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Review

The Nature of Lignin and Implications for Its Technical Use as a Source for Biogenic Aromatics—A Review

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Abstract

The composite material lignocellulose makes up the majority of biomass on earth and is characterized by a high biological and chemical resistance, which is essentially caused by the phenylpropanoid polymer lignin. Thus, the removal and depolymerization of lignin to produce aromatic chemicals can significantly enhance the material usability of all lignocellulose constituents. This review summarizes the current state of knowledge on the nature of lignin, including its biosynthesis, structure, chemistry and biodegradation. Second, it attempts to derive implications regarding the technical valorization of lignin from native biomass through depolymerization. Finally, the consequences of the findings for conventional, recently developed and future processes valorizing lignocellulose are assessed, and the associated technical and economic hurdles are discussed. It becomes clear that lignin depolymerizability is restricted in established pulping processes, primarily due to repolymerization reactions. Strategies avoiding lignin repolymerization involve an increased process complexity and additional economic expenditure but might enable an increased value creation from lignocellulosic biomass.

Keywords: biomass; properties of native lignin; valorization of lignocellulose; lignin depolymerization; lignin-first processes

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1. Introduction

The emergence of lignin-containing plant cells is regarded as a decisive milestone for the development of land plants [1]. It is assumed that phenylpropanoid precursors of lignin have provided an essential advantage for the development of land plants by protecting them against UV radiation [2,3]. The lignin polymer evolved from these phenylpropanoids provided the plants with the physical stability to stand upright and expand in size, enabled long-distance water and thereby nutrient transport in plants and offered them protection against pathogens and herbivores—all of these being essential properties for the evolution of land plants in the abundance and diversity in which they are found today [4]. However, lignin cannot be viewed in isolation but as one component of the highly cross-linked composite material lignocellulose, which it forms together with mainly two further carbohydrate polymers—cellulose (composed of glucose units) and hemicellulose (mainly composed of C5 sugars) [5]. Lignocellulose is mainly found in the secondary cell walls of plant cells, which are formed by only a subset of cells in any given vascular plant [6]. Still, secondary cell walls make up the majority of trees and herbaceous biomass, which in turn make up the majority of the total biomass on earth [7] (p. 794).

Highly relevant in nature, lignin could also play a prominent role in the chemical industry. Due to its abundance and its carbon-rich, aromatic structure, lignin is considered an attractive biogenic and renewable raw material for material utilization, for which various applications are being discussed, such as its use in phenolic resins, for carbon fibers or for the production of aromatic basic chemicals [8]. Aromatics are an important class of substances for the chemical industry, being produced almost exclusively from fossil raw materials nowadays [9]. Thus, the extraction of aromatics from lignin could make a decisive contribution to a bio-based chemistry.

Lignocellulose has been fractionated for over 100 years, but mainly for the production of cellulose, e.g., for paper production. This requires the removal of lignin from the lignocellulose matrix, which inevitably involves structural changes in the lignin. In conventional processes, this isolated lignin is heterogeneous, condensed (structurally reformed with the formation of new stable bonds) and dissolved in a complex reaction slurry. Together with other remaining process chemicals, it is mostly incinerated for energy production and the recovery of inorganic process chemicals [10]. Lignin condensation reduces lignin depolymerizability and thus makes it more difficult to obtain monomeric aromatics from technically isolated lignin compared to native lignin [11,12]. For this reason, there has been increasing research in recent years into alternative processes avoiding lignin condensation by active stabilization strategies ("lignin-first" processes) [13].

Against this background, the main goal of this review is to summarize the current state of knowledge on the nature of native lignin as it is contained in lignocellulosic biomass (i.e., its biosynthesis, structure, chemistry and biodegradation) and to derive implications for its technical utilization from the respective theoretical background (Sections 2–5). Finally, the consequences of the findings for conventional, recent and future processes valorizing lignocellulose are assessed (Section 6). Since the topics of lignin and lignocellulose are very broad, this paper is limited to the utilization of lignocellulose that is as native as possible and the depolymerization of its lignin into small aromatic oligomers and monomers. As native lignin cannot be viewed in isolation, the interplay of lignin and (hemi-) cellulose needs to be considered, as well as strategies enabling a high valorization of all these fractions of lignocellulose. The key novelty of this review article is its technical perspective on the updated state of knowledge about the nature of lignin in order to derive consequences for future process developments for the depolymerization of lignin from native lignocellulose. Topics such as the use of technically isolated lignin as feedstock or the influence of genetic modification on lignocellulose are excluded from this review.

2. Biosynthesis of Lignocellulose

Secondary cell wall synthesis: Lignin, incorporated in lignocellulose, is mainly found in the secondary cell wall of specific plant cells. The formation of the lignocellulosic secondary cell wall starts after the plant cell finishes expansion. The secondary wall grows inwards the cell, typically starting with the deposition of polysaccharides, i.e., a matrix of cellulose microfibrils, synthesized by membrane proteins, and hemicellulose, synthesized within the Golgi apparatus [6]. Following the initial deposition of polysaccharides for secondary cell wall synthesis, lignification starts at the outer middle lamella and primary cell wall and continues across the forming secondary call wall layers [14,15]. It is assumed that in addition to the chain growth of the lignin molecule itself, covalent bonds are also formed between lignin and the polysaccharides [15,16]. The highest lignin concentrations are observed in the compound middle lamella and especially in the cell corners of the compound middle lamella, whereas most lignin in terms of absolute quantities is found in the substantially thicker secondary cell wall [15,17,18]. The growing of the secondary cell wall inwards in the cell induces its programmed cell death and clearance of the protoplasm,

leaving a hollow void inside (lumen) [19,20]. However, further postmortem lignification through neighboring cells has been observed [21,22].

Lignification: The three basic monolignols p-coumaryl, coniferyl and sinapyl alcohol are synthesized within plant cells by several enzymatically catalyzed reactions via the phenylpropanoid pathway, typically starting from the amino acid phenylalanine [23]. These monolignols are then exported from the cytosol of the plant cell to the apoplast (Figure 1a) [6]. Different mechanisms for their transport via membranes are discussed; however, the exact transport procedure has not yet been clarified [24]. Before export, monolignols can be enzymatically glycosylated to form 4-*O*-β-$_D$-glucosides, which is especially observed in the case of gymnosperm species; however, this glycosylation is enzymatically reversible also after monolignol export and before polymerization [24]. The role of this glycosylation is not clear yet; its uses for monolignol transportation, regulation and storage are being discussed [25–27]. Another possible modification of monolignols before export is their acylation (e.g., with acetates, p-hydroxybenzoates, p-coumarates or ferulates, especially observed in angiosperm species) [28–30].

After monolignol export to the apoplast, oxidative enzymes (laccases and peroxidases) catalyze the radicalization of mono- and oligolignols by dehydrogenation. Two radicals produced in this way can undergo a radical coupling reaction, whereby each of them contributes a single electron to the newly formed bond so that none of them remains radicalized (termination instead of chain reaction) [31]. As intermediates, quinone methides are typically formed, which subsequently re-aromatize by reacting either with water, carbohydrates or further lignin components (Figure 1b) [32]. Successive radical coupling reactions lead to a growing lignin oligomer and lignification of the cell wall. Based on the current state of knowledge, it is assumed that this oxidative radical polymerization is mostly a purely chemical process, dependent on factors like monolignol and enzyme availability, intrinsic chemical reactivity of monolignols, local pH and carbohydrate matrix, but not the result of a direct enzymatic action, as is typical for other biochemical processes [33–37]. This assumption is supported by the fact that lignin structures are racemic and not optically active [38,39]. There is evidence for the existence of dirigent proteins that mediate lignin polymerization and thus could indicate a certain enzymatic control in lignification; however, their effect has so far only been demonstrated in certain root cells (casparian strip in root cell walls) [40,41]. In various studies in which the production of certain proteins responsible for monomer synthesis or lignification was suppressed, lignification nevertheless took place, showing the high flexibility of this process [42,43].

As supported by theoretical calculations, monolignol radicals favor coupling at their β-carbon (numbering of the carbon atoms as presented in Figure 1a), resulting in a predominance of β-O-4, β-β and β-5 bonds within the lignin oligomer [31,44,45]. Furthermore, non-covalent interactions locate the reactants in a geometrical arrangement that favors the formation of the β-O-4 ether bond according to a computational study [46]. Acylation appears to be retained during lignin polymerization so that acylated monolignol conjugates are incorporated into the lignin polymer [29]. Likewise, the incorporation of monolignol glucosides is possible, as was shown in vitro [47]. Furthermore, other unconventional lignin monomers like precursors of the monolignols (e.g., caffeyl alcohol) or phenolic compounds derived from other polyphenolic biosynthetic pathways (e.g., flavonoids like tricin or hydroxystilbenes) might be incorporated into the lignin polymer [29].

