However, extensive washing, detoxification and neutralization of the solution are required before fermentation.[176] Moreover, concentrated acids are toxic, highly corrosive compounds, which are difficult to recycle when in solution.[39,69]

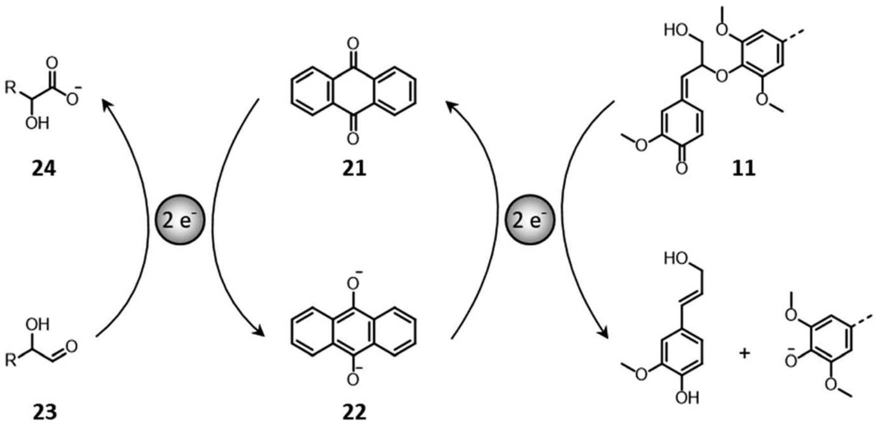


Fig. 14 Anthraquinone–anthrahydroquinone reactions with carbohydrates and lignin in alkaline conditions. Based on Sjöström.[150]

Thus, the stringent safety/equipment requirements and the large amount of neutralization waste deriving from the use of concentrated acids represent important drawbacks of concentrated acid pretreatments.[39,69,176] In general, the use of dilute acid solutions is a more suitable option for the pretreatment of lignocellulose at industrial scale, as the enzymatic digestibility of the biomass can be greatly improved, and the process is less costly and more environmentally friendly.[69,135,177]

One drawback of acid pretreatment is that the released sugars may undergo acid-catalyzed degradation reactions, leading to the formation of furans (*e.g.* furfural, 5-hydroxymethylfurfural), organic acids (*e.g.* formic acid, levulinic acid) and condensation products (pseudolignin), which inhibit the subsequent downstream processing of the cellulosic pulp.[39,69,176] Nonetheless, furans and levulinic acid can also represent attractive platforms for the manufacturing of polymers, chemicals, and fuels.[6,178–181] Therefore, severe acid pretreatment configurations are sometimes adopted with the goal of converting (hemi)cellulose toward these intermediates.[39]

During acid pretreatment, lignin is partially solubilized and undergoes depolymerization and repolymerization reactions, following the pathways discussed for LHW pretreatment. The residual amount of inter-unit ether linkages in the isolated lignin decreases with the severity of the pretreatment.[14] At higher severity, lignin fragments exhibit a greater tendency to undergo recondensation, and a larger redeposition of lignin on cellulose fibers occurs.[14] This represents a crucial shortcoming of acid pretreatment, as it negatively affects both cellulose and lignin valorization downstream. Overall, the selection of optimal process conditions for the acid pretreatment of lignocellulosic biomass is dependent on the purpose of the pretreatment and on the targeted products.

3.3.5. Oxidative pretreatment. Oxidative treatment is extensively adopted for the bleaching of pulps destined to the production of paper. During pulp bleaching, oxidizing agents (hydrogen peroxide, oxygen, ozone or peroxyacids) are used to delignify pulps and inactivate chromophore groups in the residual lignin, thereby yielding white cellulose fibers (which also have enhanced enzymatic digestibility).[39,68,176,182,183] Oxidative pretreatment is commonly carried out in an alkaline or an acidic environment, thus biomass components undergo both acid-/base-catalyzed reactions and oxidation reactions.[14,39]

Lignin oxidation follows a radical reaction mechanism, involving a multitude of possible depolymerization and repolymerization pathways.[184–187] In contrast to the previously discussed acid- and base-catalyzed lignin reactions, in which lignin depolymerization only proceeds *via* the cleavage of inter-unit ether bonds, in this case the rupture of C–C linkages can also take place.[184–187] C–C bonds in the side chains of lignin units can be broken, with the formation of phenolic aldehydes (**25**), acids (**26**) or quinones (**27**) (Fig. 15).[184–187] Additionally, aromatic rings can be cleaved, with the consequent formation of aliphatic carboxylic acids (**28**).[184,185] Condensation reactions between lignin radicals can yield biphenyl structures (**29**).[184,185]

Along with lignin, hemicellulose and cellulose undergo substantial degradation under the non-selective action of the free radical species formed during the process. As a result, various organic acid byproducts are formed (*e.g.* succinic acid, glycolic acid, formic acid, acetic acid, …), which act as inhibitors of the subsequent enzymatic and fermentative processing, thereby limiting the effectiveness of the oxidative pretreatment.[39,68,176]

In view of this, a mild oxidative pretreatment is usually preferred over harsh conditions, since partial delignification can be achieved with low degradation of lignin and carbohydrate products, leading to an enhancement of the pulp processability *via* enzymatic or chemical methods.[188,189] Moreover,

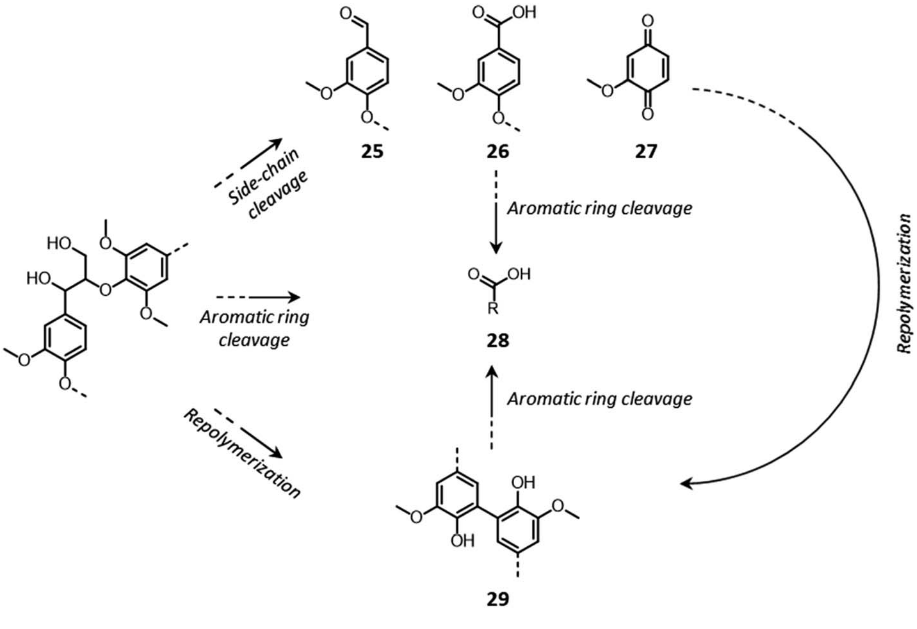


Fig. 15 Lignin chemistry under oxidative conditions. Based on Schutyser *et al.*[14]

the oxidized lignin obtained from a mild pretreatment can be further upgraded toward aromatic chemicals, thereby constituting an additional valuable product stream.[190–193] In spite of this, the high cost of the most commonly adopted oxidizing agents currently represents an obstacle to the scale-up of oxidative pretreatments.[68,82]

3.3.6. Organosolv pretreatment. Organosolv fractionation has been investigated both for paper making and as a pretreatment to be adopted in biorefineries. It relies on contacting lignocellulosic biomass with an organic solvent in the presence or in the absence of water to disrupt the linkages between lignin and hemicellulose, thereby solubilizing lignin (and hemicellulose, under certain conditions), improving the cellulose purity and the enzymatic digestibility of the residual biomass.[176,194–198] A broad range of organic solvents can be employed for organosolv pretreatment, including alcohols (*e.g.* methanol, ethanol, ethylene glycol, glycerol, …),[199,200] organic acids (*e.g.* formic acid, acetic acid, …),[201] peroxyacids (*e.g.* peroxyformic acid, peroxyacetic acid, …),[202] ketones (*e.g.* acetone, methyl isobutyl ketone, …),[203,204] ethers (*e.g.* tetrahydrofuran, 2-methyltetrahydrofuran, …),[205,206] or esters (*e.g.* γ-valerolactone, …).[207,208] The ability of different organic solvents to solubilize lignin is commonly described using the Hildebrand solubility parameter (δ), defined according to eqn (2).

$$\delta = \sqrt{\frac{\Delta\tilde{H} - R\,T}{\tilde{V}}} \tag{2}$$

wherein $\Delta\tilde{H}$ is the molar heat of vaporization of the solvent (J mol^{-1}), R is the ideal gas constant (J mol^{-1} K^{-1}), T is the temperature (K), and $\tilde{V}$ is the molar volume of the solvent (m^3 mol^{-1}). For optimal solvency, the Hildebrand solubility parameter of the solvent should match that of the solute, which, in the case of lignin, is about 23.5 MPa$^{1/2}$.[196,197,199] Depending on the solvent used, and on the use of an aqueous or a non-aqueous solution, only lignin or both lignin and hemicellulose are solubilized. Concomitantly, cellulose swelling occurs due to the action of the organic solvent (and water, when present), which disrupts the hydrogen bonds in the amorphous regions of cellulose, leading to an increased enzymatic accessibility.[39]

The treatment temperature and time are generally comprised in the ranges of 100–200 °C and 30–150 min, respectively, and they are related to the solvent adopted.[196] Moreover, acid co-catalysts (*e.g.* H_2SO_4, H_3PO_4, oxalic acid, …) or basic co-catalysts (*e.g.* NaOH, …) are often employed within organosolv processes to increase the rate of delignification or hemicellulose dissolution, and reduce the treatment duration or the operating temperature.[194–197] The use of an acid co-catalyst can also enhance the depolymerization of cellulose. However, the formation of inhibitors of fermentative microorganisms (*e.g.* furfural, 5-hydroxymethylfurfural, organic acids, phenols, …) is favored under acid-catalyzed conditions, implying that a tradeoff should be found between lignocellulose deconstruction and the formation of degradation products.[82,195,197]

During organosolv pretreatment, LCCs are ruptured by the action of the organic solvent, contributing to the solubilization of large lignin fragments. Such lignin oligomers are further broken down by cleavage of β-O-4′ inter-unit bonds, following acid- or base-catalyzed reactions (Fig. 7 and 9).[209] Repolymerization reactions between lignin moieties occur as well, and both the extent of the cleavage of ether linkages, and that of lignin recondensation increase with the process severity.[196] In the presence of aliphatic alcohols solvents, lignin etherification may take place *via* nucleophilic attack of solvent molecules at the α-carbon of β-aryl ether motifs leading to the formation of α-etherified lignin structures (Fig. 16).[17,199,210–214] The latter were shown to possess a considerably lower tendency to undergo condensation reactions and β-O-4′ bond cleavage as compared to benzylic carbenium ions or parent β-aryl ether motifs with α-hydroxyl groups.[118,199,211,215] Noteworthy, lignin etherification is a reversible reaction and native-like lignin structures may be obtained by subjecting etherified lignin to mildly acidic conditions. Lignin stabilization by aliphatic alcohols was reported to be an effective strategy for protecting lignin against repolymerization during pretreatment,[17,213,214,216] ultimately opening the way to the successful downstream conversion of lignin to chemicals.[118,211,213,215–218]

A great advantage offered by organosolv pretreatment compared to other fractionation methods is the possibility of producing three separate product streams: a cellulose-enriched pulp, an aqueous fraction enriched with hemicellulose derivatives (*e.g.* sugars, alkylated sugars, furans, organic acids, …) and an organic fraction enriched with lignin derivatives (polyphenols), as illustrated in Fig. 17.[39,194–198] This feature enables the valorization of all lignocellulose constituents, provided that no excessive degradation takes place during the pretreatment.

On the other hand, the high cost of organic solvents imposes a downstream recovery step. Moreover, when organosolv fractionation is used as a pretreatment for further enzymatic/fermentative conversion of the pulps, organic solvents should be completely removed from the pulp by extensive washing, otherwise they would cause inhibition of the subsequent saccharification and fermentation steps.[39,195,197] Clearly, this leads to the need of additional unit operations, and, therefore, additional costs. From this point of view, the selection of the solvent has a crucial impact on the economics of the organosolv process. The use of low-boiling solvents, such as methanol or ethanol, results in high operating pressures, and strict requirements for the reactor design, but allows a facile solvent recovery by distillation.[194–198] Conversely, the adoption of high-boiling solvents, such as ethylene glycol or glycerol, entails

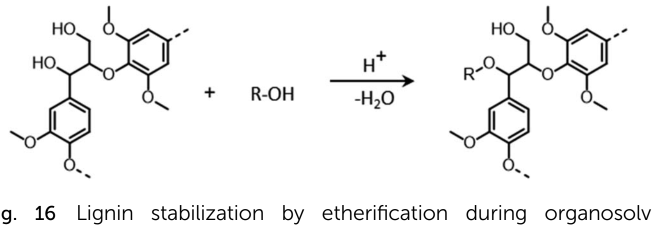


Fig. 16 Lignin stabilization by etherification during organosolv pretreatment in the presence of aliphatic alcohols.

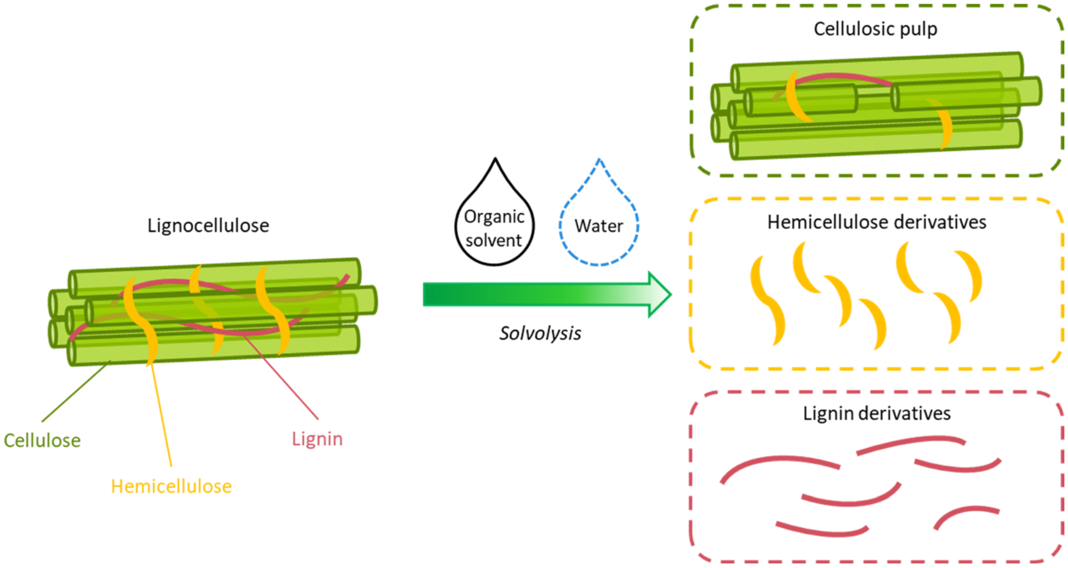


Fig. 17 Schematic outline of the organosolv process for the solvolytic extraction of lignin (and hemicellulose) derivatives from lignocellulosic biomass. Note: the isolation of the product streams enclosed in colored boxes on the right-hand side of the figure can be achieved only after a series of downstream operations. These may include a filtration step to isolate the solid pulp from the liquid extract, followed by precipitation of lignin derivatives from the liquid fraction, before further filtration to separate insoluble lignin derivatives from soluble hemicellulose derivatives, and concentration/purification of hemicellulose and lignin streams.

low operating pressure and less stringent reactor requirements, but also more energy-intensive solvent recovery by distillation.[198] In addition, for the solvent selection, the possible formation of azeotropes should also be taken into account (*e.g.* ethanol–water, *n*-butanol–water, tetrahydrofuran–water…), as it could complicate the recovery of the solvent by distillation.[198] Other aspects that are to be taken into account for the choice of a suitable organic solvent include its flammability, toxicity and sustainability.[196] Table 2 summarizes important features of some solvents commonly adopted in organosolv processes. Overall, ethanol is among the preferred solvents for organosolv pretreatment, since it possesses a high ability to solubilize lignin (δ = 26.5 MPa$^{1/2}$), a low toxicity, and can be produced from fermentation of the hydrolyzed pulp, creating an integrated biorefinery process.[219] Another alluring option is the adoption of biphasic solvent mixtures (*e.g.* *n*-butanol and water), which have been reported to facilitate the downstream products separation.[198,212,220–222]

Organosolv pretreatment has attracted a lot of attention in the recent years and, currently, different processes have been scaled-up to the pilot or industrial scale (*e.g.* organocell process, lignol process, CIMV process).[39,127,195,197] Nevertheless, the

Table 2 Physical properties and green solvent rating for organic solvents typically employed for organosolv fractionation. Based on Wei Kit Chin *et al.*[196] and Prat *et al.*[223]

Organic solvent	Boiling point (°C)	Flash point (°C)	δ^a (MPa$^{1/2}$)	Green solvent rating[b] Safety score[c]	Health score[d]	Environment score[e]	Ranking[f]
Methanol	65	12	29.6	4	7	5	P
Ethanol	78	13	26.5	4	3	3	R
Propanol	97	24	24.6	4	3	3	R
n-Butanol	118	35	23.2	3	4	3	R
Ethylene glycol	197	111	32.9	1	2	5	R
Acetone	56	−17	20.0	5	3	5	P
MIBK[g]	117	18	17.0	4	2	3	R
Acetic acid	118	44	21.4	3	7	3	P

[a] Hildebrand solubility parameter. [b] From 1 (greenest) to 10 (least green). [c] The safety score is determined based on the flash point temperature of the solvent.[223] [d] The health score reflects the occupational hazard. It is established based on the hazard statements in the Globally Harmonized System of Classification and Labelling of Chemicals.[223] [e] The environment score takes into account the toxicity toward aquatic life, bioaccumulation, the tendency to form volatile organic compounds, and the carbon footprint of the synthesis, recycling, and disposal of the solvent.[223] [f] The overall ranking is established based on the criteria: (i) a solvent is classified as hazardous (H) if one of the scores is greater than or equal to 8, or if two of the scores are greater than or equal to 7; (ii) a solvent is classified as problematic (P) if one of the scores is equal to 7, or if two of the scores are comprised between 3 and 7; (iii) in all other cases the solvent is classified as recommended (R).[223] [g] Methyl isobutyl ketone.

effective conversion of the lignin fraction into valuable products still represents a challenge. Organosolv lignin possesses a higher purity compared to lignin streams obtained from other fractionation methods (*i.e.* less contamination by carbohydrate residues or chemical additives), and a more native-like structure (*i.e.* lower degree of condensation).[11,15] These features pave the way for the upgrading of the lignin isolated from organosolv pretreatment toward aromatic chemicals. The future success of industrial scale organosolv pretreatments depends on the development of processes that allow upgrading each isolated fraction into marketable end-products.[195] Ideally operated at low pressure and with inexpensive, recoverable, green solvents, these processes must combine an effective lignin (and hemicellulose) extraction and the preservation of a digestible cellulose fraction.[207,224,225]

3.3.7. Ionic liquid pretreatment. Ionic liquids (IL)s are salts that are liquid at temperatures below 100 °C.[39,68,69,82,176,226] Typically, they are formed by large organic cations, such as quaternary aliphatic and aromatic ammonium ions, alkylated phosphonium ions, or alkylated sulfonium ions, and small (in)organic polyatomic anions, with the negative charge distributed over multiple atoms.[226–228] Despite being often derived from non-renewable sources, ILs possess several beneficial properties, such as low toxicity, high stability, and low vapor pressure, which make them recoverable and reusable in a number of unit operations.[176]

The use of ILs for the pretreatment of lignocellulosic biomass has become a popular strategy, since these solvents possess excellent performance with respect to the solubilization of biomass components at low severity conditions, with operating temperatures typically in the range of 90–130 °C, and durations of 1–24 hours.[82,176] More specifically, ILs can dissolve cellulose, hemicellulose and lignin, and their selectivity with respect to the dissolution of different biomass components can be tuned by modifying the cation and the anion.[226–228]

Cellulose solubility depends strongly on the nature of the anion, since the cellulose dissolving power of ILs is related to the capacity of their anions to form hydrogen bonds with hydroxyl groups in the cellulose structure.[82,226,228] In addition to the anion, the choice of the cation affects cellulose solubility, which decreases with the lengthening of alkyl chains in the cation.[229,230] The use of protic cations dramatically reduces cellulose solubility, due to increased interactions between cations and the anions that limit the hydrogen bonding capacity of the latter.[230]

The solubility of hemicellulose and lignin is also predominantly dependent on the type of anion used, involved in the cleavage of LCCs and inter-unit bonds (glycosidic bonds in hemicellulose and ether bonds in lignin).[226,228] During IL pretreatment, the solubilized lignin fragments undergo depolymerization and recondensation reactions, following pathways analogous to those previously discussed for LHW and acid pretreatment, with the initial formation of benzylic carbenium ions that react with the anions of the IL to generate enol ether structures, ultimately leading to the production of Hibbert's ketones (dominant pathway in the presence of strongly coordinating anions) or C_2-aldehyde-substituted phenolics (dominant pathway in the presence of weakly coordinating anions), which can then undergo further recondensation.[231,232]

Two main strategies have been developed based on the use of ionic solvents for lignocellulose pretreatment: (i) a dissolution approach aimed at dissolving the totality of lignocellulose in the ionic liquid for the subsequent recovery of the isolated fractions, and (ii) an ionosolv approach targeting the solubilization of lignin (and hemicellulose in some cases) to leave behind a cellulosic pulp.[226] In the dissolution approach, after pretreatment, the different biomass fractions are recovered with a two-stage process. Firstly, (hemi)cellulose is precipitated by addition of an antisolvent, usually an organic solvent or a mixture of an organic solvent and water. Subsequently, lignin can be precipitated in acidified water.[233–235] Conversely, in the ionosolv approach, lignin is directly precipitated after pretreatment by addition of water, while hemicellulose derivatives can be removed from the IL by solvent extraction.[236–238]

The properties of the recovered fractions are greatly modified after IL pretreatment. In the dissolution approach, the regenerated cellulose possesses a considerably lower crystallinity compared to the initial biopolymer, which results in a fast enzymatic conversion in the subsequent saccharification step.[228,233,235] On the contrary, in the ionosolv approach cellulose crystallinity remains mostly unaltered after pretreatment.[226] Hemicellulose is usually partially hydrolyzed by ILs, and is recovered in the form of oligo- and monosaccharides.[226,237] Degradation products such as furans are also formed due to the occurrence of dehydration reactions. The lignin fraction recovered after IL pretreatment possesses a lower content of inter-unit ether bonds and is partly condensed.[239,240] Additionally, condensation reactions between the lignin and the IL may occur, at an extent that increases with the operating temperature.[239,240] Overall, the IL lignin fractions possess similar features to organosolv lignin streams and are regarded as a promising substrate for further upgrading toward aromatic chemicals.[171,241]

Despite the advantages offered by ILs in terms of the selective solubilization and deconstruction of biomass, few bottlenecks exist for the development of IL-based biorefineries. First, ILs are expensive solvents, hence their effective recovery is imperative for the economic viability of the pretreatment.[176,226,228,237] While different strategies have been explored for the recovery and recycling of ILs, including liquid–liquid separation and distillation, the presence of residual biomass components (*e.g.* sugars, minerals, extractives, …) in the recovered ILs reduces their performance upon reuse.[226] Moreover, most ILs cause inactivation of saccharification enzymes and are toxic to fermentative microorganisms. Thus, a complete removal of ILs from the recovered pulp is required before further conversion, resulting in the need of extensive washing, and additional processing costs.[82,176,228]

3.3.8. Deep eutectic solvent pretreatment. Deep eutectic solvents (DES)s are a relatively new class of solvents that has increasingly attracted the interest of the scientific community since the beginning of the 2000s.[242–245] DESs are prepared by combination of hydrogen bond acceptors, such as quaternary ammonium salts, and hydrogen bond donors, such as amides, carboxylic acids or alcohols, to form an eutectic mixture, with a melting point lower than the individual components.[242–245]

Similarly to ILs, DESs are extremely versatile and their properties can be tuned by changing the hydrogen bond acceptor or donor.[242] In view of their ability of selectively dissolving biomass components, DESs have been recently explored as solvents for the pretreatment of lignocellulose.[243–247] The disruption of the lignocellulose structure follows a mechanism that is analogous to that discussed for IL pretreatment (see above). Cellulose can be dissolved in DESs thanks to the formation of extensive hydrogen bonding between the hydrogen bond acceptor of the DES and the hydroxyl groups in cellulose structure.[243,244,248] Additionally, LCCs can be cleaved during pretreatment with DESs, facilitating the solubilization of hemicellulose and lignin. Partial hydrolysis and degradation of hemicellulose may occur, depending on the properties of the DES.[243,248] Lignin undergoes depolymerization (mainly cleavage of inter-unit ether bonds) and repolymerization pathways similar to those described for the use of ILs.[246,249] Ultimately, the residual content of β-O-4′ linkages and the degree of condensation of the isolated lignin depend on the properties of the solvent and the operating temperature.[249–252]

DESs offers several advantages for the pretreatment of lignocellulosic biomass. First, in contrast to ILs, the components of DESs are inexpensive and readily available chemicals. For instance, one of the most adopted hydrogen bond acceptors, choline chloride, is a common additive used in animal feeds, and urea, a frequently adopted hydrogen bond donor, is used in fertilizers.[243,248] Second, DESs possess a much lower inhibitory effect toward cellulolytic enzymes and fermentative microorganisms, implying that the complete purification of the pulp from the solvent is not necessary after DES pretreatment.[247,248] One drawback of DESs is their high viscosity, which entails high pumping costs.[243] In addition, DESs recycling is challenging and the lack of effective methods represents a prominent limitation to the technoeconomic viability of DESs for biorefinery applications.[247,248,253,254] Nevertheless, these green solvents are considered promising candidates for the pretreatment of lignocellulose and for the subsequent valorization of the isolated lignin.[246,247,255,256]

3.4. Biological pretreatment methods

Biological pretreatments rely on the delignification of lignocellulosic biomass performed by microorganisms or enzymes.

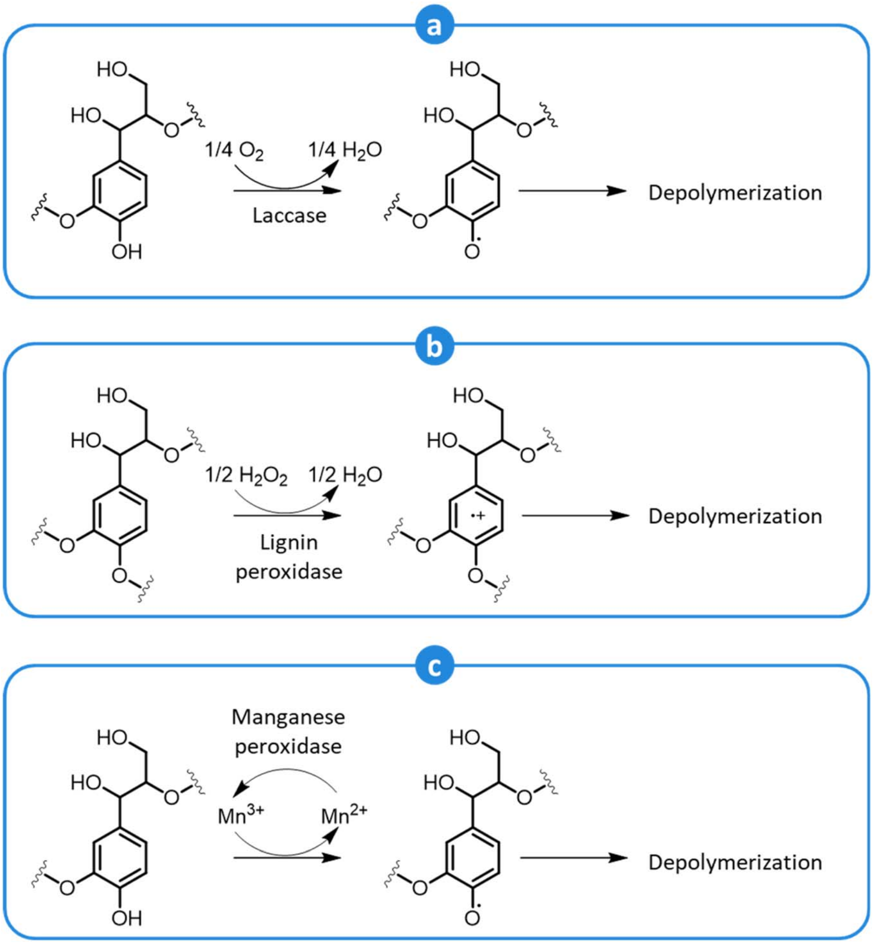


Fig. 18 Oxidative depolymerization of lignin by the action of laccase (a), lignin peroxidase (b), and manganese peroxidase (c). Adapted from Vasco-Correa *et al.*[257]

These methods are attractive since they have a low energy demand (they are carried out at ambient conditions), do not require expensive chemicals, are environmentally friendly, and do not lead to the formation of inhibitors of the subsequent saccharification and fermentation steps.[69,257–260]

Microbial decomposition of lignin can be carried out both using bacteria or fungi (principally, white-, brown-, and soft-rot fungi).[257–260] In general, white rot fungi are preferred, since they are particularly active in lignin degradation and they do not cause excessive decomposition of (hemi)cellulose.[257–260] During pretreatment, white rot fungi secrete a range of enzymes, such as laccases, lignin peroxidases, and manganese peroxidases, which contribute to depolymerize lignin by an oxidative action.[257,259] Laccases attack phenolic lignin units to form phenoxy radicals and, concomitantly, reduce oxygen to water (Fig. 18a). Due to their low redox potential, laccases cannot oxidize non-phenolic lignin units.[257,258] However, in the presence of a suitable low-MW mediator, such as syringaldehyde, acetosyringone, and other lignin-derived monophenolics, the oxidation of non-phenolic units can occur as well.[257] Lignin peroxidases possess a high redox potential and can directly attack both phenolic and non-phenolic units, generating cation radicals that can react further to cause the breakdown of C–C bonds, leading to side-chain cleavage or ring-opening reactions.[257,258] In this case, the final electron acceptor is hydrogen peroxide (Fig. 18b). Manganese peroxidases oxidize Mn^{2+} to Mn^{3+}, which forms a complex with a chelator, such as oxalate or malonate, and diffuses away from the enzyme to attack phenolic lignin units, forming phenoxy radicals (Fig. 18c).[257,258] In the presence of unsaturated lipids or thiols, their oxidation by manganese peroxidases can produce peroxyl radicals, which act as mediators in the oxidation of non-phenolic lignin units.[257] Along with these enzymes, others contribute to lignin oxidation, such as versatile peroxidases, dye-decolorizing peroxidases, and various accessory enzymes, including oxidases that produce hydrogen peroxide, and dehydrogenases that reduce lignin depolymerization derivatives, preventing their subsequent recondensation.[257,258]

Biological pretreatments lead to variable degrees of delignification, depending on the structural complexity of the feedstocks, on the bacterial or fungal strains employed, and process conditions, such as the operating temperature, the pH, the moisture content, the substrate particle size, the aeration conditions, and the incubation time.[258–260] Typically, the lignin recovered from biological pretreatments possesses a lower MW compared to native lignin, a decreased content of inter-unit ether linkages, and is partially condensed.[257,261] Noteworthy, the so-formed lignin fractions were recently reported to act as suitable electron donors for the redox cellulolytic enzymes such as lytic polysaccharide monooxygenases, paving the way for the exploration of synergies between oxidase enzymes for the simultaneous decomposition of lignin and polysaccharides.[262,263]

In spite of the inherent advantage of offering a low-severity strategy for lignocellulose pretreatment, biological methods suffer important shortcomings. The sterilization of biomass that is frequently required before microbial pretreatment to prevent outcompetition of lignolytic microbes by the indigenous microbes that are naturally present in the biomass, is an energy-intensive operation.[257,258] Moreover, the long incubation time needed for microbial growth (from few days to several weeks) is incompatible with industrial needs.[257–260] In addition, most microorganisms cannot use lignin as a carbon source and consume part of the (hemi)cellulose for their growth, leading to an undesirable loss of polysaccharides.[257–259] Such limitations can be overcome by the adoption of lignolytic enzymes for the pretreatment.[257] However, this approach requires a separate unit for the production of enzymes. Furthermore, lignolytic enzymes are typically produced in low amounts by lignin-degrading microbes and, even though they are extracellular, their recovery from the fermentation broth is challenging.[257] Overall, these drawbacks currently hamper the implementation of biological pretreatments at the industrial scale.

3.5. Comment

From the overview of pretreatments methods presented above, it appears that no simple method currently stands out as a "one-size-fits-all" solution, able to fully embrace the complexity of the task. Nevertheless, important progress is currently being made in the development of novel approaches to biomass processing. In this perspective, lignin depolymerization will probably play a major role, giving access to (industrially) useable lignin streams, but complementary methods will be needed for certain biomasses or for certain applications. In this context, the research community is rightfully focused on developing the knowledge that will allow scaling up the most effective pretreatment methods.

4. Valorization of the isolated lignin fractions

Lignocellulose pretreatments produce large amounts of lignin as a byproduct. While pulp and paper facilities generate about 50–70 million tons of lignin per year, lignin production from lignocellulose biorefineries is expected to reach nearly 225 million tons per year by 2030, in view of to their rapid diffusion.[264] Thus, the development of processes for the effective valorization of lignin is essential for improving the economic viability of second generation biorefineries.

Although in pulping processes the lignin fraction is often employed as an energy source, alternative conversion routes for lignin streams isolated from biomass pretreatment have been developed, thanks to which a range of lignin-derived products can be manufactured (Fig. 19), including materials (*e.g.* thermosets, thermoplastics, elastomers, …), fine chemicals (*e.g.* vanillin, eugenol, …), and bulk chemicals (*e.g.* benzene, toluene, xylene, phenol, …).[265–268] The choice of the most suitable valorization routes for lignin streams isolated from biomass pretreatment is primarily dependent on the features of lignin fractions (*e.g.* MW, degree of condensation, presence of contaminants, content of β-O-4′ linkages, …). Lignin streams possessing a high purity are suitable for high-value materials applications, such as the manufacture of carbon fibers or resins

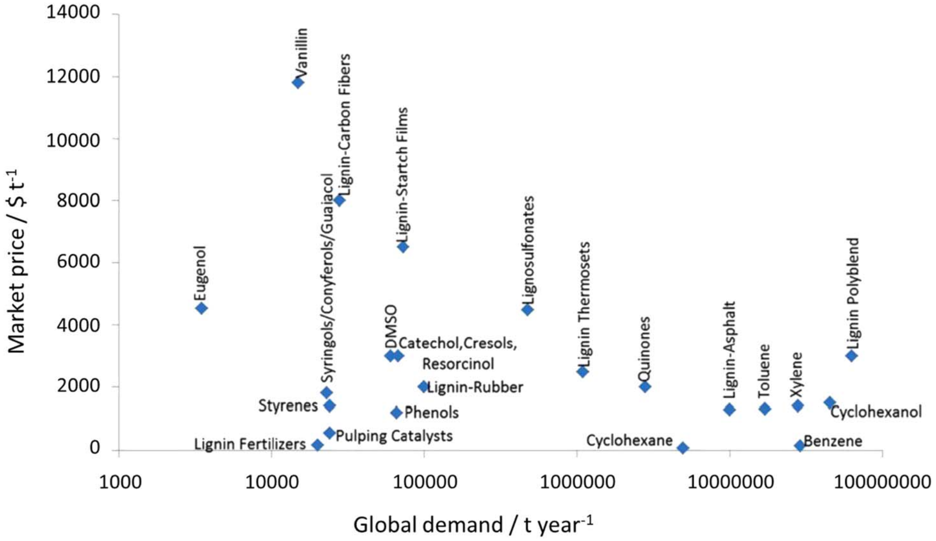


Fig. 19 Market price and global demand of some lignin products (price estimations are from 2006). Adapted from Gillet *et al.*[265]

(Fig. 20).[265,267,269] In addition, the residual presence of a high content of labile inter-unit ether linkages in the isolated lignin is convenient for its further conversion toward chemicals (Fig. 20).[16,265,267,270] On the other hand, highly condensed, contaminated lignin streams typically require extensive purification and harsher treatment conditions for their upgrading to chemicals and materials, which is why low-value applications, such as the production of syngas and power, are often preferred in this case (Fig. 20).[264,265,267]

The most alluring options for lignin valorization include the manufacturing of polymers and chemicals, as they entail a high economic potential, in terms of market price and size (Fig. 19). The production of polymers may represent a direct valorization route, in which the lignin streams isolated from lignocellulose pretreatment can be employed in the manufacturing process as they are, or after minor purification/chemical modification. Conversely, the production of chemicals involves an extensive depolymerization of lignin into monomeric products before commercialization of lignin derivatives or further upgrading toward selected chemicals.[264,266,271] An overview of the strategies adopted for the utilization of isolated lignin streams in polymer manufacturing and for their depolymerization into low-MW aromatics is presented in the following sections.

4.1. From lignin to polymeric materials

The use of lignin as a substitute for fossil-derived building blocks in the manufacture of polymers is a convenient way for reducing the environmental impact of these products, while improving material properties such as flame-retardant ability, UV- and thermo-oxidative resistance, and antimicrobial resistance.[269] In this context, the most widespread applications include the manufacturing of thermoplastic blends, phenol-formaldehyde resins, epoxy resins, polyurethanes, and carbon fibers.[269,271,274–277]

4.1.1. Thermoplastic blends. A polymer blend is a mixture of two or more polymers in which the components interact through interdiffusion, according to their mutual solubility. Weak interactions between the polymers in a blend result in a heterogeneous blend, with dispersed polymer particles and poor mechanical properties, whereas strong interactions produce a homogeneous blend with uniform morphology and enhanced mechanical properties.[278] The blending of lignin with thermoplastic polymers may yield both homogeneous and heterogeneous blends, depending on the compatibility between the lignin fraction and the other polymer(s) in the blend (Fig. 21).[275,279–281] From this point of view, the wide array of lignin streams available from biomass pretreatments offers many opportunities to manufacture lignin–polymer blends with superior performance.[275]

Lignin blends with polyolefins, such as polyethylene and polypropylene, have been studied with the goal of exploiting the radical scavenging ability of lignin to enhance the stability of polyolefins against UV radiation and thermal oxidation.[269,275] While a low lignin content in the blend can effectively stabilize polyolefins, the introduction of larger amounts of lignin results in a higher tensile modulus of the blends, due to the inherent stiffness of lignin molecules, but also in a lower strength and deformability, determined by the poor interactions between the components in the blend.[280] An important point to consider with respect to the manufacturing of blends with lignin is the compatibility of the different components in the blends. The presence of a large amount of hydroxyl groups in lignin structures imparts lignin with a polar character, which results in weak interactions with apolar polymers, such as polyolefins, and, typically, in the formation of heterogeneous blends with large dispersed particles.[279,281,282] A better compatibility can be expected for the blending of lignin with polymers containing aromatic rings (*e.g.* polystyrene, polyethylene terephthalate, …), by virtue of π-stacking interactions.[283] However, also in this case, a complete miscibility between lignin and aromatic polymers is seldomly achieved and the produced blends usually exhibit poor deformability.[275,282,283] A similar scenario is

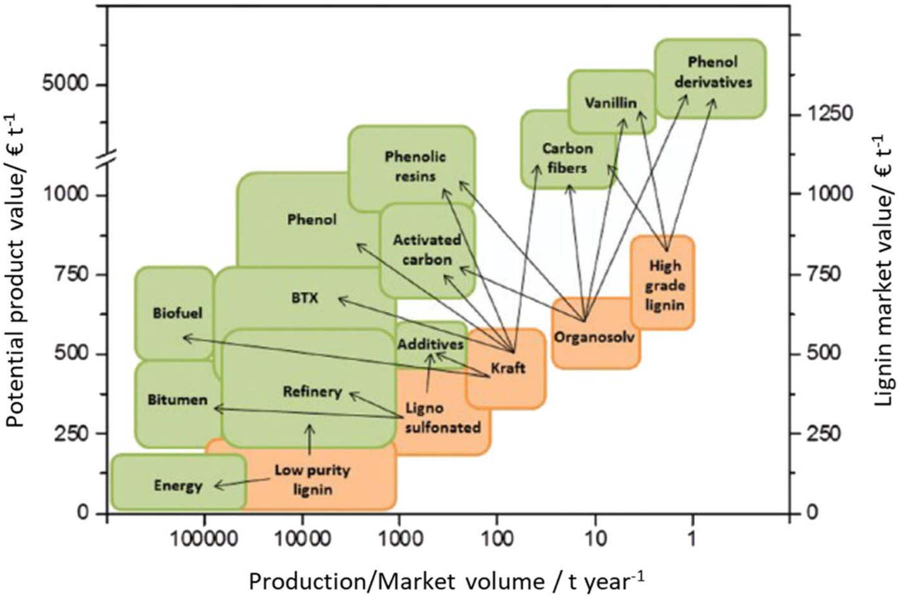


Fig. 20 Market value of isolated lignin streams (orange) and potential market value for lignin-based products (green) with respect to their production/market volume (price estimations are from 2011). Adapted from Behling *et al.*[272] Note: high-grade lignin indicates lignin fractions that were subjected to extensive purification after isolation using techniques such as liquid–liquid extraction, vacuum distillation, liquid chromatography, crystallization, *etc.*[273]