Some of the oxidative enzymes catalyzing lignification are anchored to the cell wall and not mobile; it is anticipated that they are co-secreted together with hemicellulose components [48]. The monolignols, on the contrary, appear to be highly mobile and diffuse through both primary and secondary cell walls [6]. Thus, the spatial distribution of

lignin deposition on the cell wall might be controlled by the localization of the oxidative enzymes [49].

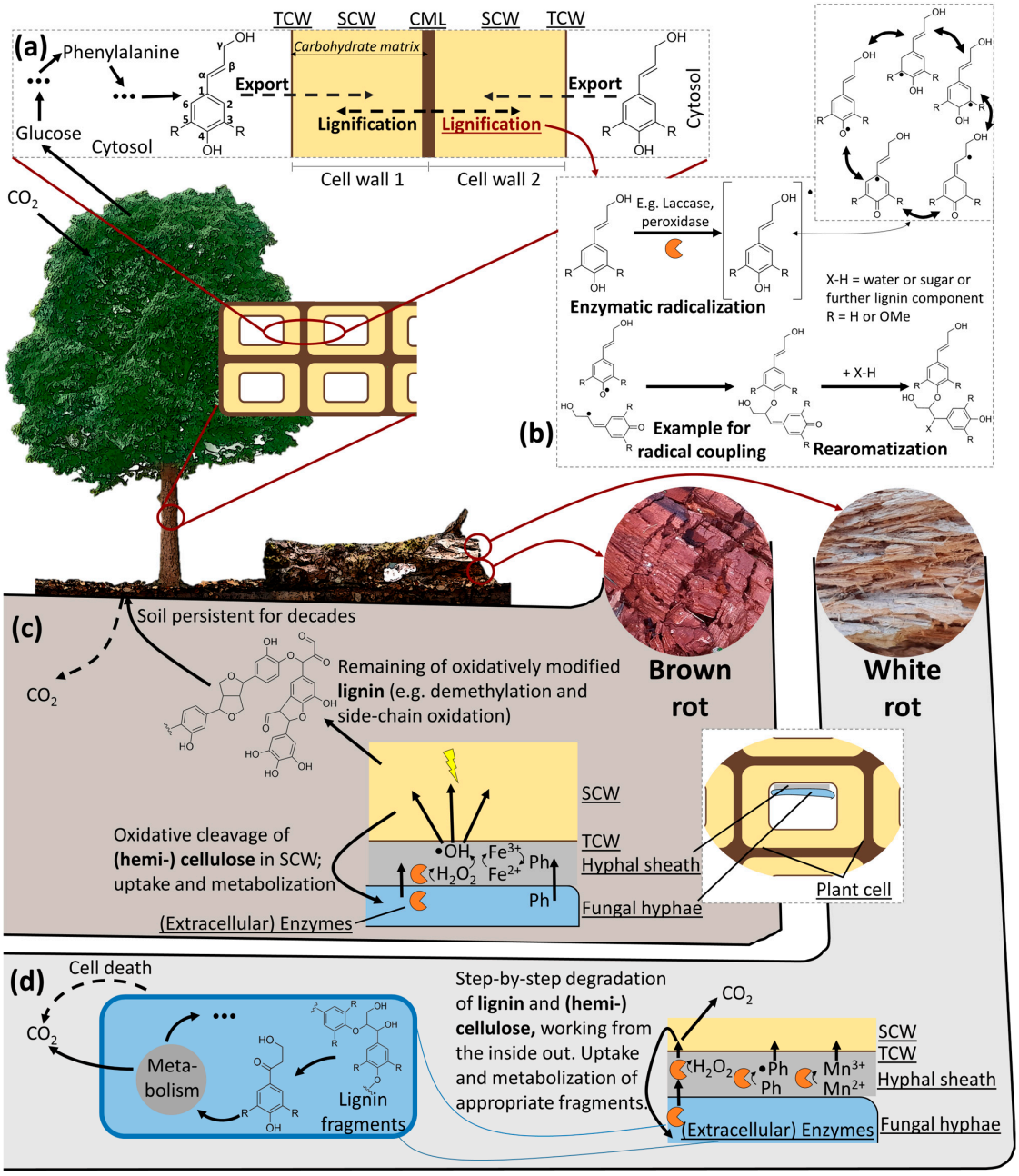


Figure 1. Lifecycle of lignin. For biosynthesis, as described in Section 2, (**a**) lignin monomers are synthesized in the cytosol of plant cells and then exported to the cell wall, which is composed of a thin tertiary cell wall (TCW), a thick secondary cell wall (SCW) and the compound middle lamella (CML). (**b**) Within the cell wall, monomers are radicalized by enzymes, leading to phenolic radicals with a delocalized unpaired electron. If two radicals react with each other, quinone methide structures might form, which re-aromatize via the reaction with, for example, water, sugars or other lignin components (X-H). Biodegradation might take place via (**c**) brown rot or (**d**) white rot, as further described in Section 5.

Key findings and implications for technical lignin valorization by depolymerization: The following considerations can be derived from the brief overview of the biosynthesis of lignin and lignocellulose.

- Apparently there is a clear order in the synthesis of lignocellulose: first, a matrix of carbohydrate polymers is built up, into which lignin is then incorporated and where it acts as a "curing agent" [16]. It seems logical to proceed in the opposite direction when degrading the material and remove the lignin first.
- Regions with highest lignin concentrations are more difficult to access as they are found in the compound middle lamella in between two cells, thus surrounded by secondary cell walls. Lignified plant cells are typically hollow on the inside and can therefore be accessed from the inside. However, the high mobility of lignin monomers within the cell wall indicates a certain diffusibility of the cell walls, which is examined further in Section 4.1.
- Unlike the formation of other biopolymers like cellulose, lignin polymerization is not the result of a direct enzymatic action, but a chemical process. Accordingly, a reverse, selective enzymatic cleavage of lignin bonds does not appear to be the obvious solution for depolymerization. The natural biodegradation of lignin is further explored in Section 5.
- The lack of regulation leads to a high degree of heterogeneity and poses a challenge for lignin depolymerization. The insight that the formation of β-O-4 ether bonds is favored may prove helpful for the development of depolymerization approaches.

3. Structure of Lignocellulose

Lignin structure: Besides the defining common criterion that lignin comprises phenolic subunits, covalently connected by carbon–carbon, ether or ester bonds forming optically inactive oligomers or polymers, there is a huge structural variety among lignins in different biomasses, plant cells and even sections of one plant cell with regard to the exact quantities and types of monomers and bonds between them [15,16,29]. Typically, the main polymer is formed by the three basic monolignols p-coumaryl (H-unit), coniferyl (G-unit) and sinapyl alcohol (S-unit), which only differ in the extent of methoxylation (0, 1 or 2 methoxy groups in H-, G- or S-units, respectively). Softwood is primarily composed of G-units with traces of H-units, whereas hardwood and herbaceous biomass typically consist of significant amounts of both S- and G-units with traces of H-units (Table 1) [50]. H-units are often overestimated due to interferences with protein residues or other cell-wall phenolics such as p-coumarate and p-hydroxybenzoate; H-levels are rarely above 5 % in native lignin [43,51]. A high content in H-units is often observed in the middle lamella of plant cells, where lignin is typically highly concentrated, but that, however, only make up a small part of the total cell wall [15].

The monolignols are mainly connected by β-ether bonds (β-O-4) in native lignins (60 to 80 %, Table 1) [52]. Furthermore, computer models have recently shown the thermodynamic favorability of the formation of α-O-γ linkages between β-O-4 complexes and further monomers [53]. Such alkyl ether bonds only involving α- and γ-carbons and no carbon from the aromatic ring are assumed to be present in combination with β-O-4 and β-β complexes [54] and were also assumed from NMR analyses but are difficult to assign due to signal overlap [53–56].