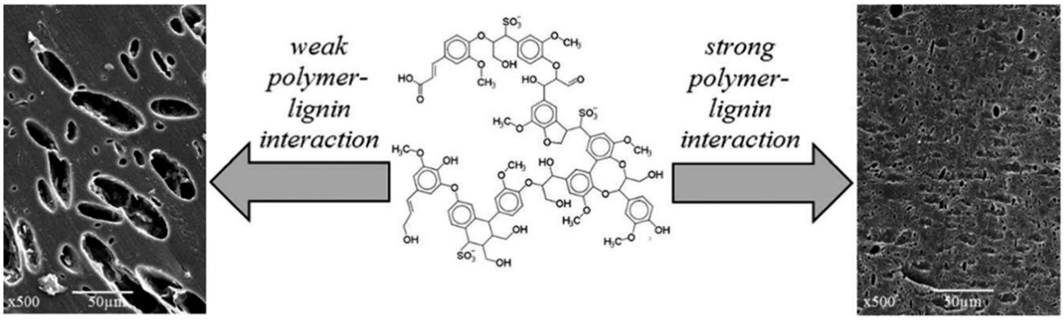


Fig. 21 Possible morphologies of lignin–polymer blends: heterogeneous blend with large dispersed particles (left) and homogeneous blend with no observable particles. Adapted from Kun *et al.*[275]

observed also for blends between lignin and more polar polymers, such as polyvinyl chloride, polyvinyl alcohol or polylactic acid, despite their ability to form hydrogen bonds.[275,282]

To improve the homogeneity (and the mechanical properties) of lignin–polymer blends different approaches have been developed. The introduction of a plasticizer in the blend is often adopted as a method to reduce lignin–lignin interactions, favoring the dispersion of lignin in the blend.[274,275,280] Additionally, chemical modification of the lignin (*e.g. via* esterification) can be used to reduce its polarity and increase its compatibility with apolar polymers.[275,280,281,284,285] Lignin depolymerization and/or fractionation can also be used to generate lignin fractions possessing a narrowed molecular-weight distribution and specific structural features that enhance compatibility.[279,286]

Another crucial challenge in the manufacture of thermoplastic blends with lignin is the high glass transition temperature of lignin streams.[274,280] While lignin exhibits a thermoplastic behavior at low temperature, at high temperature crosslinking reactions are initiated and lignin acts as a thermoset.[269,274] This transformation is observed already at temperatures close to the glass transition temperature of lignin, which makes thermal blending particularly complicated, as it leads to blends that possess an inherent brittleness.[269] However, the use of a plasticizer, or chemical modification/depolymerization of lignin are strategies that can be adopted also for lowering the glass transition temperature of lignin, thereby facilitating the blending process.[269] Overall, the manufacturing of thermoplastic polymer blends is regarded as a rather simple and inexpensive way of producing lignin-based materials for high added-value applications.[269,287]

4.1.2. Phenol-formaldehyde resins.

The global market of phenol-formaldehyde (PF) resins underwent a rapid expansion during the last decade, with an annual growth rate of over 5% in the period from 2013 to 2019.[288] Thanks to their excellent adhesive strength, superior mechanical properties and high thermal stability, these resins are adopted for a wide range of applications, including the fabrication of coatings, molding materials and wood adhesives.[271,288] Currently, the largest application of PF resins is as a wood adhesive for the manufacturing of plywood.[271]

Traditionally, PF resins are prepared by reacting phenol with formaldehyde. More specifically, formaldehyde reacts with the aromatic ring in the *ortho*- or *para*-position to yield hydroxymethyl groups, which subsequently condense to form methylene or ether bridges.[289] Upon curing of the resin, further crosslinking between residual free hydroxymethyl groups polymer chains occurs, and a rigid thermoset is obtained.[289]

Since the phenol employed for the fabrication of PF resins, is typically derived from fossil resources *via* the cumene hydroperoxide process, the use of lignin as an alternative to phenol represents an attractive opportunity to simultaneously decrease the price and increase the sustainability of PF resins.[288,290–292] Nevertheless, the poor solubility of lignin in common organic solvents complicates its incorporation in the polymers.[288,293] In addition, the reactivity of the isolated lignin fractions with formaldehyde is lower than that of phenol, due to the presence of methoxy groups in the *ortho*-positions of lignin units, and also due to the higher steric hindrance of large lignin molecules.[269,271,288,294] For these reasons, only part of the phenol can be replaced by lignin (usually less than 30%), and a higher reaction temperature as well as longer reaction times are often required to manufacture resins with satisfactory mechanical properties.[288,290,295] Moreover, the low reactivity of lignin with formaldehyde can constitute an issue since it may lead to the presence of residual formaldehyde after curing, and to the subsequent release of this toxic chemical.[292,296]

Several strategies have been developed to overcome these limitations and improve the reactivity of lignin fractions. Chemical modification of the raw lignin streams *via* hydroxymethylation, demethylation, or phenolation can be adopted to increase lignin reactivity with formaldehyde.[284,288,290,291,293,294,297–299] In addition, the partial depolymerization of lignin into low-MW aromatics is another way to increase the number of active sites available for crosslinking reactions.[288,290,300] Thanks to these modifications of the lignin structure, a higher degree of phenol replacement by lignin in PF resins is achieved (>50%) and the adhesive properties of the lignin-based resins are improved.[290,291,294,300]

4.1.3. Epoxy resins. Epoxy resins are among the most popular thermosetting polymers, with a current global market of about $30 billion, and an annual growth rate of nearly 7%.[301] In view of their superior properties, such as a high chemical and thermal resistance, strong adhesion, excellent electrical insulation (low dielectric constant), and good mechanical properties, epoxy resins are used in various applications, such as the fabrication of adhesives, coatings, and electrical insulators.[269,301,302]

Currently, about 80–90% of commercial epoxy resins are prepared by reacting bisphenol-A (BPA) with epichlorohydrin.[301] During the last three decades, the use of BPA for the fabrication of epoxy resins has raised increasing concerns, since BPA is a renowned endocrine disruptor, and leaching of this chemical from polymeric materials had been reported.[303] From this point of view, the adoption of lignin as a replacement for BPA in epoxy resins constitutes an attractive option for eliminating the risks related to the use of such harmful chemical, while concomitantly reducing the environmental impact of these polymeric products.[304–306] However, few downsides exist with respect to the use of isolated lignin fractions as a replacement for BPA. The low purity and the high content of minerals constitute a limitation to the use of kraft lignin, lignosulfonates, and soda lignin, imposing an initial purification step.[269,301,302,307] Moreover, the low solubility of lignin in both aqueous and organic media constitutes another limitation to the employment of lignin for the production of epoxy resins.[293,301,305] In addition, lignin possesses a lower reactivity compared to BPA, due to the typically high MW and the lower content of hydroxyl groups.[301,304] For these reasons, chemical modification (*e.g. via* hydroxyalkylation, demethylation, phenolation)[304,308,309] and partial depolymerization of isolated lignin streams are often adopted to increase lignin solubility and the content of reactive functional groups in lignin molecules.[269,284,293,301,310,311] Overall, lignin can be employed to replace over 50% of the BPA, to yield epoxy resins with electrical, mechanical, and thermal properties comparable to lignin-free polymers.[269,301,307,310–312] Most promisingly, the use of high-purity, low-MW lignin streams has been recently reported to allow for the full replacement of BPA in the production of bio-based epoxy resins.[307,313–317]

4.1.4. Polyurethanes. The global market for polyurethanes (PU)s was valued nearly $50 billion in 2014 and has undergone an annual growth rate of about 6% in the recent years.[318] The majority of the produced PUs are soft and rigid foams, the former being applied mainly for cushioning in automobiles and furniture, and the latter being employed for heat and sound insulation in construction materials. PUs are also employed as elastomers or as adhesives and coatings.[318,319] They are prepared by polyaddition of polyisocyanates with polyols, typically in the presence of a catalyst (*e.g.* diazobicyclo[2.2.2]octane, dimethylethanolamine).[318–320]

Driven by the increasing awareness of the impact of fossil-based materials on climate change, as well as by an escalation of the prices of fossil-based polyols, the use of lignin as a sustainable, inexpensive alternative has attracted conspicuous attention.[271,302,318,319] Isolated lignin fractions can be employed for the synthesis of PUs either directly or after chemical modification/fractionation.[321–323] The latter is aimed at increasing lignin solubility and reactivity with cyanate groups.[318,319,324,325] In particular, oxypropylation is commonly employed to extend the distance between hydroxyl groups in the lignin matrix and reduce steric hindrance effects.[284,319,324,326] Lignin depolymerization is also adopted prior to polymer synthesis to increase the number of reactive groups in lignin molecules.[318,319,327] When unmodified lignin is employed for PUs synthesis, it can replace only a limited fraction of the polyol (typically below 30%) without compromising the polymer performance.[271,318,328] On the contrary, the prior chemical modification of the lignin makes it possible to achieve a higher degree of incorporation of the biopolymer in PUs (>50%).[302,318,319,329] In general, the introduction of lignin in PUs results in polymers with increased rigidity (larger tensile modulus) and a higher thermal stability.[302,318,319] In addition, the use of lignin in PU foams advantageously reduces the polymer flammability, which is one of the major drawbacks of these polymeric materials.[319]

4.1.5. Carbon fibers. In view of a unique combination of properties, such as low density, high tensile modulus and strength, elevated fatigue resistance, high thermal stability, low thermal expansion coefficient, excellent chemical resistance, biocompatibility and superior electrical conductivity, carbon fibers are recognized as promising components for the fabrication of high-performance structural materials.[330–332] In 2013, the global market of carbon fibers was about $2 billion and, since then, it has expanded continuously with an annual growth rate of nearly 10%.[333] Carbon fibers are employed in various sectors, such as the marine, aircraft, and automotive industries, and the fabrication of sport equipment.[330,333] Notably, carbon fibers have attracted a lot of interest from the automotive industry, since these materials allows to achieve a major weight reduction of the vehicles, lowering fuel consumption.[334]

On the other hand, the high cost of carbon fibers considerably restricts the range of applications of these materials.[271,330,331,334,335] It is estimated that over 50% of the cost of carbon fibers is related to the production of their precursor, which is typically polyacrylonitrile, a fossil-based polymer made by condensation of acrylonitrile, methyl methacrylate and itaconic acid.[271,334] The adoption of lignin as an alternative precursor for carbon fibers is a promising solution to simultaneously reduce the cost and improve the sustainability of final products.[336–339]

The preparation of carbon fibers follows three main steps: a spinning of the precursor, a thermal stabilization step, and a carbonization step.[330–332,336] When lignin is adopted as a precursor, the properties of the isolated lignin fraction, such as the presence of contaminants and the degree of condensation have a substantial impact on the requirements for the manufacturing process as well as on the features of the final products.[271,330–332] The lignin feedstock has to be purified to remove minerals and sulfur, as well as to reduce the heterogeneity of the precursor prior to spinning.[271,337,338,340] Hardwood lignin possesses a less crosslinked structure and a lower glass transition temperature compared to softwood lignin, which makes the latter less suitable for spinning.[341] To enhance the spinnability of softwood lignin, the use of a plasticizer or chemical modification (*e.g.* acetylation) are usually adopted.[269,271,335,338] After spinning, the lignin fibers undergo a thermal stabilization during which crosslinking occurs and lignin glass transition temperature increases, as lignin gains a thermosetting behavior.[330,331] Thermal stabilization is performed at temperatures comprised between 200 and 300 °C, and a slow heating rate is typically applied to enhance the fibers stability.[269,330,331,336] In this step, the oxygen content of the lignin initially increases due to oxidation reactions, then decreases due to dehydration, condensation, and crosslinking reactions.[331] Subsequently, the stabilized lignin fibers are carbonized at high temperature (≥1000 °C) and under inert atmosphere to eliminate all elements other than carbon.[330,331] During carbonization a considerable weight loss occurs, due to the release of volatile components, which can also result in microstructural defects. A fast heating rate produces more stable and less brittle fibers.[331,337]

Lignin-based carbon fibers with tensile strength up to 1.07 GPa and modulus up to 82.7 GPa have been reported, which, however, do not reach the mechanical performance of synthetic carbon fibers (tensile strength ~7 GPa, and modulus ~900 GPa).[271,331] This is mainly due to a less ordered structure of the lignin-based fibers, ultimately ascribable to the nonuniform structure of the lignin precursor.[271,342] Thus, overcoming lignin heterogeneity still represents a critical challenge for the manufacturing of lignin-based carbon fibers with higher performance.[337,338]

4.2. Depolymerization of isolated lignin

The conversion of isolated lignin streams into chemicals encompasses an extensive depolymerization of lignin to produce monomeric intermediates that can subsequently be funneled toward target end-products. The goal of lignin depolymerization methods is to maximize the yield of phenolic monomers, which are obtained by the disruption of inter-unit linkages in lignin polymers. However, not all these linkages can be easily disrupted without causing extensive defunctionalization of lignin derivatives. As previously illustrated, ether bonds in lignin structures possess a lower dissociation energy and are more easily cleavable compared to C–C bonds.[11,15,55] For this reason, ether linkages are the primary target of lignin depolymerization methods. The maximum yield of monomers that can be achieved during lignin depolymerization is directly dependent on the amount of β-O-4′ bonds in the isolated lignin.[11,15,16] Mathematically, assuming an infinite linear structure for the lignin polymer, the maximum theoretical yield of monomers corresponds to the square of the fraction of cleavable linkages (β-O-4′ bonds) contained in the lignin polymer.[343] Several strategies have been developed for the depolymerization of isolated lignin streams, which can be divided into five main groups, based on the exploited cleavage mechanism: reductive, oxidative, acid- or base-catalyzed, solvolytic, and thermal depolymerization. The following sections provide an overview of these methods.

4.2.1. Reductive depolymerization. Reductive depolymerization approaches rely on a reducing agent and (commonly) a redox catalyst to achieve the hydrogenolysis of inter-unit ether linkages in lignin polymers.[344–351] Along with hydrogenolysis, hydrodeoxygenation (HDO) and hydrogenation reactions occur in reductive depolymerization processes.[152,349–351] On the other hand, the rupture of C–C bonds does not usually occur.[16,349–351] Both noble metals (*e.g.* Ru, Pd) and base metals (*e.g.* Ni, Cu) can be employed as catalysts within the reductive depolymerization of lignin, and the catalyst choice, together with the properties of the isolated lignin and the operating conditions of the depolymerization process, plays a major role with respect to the final yield of monomers and the selectivity toward different products.[346–351] The reducing agent employed in the process can either be hydrogen gas, or a hydrogen donating species, such as the solvent or lignin itself.[344,347,349–351] When hydrogen gas is employed, the process is termed hydroprocessing. Conversely, when the solvent or lignin act as a hydrogen source, the process is referred to as liquid-phase reforming.[14,351]

Hydroprocessing is further divided into three subcategories, according to the applied process conditions: mild, harsh, and bifunctional hydroprocessing (Fig. 22).[152,351] Mild hydroprocessing is performed at relatively low temperatures (≤300 °C), in the presence of a solvent (either water, an organic solvent, or a combination of the two). Methoxy groups in lignin units are preserved, and the obtained pool of monomeric products comprises mainly *p*-alkylated methoxyphenols, which are obtained with a high selectivity and a yield that is generally below 20% (Fig. 22).[152,351] Harsh hydroprocessing is conducted at higher temperatures (≥320 °C) and, most often, in the absence of a solvent. Extensive demethoxylation of lignin derivatives occurs, and a much broader distribution of monomeric products is obtained, comprising phenols, alkylated phenols, along with various amounts of mono- and polycyclic deoxygenated aromatics, alkanes, catechols, and methoxyphenols.[349–351] The yield of monomers is usually below 20%.[14,152,351] In bifunctional hydroprocessing an acid catalyst is introduced in the system, in such a way that hydrolysis and dehydration reactions occur, along with hydrogenolysis and hydrogenation reactions.[16,349–351] The operating temperature is usually below 320 °C.[152,351] Under these conditions, extensive HDO of lignin derivatives is achieved, with the selective formation of cycloalkanes.[351] Monomer yields of up to 50% toward C_6–C_{18} cycloalkanes (including both monomers and dimers) have been reported for these processes (Fig. 22).[14,152,351]

As opposed to hydroprocessing, liquid-phase reforming is performed under inert atmosphere, and in the presence of a hydrogen donor.[344,347–351] The operating temperature range spans from 150 °C to 400 °C.[349,351] Hydrogen donating solvents commonly employed in liquid-phase reforming include isopropanol, tetralin, formic acid, methanol, and ethanol.[344,347–351] The advantages of this method are a lower operating pressure (*i.e.* less stringent reactor requirements), and thus reduced safety concerns.[152] Notably, the utilization of hydrogen gas is usually still required for the subsequent reduction of the oxidized hydrogen donor.[152] A large pool of monomeric products is obtained from liquid-phase reforming, comprising alkyl-substituted phenols and methoxyphenols (possibly with

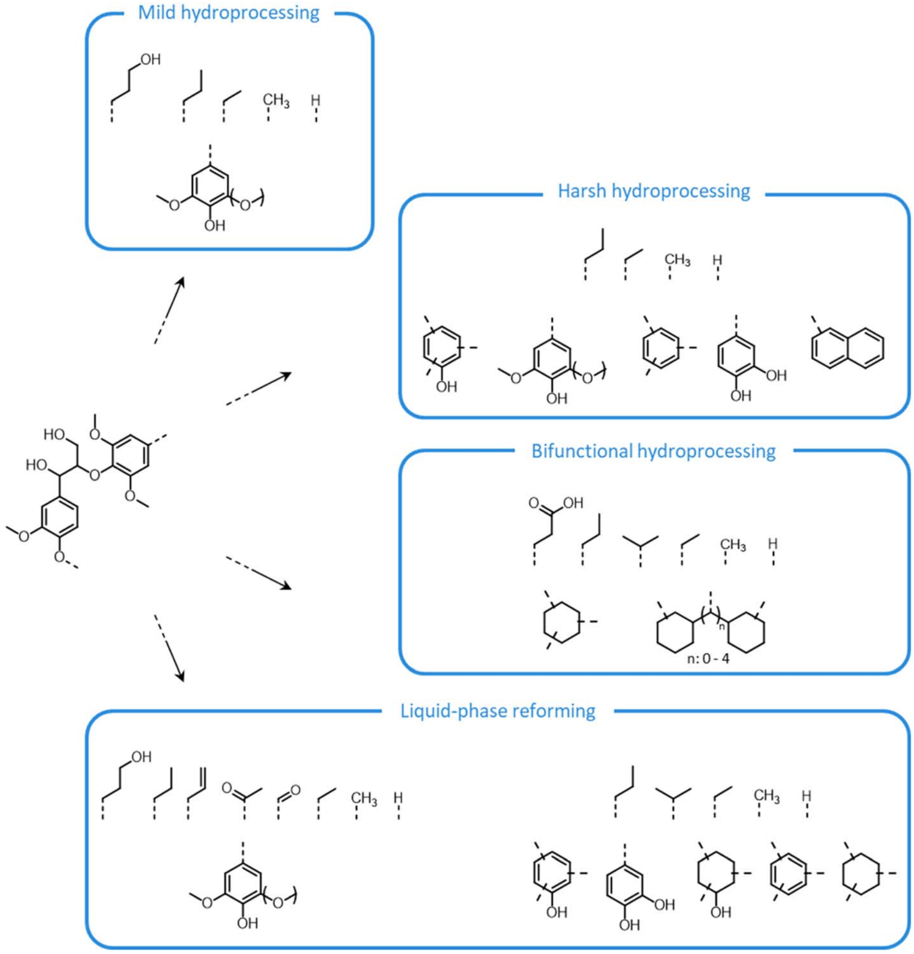


Fig. 22 Overview of phenolic monomers produced upon mild, harsh, and bifunctional hydroprocessing, and liquid-phase reforming of isolated lignin. Based on Schutyser *et al.*[14]

oxygenated side-chains), catechols, deoxygenated aromatics, and cycloalkanes (Fig. 22).[16,349–351] Monomer yields up to 30% are frequently reported for liquid-phase reforming processes.[14,351]

An additional subcategory of reductive depolymerization processes includes recently developed two-step methods for the breakdown of β-O-4′ linkages relying on an initial oxidation of lignin by conversion of the hydroxyl group at the α-position into a ketone, followed by a reductive cleavage of the ether bond.[191,352–355] The oxidation step reduces the dissociation energy of β-O-4′ bonds, facilitating their subsequent rupture.[191,352–355] One of the key advantages of these methods is that they allow achieving lignin depolymerization at ambient or near ambient conditions (without external pressurization, and at temperatures below 100 °C),[191,192,352–355] thereby reducing the energy and equipment requirements. Lignin oxidation can be performed using 2,2,6,6-tetramethylpiperidinyloxy (TEMPO),[352,355–357] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[353,356,358–360] electrocatalytic oxidation,[354,361] or a mild oxidative biomass pretreatment.[191,192] The reductive cleavage of oxidized lignin can then be conducted in the presence of different reducing agents, such as zinc,[353] photo-reductive iridium complexes,[354,355] or nucleophilic thiols.[191,192] A redox neutral process for the cleavage of oxidized lignin in the presence of formic acid and sodium formate has also been proposed.[352] The monomeric products produced with these depolymerization methods mainly include methoxyphenols possessing oxidized (hydroxy)alkyl side chains, typically obtained with a high selectivity, and a yield that can vary from ∼2% to over 60%, depending on the features of the isolated lignin fraction, and on the oxidation/depolymerization method applied (Fig. 23).[191,192,352–355]

Other methods rely on the etherification of the hydroxyl group at the α-position of β-O-4′ motifs, followed by the catalytic hydrogenolysis of β-O-4′ bonds.[362,363] The initial etherification reduces the dissociation energy of β-O-4′ linkages, thereby favoring their subsequent cleavage.[362,363] The use of an acidic environment in the presence of methanol was shown to promote the nucleophilic substitution of the α-hydroxyl groups in lignin β-aryl ether motifs by the alcohol molecules.[364] The so-formed α-methoxylated intermediates were reported to possess enhanced susceptibility toward catalytic hydrogenolysis, ultimately leading to higher yields of monophenolics possessing (hydroxy)alkyl side chains (Fig. 23).[362,363]

Alternatively, non-metal-based systems for the reductive depolymerization of lignin streams have been developed. For instance, silanes (*e.g.* Et_3SiH, polymethylhydrosiloxane, and tetramethyldisiloxane)[365–367] in combination with Lewis acids (*e.g.* $B(C_6F_5)_3$)[365] or bases (KO*t*-Bu)[367] were reported to act as effective reducing agents for the cleavage of inter-unit ether linkages in lignin structures, affording silylated monoaromatics, which could be subsequently purified and hydrolyzed to form phenolic products with yields up to about 25%.[366] The use of sodium or potassium dithionite as a reducing agent was also reported to enhance the depolymerization of pre-isolated lignin fractions.[368]

4.2.2. Oxidative depolymerization. Oxidative depolymerization strategies employ oxidants, such as oxygen, hydrogen peroxide, nitrobenzene, or metal oxides, to enable the cleavage of both ether and C–C bonds in lignin structures.[185,272,349,350,369–371] Alternative strategies based on electrocatalysis or photocatalysis have been developed as well.[372–377] The disruption of ether and C–C bonds in the side chains of lignin units results in the formation of phenolic compounds, whereas the cleavage of C–C bonds in aromatic rings produces aliphatic carboxylic acids.[349,350,369,370] A key feature of oxidative depolymerization is that oxidation products are polyfunctional monomers, such as aromatic aldehydes or carboxylic acids.[272,369,370] If, on the one hand, this increases the complexity of the product mixture, on the other, many of these monomers can serve as precursors of high-value chemicals.[272,370,371,378] Oxidative methods possess also the potential advantage of requiring relatively mild process conditions compared to other strategies.[272,371] However, controlling the yield and selectivity of

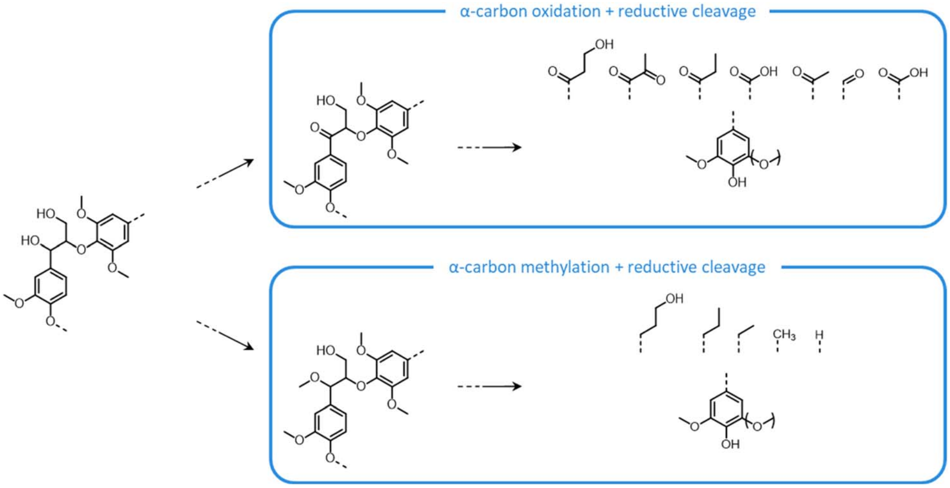


Fig. 23 Overview of phenolic monomers produced upon two-step reductive depolymerization of isolated lignin. Based on Schutyser *et al.*[14] and Sun *et al.*[16]

monomeric products during oxidative depolymerization can be difficult, and excessive oxidation toward gaseous products or repolymerization of radical intermediates frequently occurs.[185,272,370]

Oxidative depolymerization of lignin is most commonly performed in aqueous alkaline media (*e.g.* NaOH, KOH), but acids (*e.g.* acetic acid, H_2SO_4), and organic solvents (*e.g.* methanol) can also be applied.[349,350,369,370] Additionally, a large number of homogeneous and heterogeneous catalysts have been investigated to enhance the yield and selectivity of oxidative depolymerization methods.[185,272,349,350,369,370] The frequent selection of alkaline media for oxidative methods is related to the rapid formation of phenolate ions at high pH, which facilitates the subsequent oxidation to generate phenoxy radicals.[272,370] The latter is considered a pivotal step for the initiation of C–C bonds rupture.[14,152] In addition, a high pH slows down the degradation of the produced aromatic aldehydes.[14]

When the target products are phenolic monomers, the operating temperature is usually between 120 and 190 °C, and the oxidant is either oxygen or air (with a partial pressure of oxygen comprised between 2 and 14 bar).[272,369,370] The obtained monomeric products include aromatic aldehydes (vanillin, syringaldehyde, 4-hydroxybenzaldehyde), and their acetyl-substituted (acetovanillone, acetosyringone, 4-hydroxyacetophenone), and acid (vanillic acid, syringic acid, 4-hydroxybenzoic acid) analogs (Fig. 24).[272,370,371] The most renowned example of oxidative depolymerization of lignin toward monophenolics is the Borregaard process, which produces vanillin from sulfite liquor, and currently contributes to about 15% of the global supply of vanillin.[379,380]

While the final product distribution depends on the properties of the lignin fraction and on the conditions of the depolymerization process, these compounds are prone to undergo repolymerization reactions.[14,371] As a result, the yields of monophenolics for oxidative depolymerization processes are typically below 10%.[14,152]

An alternative strategy for the oxidative depolymerization of lignin relies on targeting the further conversion of the phenolic compounds initially obtained from lignin oxidation toward carboxylic acids, *via* the cleavage of aromatic rings.[371,381,382] This can be achieved by the adoption of prolonged reaction times, higher temperatures, or by the use of stronger oxidants (*e.g.* H_2O_2).[369,370,381,382] The process can be performed in neutral, acidic, or alkaline media, and the operating temperature is commonly in the range of 60–225 °C.[272,371] Under such conditions, the main products are organic acids such as, formic, acetic, succinic, oxalic, and malonic acid, with yields that vary between ∼10% and ∼60%, depending on the properties of the isolated lignin stream and on the applied process conditions (Fig. 24).[14,152]

4.2.3. Acid- or base-catalyzed depolymerization. Acids or bases are often applied as co-catalysts within the reductive or oxidative depolymerization of isolated lignin fractions, but they can also be employed in the absence of reducing or oxidizing agents. In this case, harsher operating conditions, such as higher temperatures or larger concentrations of acid or base catalysts are required to achieve an effective cleavage of the residual ether bonds in the lignin matrix.[344,347,350,383,384]

Acid-catalyzed lignin depolymerization is usually performed at temperatures in the range of 250–400 °C, and various types of acids can be employed in the process, including Lewis acids, Brønsted acids, zeolites, and ionic liquids.[350,383,384] The chemistry of acid-catalyzed cleavage of β-O-4′ linkages follows the pathways illustrated in Fig. 7, and the final monomeric products principally include methoxyphenols possessing side chains with alkyl, alkenyl, carbonyl, and carboxyl functionalities (Fig. 25).[344,350,384] Increasing the process temperature causes a gradual shift of the product selectivity toward catechols and

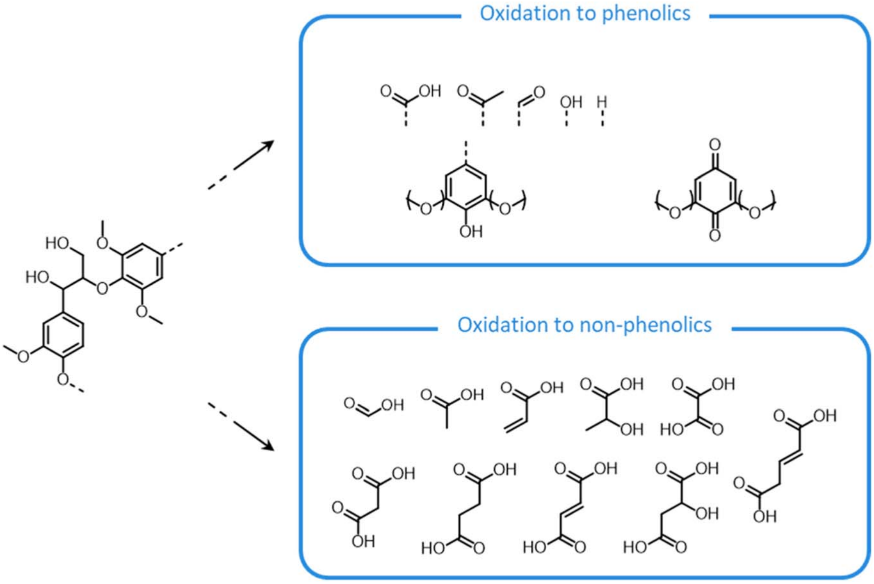


Fig. 24 Overview of phenolic monomers produced upon oxidative depolymerization of isolated lignin. Based on Schutyser *et al.*[14] Note: bonds other than β-O-4′ linkages are cleaved during oxidative depolymerization, including both C–O and C–C bonds.

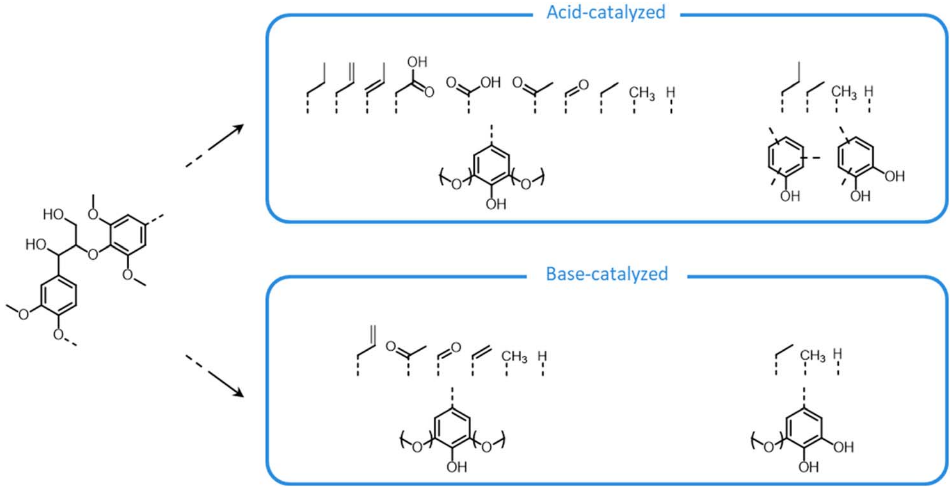


Fig. 25 Overview of phenolic monomers produced upon acid- and base-catalyzed depolymerization of isolated lignin. Based on Schutyser *et al.*[14]

alkylcatechols.[152,344,384] In general, the monomer yields obtained for acid-catalyzed depolymerization do not exceed 20%.[14,152]

Base-catalyzed lignin depolymerization is commonly performed at temperatures comprised between 240 and 330 °C, and in the presence of soluble or insoluble base catalysts.[350,383–385] Under alkaline conditions, the cleavage of β-O-4′ linkages follows the pathways illustrated in Fig. 9, and monophenolic products with functionalities analogous to those described for acid-catalyzed lignin depolymerization are obtained (Fig. 25).[350,384,385] Most frequently, the monomer yields achieved with base-catalyzed depolymerization are below 10%.[14,152]

An important limitation is the fact that the high temperature and the presence of acid and base catalysts do not only enhance the cleavage of inter-unit ether bonds, but also promote the repolymerization of the so-formed lignin moieties, which tend to recondense yielding insoluble products.[344,347,350,383–385] In order to partially overcome this issue, organic solvents can be adopted in the place of pure water to increase the solubility of lignin products, and, ultimately, improve the monomer yield.[14,152] Moreover, the introduction of redox catalysts in the reaction system is another way to quench the reactive lignin fragments and to improve the yield of low-MW products.[16,349] In addition, in the case of acid-catalyzed depolymerization, the yield of monophenolics may be enhanced through the stabilization of C_2-aldehyde-substituted phenolics, which otherwise possess a high tendency to undergo repolymerization.[118,152]

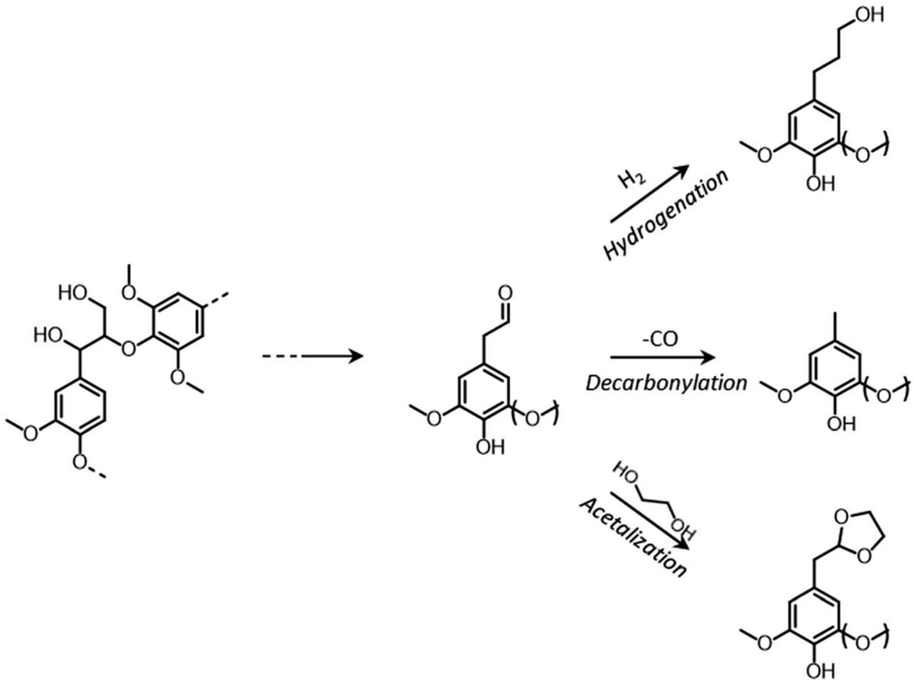


Fig. 26 Possible routes for the stabilization of C_2-aldehyde-substituted phenolics during acid-catalyzed depolymerization of isolated lignin.

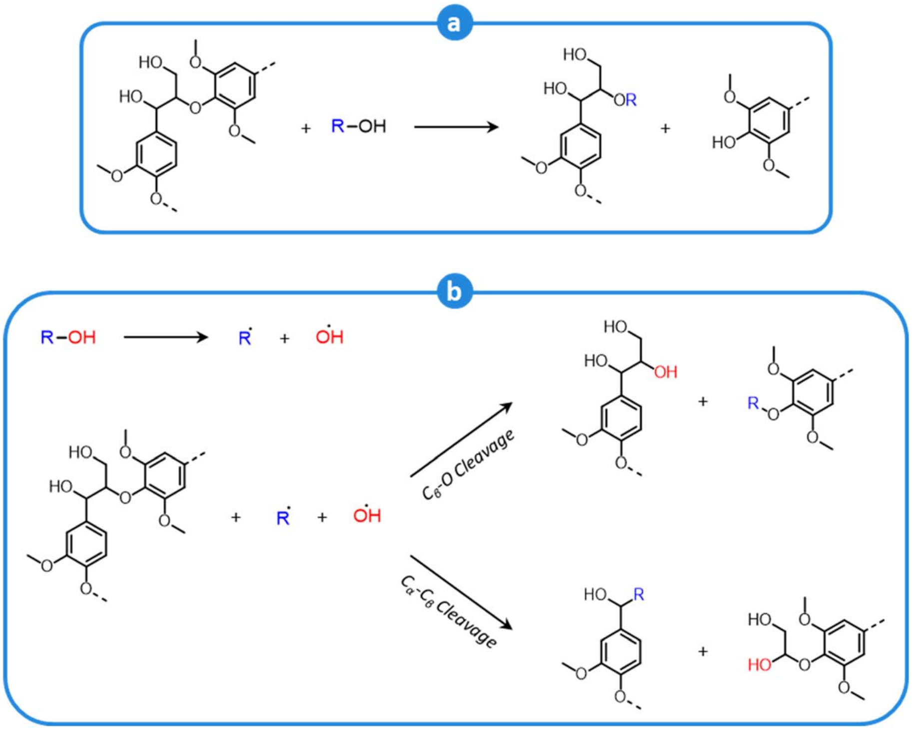


Fig. 27 Possible pathways for the non-radical- (a) and radical-mediated (b) cleavage of lignin inter-unit linkages during the solvolytic depolymerization of lignin in the presence of alcohols. Based on Jensen *et al.*[387]

Suitable routes for trapping these reactive intermediates include hydrogenation, decarbonylation, or reaction with glycols to form stable acetal structures (Fig. 26).[16,118] Recently, acid-catalyzed depolymerization was reported to be effective for the depolymerization of pre-oxidized lignin, leading to a monomer yield of up to about 30%.[386]

4.2.4. Solvolytic depolymerization. In the absence of reducing or oxidizing agents and acid or base catalyst, lignin depolymerization can be accomplished by solvolytic and thermal action.[270,347,348,383,384,387] In this case, the solvent applied can be either water, an organic solvent (often methanol or ethanol), or a mixture of the two.[270,347,383,384,387] The operating temperature of solvolytic depolymerization processes typically varies between 250 and 450 °C.[270,347,383,384,387] Under these conditions, β-O-4′ linkages in the isolated lignin fractions can be cleaved by solvolytic cleavage.[387] A polar organic solvent, such as methanol or ethanol, performs a nucleophilic attack on the carbon atom at the β-position, leading to the rupture of the β-O-4′ bond (Fig. 27a).[387] Alternative reaction pathways involving the formation of alkyl and hydroxyl radicals from the solvent have also been proposed to explain the cleavage of inter-unit linkages during solvolytic depolymerization. Here, hydroxyl radicals are supposed to attack the β-carbon, while alkyl radicals may attack either the oxygen, resulting in the cleavage of the ether bond, or the α-carbon, resulting in C–C bonds disruption (Fig. 27b).[387]