As further ether bonds, biphenyl ethers (4-O-5) were detected [57]. Besides being connected by such pure ether bonds, monolignols might be incorporated by a combination of ether and carbon–carbon bonds. In native lignin, these are assumed to include phenylcoumarans (combination of β-5 and α-O-4) [58], resinols (two α-O-γ ethers and one β-β bond) [58], tetrahydrofurans (one α-O-γ ether and one β-β bond; alternative to resinols, e.g., in case of existing γ-acylation or an α-carbonyl group) [59,60], dibenzodioxocins (involves three monolignols bound by a 5-5, an α-O-4 and a β-O-4 bond) [61] and, to a minor

extent, spirodienones (combination of a β-1 and an α-O-α bond) [62] according to a recent review on lignin structure [43]. All bond types named are illustrated in Figure 2.

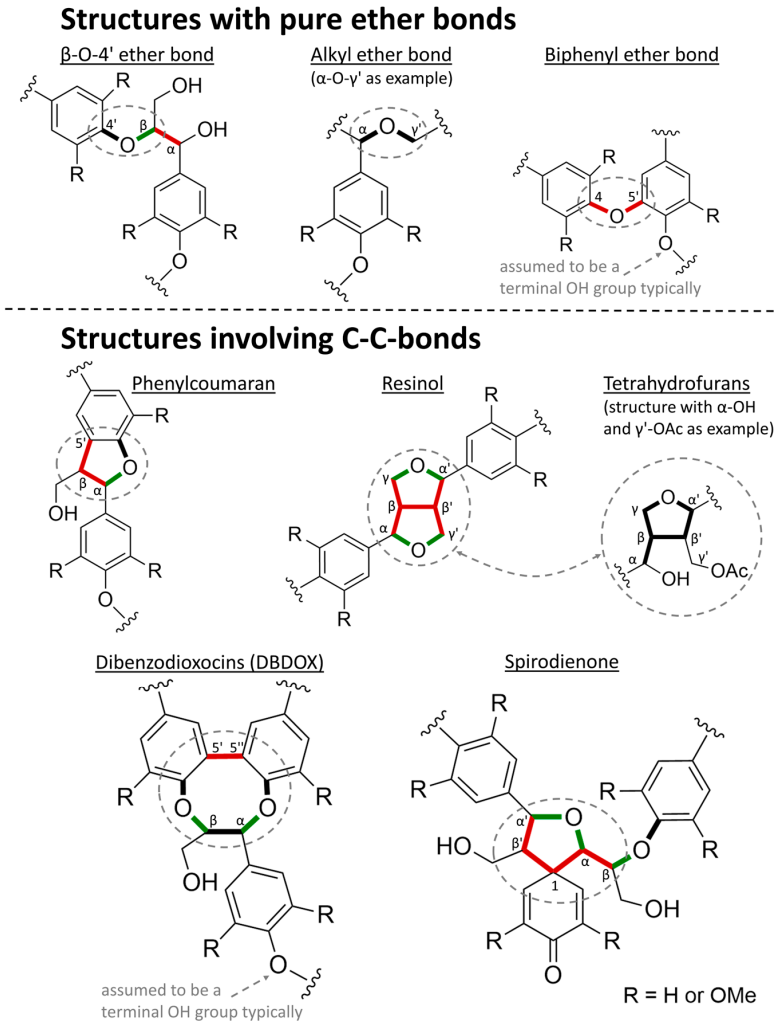


Figure 2. Representation of the main types of bonds that are assumed to be present in lignin. Typical frequencies of these bond types are given in Table 1. For bonds marked in color (green in the case of ether bonds and red in the case of carbon–carbon bonds), the homolytic bond dissociation enthalpies are shown in Table 2.

Besides the three basic monolignols, many further compounds were identified as being incorporated in lignin during radical polymerization reactions [29]. Lignin can be acylated due to the incorporation of acylated monolignols, e.g., by acetates (in many hardwoods), p-hydroxybenzoates (observed for some types of hardwood) or the hydroxycinnamate p-coumarate (mainly in grasses), all of them being typically connected by an ester-bond to the γ-carbon of a monolignol [63]. Another hydroxycinnamate playing a prominent role, especially in divers angiosperms species, is ferulate [30]. In contrast to p-coumarate, it is not only connected by ester bonds, but also forms ether and different carbon–carbon bonds with the basic monolignols [63]. A further prominent example for an unconventional lignin monomer, even derived from another polyphenolic biosynthetic pathway than the phenylpropanoid pathway, is the flavonoid tricin, which is found in particular in certain types of grass and seems to bind to other monolignols only via 4-O-β ether bonds [64].

After this brief overview of the current knowledge regarding the types of monomers and the bonds between them in lignin, the question of the 3D organization and size of the resulting macromolecule is still to be investigated. The huge difficulty of measuring such properties for native, non-isolated lignin poses a major challenge in this regard. Dibenzodi-

oxocins (involving a 5-5 bond) and biphenyl ethers (4-O-5) bonds are possible branching points within lignin, as they theoretically allow the connection of three further monomers at the 4- and β-carbons typically involved in bonding. Historically, a three-dimensional branched conformation of lignin was assumed [65]. However, the finding that the structures considered as possible branching points mostly contain free phenolic end units (4-OH) instead of bonds to further monolignols at the 4-carbon led to the assumption of a rather linear lignin structure (Figure 2) [43,57,66]. Around 7 to 13% of basic units in different native woods were found to carry a free phenolic hydroxyl group [67]. However, different analytic methods applied in recent studies have indicated a highly branched structure for softwood, including the detection of etherified, thus branching 5-5-units [56,68]. The existence of α-O-γ bonds recently indicated by computer simulations might harmonize the assumption of a branched structure and the assumption that dibenzodioxocins and biphenyl ethers do not abundantly act as branching points, as α-O-γ bonds could also act as branching points [53]. Similarly, there is uncertainty regarding the average degree of polymerization of one lignin macromolecule. Some studies report values around and even below 25 units per molecule for milled wood lignin [56,66]. Significantly larger molecular weights are often observed for isolated lignins; however, these do not provide reliable information concerning the native lignin due to structural rearrangements by depolymerization and repolymerization reactions [69,70]. Artificially synthesized lignins have very different degrees of polymerization depending on the method of synthesis, ranging from below 20 to 500 [71,72]. Again, these findings show how difficult the analysis of lignin in its native form is, since any analysis methods require a prior treatment of biomass, at least grinding, which in turn already leads to structural changes [56]. Similarly difficult is the analysis of the interactions between lignin and carbohydrate polymers.

Table 1. Lignin characteristics for the typical lignocellulose-rich plant classes; ranking abundances of the monolignols H, G, S—p-coumaryl, coniferyl and sinapyl alcohol, respectively—and abundances of β-O-4 ether (β-O-4), phenylcoumaran (PC), resinol (Res), tetrahydrofuran (THF), dibenzodioxocin (DBDOX), spirodienone (Sp) and biphenyl ether (BP) bond structures.

	Classification	Examples	Lignin Content in % [73,74]	Monolignol Shares in % [43,74–76]	Typical Unconventional Monomers [29]	Bond Frequencies in % [2]
Gymnosperms	↦ Softwoods	Spruce, Pine	27–31	H: <5 G: >95 S: →0	Dihydroconiferyl alcohol, guaiacylpropane-1,3-diol	β-O-4: ~60 [30–50] [2] PC: ~10 Res: ~5 DBDOX: ~10 Sp: 1–2 BP: ~1
Angiosperms	↦Dicots [1] ↦Hardwoods [1]	Poplar, birch, Beech	19–25	H: <5 G: 20–50 S: 45–75	Acylation with p-hydroxybenzoates and acetates	β-O-4: ~80 [60–75] [2] PC: ~5 Res: ~5 DBDOX: ~3 Sp: 1–2 BP: 1–2
	↦Monocots [1] ↦Grasses [1]	Straw, switch-grass, corn stalk, Miscanthus	6–23	H: <5 G: 23–80 S: 20–75	Acylation with p-coumarates and acetate; ferulate-polysaccharide-esters; tricin	β-O-4: ~75 [30–60] [2] PC: <10 THF: ~5 DBDOX: ~10 Sp: 1–2 BP: 1–2

[1] These group subdivisions are frequently found in the lignocellulose context, but they are not official and unambiguous taxonomic groups. [2] Bond frequencies were adopted from the lignin models recently published by Ralph, Lapierre and Boerjan [43], which are mainly based on NMR investigations. If wet chemical, ether-selective methods like thioacidolysis or reductive catalytic fractionation are applied, lower ether bond contents are typically estimated, especially for grasses [77,78]. Values typically obtained by such methods are given in brackets.

Cross-linking with carbohydrates: Lignin is tightly cross-linked with hemicellulose and cellulose in lignocellulose. Cellulose is a large, linear polymer composed of d-anhydroglucopyranose units (with a degree of polymerization typically between 500 and 15,000) linked by β-1,4-glycosidic bonds [79]. Several of such chains (estimates ranging from 18 to 36 chains) bind together by different physical interactions to form microfibrils, which are then further surrounded and interconnected by hemicellulose and lignin [80,81]. Hemicelluloses are branched polymers composed of pentoses (e.g., xylose), hexoses (e.g., mannose) and sugar acids (e.g., glucoronic acid), also connected mostly by β-1,4-glycosidic bonds [82,83]. Hemicellulose appears to act as binding material between cellulose and lignin, having specialized domains with varying hydrophilicities depending on the side groups [84,85]. Cellulose and hemicellulose seem to bind with each other mostly via physical interactions like hydrogen bonds; however, the overall architecture of the cellulose–hemicellulose matrix is still "very poorly understood" [86].

Primarily, lignin interacts with hemicellulose, both of them forming a matrix that surrounds the cellulose fibrils [87]. However, especially in wood, secondary interactions between lignin and cellulose seem to occur to a considerable extent as well [86,88,89]. These interactions between lignin and both hemicellulose and cellulose are believed to be mainly non-covalent (physical interactions, e.g., hydrophobic interactions) [86,88,90]. However, the existence of covalent bonds between lignin and carbohydrates (so-called lignin–carbohydrate complexes, LCCs) has long been suspected, and their existence is now supported by many strong indications [47,91,92]. Lignin–carbohydrate complexes (LCCs) are regarded as one important contributor to the recalcitrance of lignocellulosic biomass [93,94]. As already stated in the context of lignin structure, the extent to which isolation methods lead to structural changes in the lignin–carbohydrate bonds is uncertain, as irreversible structural changes were observed to occur during milling and even simple drying [56,95,96]. Furthermore, there is still a lack of reliable methods for quantifying such lignin–carbohydrate complexes (LCCs), so no precise statements on the occurrence of LCCs are currently possible [97].

As to the covalent bonds between lignin and carbohydrates, possible candidates discussed so far are α-ether (also termed benzyl ether), α-ester (benzyl ester), γ-ester, phenyl glycoside bonds and, predominantly in grasses, ferulate cross-links involving an ester and possibly ether or carbon–carbon-bonds (Figure 3). More than 60 years ago, the formation of an α-ether between a monolignol and a monomeric sugar was shown to be formed via the nucleophilic attack of the sugars hydroxyl group on the α-carbon of the quinone methides formed as intermediates during radical lignin polymerization [92]. This nucleophilic attack then leads to the re-aromatization of the quinone methide (Figure 1b). Recently, computational modeling has revealed that the formation of an α-carbon ether bond with carbohydrates is even thermodynamically favorable compared to the addition of a water molecule for re-aromatization, which would lead to an α-OH group and thus only enable physical interactions (hydrogen bonds) between the polymers [98]. Furthermore, the reaction showed to be kinetically facile, leaving questions of transport and availability of sugar groups as remaining uncertainties that are hard to investigate [98]. In harmony with this computer model, the existence of such α-ether lignin bonds has been evidenced in isolated lignocellulose fragments [99]. In a similar manner, it is believed that the nucleophilic attack of a carboxylic acid (e.g., glucuronic acid, which is a common side-chain on xylan) on the α-carbon of a quinone methide might lead to an α-ester, which might consequently migrate to a γ-ester [16,98,100]. Computer modeling indicated a higher activation barrier compared to the addition of sugars and a lower kinetic favorability compared to the addition of water, so that the abundance of such esters with sugar acids is assumed to be low [98]. However, different studies report the detection of both α- and γ-ester [68,101].

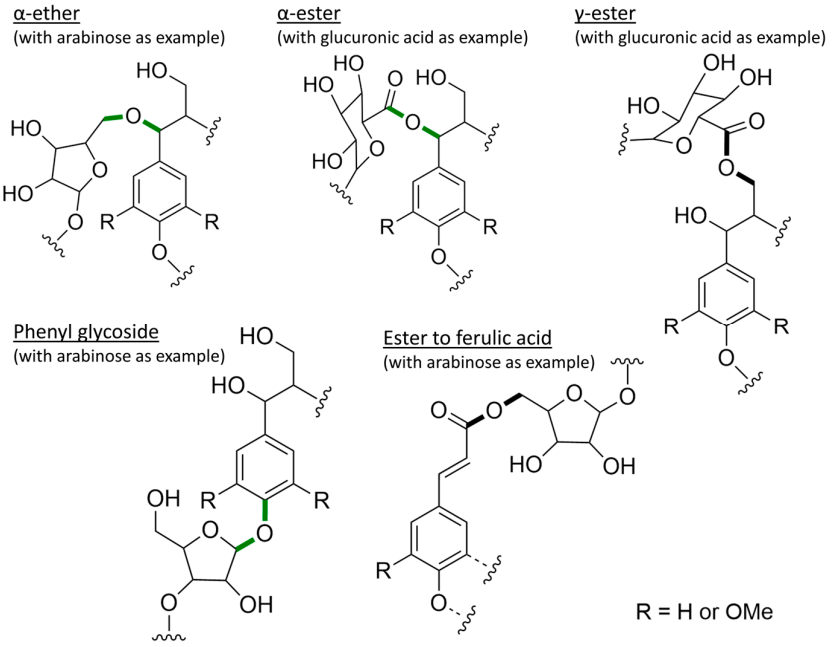


Figure 3. Representation of the main types of bonds that are assumed to be present between lignin and carbohydrates (lignin–carbohydrate complexes, LCCs). For the carbon–oxygen bonds marked in green, the homolytic bond dissociation enthalpies are shown in Table 2.

Furthermore, glycosidic bonds possibly form between lignin and carbohydrates. Phenyl glycoside bonds are usually detected in considerable amounts in isolated lignocellulose fragments and the mechanism of their formation is still not clear [56,101,102]. One possible mechanism, the incorporation of monolignol glucosides, was recently demonstrated via in vitro experiments [47]. Hydroxycinnamic acids, mainly ferulic acids, can act as linking molecules, which is a characteristic feature mainly found in grasses and other commelinid monocots. Ferulic acid can be linked to both hemicellulose and lignin via ester bonds and furthermore undergo radical coupling with lignin or other ferulates. Thus, ferulic acid is able to also form ether and carbon–carbon bonds with lignin to cross-link hemicelluloses with lignin [28,63,103,104].

Similarly to the physical interactions, it is assumed that lignin binds covalently mainly with hemicellulose, but also with cellulose to a lesser extent [105,106]. The composition and structure of hemicellulose vary depending on the biomass type, which presumably results in variations within the lignin–carbohydrate complexes. Regarding the hemicelluloses in the secondary cell walls, mannans (galactoglucomannans) typically dominate in gymnosperms, whereas xylans typically dominate in angiosperms, mainly in the form of glucoronoxylan in dicots and in the form of glucuronoarabinoxylan monocots (Table 1 for species classification and respective examples) [83]. It is even hypothesized that the type of hemicellulose might influence the lignin structure, e.g., by pH changes due to carboxylic acids that might induce an increase in β-O-4 in lignin [107].

Microscopic secondary cell wall structure: Mature lignocellulosic secondary cell walls make up the majority of the plant cell wall, reaching a thickness of several µm (e.g., 2 to 4 µm) and surrounding the void cell lumen, which is in the size range of tens of micrometers in diameter [108–110]. For cellulose aggregates in native spruce wood cell walls, mean side lengths of 11–20 nm of the (approximately square) cross-section were determined, whereas a thickness of about 4 nm was estimated for the surrounding matrix of lignin and hemicellulose [111]. Secondary cell walls typically have a density of around 1500 kg/m^3 and porosities below 5% [112,113]. For different types of lignocellulosic biomass, it was found that the majority of the pore volume in the secondary cell

wall is made up by micropores below 2 nm [112,114]. However, pore size determination is difficult and different analysis methods show huge deviations [115]. Furthermore, pore sizes are affected by water content and vary among the different cell wall layers [116,117]. Porosity decreases substantially as lignin is deposited in the carbohydrate matrix during lignification [14].