Overall, a broad spectrum of monomeric products is obtained from solvolytic depolymerization of lignin, mainly comprising unsubstituted methoxyphenols or methoxyphenols possessing saturated, unsaturated, or oxygenated side chains (Fig. 28).[383,384,387] Notably, processing at higher temperatures or in the presence of a larger fraction of water in the solvent results in a higher selectivity toward unsubstituted/alkylated methoxyphenols and catechols.[14] A limitation of solvolytic processes lies in the lack of stabilization routes for the reactive intermediates produced upon the disruption of inter-unit ether linkages in lignin, which ultimately restrain the yield of monomeric products.[348] Thus, the yields of phenolic monomers generally do not exceed 10%.[152,270]

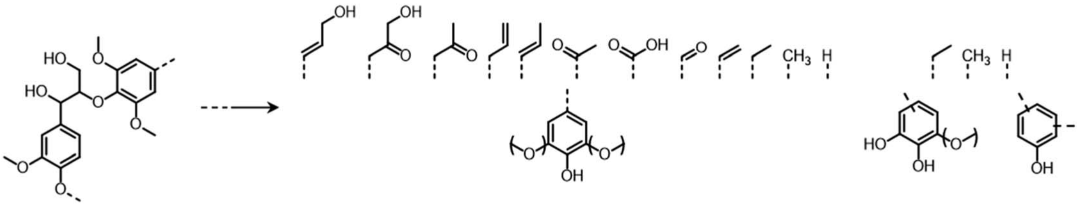


Fig. 28 Overview of phenolic monomers produced upon solvolytic depolymerization of isolated lignin. Based on Schutyser *et al.*[14]

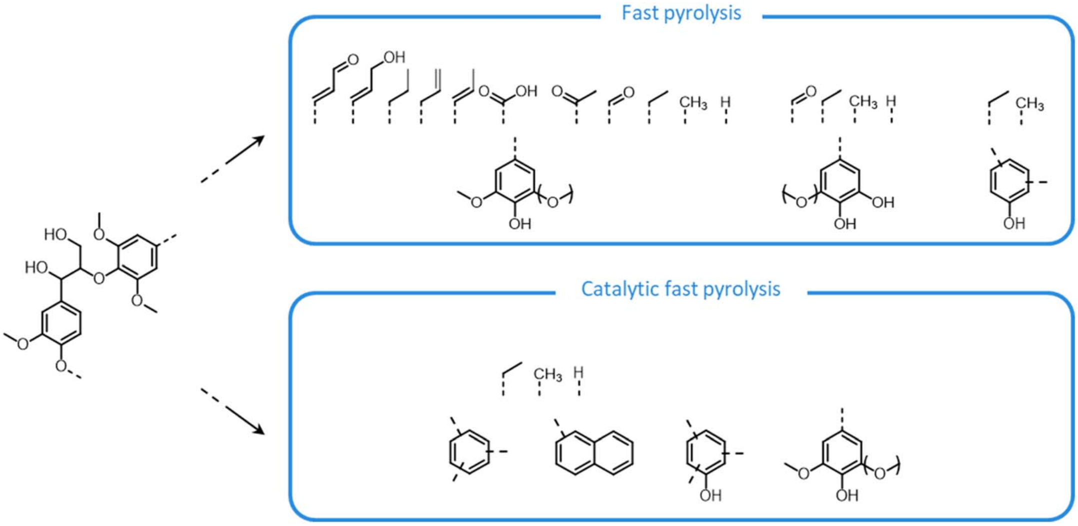


Fig. 29 Overview of phenolic monomers produced upon fast pyrolysis and catalytic fast pyrolysis of isolated lignin. Based on Schutyser *et al.*[14] Note: bonds other than β-O-4′ linkages are cleaved during pyrolysis, including both C–O and C–C bonds.

4.2.5. Thermal depolymerization. The routes for the thermal depolymerization of lignin include gasification and pyrolysis.[270,347,350,383,387–390] The former relies on the treatment of lignin at high temperature (>800 °C), in the presence of water or sub-stoichiometric oxygen.[270,347,387] Under such conditions, syngas is produced, which can subsequently be converted into liquid fuel through the Fischer–Tropsch synthesis or methanol-dimethyl ether synthesis.[270,350,387] Pyrolytic depolymerization is based on the heating of lignin at temperature usually comprised between 400 and 800 °C, under inert atmosphere.[270,345,347,350,383,387,390] The final products obtained from pyrolysis are a liquid bio-oil, comprising depolymerized lignin fragments, a solid biochar, possessing a high carbon content, and gaseous products (*e.g.* CO, H_2, …). Clearly, for the

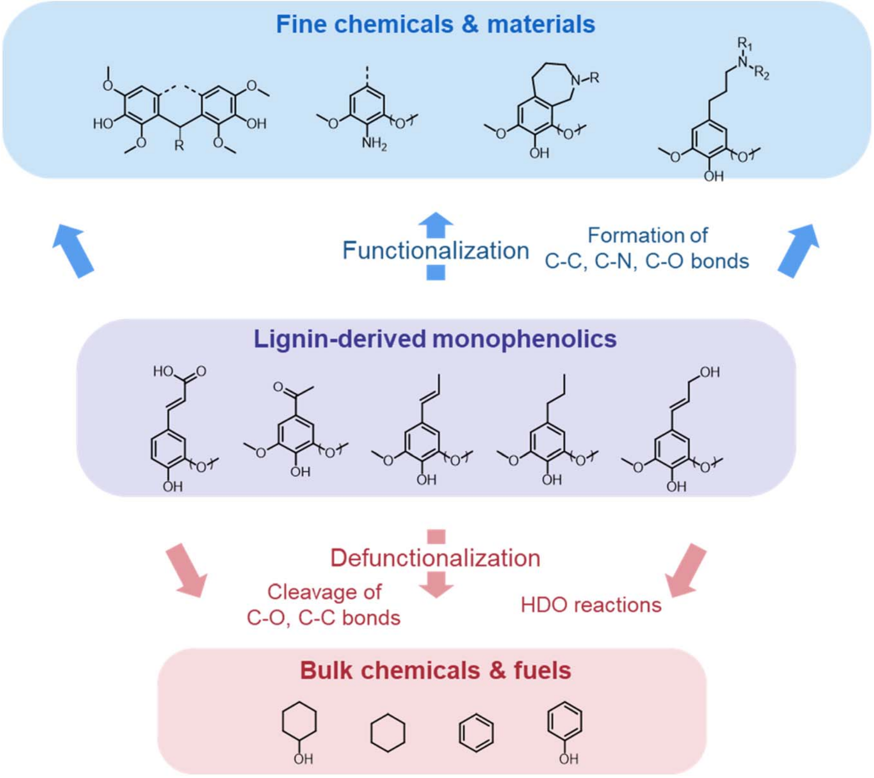


Fig. 30 Strategies for the conversion of lignin-derived monophenolics into fine and bulk chemicals.

depolymerization of lignin toward monomeric products, pyrolysis is preferred over gasification.[270,350,387]

During lignin pyrolysis, the treatment time and the operating temperature have a critical impact in steering the selectivity toward liquid, solid, or gaseous products. Slow pyrolysis, with a heating rate well below 100 °C h^{-1} and a duration greater than 30 minutes, favors the formation of gaseous products and biochar.[345,391] On the other hand, fast pyrolysis, with higher heating rates and durations in the order of seconds, promotes the formation of liquid bio-oil.[345,391] Within fast pyrolysis, a temperature comprised between 400 and 600 °C is commonly required to maximize the yield of bio-oil and low-MW phenolic products.[345,390,392,393] In view of this, fast pyrolysis represents the main thermal approach for the depolymerization of lignin into monomers.

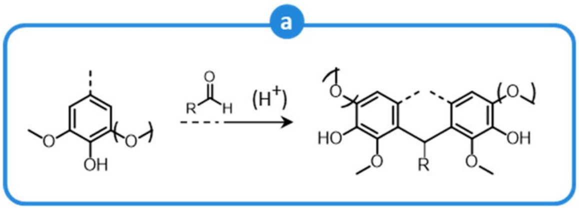


Fig. 31 Formation of bisphenols (a) and aniline derivatives (b) from lignin monomers. The structure of the R-group in aniline derivatives is dependent on the synthesis conditions.

Several chemical reactions, typically involving the formation of free radical species,[350,394] take place over the broad temperature range of pyrolytic depolymerization processes.[395,396] Below 400 °C, the cleavage of labile inter-unit ether bonds occurs, while C–C bonds and methoxy substituents on aromatic rings are stable.[350,383,390] As the temperature increases above 400 °C, C–C linkages are broken, and methoxy, hydroxyl and methyl substituents on aromatic rings are cleaved.[350,383,390] At the same time, the higher temperature boosts lignin recondensation and the formation of biochar and polycyclic aromatic hydrocarbons.[383] Finally, at temperatures greater than 550 °C, aromatic rings are broken down and an increasingly larger amount of gaseous products is obtained.[350,383,390]

Due to the complex network of reactions occurring during fast pyrolysis, a broad pool of monomeric products is generally obtained, comprising unsubstituted and substituted (methoxy)phenols and catechols, possessing unsaturated, saturated, or oxygenated side chains (Fig. 29).[350,383,392,397] Overall, as a result of the extensive recondensation of the unstable lignin moieties formed during the depolymerization process, the monomer yield from fast pyrolysis of lignin does not exceed 10%.[14,152]

Fast pyrolysis can also be performed in the presence of a catalyst, which improves the stability of the produced monomeric species, reducing excessive repolymerization and biochar formation, and increasing the selectivity toward target products.[270,350,383] Most frequently, acid zeolites (*e.g.* H-ZSM-5) are employed, and tuning the acidity and the pore size of the zeolites can drastically enhance the selectivity toward deoxygenated aromatics (*e.g.* benzene, toluene, xylene) (Fig. 29).[270,350,383,398] Namely, a higher density of acid sites boosts

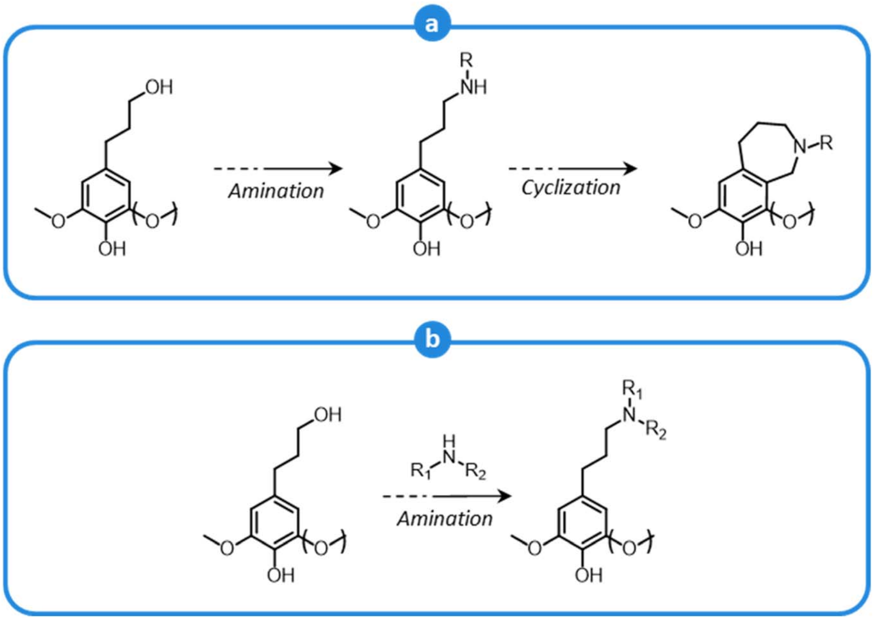


Fig. 32 Formation of benzazepines (a) *via* amination and subsequent cyclization of lignin monomers and (b) formation of tertiary amines from lignin monomers, as examples of upgrading toward effective antioxidants.

deoxygenation reactions, while a small pore size may limit the access of methoxyphenols to the active catalytic sites.[152,350,397] Along with acid zeolites, other catalysts such as mesoporous silica, metal oxides, and supported metals have been explored within catalytic fast pyrolysis.[350,383,397,399] A common issue of these processes is the considerable catalyst deactivation that occurs due to the formation of char on the catalyst surface (coking), which imposes frequent catalyst regeneration.[350,383] In general, despite a higher selectivity, monomer yields from catalytic fast pyrolysis remain lower than 20%.[152]

4.3. Upgrading lignin monomers to chemicals

The phenolic monomers obtained after lignin depolymerization typically possess structures resembling native lignin units, with aromatic rings featuring methoxy and hydroxyl groups, as well as side chains comprising alkyl, alkenyl, carbonyl, carboxyl, or hydroxyl functionalities. Although such mixtures of monophenolics are substantially less complex than the native lignin polymer, further purification and/or chemical modification is required before they can be commercialized.[120,267,268] The series of transformations to which these monomers are subjected prior to being marketed are termed “upgrading”. Two distinct approaches exist for upgrading phenolic monomers: (i) functionalization strategies, which aim at introducing new chemical groups in lignin moieties to yield high-value fine chemicals and materials,[400,401] and (ii) defunctionalization strategies, which target the removal of functional groups from lignin derivatives to yield bulk chemicals and fuels (Fig. 30).[16,267,268]

Functionalization strategies are emerging approaches that rely on the conversion of aromatic or aliphatic hydroxyl groups in lignin monomers toward amines, or on the formation of new C–C or C–O bonds exploiting aromatic and side chain reactive functionalities.[268,402–404] Various value-added polymer building blocks can be obtained in this way, as precursors for epoxy resins, polyurethanes, and polyesters.[267,268,405] One example is the dimerization of lignin monomers to form bisphenols that can be employed as renewable alternatives to BPA. The acid-catalyzed hydroxyalkylation of stoichiometric amounts of monophenolics and formaldehyde is a suitable route for the synthesis of lignin-derived bisphenols (Fig. 31a).[313,316,406,407] In this context, the selective preservation of natural lignin functionalities in the building blocks (*e.g.* methoxy groups, side chains, …) may be exploited to improve the features of the bisphenols, as reported for bisguaiacols or bissyringols, which possess a substantially reduced endocrine disrupting activity compared to BPA, while their use in the synthesis of polyesters and epoxy resins gives materials possessing properties similar to their synthetic counterparts.[313,316,408] Another example of functionalization pathway is the amination of phenolic hydroxyl groups of lignin monomers to yield anilines (Figure 31b),[409,410] which are employed as building blocks for the synthesis of polyurethanes, as well as in the fabrication of dyes.[411]

Alternatively, the chemical functionalization of phenolic monomers can be directed toward the synthesis of high-value bioactive compounds, such as benzazepines, benzoxepines, carbazoles, and many others.[412–415] For instance, the amination of terminal hydroxyl groups in the alkyl side chains of methoxyphenols can be used to form aminoalkyl-substituted monomers, which, upon cyclization, yield benzazepine-like structures (Fig. 32a).[412,414] Recently, valuable tertiary amines with proven antioxidant properties have been obtained from series of lignin monomers, using an atom-efficient Cu-catalyzed “hydrogen

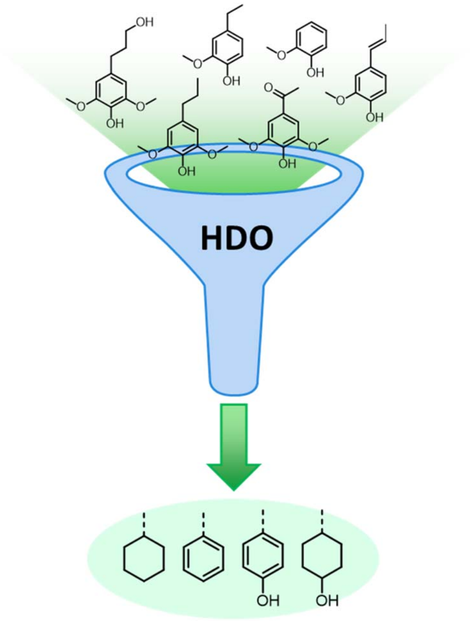


Fig. 33 Schematic representation of the chemocatalytic upgrading of lignin monomers *via* HDO reactions to yield substituted alkanes, aromatics, phenols and cyclohexanols.

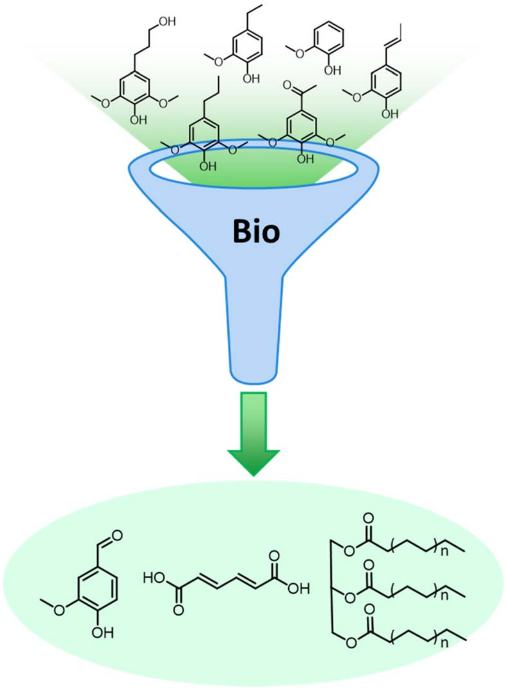


Fig. 34 Schematic representation of the biological upgrading of lignin monomers toward platform chemicals.

borrowing" strategy (Fig. 32b).[416,417] Although the market volume of these bioactive compounds and pharmaceuticals is smaller compared to that of bulk chemicals or commodity polymers, the value of such compounds is considerably higher.[413,414] Such approach may be a promising way to significantly improve the profitability of existing and future biorefineries.

However, a crucial limitation of such functionalization strategies lies in the need of isolating and purifying single components from the complex mixtures of monomers usually obtained upon lignin depolymerization. In particular, for processes characterized by a low product selectivity, the separation step(s) may be technically challenging, energy-intensive, and, ultimately, not economically viable. A defunctionalization approach may be preferable for funneling the heterogeneous mixture of monomers into a handful of drop-in platform chemicals, which can serve for a variety of applications (*e.g.* fuels, polymers manufacturing, solvents, …), thereby reducing the cost associated with downstream product isolation.[267,268] From this point of view, both chemocatalytic and biological pathways have been developed for the defunctionalization of lignin monomers.[267,405,418–421]

Among the possible routes for chemocatalytic upgrading of phenolic monomers, their defunctionalization through HDO reactions is particularly attractive for decreasing the complexity of the mixture of monomeric products, as well as the oxygen content of the produced molecules.[267,405,422,423] Depending on the applied process conditions, HDO of phenolic monomers can yield alkanes, aromatic hydrocarbons, phenols, or cyclohexanols (Fig. 33).[419,420,422,423] Lignin-derived alkanes (*e.g.* alkyl cyclohexane) can be produced from substituted methoxyphenols by the combined action of a redox catalyst (noble- or base metal) and an acid catalyst (homogeneous or heterogeneous).[405,422,423] The obtained mixture of alkanes may be directly exploited as fuel additives in midrange fuels.[16,152] Alternatively, aromatic hydrocarbons (*e.g.* alkylbenzene) can be produced when reaction conditions are tuned in such a way to prevent the hydrogenation of aromatic rings.[405,422] To achieve this goal, gas-phase reactions at high temperature, with a low hydrogen pressure, and in the presence of redox catalysts are often employed.[419,422,424] The preservation of phenolic hydroxyl groups can be achieved when the HDO conditions are adjusted to target the selective demethoxylation of lignin-derived monophenolics, yielding alkylphenols.[422,423] Further dealkylation of alkylbenzenes and alkylphenols yields benzene/phenol and short olefins (*e.g.* ethylene, propylene), which can be exploited as building blocks for the production of chemicals, fuels, or polymer precursors.[405,420] Finally, alkylated cyclohexanols can be obtained from lignin monomers *via* demethoxylation and aromatic ring hydrogenation.[405,422] Notably, alkylated cyclohexanols can be oxidized into the corresponding cyclohexanones, which may be further transformed into (alkylated) caprolactone, caprolactam, or adipic acid.[267,268,405,425] The latter are widely adopted polyester building blocks. In this context, as mentioned above, the presence of alkyl side chains may impart new properties to the polymeric materials, possibly resulting in an added value.[311,423,426]

As an alternative to chemocatalytic funneling, biological approaches have been investigated for the conversion of lignin monomers toward valuable platform chemicals.[418,427,428] These strategies rely on the exploitation of metabolic pathways that defunctionalize aromatic compounds to yield few central intermediates, which then undergo ring-opening and ultimately enter central carbon metabolism.[427–431] Microbial strains (*e.g. Pseudomonas putida*, *Rhodococcus opacus*, …) have been genetically engineered to convert lignin-derived monomers toward value-added chemicals, such as vanillin, muconic acid, triglycerides, and others (Fig. 34).[418,430] These chemicals can then be directly marketed or transformed into polymer precursors or fuels. Although promising, biological pathways require further research efforts to improve the concentration of final products in fermentation broths and the resistance of microbes and enzymes against toxic aromatic chemicals.[428,430]

5. Critical considerations about isolated lignin valorization

The sections above illustrate a plethora of routes that have been explored for the valorization of lignin streams isolated from

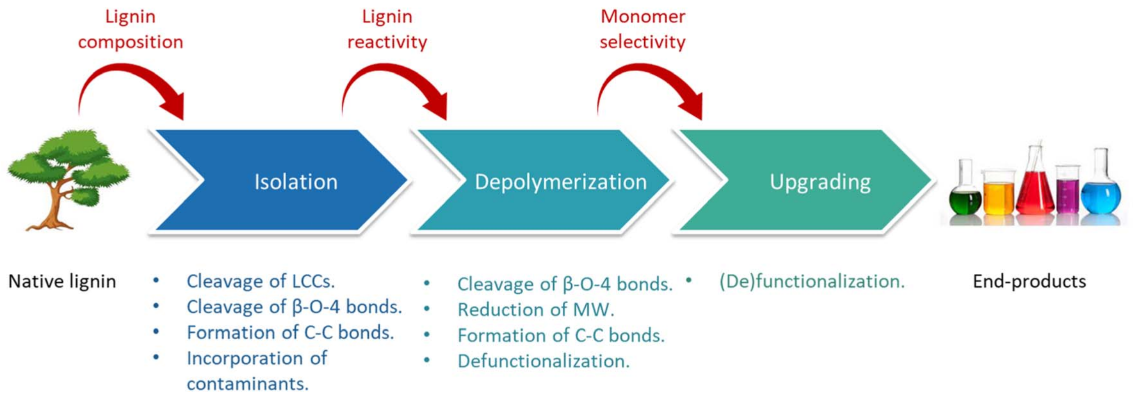


Fig. 35 Outline of the sequence of operations involved in the valorization of lignin to chemicals: lignin isolation, depolymerization and upgrading. The main structural modifications occurring in the lignin polymer and its derivatives during the different operations are reported below each block. The properties of lignin streams affecting subsequent steps are reported above the red arrows.

biomass after pretreatment. While the direct utilization of lignin fractions for the manufacturing of polymeric materials represents a relatively facile and alluring route for generating value from lignin, it has been shown that the implementation of lignin within the polymeric frameworks is typically hindered by the low reactivity and solubility of isolated lignin streams. The manufacturing of polymer blends possessing large contents of lignin (>∼30%) often requires a prior chemical modification or a partial depolymerization of the isolated lignin in order to attain mechanical properties comparable to those of synthetic materials.