Key findings and implications for technical lignin valorization by depolymerization:

- Lignin represents a group of phenolic macromolecules with an extremely heterogeneous composition. It consists of a large number of monomers that are connected by very different types of bonds, and furthermore, lignin concentration, composition and structure vary within the cell wall. This means that, firstly, there is no single type of bond that can be used as a point of attack to cleave all monomers from one another. Secondly, this heterogeneity naturally imposes restrictions on the maximally achievable product selectivity.
- The majority of the bonds are ether bonds, in particular β-O-4 bonds. These bonds are therefore the most suitable effective target for selective cleavage. Thus, a focus will be set on the chemistry of these ether bonds. The maximally achievable monomer yield by cleaving the ether bonds can then be estimated by the square of the ether bond content [118].
- In order to release lignin from the cell wall, not only the bonds between lignin monomers have to be considered but also the bonds between the lignin molecules and the carbohydrates. These appear to be cleavable mainly through the cleavage of carbon–oxygen bonds (ester, ether and glycosidic bonds). However, there are still many unknowns regarding the covalent linkages between lignin and carbohydrates.
- Lignin cross-links primarily with hemicellulose, thus filling the space between aggregates of cellulose microfibrils and also filling existing pores in the carbohydrate matrix. The removal of lignin could thus lead to a considerably higher porosity and hence diffusibility of the cell wall.

4. Chemistry of Lignocellulose and Lignin

As outlined above, native lignin is incorporated into the lignocellulose network in a complex and heterogeneous way. In the following, special attention is paid to its chemical properties considered important for understanding and developing technical utilization options; including solubility properties, bond stabilities and the effects of various thermochemical influences.

4.1. Solubility

High-polymeric native lignocellulose and the embedded lignin interlinked with carbohydrates are not easily soluble in most solvents. Nevertheless, it is important for the design of treatment processes to understand the interaction of lignocellulose with a solvent (e.g., to ensure a high diffusibility) and the solubility of released lignin oligomers in a solvent (e.g., to ensure their removal). In the following, findings from established lignin isolation methods and theoretical studies will be used to develop an understanding of the solubility characteristics of native lignocellulose and lignin.

Lignin solubility characteristics cannot be directly inferred from the solubility characteristics of isolated lignin, as the isolation process often leads to different types of lignin functionalization, making lignin soluble in the process media used under the reaction conditions applied. Thus, the solubility of isolated lignin depends largely on the method of isolation. Some isolated lignins are water soluble (e.g., lignosulfonates), some are soluble in organic solvents (e.g., organosolv lignin), and many are insoluble at room temperatures in most solvents, both aqueous and organic (e.g., Kraft lignin, which is only soluble in

alkali) [119,120]. However, it can be concluded from the study of isolated lignins that lignin rather tends to be alkali-soluble than acid soluble in aqueous media. Aqueous alkaline media typically lead to delignification, whereas limited delignification with an insoluble lignin residue remaining is typically reached in aqueous acidic media, unless a functionalization (e.g., by sulfonation) takes place [78,121]. Deprotonation of phenolic OH groups is regarded as cause for alkali solubility [78]. In aqueous acid, on the contrary, lignin translocation and redistribution in the form of droplets or agglomerates was observed [121]. Investigating organosolv lignins, it was found that solubility increases with decreasing molecular weight of lignin and that a certain polarity and hydrogen bonding capacity of the solvents is decisive for lignin dissolution [122]. The investigation of many differently isolated, but thereby hardly functionalized lignins revealed that mixtures of two solvents often led to better dissolution than pure solvents, and that with decreasing molecular weights of the lignin fragments, a broader range of solvents was successful in their dissolution [123].

Theoretical considerations and computer simulations can help to understand the solubility of lignin molecules with native structure as assumed according to current knowledge. Native lignin comprises both nonpolar (e.g., aromatic rings) and polar (e.g., hydroxyl groups) moieties and thus a medium polarity with both polar and nonpolar interactions is possible between lignin and a solvent. It can be assumed that its hydrophobicity increases with higher degrees of polymerization, due to a lower content in free phenolic hydroxyl groups. In general, solubility is expected to decrease with increasing molecular weight [124]. Molecular dynamics simulations of uncharged lignin oligomers of different sizes, dimers and monomers indicate that solvents like dimethyl sulfoxide (DMSO) and methanol, with an intermediate solvent polarity, are good lignin solvents, whereas polar solvents like water or unpolar solvents like hexane are poor lignin solvents [125]. Mixtures containing water and an organic co-solvent could be used to set an optimal polarity and indeed, such mixtures showed to be powerful in solubilizing lignin through local interactions of the respective solvents with lignin regions with corresponding polarity, e.g., methanol solvating nonpolar segments of lignin and water solvating polar functional groups in a water/methanol mixture [125–130]. Due to the additional methoxy group increasing the possibility for hydrophilic hydrogen bonds and reducing the possibilities for hydrophobic π–π interactions, S-monomers and lignin rich in S-monomers seem to be slightly more water soluble and less soluble in organic solvents compared to G-monomers and lignin rich in G-monomers [125,131].

Solubility parameters like the Hildebrand solubility parameter and the Hansen solubility parameters were developed to predict and quantify solubility properties following the basic "like seeks like" principle [132]. The Hildebrand solubility parameter δ is defined by the molar volume V of a pure solvent and its energy of vaporization E according to Equation (1) [132]:

$$\delta = \left(\frac{E}{V}\right)^{\frac{1}{2}} \quad (1)$$

Molecular dynamics simulations predicted Hildebrand solubility parameters in the range of 23 to 27 $MPa^{1/2}$ for lignin model oligomers with degrees of polymerization from 8 to 26 [133]. Comparable solubility parameters were detected for isolated lignins, e.g., around 24 to 25 $MPa^{1/2}$ for different Kraft lignins [134] and around 25 to 28 $MPa^{1/2}$ for different types of organosolv lignin [135,136]. And indeed, the best solubility for isolated lignins was obtained with water–alcohol mixtures when the mixing ratio of the solutions was adjusted so that the Hildebrand parameters of the solvents and the lignins were about the same [136–138].

Lignin fractions with lower molecular weight showed to be soluble in different solvents with a broader range of solubility parameters than larger lignin molecules [123].

However, even solvents with similar Hildebrand solubility might still have very different affinities, and thus a further, more detailed subdivision into three so-called Hansen solubility parameters was undertaken [132]. These are calculated similarly to the Hildebrand parameter; however, the cohesion energy (i.e., energy of vaporization) is split into three individual energies arising from dispersion forces, permanent dipole–dipole forces and hydrogen bonding, leading to the three different Hansen solubility parameters δ_D, δ_P and δ_H, respectively, and also, the similarity of these parameters determines miscibility [132]. For lignin, the determined Hansen solubility parameters vary depending on the source, isolation technique and determination method from around 15.6 to 22.7 $MPa^{1/2}$ for δ_D, from 8.6 to 14.1 $MPa^{1/2}$ for δ_P and from 9.2 to 21.9 $MPa^{1/2}$ for δ_H [139]. These values show that lignin has a medium polarity and typically interacts with dispersion-type interactions as the main interactions. Molecular dynamics simulations with assumed native structures revealed that for smaller lignin molecules (e.g., degree of polymerization of around 8), electrostatic interactions (i.e., dipole–dipole and hydrogen bonding) make a larger contribution than dispersion-type interactions, whereas for larger lignin molecules (e.g., degree of polymerization of 26), the dispersion-type interactions start to dominate [133]. The Hansen solubility also reveals that lignin and cellulose are not compatible with each other, whereas hemicellulose has portions with solubility parameters closer to cellulose and portions closer to lignin; this indicates the role of hemicellulose as a surfactant between these two macromolecules [140].

The solubility is furthermore an important factor influencing the ability of a solvent to diffuse into the secondary plant cell wall, which is a decisive parameter regarding the competition of mass transfer and repolymerization reactions during cell wall fractionation processes [109]. Small polar molecules such as water, salts (as concentrated aqueous solutions) and ethanol can be used for wood swelling, whereas hardly any swelling is achieved with non-polar molecules such as benzene or heptane [141,142]. Consistent with the trends observed for the solubility, water/alcohol mixtures led to higher swelling than pure solvents [143]. Whereas amino acids are able to penetrate the cell wall, enzymes are too large [144]. The moisture content is an important parameter regarding the diffusibility and typically, diffusibility increases with higher moisture content [141,145,146]. Polyethylene glycol with molecular weights smaller than 400 Da could be used to swell dry wood cell walls, which provides an order of magnitude regarding molecular sizes that might be able to diffuse through cell walls [147]. With increasing water content, more and also larger Polyethylene glycol molecules could be absorbed by the wood cells [147]. The transition of the cell wall polymers from a glassy to a rubbery state, which is favored by higher temperatures and moisture contents, is expected to facilitate diffusion [141].

Some studies dealt with the modeling of reaction and mass transfer kinetics during lignocellulose fractionation and the estimated lignin diffusion coefficients within cell walls show an extremely high variety (e.g., ranging from 10^{-20} to 10^{-9} m^2/s) depending on process type and conditions [148]. However, such studies show that the internal diffusion of lignin might be a determining factor for reaction kinetics and redeposition and repolymerization reactions if a certain biomass particle size is exceeded [109]. From a study regarding the reductive catalytic fractionation of poplar as a specific process, it is concluded that extremely fine poplar particles with an average particle length of around 0.2 mm are required to completely avoid diffusion limitations [109].

Key findings and implications for technical lignin valorization by depolymerization:

- Lignin appears to be rather alkali-soluble than acid-soluble in aqueous media.
- Lignin has an intermediate solubility with both rather polar and rather non-polar moieties. As evidenced by different approaches, mixtures of water with an organic solvent

appear to be optimal for solubilizing native lignin and thereof derived structures that are not further functionalized.
- Smaller lignin fragments tend to be more soluble in a broader range of solvents.
- Besides a matching solubility, a high moisture content is essential for a good diffusion of small molecules through the secondary cell wall.

4.2. Bond Stabilities

In different theoretical studies, the homolytic bond dissociation enthalpies (BDEs) of the typical lignin linkages in lignin models (mostly models of dimers) were investigated (Table 2) [149–156]. In general, the dissociation enthalpies of bonds directly involving an aromatic ring are much higher than bonds within the aliphatic chain, which can be explained by the stability of the aromatic ring resulting from electron delocalization [152]. Furthermore, ether bonds are considered to be weaker than carbon–carbon bonds (for otherwise similar complexes) [149]. Taking these considerations together, alkyl ether bonds and the β-O bond in β-O-4 ether bonds are believed to be rather instable compared to the other lignin bonds, followed by aliphatic carbon–carbon bonds like α-β-bonds [54,149].

There are contradicting results from theoretical studies with dimer models for the β-O-4 linkage, as to whether the existence of an α-OH functionality instead of α-H slightly increases or decreases the homolytic bond dissociation enthalpy [157,158]. However, there is an agreement among many studies that the oxidation of α-OH to an α=O carbonyl group effects a reduction in homolytic bond dissociation enthalpy of more than 40 kJ/mol [149,150,154,157,158]. A similar effect is achieved by oxidation of γ-OH, and the reduction is even higher if both α- and γ-hydroxyl groups are oxidized [150,154]. Replacing α-OH by α-OMe also effects a reduction in homolytic bond dissociation enthalpy of around 20 kJ/mol, which can be explained by the disruption of intramolecular hydrogen bonds between the α-OH proton and the β-oxygen [159]. The existence of the γ-carbon, representing an important difference between native lignin and many model compounds, lowered the α-β bond energy in the phenylcoumaran and β-O-4 ether linkages [149,153].

With regard to the covalent bonds between hemicellulose and lignin, mainly carbon–oxygen bonds (ester, ether and glycosidic bonds) are expected, as described above. Fewer theoretical studies can be found regarding the homolytic bond dissociation enthalpies for the cleavage of the lignin–carbohydrate complexes (LCCs). However, these studies indicate comparable homolytic bond dissociation enthalpies to the cleavage of β-O-4 bonds, with phenyl glucosides apparently having slightly lower and benzyl ether and ester having slightly higher homolytic bond dissociation enthalpies [160,161]. Within the phenyl glycoside, the bond between lignin and the connecting oxygen atom is significantly stronger than the connection between the oxygen and the sugar, as an aromatic ring is involved on the lignin side [160,161]. The homolytic bond dissociation enthalpies within benzyl ethers and esters differ less clearly, with benzyl ether bonds being more likely to be cleaved on the sugar side and the benzyl ester being more likely to be cleaved on the lignin side [160].

In the context of the homolytic bond dissociation enthalpies, it must be noted that these only provide the theoretical cleavage energy for a simple homolysis in empty space and that in chemical processes many other effects such as solvent effects and the actual reaction mechanism influence the actual activation energy of the bond cleavage. As examples, activation energies of around 170 kJ/mol in methanol (temperatures of 150 °C to 190 °C) or even 85 kJ/mol in supercritical methanol were measured for the cleavage of β-O-4 model compounds, which is much lower compared to its calculated homolytic bond dissociation enthalpy of around 280 kJ/mol [162,163]. Furthermore, the theoretical studies cited focused on the enthalpies needed to cleave bonds between two units. However, lignin modifications

by cleavage of side groups might occur already at milder conditions. In particular, the α-OH group is rather unstable, and typically, modifications of this group (e.g., dehydration) occur at milder conditions than the cleavage of any inter-unit bond among lignin, cellulose or hemicellulose [164].

Key findings and implications for technical lignin valorization by depolymerization:

- Lignin bonds directly involving the aromatic ring (4-O-5, β-1, 5-5, β-5) are clearly more stable than bonds involving only aliphatic carbon or oxygen (α-O, α-β, β-O). Based on the calculated bond dissociation enthalpies (BDEs) regarding homolytic bond dissociation, the β-O-4 structure and the α-β bond in phenylcoumaran structures appear to be the simplest target for complete cleavage of two monomers.
- The oxidation and, to a lesser extent, the methoxylation of aliphatic OH groups apparently decrease the stabilities of the β-O-4 bond.
- The lignin–carbohydrate complexes (LCCs) predominating according to the current state of knowledge contain bonds not directly involving the aromatic ring; consequently, their stability seems to be in a similar range to the stability of the β-O-4 bond.
- Side groups, especially the α-OH group, are less stable than the inter-unit bonds, so lignin modifications typically occur at much milder conditions than depolymerization reactions.

Table 2. Theoretically calculated homolytic bond dissociation enthalpies (BDEs) in kJ/mol of certain lignin bonds and lignin carbohydrate linkages (LCCs) at 298 K. The respective bonds are highlighted in color in Figures 2 and 3.

	Bond Structure	Specific Bonds and Their BDE in kJ/mol
Lignin bonds	β-O-4 ether [149,150]	β-O ≈ 268–301, α-β ≈ 314–322
	Biphenyl ether [149]	4-O/O-5 ≈ 326–347
	Phenylcoumaran [152]	β-5′ ≈ 393–422, α-O ≈ 188–226, α-β ≈ 238–293
	Resinol [155]	β-β′ ≈ 339–343, α-β ≈ 272–280, β-γ ≈ 330–339, α-O ≈ 284, γ-O ≈ 330–334
	DBDOX [149,150,155]	5′-5″ ≈ 468–497, α-O ≈ 176–192, β-O ≈ 238
	Spirodienone [156]	α-β ≈ 380, α′-β′ ≈ 301, α-O ≈ 343, α′-O ≈ 376, 1-α′ ≈ 192, 1-β′ ≈ 213, β-O ≈ 301
LCCs	α-ether [1] [160]	α-O ≈ 319-340, O-S5 ≈ 274-291
	α-ester [1] [160]	α-O ≈ 327, O-S5 ≈ 413
	Phenyl glycoside [1] [160]	4-O ≈ 415-427, O-S1 ≈ 243–280

[1] The cited study did not further specify the temperature at which BDE was calculated.

4.3. Effect of Thermo-Chemical Treatments

In the following, the behavior of lignin under specific thermo-chemical influences is roughly discussed, with a focus on the behavior of the β-O-4 bond, as it is the most common type of bond, and on lignin–carbohydrate complexes (LCCs), as these bonds are decisive for the retention of lignin in the cell wall. Typically, several different treatment types are combined, e.g., acids with heat, and for each treatment, there is a large number of variation options and special features not fully coverable here but further elaborated in thematically appropriate reviews. Here, the goal is to identify the general influence of the different individual treatment options.

4.3.1. Effect of Heat

Most thermo-chemical processes operate at high temperatures. The influence of heating under the absence of any solvent and oxygen on the behavior of lignin (i.e., pyrolytic decomposition) will be addressed in this section. For lignin in native lignocellulose, a transition from a glassy to a rubbery state (glass transition) has been observed already at temperatures below 100 °C; various properties, in particular the moisture content, have

an influence on this transition [141,165–167]. Due to this transition to a rubbery state at (relatively) low temperatures, lignin can serve as a binding agent when appropriate temperatures and increased pressure are applied; this is an important and often used property for wood processing (e.g., during pellet or briquette production) [168,169]. Compared to polysaccharides, lignin appears to have the highest molecular mobility, at least, this was observed during the analysis of isolated fractions [170]. Above the glass transition temperature, the mobility of the isolated lignin increased with increasing temperature, and above temperatures around 200 °C, it became completely fluid [170].