An alternative strategy is to subject lignin to a depolymerization process, and to selectively upgrade the low-MW lignin derivatives toward target high-value products. This approach entails the potential of developing fully lignin-based chemicals, pharmaceuticals, and materials, exploiting the natural functionalities of lignin units. However, the low susceptibility of isolated lignin fractions toward depolymerization constitutes a significant limitation to the yield and selectivity of low-MW products, and, eventually, to the yield of (de)functionalized products after upgrading. In this respect, it is important to recognize that lignin isolation, depolymerization, and upgrading are consecutive processes, and each one of them affects the following steps (Fig. 35). Namely, biomass fractionation induces chemical modifications in the isolated lignin streams which may reduce the efficacy of lignin depolymerization (*e.g.* reduced content of β-O-4′ linkages, increased degree of condensation, presence of contaminants), resulting in a lower yield toward phenolic monomers and, ultimately, undermining the production of final end-products from lignin upgrading.

Overall, the yield of valuable lignin-derived products that can be obtained from biomass processing is influenced by the biomass source from which the lignin is extracted, by the fractionation method applied for lignin isolation, by the depolymerization method adopted, and by the effectiveness of the (de) functionalization strategy employed.

A crucial parameter correlated with lignin reactivity toward depolymerization is the content of labile β-O-4′ bonds in the lignin structure. The lower the content of β-O-4′ linkages, the less susceptible the isolated lignin is toward depolymerization.[11,15] In addition, the incorporation of impurities deriving from additives (*e.g.* sulfur), carbohydrates (*e.g.* pseudolignin), or minerals during biomass pretreatment may also increase lignin recalcitrance toward further depolymerization and upgrading.[11,12,15] Indeed, such impurities may cause deactivation of the catalysts that are typically employed in these processing steps.[11,12] From this point of view, the drawback of many of the methods adopted for biomass fractionation within biorefining and the pulping industry is that they are predominantly focused on the valorization of the carbohydrate fraction, while little attention is given to preventing excessive lignin degradation.[12,15]

The formation of valuable lignin products may be enhanced by following two leading principles during biomass pretreatment. The first one relies on minimizing lignin degradation reactions by preserving β-O-4′ linkages and preventing the incorporation of contaminants. This objective may be realized by adopting mild fractionation methods, with a low process severity and, ideally, not employing chemical agents that can irreversibly bind lignin derivatives hindering their subsequent processing.[14] Notably, a compromise should be established between biomass delignification, and the isolation of well-preserved lignin. The second principle is based on minimizing lignin recondensation reactions and in particular the formation of new C–C bonds. One way to achieve this goal is to adopt flow-through reactor configurations instead of a conventional batch configurations for biomass pretreatment, so that the reactive intermediates formed during fractionation are promptly removed from the heating zone, thereby reducing their tendency to undergo repolymerization.[14,17]

Importantly, these two principles can also be applied upstream of biomass fractionation, when biomass feedstocks are selected or designed on purpose for their subsequent conversion to chemicals and materials. Genetic modification of plants may be exploited to create lignin structures that are less networked, with larger contents of labile β-O-4′ linkages, and possessing a higher ratio of S-units, which are less prone to undergo recondensation due to the presence of methoxy groups in the *ortho*-positions.[432–436] In addition, labile ester bonds may be introduced in the lignin backbone to facilitate its fragmentation. A well-known example is the incorporation of ferulate linkages to create a so-called zip-lignin,[436–438] which can be more easily extracted and depolymerized during biomass pretreatment.[438] However, these alterations can typically be realized only up to a certain extent, since they also exert an impact on other key biological functions of the lignin polymer, such as imparting structural resistance to plant cells, ultimately hampering plant growth, and reducing biomass yields.[432,434–436,439] The improvement of the yield and selectivity of lignin derivatives from biomass processing also encompasses the design of the depolymerization step. In this context, the suppression of recondensation reactions that occur at the high temperatures typically applied for lignin depolymerization processes is a crucial objective.

Finally, developing strategies for upgrading lignin-derived monomers toward marketable fine or bulk chemicals and materials also entails expanding the market of lignin-derived products, finding applications which benefit of the unique functionalities of lignin derivatives that are not found in their fossil-derived counterparts.[152] The latter is certainly a decisive aspect for creating added-value from lignin and for drawing an increased attention on this subject from industrial players in the field of biomass processing.

Recognizing the interdependence of native lignin properties, lignin isolation conditions, depolymerization conditions, upgrading methods, and the yield and selectivity of end-products, naturally implies that a process aimed at valorizing lignin should take all these aspects into account since its initial design. In other words, biomass fractionation should be performed in such a way to produce a lignin stream that is suitable for the subsequent depolymerization. Similarly, the depolymerization process should be tuned to maximize the yield and selectivity toward target monomers in view of further upgrading.

Nevertheless, the conversion of lignin to products should not be carried out at the expense of the valorization of cellulose and hemicellulose. To achieve the fullest utilization of biomass potential, a holistic approach is required that considers the interplay of biomass components and their derivatives in each stage of the process. In this regard, biomass pretreatment represents a pivotal aspect of biomass valorization, being the first step of the processing sequence in which all biomass components are present and potentially subject to alteration. Driven by the need of alternative pretreatment approaches that could facilitate the upgrading of all biomass fractions, new biorefinery schemes termed "lignin-first" biorefineries have been recently developed, which aim at extracting lignin from biomass while preventing the occurrence of repolymerization reactions.[17,19] The next section discusses in detail these innovative methods.

6. Lignin-first biorefineries

Throughout the last few decades, a wide variety of biomass pretreatment methods have been developed with the main goal of delignifying lignocellulose to enhance the processability of the residual carbohydrate fraction toward materials (*e.g.* paper), or chemicals and fuels (*e.g.* bioethanol). More recently, the perspective of exploiting also the lignin fraction as a source of renewable aromatics directed an increased attention toward the effect of biomass pretreatment on the properties of the isolated lignin streams. In this context, the adoption of organosolv fractionation has been shown to effectively extract lignin from lignocellulose with minor chemical modifications compared to many other pretreatment methods (*e.g.* kraft, sulfite, hydrothermal, …), while producing a processable carbohydrate pulp.[14,15,39] Yet, the acidic conditions frequently applied within organosolv treatments cause a partial depletion of native ether bonds in lignin structures, leading to the formation of reactive intermediates that tend to recondense creating C–C linkages, and, ultimately, boosting lignin recalcitrance toward further depolymerization.[12,15,39]

With the goal to produce isolated lignin streams possessing an improved reactivity, a new class of so-called "lignin-first" processes has been developed. Lignin-first approaches are biomass fractionation methods that aim at (i) extracting a relatively pure lignin stream from lignocellulosic biomass in high yields, while concomitantly (ii) suppressing recondensation reactions between the lignin fragments liberated in the medium, ultimately yielding a lignin fraction (typically in the form of a lignin oil) that is either depolymerized or prone to undergo subsequent depolymerization, purification by fractionation, or upgrading. These methods typically rely on catalysis or protection-group chemistry to achieve the active stabilization of lignin derivatives.[19,440,441] The lignin-first concept was clearly defined in a recent review by Abu-Omar *et al.* as "an active stabilization approach that liberates lignin from the plant cell wall and prevents condensation reactions through either catalysis or protection-group chemistry".[19] Importantly, the stabilization strategies that characterize lignin-first processes are often suitable also for suppressing undesirable condensation of the released carbohydrate fragments toward humins.[18,441–443] Hence, lignin-first methods are integral approaches, designed for the valorization of both lignin and (hemi)cellulose, thus aiming at a more complete utilization of lignocellulose potential.[19,441]

Lignin-first processes commonly involve a solvolytic extraction of lignin, analogous to that occurring during organosolv processes, followed by a stabilization of the reactive lignin (and carbohydrate) intermediates and, finally, by the depolymerization of the isolated lignin fraction (when this is not achieved concomitantly with lignin stabilization).[19,441] The passivation of reactive lignin (and carbohydrate) moieties may be realized through physical protection, as in the case of flow-through

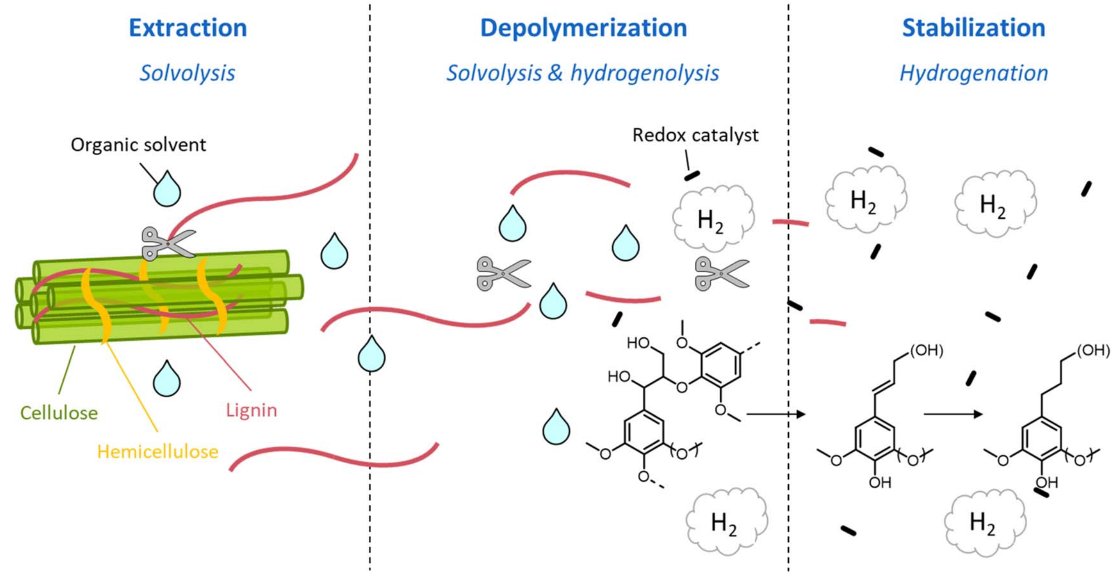


Fig. 36 Schematic representation of lignin extraction, depolymerization, and stabilization during the RCF. Based on Van den Bosch *et al.*[460]

reactors, *via* chemical functionalization (*e.g.* hydrogenation, acetalization, …), or by a combination of the two.[17,18,216,441,442] The lignin oil can also undergo purification through fractionation (*i.e.* successive solvent extractions).[417]

Different strategies have been reported within the scope of lignin-first pretreatment. The following sections provide an overview of the most widely acknowledged methods: reductive catalytic fractionation (RCF), aldehyde-assisted fractionation (AAF), and diol-assisted fractionation (DAF). We also present an emerging method based on the use of sodium dithionite. It should be mentioned that alternative methods are currently being developed and could arguably lead to further progress in the field in the years to come (*e.g.* shape-selective catalysis).[444–446]

6.1. Reductive catalytic fractionation

Reductive catalytic fractionation, also termed Early-Stage Catalytic Conversion of Lignin (ECCL) or Catalytic Upstream Biorefining (CUB), relies on catalytic hydrogenation for stabilizing the reactive intermediates released during lignocellulose solvolysis.[447–449] This method was originally exploited in the 1940s as a means to gain insight in the structural composition of the lignin from different biomass sources.[450–453] However, the potential of the RCF as a biomass pretreatment for the development of integrated biorefineries was recognized only in the last decade, leading to a renewed interest in this approach.[448,454–457]

RCF is performed in an organic solvent (typically an alcohol), possibly in combination with water or an acid catalyst, in the presence of a reducing agent (most often H_2) and a heterogeneous redox catalyst (*e.g.* Ru/C, Pd/C, Raney® Ni, …), at a temperature in the range between 180 and 250 °C.[458,459] Similarly to organosolv pretreatment, during the RCF, LCCs are ruptured by the action of the organic solvent, and large lignin fragments are released in the medium, which undergo further solvolysis and hydrogenolysis of labile inter-unit ether linkages to generate smaller lignin moieties (Fig. 36).[460,461] The latter are characterized by reactive alkenyl functionalities in the side chains of lignin units, which make them prone to undergo repolymerization.[460] Notably, the formation of (hydroxy)alkenyl-substituted lignin derivatives implies the occurrence of a reductive cleavage of ether linkages, in which hydrogen gas or a hydrogen donor act as reducing agents.[460] When water is employed as a co-solvent, or when an acid co-catalyst is used, acidolysis of ether bonds occurs along with solvolysis, and lignin fragments possessing reactive carbonyl functionalities, prone to recondensation, are produced as well (*i.e.* Hibbert's ketones and C_2-aldehyde-substituted phenolics).[17,462] However, by virtue of the presence of the redox catalyst and H_2 (or a H-donor), the catalytic hydrogenation of reactive moieties is favored over repolymerization, and stable (hydroxy)alkyl-substituted phenolic compounds are ultimately formed (*e.g.* 4-propanol, 4-propyl, 4-ethyl guaiacol/syringol) (Fig. 36).[458,460] Since the stabilization of lignin derivatives occurs after the cleavage of inter-unit bonds, RCF integrates lignin isolation and depolymerization in a single operation, producing a low-MW lignin stream, rich in phenolic monomers.[458]

Thus, as illustrated in Fig. 36, the RCF can essentially be divided into three main steps: lignin extraction, depolymerization, and stabilization. While the extraction of lignin is only determined by solvolysis (and acidolysis),[460] and the stabilization of reactive intermediates is exclusively governed by redox catalysis,[460,463,464] the depolymerization step involves an interplay of the two phenomena.[460,461,465,466] In particular, the lignin oligomers released during solvolysis (and acidolysis) may reach the catalyst surface to undergo further catalytic hydrogenolysis of residual ether bonds.[461,465,466] The contribution of

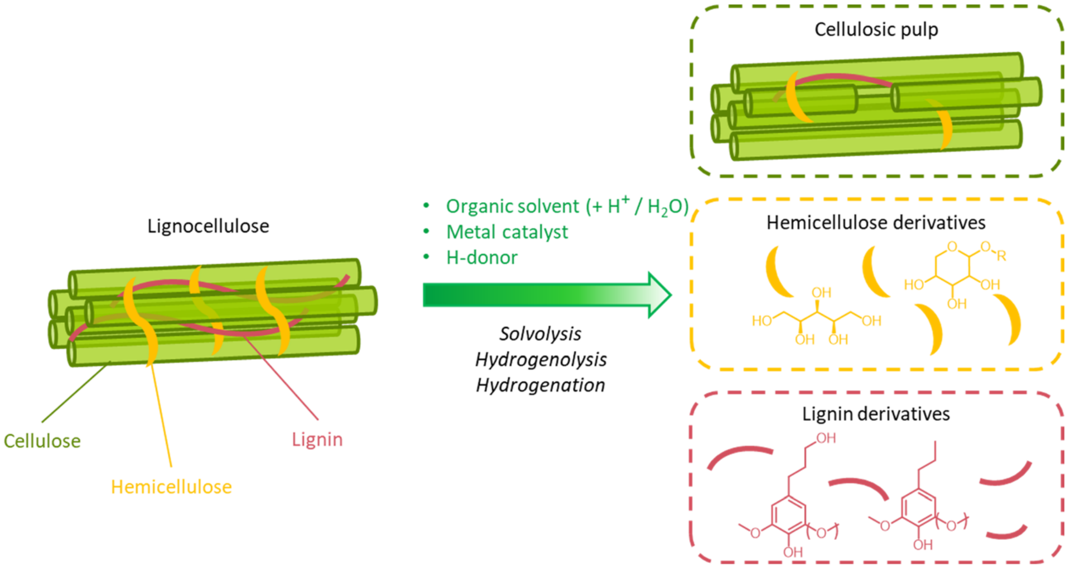


Fig. 37 Schematic outline of the RCF process for the extraction, depolymerization, and stabilization of lignin (and hemicellulose) derivatives from lignocellulosic biomass *via* solvolysis, solvolysis/hydrogenolysis, and hydrogenation, respectively. Note: when RCF is performed in the absence of water or without an acid co-catalyst, hemicellulose is mainly retained in the solid pulp.

hydrogenolysis to lignin depolymerization is more evident when the RCF is performed under low severity conditions, at which solvolysis (and acidolysis) are less effective.[466]

Although RCF shares some similarities with organosolv pretreatment concerning the solvolytic disassembly of lignin, a key difference exists in the criterion to be adopted for solvent selection. While for organosolv processes the best solvents are typically weakly polar solvents, exhibiting the highest lignin solubility, for the RCF more polar solvents (*e.g.* methanol, ethylene glycol) are preferred in view of their improved ability to depolymerize lignin.[467] Moreover, the type of solvent also contributes to affect the features of the phenolics products obtained from the RCF, such as their molecular weight distribution,[467] and the residual presence of alkenyl or hydroxyl functionalities in the side chains of lignin moieties.[468] Other factors affecting the properties of the RCF lignin streams are the type of metal catalyst employed and the hydrogen pressure (when H_2 is used). For instance, the use of Ru/C or Rh/C has been shown to afford a high selectivity toward alkyl-substituted phenolics,[469,470] whereas Pd/C preferentially yields hydroxyalkyl-substituted phenolics,[469,470] and Raney® Ni leads to the partial hydrogenation of aromatic rings.[448,468] Additionally, the adoption of a low hydrogen pressure favors the hydrogenolysis of terminal hydroxyl groups in the side chains of lignin units, ultimately leading to alkyl-substituted phenolics, while at higher hydrogen pressure terminal hydroxyl groups are preferentially preserved.[470] The process severity is another element that influences the features of the isolated lignin fraction, with lignin extraction and defunctionalization of lignin derivatives both being favored at higher severity conditions.[462,471,472]