In the native polymer network, a reduced mobility was observed due to the interactions among the different polymers [171]. An increase in mobility is expected to be achieved by the addition of a solvent or an acid [170,171]. Starting from temperatures around 200 °C, splitting reactions start to occur. One reaction is the γ-elimination, where formaldehyde is released from γ-alcohol groups, whereas CO_2 is released from γ-carboxyl groups [172]. Water is released from hydroxyl groups [172]. Higher temperatures of around 400 °C are needed to release methane or methanol from methoxy groups [172–174]. The cleavage of ether bonds can already occur at much lower temperatures based on studies on the pyrolysis of model dimers [175,176]. The observed behavior of various bonds between monomers was consistent with the theoretical calculations of bond dissociation enthalpies for homolytic cleavage described above; α-ether exhibited the lowest stability (cleavage already at 200 °C), while ß-ether and ß-1 bonds were slightly more stable and 5-5 biphenyl were clearly more stable [175,176]. The phenolic OH group was found to have a strong influence; dimers with methyl groups instead of phenolic groups at the 4-position were significantly more stable (increase in decomposition temperatures by 150 to 200 °C) [176]. The overall structure of the molecule therefore has a major influence, so that the behavior of the lignin in native lignocellulose cannot be directly inferred from the investigation of the model dimers.

Furthermore, interactions with other cell wall constituents have an impact, i.e., the pyrolysis of lignocellulose is much more complex [177]. In fact, significant lignin depolymerization in native lignocellulose has only been shown at higher temperatures from about 350 °C upwards [176].

For the homolytic cleavage of $O-CH_3$ bonds, temperatures above 400 °C are needed; however, β-O-4 ether bonds have a comparable, even slightly higher bond dissociation enthalpy (234 to 242 kJ/mol for $O-CH_3$ bonds compared to 268 to 301 kJ/mol for β-O-4 bonds, Table 1) [177,178]. Consequently, it can be assumed that comparably high temperatures are needed for the homolytic cleavage of β-O-4 ether bonds [177,178].

The observed cleavage of β-O-4 ether bonds in phenolic dimers with free phenolic hydroxyl groups at significantly lower temperatures is hypothesized to occur by conversion to quinone methides, which results in a reduction in the bond dissociation enthalpy (to around 184 kJ/mol) according to theoretical calculations; however, this is only possible for structures with free phenolic hydroxyl groups [177,179]. Such free phenolic hydroxyl groups are rather rare in lignocellulose due to the strong cross-linking of lignin with other lignin monomers and carbohydrates (Section 3), but theoretically a chain reaction would be conceivable in which, starting from one free phenolic hydroxyl group, increasing numbers of such free ends are formed by stepwise ether cleavage. However, the quinone methide structure is reactive, so further polymerization reactions are likely to occur in competition with this depolymerization chain reaction [176,177,180].

At low temperatures around 120 to 180 °C, lignin repolymerization (condensation) reactions already start to occur in native wood [181]. The main condensation reactions at such lower temperatures seem to be the formation of α-aryl-linkages (diarylmethane structures) and 5,5-biphenolic structures [181,182]. From investigations with the pyrolysis

of coniferyl alcohol as a model substance, the condensation via the formation of reactive quinone methides already mentioned above has been suggested as one important condensation reaction intermediate step [183]. At even higher temperatures (from about 400 °C), carbonization (i.e., the formation of a multiple aromatic ring system) is observed [176].

Key findings and implications for technical lignin valorization by depolymerization:

- When only heated, lignin might already change from a glassy to a rubbery state at temperatures below 100 °C. Significant depolymerization of native lignin in the lignocellulose complex, however, starts to occur only at temperatures around 350 °C. Repolymerization reactions are already possible at lower temperatures than 250 °C and might lead to the formation of new, stable bonds to aromatic nuclei.
- Lignin apparently has a higher mobility than the carbohydrate polymers.

4.3.2. Effect of Solvents

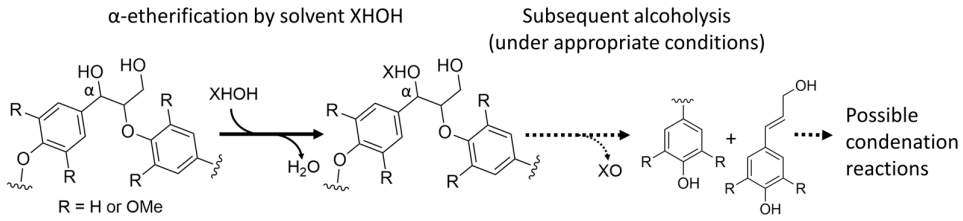
In addition to thermal energy, solvents clearly have an influence on the chemistry of lignocellulose. One indication is that a significant lignin depolymerization by ether bond cleavage in polymeric lignin and model dimers has been observed even at neutral conditions and in the absence of any catalyst in an alcoholic solvent at low temperatures around 160 to 250 °C, and thus lower temperatures than those needed for depolymerization by simple heat application [184–186].

The interactions of solvents with reactants, transition states, catalysts and products influence the reaction thermodynamics. An important, reaction-decisive factor in this regard is the solubility of the lignocellulose and the released fragments into the used solvent, as this influences the accessibility (e.g., for catalysts) and removal of lignin [187,188]. An illustrative example for the influence of the solvent is the application of an inorganic acid with water, in which lignin is insoluble (Section 4.1). Consequently, lignin is difficult to remove and rather self-condensing in such a solvent, whereas the addition of an organic solvent offering better lignin solubility largely increases lignin removal, maintaining the same acidity and temperature [187]. For organosolv processes, a clear relation between delignification and lignin solubility in the applied solvents was observed [188–190]. As presented in Section 4.1, solvents with medium polarity like alcohols, especially their mixtures with water, appear to be good solvents for lignin, whereas the spectrum of suitable solvents gets broader the smaller the lignin fragments are. Accordingly, the relationship between delignification (and thus lignin yield) and suitability of the solvent for lignin dissolution appears to become less important the smaller the lignin fragments released during a process are. Pure water appears not to be suitable to remove larger lignin fragments [191,192]. However, in processes that quickly lead to significantly smaller lignin fragments (monomers and dimers, e.g., by reductive catalytic fractionation) due to a catalytically increased cleavage and stabilization, solvents such as water with high polarity and lower lignin solubility even lead to higher delignification and yield than solvents with medium polarity under otherwise identical reaction conditions [193]. In contrast to organosolv processes, delignification was more related to the polarity, Lewis acidity and hydrogen-bond donating capacity of the solvent rather than the lignin solubility for such a process [128,193]. However, higher polarity is associated with higher total biomass degradation (i.e., higher carbohydrate solubilization and enhanced fragmentation of lignin oligomers to mono- and dimers) [193]. Consequently, the solvents have a greater influence than merely enabling the availability and removal of lignin by its dissolution.

Solvents appear to be directly involved in reactions with lignin, and therefore, properties such as the nucleophilicity and reactivity of free protons are discussed as additional important factors regarding the solvent [188,193]. As one example of reactions with a solvent, it became obvious from experiments with deuteriated methanol that methanol can

act as a hydrogen donor for both hydrogenolysis and hydrogenation reactions [184,185]. Similar effects were observed for other alcohols like 2-propanol [194]. These reactions are significantly enhanced by the addition of a suitable catalyst [184].

Furthermore, the binding of a solvent to the lignin molecule can play an important role. Alcohols (e.g., methanol, ethanol, butanol and also diols like 1,4-butanediol) can react with lignin at typical organosolv reaction conditions; typically, their etherification to the α-carbon of lignin is observed (Scheme 1) [185,195–197]. This α-etherification was observed to already occur to lignin, prior to extraction [198]. Supposedly, alcohols react by nucleophilic attack with benzyl cations of reactive intermediates and through this stabilize them against repolymerization reactions and also typically lead to an increase in solubility in the reaction media [195,198,199]. Especially interesting is the finding that such an addition of an alcohol at the α-position could facilitate the further β-O-4 ether bond cleavage by reducing the bond dissociation enthalpy, as was shown for the addition of a methoxy-group at the α-carbon (Section 4.2) [159,186]. Thus, it is believed that the alcoholysis cleavage mechanism (e.g., occurring under neutral conditions in methanol at 160 °C) involves the nucleophilic attack of the alcohol at the α-carbon and a subsequent synchronous cleavage of both α-O and β-O as a concerted hydrogenolysis/elimination reaction where the alcohol acts as hydrogen donor (Scheme 1) [184,186,200]. However, the exact reaction mechanisms in neutral solvents are not fully understood yet and different reaction pathways (possibly existing in parallel) are most likely to occur.