A schematic outline of the RCF process summarizing the features of each product fraction is displayed in Fig. 37. Notably, high yields of delignification (up to ~90%) and near-theoretical yields of monophenolics (based on the content of β-O-4′ linkages) have been reported for the RCF of hardwood biomass (*e.g.* birch,[447,454,460] poplar,[448,455,466] eucalyptus,[470,473,474] …). The treatment of softwood biomass (*e.g.* pine,[315,446,475] spruce,[447,476,477] …) resulted in lower yields of lignin extraction (≤~60%)[447,475] and in a higher molecular weight of the isolated lignin streams, due to a lower fraction of cleavable β-O-4′ linkages and to a typically more networked structure of softwood lignin.[447,477] The RCF of herbaceous feedstocks (*e.g.* miscanthus,[465,478] corn stover,[472,479] wheat straw,[478,480,481] …) has been explored as well, and relatively high yields of delignification have been reported (up to ~90%),[478] along with a yield of monophenolics that varies in the range of ~10 –~60% of the initial lignin content.[465,478,482]

Next to lignin, the fate of hemicellulose is also greatly dependent on RCF conditions. Similarly to organosolv pretreatment, RCF can extract hemicellulose from lignocellulosic biomass when water or an acid co-catalyst are added to the system.[462,467,470,472,477] Under such conditions, hemicellulose is hydrolyzed and the so-formed sugars are typically alkylated by the action of the alcoholic solvent,[462,472,477] or hydrogenated,[462,470] to yield alkyl glycosides or polyols, respectively. Importantly, the latter are more stable toward dehydration and condensation reactions compared to monosaccharides, which reduces the formation of pseudolignin.[17]

Cellulose is not hydrolyzed in RCF processes, and is mostly retained in the form of solid pulp. Nonetheless, cellulose morphology is partially altered during the treatment, as swelling occurs due to the disruption of lignocellulose structure, with a consequent increase of cellulose surface area.[39,483] The size of the isolated cellulose fibers varies depending on the solvent adopted for the RCF treatment.[467] In contrast to organosolv fractionation, the redeposition of condensed pseudolignin on the pulp surface is largely prevented within RCF, thanks to the active stabilization of lignin and hemicellulose derivatives formed in the process.[483] As a result, the cellulosic pulps produced by RCF commonly possess an excellent enzymatic digestibility (up to over 90% of glucan converted to glucose).[472,477,483]

A few challenges exist that need to be addressed to facilitate upscaling. In this respect, the design of continuous RCF process configurations may help reducing processing costs.[458,459,484] Furthermore, the use of hydrogen gas as a reducing agent constitutes a liability of RCF, imposing strict safety, environmental, and equipment requirements.[485] The solvent selection is another crucial parameter impacting the operation performance and processing costs.[485] Moreover, the development of *ad hoc* catalysts that are able to steer the process selectivity toward the desired products, and to preserve catalytic activity over time is important for ensuring operational stability.[484,486,487] Current research efforts are directed toward addressing these potential limitations. The adoption of semi-continuous flow-through reactors, in which the biomass and the heterogeneous catalyst are loaded in two separate compartments to facilitate the post-fractionation catalyst recovery and re-use, has been explored for RCF processes.[466,488,204,489–492] In addition, various works explored the development of H_2-free RCF configurations in which the solvent or hemicellulose itself act as alternative reducing agents, reporting moderately high yields of lignin and carbohydrate products,[448,468,477,481,491,493–495] and a positive impact on the overall biorefinery economy.[485] Recently, the influence of solvent selection and on the RCF performance was inspected, and the choice of high-boiling solvents was reported to minimize capital costs.[485] The use of membrane separation instead of the conventional distillation for solvent recuperation was indicated as a potentially convenient approach to further mitigate energy consumption.[268,485,496] Alternatively, for the use of low-boiling solvents, the recycling of a portion of the fractionation liquor was reported as an effective strategy to reduce the heat duty for distillation.[497] Various supported redox catalysts were explored for RCF at lab scale, as alternatives to the widely adopted commercial ones.[486] Transition metal carbide catalysts were synthesized which exhibit improved stability of the metal active phase and a higher activity toward lignin hydrogenolysis.[498,499] Transition metal sulfides were reported to excellently adsorb oxygen atoms on sulfur vacancies, boosting ether bonds cleavage in lignin species.[479,500] Solid catalysts with adjustable acidity (*e.g.* with supports based on zeolites, niobium phosphate, silica, alumina, …) were shown to substantially enhance C–O reductive cleavage in lignin species.[486,501–503] Notably, while most studies focused on the development of redox catalysts that could favor the hydrogenolysis of lignin toward monophenolics, the catalyst properties may also be tuned to achieve the stabilization of macromolecular intermediates released during lignin depolymerization, such as lignin dimers, trimers or tetramers.[446] This approach is particularly intriguing as it entails the idea of using the redox catalyst for selectively controlling the fate of lignin species during RCF.

In spite of the current challenges, the RCF is considered a promising method for future lignin-first biorefineries, as highlighted in recent techno-economic and environmental assessments of this technology.[485,497,504,505] Presently, the RCF technology is being scaled-up to multi-kg scale at the BioCon Pilot facilities (KULeuven, Belgium), with the prospect of bringing the process to the multi-ton scale by 2030.[506,507]

6.2. Aldehyde-assisted fractionation

Aldehyde-assisted fractionation entails the use of aldehydes (*e.g.* formaldehyde, acetaldehyde, propionaldehyde, …) within the organosolv treatment of biomass under acidic conditions, to suppress the repolymerization of the solubilized lignin and hemicellulose intermediates by formation of relatively stable acetal structures.[508–515] AAF is carried out in acidified aqueous mixtures of aprotic organic solvents (*e.g.* dioxane), at temperatures in the range of 80–120 °C.[508,509,511] Aprotic organic solvents are the most suitable, since hydroxyl groups in protic solvents would react with aldehydes causing their depletion.[17] Under these conditions, lignin is extracted from lignocellulose by solvolysis and acidolysis of LCCs, similarly to an acid organosolv pretreatment, and large lignin fragments are released in solution (Fig. 38). However, in this approach, the cleavage of β-O-4′ linkages is prevented. The aldehyde molecules react with the α- and γ-hydroxyl groups in the side chains of lignin moieties to yield 1,3-dioxane structures within β-O-4′ linkages, trapping the hydroxyl groups in the form of a stable cyclic acetal, thereby avoiding the generation of reactive benzylic carbenium ions, and the occurrence of lignin repolymerization reactions.[508–512,516,517] The formation of acetals is a reversible reaction that releases H_2O, and is favored in water-deficient environments.[508,509,512,517]

Moreover, when formaldehyde is employed, it contributes to lignin stabilization also by blocking reactive electron-rich *meta*-positions on aromatic rings of lignin units to form hydroxymethyl groups.[508,509,511] While this can enhance repolymerization in the presence of small amounts of formaldehyde (*e.g.* only generated *in situ* by cleavage of lignin side chains), an excess of formaldehyde completely depletes free *meta*-positions, effectively suppressing the formation of methylene bridges, and lignin recondensation.[511]

The features of the different product streams obtained *via* AAF are summarized in Fig. 39. Lignin is extracted in high yields (up to ~80% delignification for hardwood biomass),[508] and the isolated lignin fractions possess a high content of reactive inter-unit ether linkages, prone to be cleaved during a subsequent depolymerization step.[508–512] The latter is commonly realized by subjecting the lignin stream to reductive depolymerization at conditions analogous to those applied for the RCF,[508–510,512,514,518] as illustrated in Fig. 40a. In this way, near-theoretical yields of monophenolics (up to 40–50% for hardwood biomass) are obtained.[508–510,512] One limitation to this approach is that, when formaldehyde is utilized as a protecting agent, the hydroxymethylation of aromatic rings leads to additional (hydroxy) methyl groups in lignin units after reductive depolymerization, decreasing product selectivity.[508] The use of longer aldehydes (*e.g.* acetaldehyde, propionaldehyde), which do not result in electrophilic substitution on aromatic rings, provides a solution

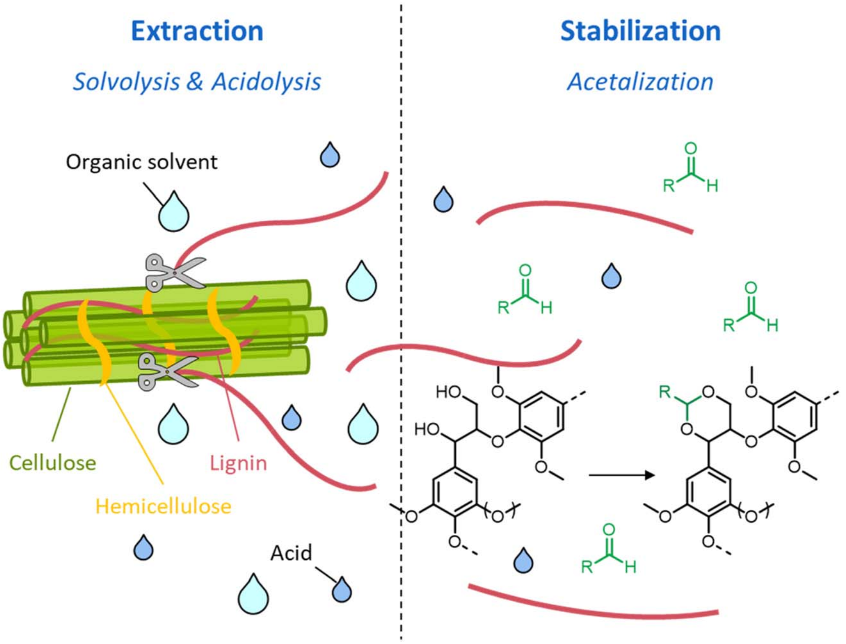


Fig. 38 Schematic representation of lignin extraction and stabilization during AAF.

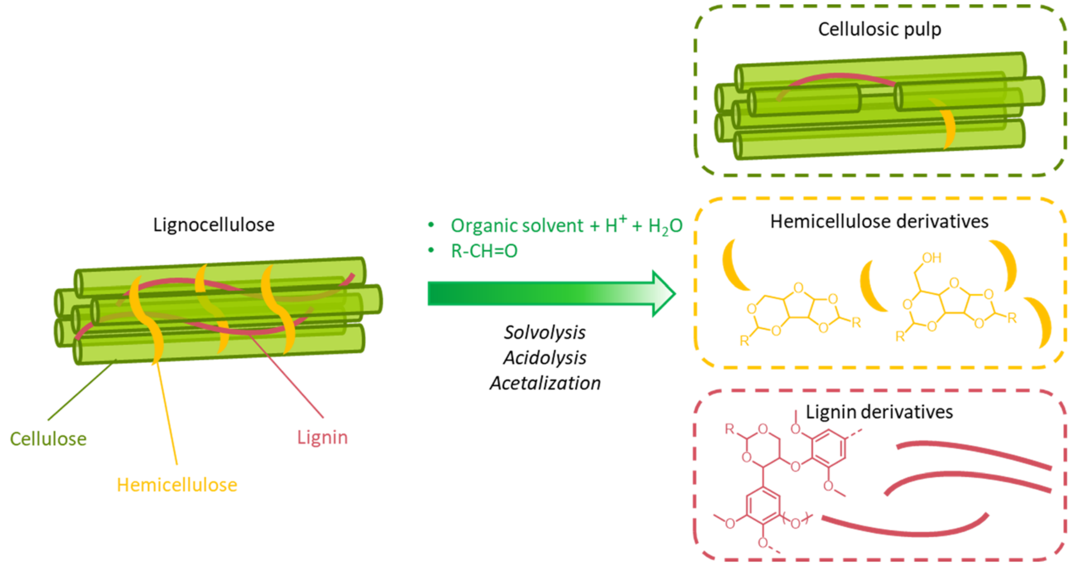


Fig. 39 Schematic outline of the AAF process for the extraction and stabilization of lignin (and hemicellulose) derivatives from lignocellulosic biomass *via* solvolysis/acidolysis and acetalization, respectively. Note: the organic solvent should be an aprotic solvent to avoid reaction of the solvent's hydroxyl groups with the aldehyde.[17] Moreover, the water fraction should be limited (<20% w/w) to achieve effective acetalization of lignin and carbohydrate derivates.[17,18]

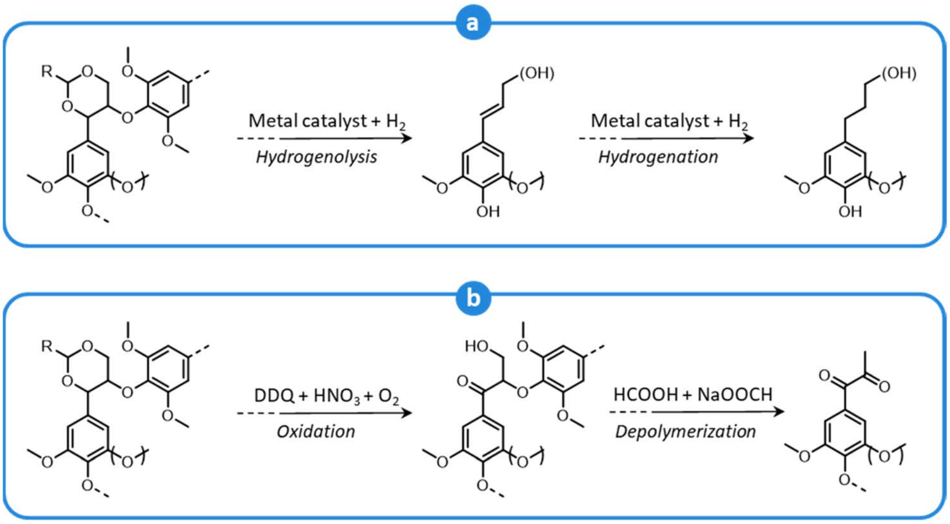


Fig. 40 Cleavage of β-O-4′ acetals structures by tandem hydrogenolysis and hydrogenation (a), and by consecutive oxidation and depolymerization (b).

to this issue, and allows achieving a high selectivity (over 90% for 4-propanolsyringol/guaiacol for the treatment of hardwood biomass) with analogous near-theoretical monomer yields.[510]

An alternative strategy for the depolymerization of AAF lignin is the adoption of a two-step oxidation and depolymerization of acetal-stabilized β-O-4′ structures (Fig. 40b). The oxidation is realized by treating the isolated lignin in a wet organic solvent solution (with 5% H_2O), in the presence of DDQ and HNO_3, under O_2 pressure.[519] Under such conditions, the acetal is cleaved, and the α-hydroxyl group is oxidized into a ketone.[519] The oxidized lignin subsequently undergoes depolymerization in an aqueous solution of formic acid/sodium formate, to give diketones with high yield (30–35%) and selectivity (over 90% for syringyl/guaiacyl propane dione) when treating hardwood biomass.[519]

Along with lignin, hemicellulose is also extensively hydrolyzed due to the acidic conditions applied within AAF. The released monosaccharides promptly react with the aldehydes to form acetal structures that are stable against dehydration and subsequent recondensation, thus limiting the formation of pseudolignin during the fractionation process.[508,509,513] The acetal functionalities can be subsequently removed by dilute acid hydrolysis to give monosaccharides.[508,509,513,520] Alternatively, the acetal-functionalized sugars can be directly converted

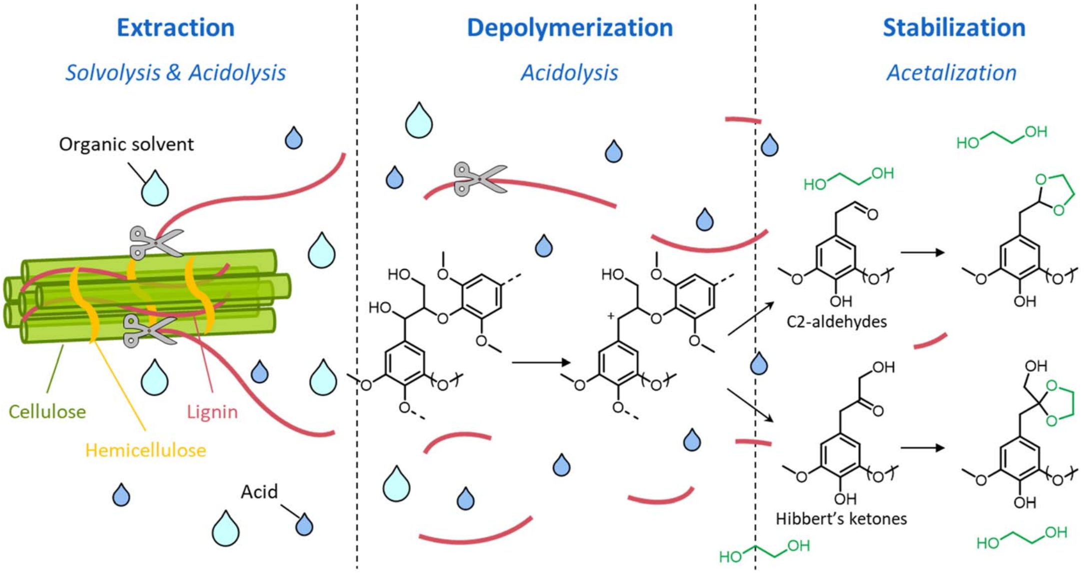


Fig. 41 Schematic representation of lignin extraction, depolymerization, and stabilization during the DAF. Note: in this example, ethylene glycol is shown as a diol, but other diols can be adopted as well.

to furfural by hydrothermal treatment (at a temperature of ∼160 °C), in the presence of a Brønsted acid catalyst (*e.g.* sulfuric acid).[513] Importantly, acetal-functionalized sugars possess a high volatility (*e.g.* diformyl-xylose exhibits a boiling temperature of 250 °C)[508] compared to the parent sugars (*e.g.* xylose exhibits a boiling temperature of 415 °C), which makes it possible to purify these compounds by distillation before further upgrading, thereby circumventing the need of expensive chromatography separations.[17,513]

The extraction of lignin and hemicellulose leaves behind a highly pure cellulosic pulp, possessing a good enzymatic digestibility.[508,509] The latter can be further improved (up to over 90% of glucan to glucose conversion) by subjecting the pulp to dilute acid hydrolysis prior to enzymatic processing to remove the aldehyde molecules grafted on the pulp surface.[508,509] Another possibility is to perform an aldehyde-assisted acid depolymerization of cellulose in an organic aprotic solvent (*e.g.* γ-valerolactone) to produce glucose acetals (with yields of up to 70% and concentrations of ∼5% w/w).[513] In this case, a higher temperature (∼200 °C) is required compared to that needed for hemicellulose hydrolysis. The acetal protection groups can subsequently be removed by treatment in aqueous conditions, and the aldehyde can be recovered.[513]

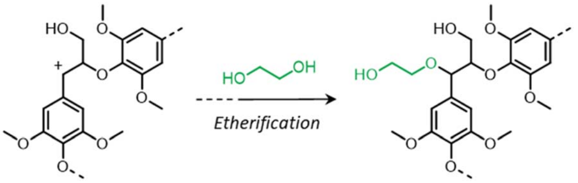


Fig. 42 Stabilization of benzylic carbenium ions by etherification with the diol during the DAF. Note: in this example, ethylene glycol is shown as a diol, but other diols can be adopted as well.

Overall, AAF offers the advantage of allowing to optimize lignin extraction and depolymerization as two separate steps. Thus, mild fractionation conditions can be applied to minimize degradation of biomass components, while harsher conditions can be used for the subsequent lignin depolymerization. On the other hand, an important limitation of this methodology lies in the toxicity of the organic solvents (*e.g.* dioxane) and of the aldehydes that are employed.[216,509,511] Moreover, the recovery of aldehyde derivatives upon deprotection of the products is not straightforward. From this point of view, the aldehydes incorporated in lignin acetals are transformed into alkanes during reductive depolymerization (*e.g.* formaldehyde is converted into methane), implying the need to reconvert alkanes into aldehydes in a separate process, or to feed fresh aldehydes for every run.[508] The fate of aldehyde derivatives during the oxidative deprotection of acetal-stabilized lignin has been less investigated, but it has been postulated that the cleavage of the acetal groups would lead to the release of aldehyde molecules in the medium.[519] Thus, the protecting agent may be recovered thereafter, provided that aldehyde molecules are not irreversibly incorporated in lignin structures (*e.g.* in the form of hydroxymethyl groups in aromatic rings) under the applied conditions. Despite these challenges, a preliminary economic assessment of formaldehyde-assisted fractionation highlighted the potential profitability of such technology.[513] Notworthy, the AAF process is currently being upscaled by the Swiss company Bloom Biorenewables, with the aim of exploring commercial opportunities for the obtained product streams.[512]

6.3. Diol-assisted fractionation

Diol-assisted fractionation (DAF) relies on the adoption of diols within the acid-catalyzed organosolv pretreatment of lignocellulose to stabilize lignin and hemicellulose derivatives against recondensation through the formation of acetals.[118,521–525] While

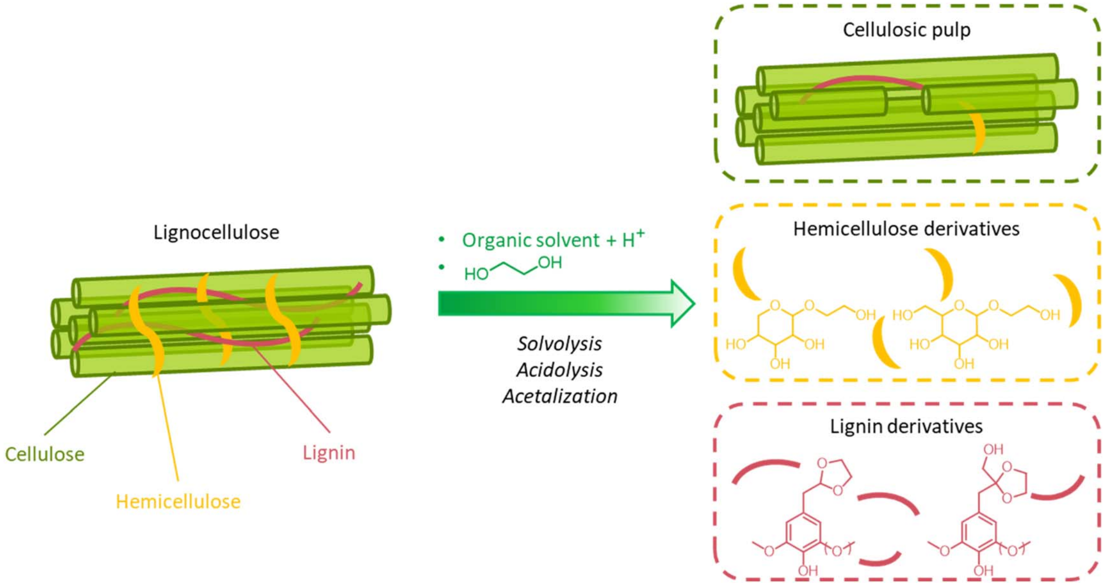


Fig. 43 Schematic outline of the DAF process for the extraction, depolymerization and stabilization of lignin (and hemicellulose) derivatives from lignocellulosic biomass *via* solvolysis/acidolysis, acidolysis, and acetalization, respectively. Note: in this example, ethylene glycol is shown as a diol, but, in general, other diols can be adopted as well. The organic solvent should be an aprotic solvent, to prevent possible condensation reactions with the diol.

diol-assisted acidolysis has been initially explored as an approach to depolymerize isolated lignin fractions,[118,523,525] it has been recently shown that it can be effectively integrated within biomass fractionation to develop a lignin-first process.[521,522,524,526]

DAF is typically performed in organic aprotic solvents (*e.g.* 1,4-dioxane, dimethylcarbonate, ethylene carbonate),[118,521,524] in the presence of an acid catalyst (*e.g.* triflic acid, H_2SO_4),[118,521,524,525] and a diol (*e.g.* ethylene glycol, 1,3-propanediol, …),[118,521,524,525] at mild temperature (∼140 °C).[521,524] Under such conditions, LCCs are cleaved by the combined action of the organic solvent and the acid catalyst and lignin is extracted in the medium (Fig. 41).[521,524] Lignin fragments are further cleaved, most prominently by acidolysis of inter-unit β-O-4′ linkages, which encompasses the formation of benzylic carbenium ions, and, ultimately, the formation of Hibbert's ketones and C_2-aldehyde-substituted phenolics.[115–118,521–523,527–530] Once formed, these species are prone to participate in repolymerization reactions. In particular, C_2-aldehyde-substituted phenolics are extremely reactive, which is why they are only found in trace amounts in typical acid-catalyzed organosolv processes.[118,523] On the other hand, during the DAF, these species react with diols to form cyclic acetals, thus their recondensation is avoided (Fig. 41).[118,521–523] Similar acetal structures can be formed as well by reaction of Hibbert's ketones with diols.[521]

By virtue of the stabilization of reactive lignin derivatives, the yield of monophenolics obtained from DAF is considerably larger compared to that achieved for an acid organosolv pretreatment, albeit lower than theoretical monomer yields.[17,118,521,522] From this point of view, even though benzylic carbenium ions can also be stabilized by etherification with the diol (Fig. 42),[217,521] the repolymerization of reactive lignin derivatives is not completely suppressed during DAF, posing a limitation to the yield of monophenolics.[217,521,522] Notably, the extent of formation of C_2-aldehydes and Hibbert's ketones is largely dependent on reaction conditions; hence, it is difficult to determine individual theoretical monomer yields for C_2- and C_3-acetals, respectively. Overall, for softwood biomass, DAF enables to effectively extract lignin from lignocellulosic biomass (up to about 80%) and to simultaneously depolymerize it, resulting in moderate yields of phenolic monomers (up to about 9%).

In addition to lignin, hemicellulose is also extracted during DAF. The acidic environment contributes to realize an extensive depolymerization of the released sugar fragments, yielding monosaccharides, which are hydroxyalkylated by further reaction with the diol.[521,524] Notably, the modified sugars are more stable against dehydration and recondensation reactions.[17] This reduces the formation of pseudolignin, thereby improving the quality and the processability of the recovered pulp. Hydroxyalkylated sugars can subsequently be converted back to their parent sugar forms by dilute acid hydrolysis in aqueous medium.[521,524]

The cellulosic pulp obtained from DAF possesses a high cellulose purity, and superior digestibility (up to ∼90% of glucan recovered as glucose upon enzymatic hydrolysis).[521,524] Incorporation of the diol in the pulp may occur, due to glycosylation reactions, and the diol can be subsequently removed by dilute acid hydrolysis of the pulp.[521] Importantly, the presence of the hydroxyalkylated sugars within the cellulose backbone does not have adverse effects on enzymatic hydrolysis.[521]

The features of the different product streams obtained *via* DAF are summarized in Fig. 43. In general, this process offers

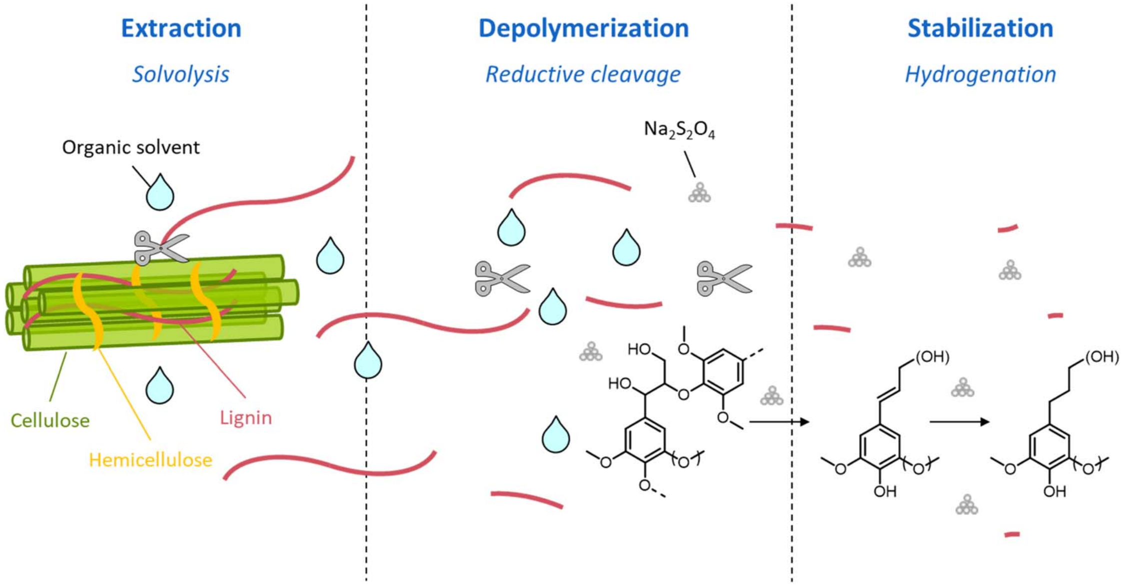


Fig. 44 Schematic representation of lignin extraction, depolymerization, and stabilization during DAOF. Based on Brienza *et al.*[531]

the advantage of affording moderately high yields of stable lignin and carbohydrate derivatives without requiring the use of a heterogeneous metal catalyst, thereby circumventing the issues related to catalyst deactivation and recovery-regeneration. However, the incorporation of diols in the products implies the need to recover this reagent downstream, or to feed fresh diols for every run, which result in additional costs. In spite of this, the DAF represents a relatively facile lignin-first process that is compatible with current industrial organosolv pretreatments.[17] This aspect potentially simplifies further scale-up of the DAF.

6.4. Dithionite-assisted organosolv fractionation

Dithionite-assisted organosolv fractionation (DAOF) is based on the use of sodium dithionite ($Na_2S_2O_4$) as a reducing agent within the organosolv pretreatment of lignocellulosic biomass to enhance the reductive depolymerization of lignin and to suppress the occurrence of lignin recondensation.[531–533] Typically, DAOF is carried out in mixtures of *n*-butanol and water, at temperatures in a range of 150 and 250 °C.[531–533] Lignin is extracted from lignocellulose by solvolysis of LCCs, similarly to an organosolv pretreatment, and large lignin fragments are released in solution. The latter are further broken down by the

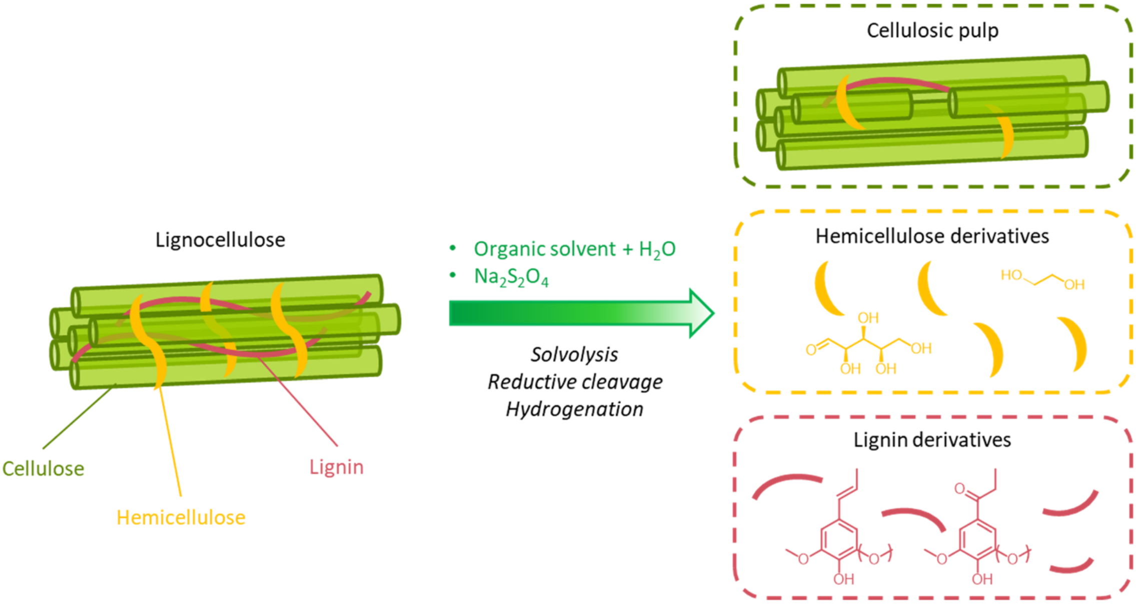


Fig. 45 Schematic outline of the DAOF process for the extraction, depolymerization, and stabilization of lignin derivatives from lignocellulosic biomass *via* reductive cleavage, and hydrogenation, respectively.

action of dithionite, which promotes the reductive cleavage of β-O-4′ linkages in lignin structures, leading to the formation of lignin moieties characterized by the presence of alkenyl functionalities in the side chains of phenolic units (Fig. 44). Such functionalities may ultimately be stabilized against recondensation by the reducing effect of dithionite. Along the formation of alkenyl and alkyl-substituted phenolics, lignin units possessing oxidized side chains are observed as well during DAOF and their presence has been explained by the occurrence of acid-catalyzed cleavage reactions of β-O-4′ linkages under DAOF conditions.

Thanks to the action of dithionite, the yield of phenolic monomers achieved during DAOF is superior to that obtained during typical organosolv pretreatments, but remains below the theoretical monomer yield, due to an incomplete prevention of lignin recondensation. Overall, DAOF has been shown to be partially effective for the treatment of hardwood and herbaceous biomass, resulting in excellent yields of delignification (up to about 80%)[532] and moderately high yields of phenolic monomers (up to about 20% for hardwood biomass).[532]

Next to the lignin fraction, hemicellulose is also extensively extracted from the biomass. However, only a minor fraction of hemicellulose is converted toward sugars, glycols, or other non-condensed carbohydrate derivatives, whereas a considerable part of it is recovered as humic products in the lignin stream.[531] Conversely, cellulose is almost completely preserved in the form of a highly pure cellulosic pulp possessing an excellent digestibility (up to ∼90% of glucan recovered as glucose upon enzymatic hydrolysis).[531]

Importantly, the use of various organic solvents may be envisaged for DAOF.[533] The adoption of the *n*-butanol/water solvent system has been illustrated to be effective for enhancing lignin extraction and depolymerization (which would be hampered in the pure solvents)[532] and to facilitate downstream product separation. The immiscibility of *n*-butanol and water at ambient conditions allows achieving the effective isolation of three distinct product fractions after DAOF: a solid fraction containing cellulose, an organic liquid fraction containing extracted lignin and humin derivatives (monomers and oligomers), and an aqueous fraction containing non-condensed carbohydrate derivatives (sugars, glycols, and organic acids).[531]

The outcomes of DAOF are schematically summarized in Fig. 45. Overall, DAOF is a less mature technology compared to other lignin-first pretreatments such as the RCF, AAF, or DAF. As such, some limitations currently exist for the adoption of DAOF. For instance, dithionite derivatives have been reported to be incorporated in the product streams,[531,532] thereby complicating their subsequent upgrading, and making the potential recuperation of the reducing agent more challenging. In addition, the valorization of hemicellulose is hampered by the extensive condensation of carbohydrate derivatives and the consequent formation of humins.[531] Nevertheless, a recent techno-economic assessment of the DAOF of birch wood has shown that this method could be economically feasible, especially in wood-abundant regions.[532] Most promisingly, the flexibility of this method with respect to the treatment of various lignocellulosic feedstocks makes it an attractive candidate for the lignin-first pretreatment of highly heterogeneous waste streams (*e.g.* agricultural residues, waste wood).

7. Conclusions and outlook

Traditionally, biomass pretreatment approaches applied in the pulping industry and in biorefineries have been principally focused on the valorization of the carbohydrate fraction of biomass, while much less attention has been dedicated to the conversion of the lignin fraction. (Hemi)cellulose is typically employed for papermaking, or for the production of biofuels (*e.g.* bioethanol). On the other hand, lignin streams isolated from biomass pretreatment are mainly exploited for energy production (*e.g. via* combustion), but can actually be employed also for other higher-value applications, such as the manufacturing of polymeric materials (*e.g. via* blending or copolymerization with synthetic polymers), or the production of bulk and fine chemicals (*e.g. via* lignin depolymerization and upgrading). From this point of view, the choice of the most suitable pathway for lignin valorization is related to the properties of the isolated lignin fractions.

More recently, the perspective of utilizing lignin as a renewable source of aromatic chemicals and polymer precursors stimulated a renewed interest in the development of strategies for the depolymerization and upgrading of isolated lignin streams. Thus, a variety of methods have been developed for the depolymerization of pre-isolated lignin fractions toward phenolic monomers, and for the upgrading of the latter into marketable products through functionalization or defunctionalization pathways. However, lignin conversion has often been found to be tedious due to the high degree of condensation of lignin structures or to the presence of impurities (deriving from other biomass components or from additives employed within the pretreatment), which makes "technical lignin" recalcitrant toward further depolymerization, limiting the yield and the selectivity for target monomeric products. Clearly, achieving an effective transformation of lignin into products cannot prescind from taking into consideration the impact of the structural features of the isolated lignin fractions on the subsequent processing steps.

Studies on biomass fractionation highlighted that the reactivity of isolated lignin streams depends on the properties of the biomass feedstock employed (*e.g.* lignin content, β-O-4′ linkages content, G-/S-/H-units composition, …) and on the conditions applied within the pretreatment (*e.g.* process severity, use of chemical additives, …). The interplay between these factors ultimately determines the extent of cleavage of native labile inter-unit ether linkages in lignin matrices, and that of undesirable repolymerization reactions occurring during the fractionation. On the one hand, the genetic modification of plants can serve as a powerful means for creating less networked lignin structures, possessing an elevated content of cleavable inter-unit ether linkages. On the other hand, the careful design of biomass pretreatment methods is of paramount importance for taking full advantage of the potential reactivity of native lignin toward depolymerization. In this respect, suppressing the formation of stable C–C bonds during lignin isolation (and depolymerization) is a key aspect with respect to the production of lignin streams amenable toward further processing. While the adoption of low-severity fractionation methods may appear as a suitable solution, in that it allows to better preserve ether linkages in lignin structures, a tradeoff typically exists between the preservation of native β-O-4′ bonds and lignin extraction. Thus, low severity pretreatment methods are often coupled with low yields of isolated lignin derivatives.

A better response to the need of extracting non-condensed lignin streams from lignocellulosic biomass requires a thoughtful, on-purpose design of the fractionation process. In the last decade, novel so-called lignin-first strategies have emerged that rely on physical protection strategies (*e.g.* flow-through reactors), chemical protection strategies (*e.g.* catalytic hydrogenation, reduction, acetalization), or a combination thereof, to achieve a passivation of reactive lignin derivatives, while concomitantly allowing to effectively extract lignin from biomass, leaving behind a carbohydrate fraction amenable to further upgrading. Moreover, when hemicellulose is extracted along with lignin, carbohydrate fragments in solution are stabilized as well against recondensation. As a result, lignin-first approaches allow for a more complete valorization of lignocellulose compared to traditional pretreatments. In particular, lignin depolymerization can be achieved either concomitantly with its extraction, when inter-unit ether linkages are cleaved and the so-formed lignin fragments are stabilized (as in the RCF DAF, or DAOF), or in a subsequent step, when the protection strategy targets the stabilization of inter-unit ether linkages (as in the AAF). For both scenarios, the yield and selectivity toward monomeric products are substantially higher compared to those obtained upon the depolymerization of lignin streams isolated from traditional pretreatments. In addition, native lignin functionalities are better preserved within lignin-first processes, which allows to expand the range of potential products.

Currently, the upscaling of lignin-first strategies remains challenging for different reasons. For instance, the use of heterogeneous catalysts, which need to be recovered and regenerated, within some lignin-first approaches (*e.g.* RCF) represents a considerable complication compared to a typical organosolv pretreatment, and requires *ad hoc* solutions. One way could be envisaging facile and easily scalable strategies for catalyst recuperation (*e.g.* the use of flow-through reactors). Next to that, the development of new lignin-first approaches that do not require heterogeneous catalysis is also highly desirable for expanding the range of processing opportunities (*e.g.* DAF or DAOF). Moreover, suitable replacements for the toxic or explosive chemicals (*e.g.* aldehydes, H_2, …) adopted within lignin-first processes should be envisaged to reduce the environmental and safety risks associated to their industrial implementation. Finally, the profitability of lignin-first pretreatments should be thoroughly investigated. From this perspective, the choice of the final market applications for lignin and carbohydrate derivatives has a crucial impact on the economic viability of lignin-first biorefineries, which can generate a wide spectrum of functionalized platform molecules. Hence, the exploration of new market sectors for the produced biomass derivatives represents a key strategy for maximizing the revenues from lignin-first processes.

Future research efforts should therefore be oriented toward improving the compatibility of lignin-first strategies with existing industrial pretreatments to facilitate their implementation within biorefinery schemes. In parallel, further studies should explore the use of lignin and carbohydrate derivatives for the manufacturing of high-value chemicals, pharmaceuticals, or polymers, to highlight what applications would benefit the most from the unique properties of such biomass-derived intermediates, and, ultimately, to pave the way for new, remunerative application routes.

In spite of the existing challenges, lignin valorization has come a long way throughout the last few decades. The initial (mis)conception that "one can make anything from lignin except money", which used to be widespread within the pulp and paper sector, is much less popular today, as lignin-first processes are steps away from entering the industry. The long-desired waste-to-resource transition of lignin is gradually becoming a reality and the promising advancements made in the last few years project an exciting future for lignin valorization.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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