Scheme 1. α-etherification with an alcohol solvent XHOH and a possible subsequent alcoholysis of a β-O-4 ether bond structure.

As an alternative to the concerted process, a homolytic cleavage of liberated phenolic β-O-4 ether structures via the formation of quinone methide intermediates in neutral alcoholic solvents as well as in neutral water is proposed as an important reaction pathway [201–204]. However, experiments with non-phenolic β-O-4 ether bond models (carrying a 4-OCH_3 group instead of 4-OH) in methanol revealed that a free phenolic OH group (necessary for quinone methide formation) is not necessary for bond cleavage; thus, the proposed homolytic cleavage mechanism possibly, but not necessarily, plays an important role [184].

Applying solvents under neutral conditions and low temperatures is regarded to be suitable for preserving lignin–carbohydrate complexes (LCCs) and is thus used for their isolation [205,206]. However, few studies have investigated the fate of lignin–carbohydrate complexes in neutral solvents at higher temperatures. It has often been said that the organosolv process leads to very pure lignin and carbohydrate streams, which could indicate a high cleavage rate of the lignin–carbohydrate complexes during organosolv processes, but precise statements cannot be made without detailed investigations [207]. It can be deduced that ester bonds between lignin and phenolic acids or between carbohydrates and phenolic acids seem to be cleavable in organic solvents at 200 °C, even without the presence of a catalyst (e.g., by transesterification in organic solvents) [208,209].

At neutral conditions, unsaturated C=C double bonds can be formed by dehydration of α-OH and might repolymerize with further unsaturated double bonds [210]. Furthermore, radicals formed at increased temperatures might undergo diverse repolymerization

reactions [202,203]. In the presence of high temperatures and the absence of any active stabilization, lignin repolymerization reactions have been observed using simply water [211] or alcohols [186,202,203,212] as solvents. Significantly, more condensation occurred in wet wood compared to dry wood, when heat was applied, indicating an influence of the presence of water on depolymerization and repolymerization reactions [181]. However, even if solvents without any further acids or bases are applied, conditions are only neutral in the initial state, as a pH reduction is typically observed during biomass fractionation due to solubilized biomass components (especially acetic acid) [194,213]; therefore, there is an overlap with the reaction mechanisms caused by acidic environments (Section 4.3.3). Alcohols can act as scavenger for reactive degradation products like formaldehyde or reactive lignin fragments (e.g., α-carbocation as described above) and thereby also reduce repolymerization to a certain extent [195,214].

Key findings and implications for technical lignin valorization by depolymerization:

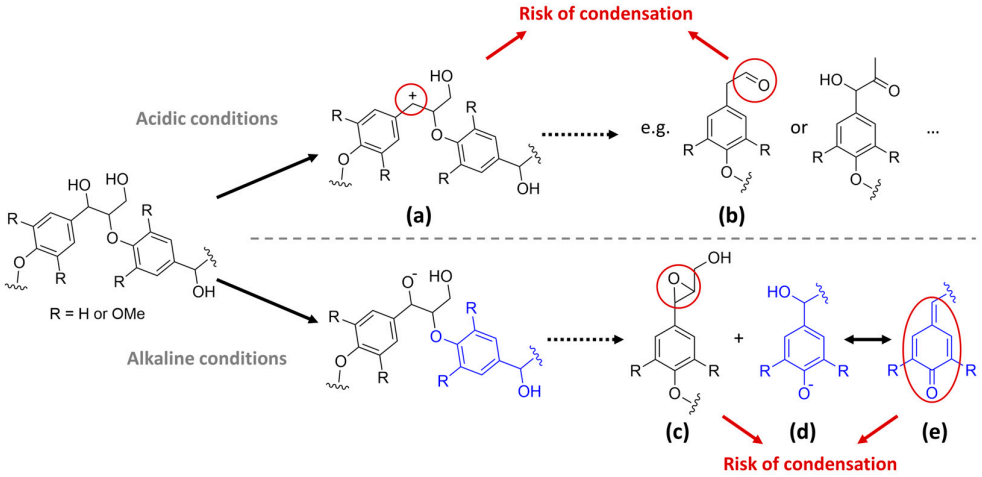
- In combination with the application of heat, solvents clearly have an important effect on lignin reactions in various ways.
- The important tasks are the stabilization and transport of released lignin fragments, and the implementation of these tasks is essential for which reactions occur next. Thereby, the suitability of a solvent depends on the solubility and thus on the characteristics of lignin fragments released by a process.
- Solvents can act as reactants themselves and donate hydrogen or attach by nucleophilic attack and thereby influence cleavage reactions but also condensation reactions.

4.3.3. Effect of Acidic Environments

Acidic treatments can be applied to separate and hydrolyze the polysaccharide fraction of lignocellulose (primarily hemicellulose, at harsher conditions also cellulose). Highly concentrated acid (e.g., phosphoric acid > 80 wt-%) can be applied to swell or even dissolve the polysaccharides and disrupt cellulose crystallinity [215,216]. The hydrolysis to monosaccharides is achieved at a higher temperature of above 90 °C, even in diluted acids [215]. With just water as a solvent and higher temperatures (e.g., 180 °C) applied, partial carbohydrate hydrolysis (predominantly of hemicellulose) and an increase in the accessibility of carbohydrates for enzymatic hydrolysis is achieved by acidic autohydrolysis reactions [217]. Whether any lignin solubilization occurs largely depends on the choice of solvent. After acidic treatments in aqueous environments, isolated lignin typically remains as an insoluble solid [218]. On the contrary, in appropriate acidic organic environments (e.g., alcohol solvents, 0.1 to 0.5 M of inorganic acids, typically 80 to 120 °C), solubilization of released lignin fragments can be achieved [195,197].

Many different structural modifications occur to lignin during acidic treatments, among them depolymerization reactions by breaking lignin–carbohydrate complexes (LCCs) and lignin bonds, but also repolymerization reactions and—especially in aqueous environments—the coalescence and redeposition of lignin fragments [219,220]. The predominant β-O-4 bond is assumed to be heterolytically cleaved by acidolysis under appropriate acidic conditions. The cleavage of both phenolic and non-phenolic β-O-4 structures is possible; however, phenolic structures (with free phenolic hydroxyl groups) are cleaved significantly faster, so that an unzipping, progressing cleavage starting from the phenolic ends moving along the lignin polymer is anticipated [221]. As typical primary reaction under acidic conditions, benzylic carbocations are formed as intermediates by elimination of a protonated α-OH (Scheme 2a), which can be followed by different hydrolysis reactions cleaving β-O-4 ether bonds [222]. However, the benzylic carbocations (Scheme 2a) or products containing aldehyde groups (Scheme 2b) or carbon–carbon double bonds formed after acidic cleavage are susceptible to nucleophilic attacks, e.g., by carbons on

aromatic rings to form carbon–carbon linkages (condensation reactions) [210,211]. Typically, such condensation reactions are energetically more favorable than the depolymerization reactions [164]. By adding an efficient scavenger for carbonium ions (e.g., 2-naphtol) to the reaction, repolymerization reactions could be reduced and extractable lignin of lower molecular weight could be obtained [211].



Scheme 2. Typical intermediates and possible products observed from the cleavage of β-O-4 bond structures under acidic (above) and alkaline (below) conditions, highlighting (**a**) benzylic carbocations and (**b**) possible aldehyde groups possibly appearing under acidic conditions, and (**c**) epoxide structures and (**d**) deprotonated new free phenolic hydroxyl groups forming an equilibrium with (**e**) quinone methide structures possibly appearing under alkaline conditions.

The most prominent lignin–carbohydrate complexes (LCCs), benzyl ether and ester, phenyl glycosidic bonds and ester bonds involving ferulic acid, are believed to be cleavable by acids under typical conditions; however, a certain process severity must be given [105]. Benzyl ethers as examples were observed to be cleavable at milder acidic conditions (e.g., 0.2 M HCl, 60 °C, 24 h) than β-O-4 ether bonds [223]. Ester bonds with the phenolic acids p-coumaric and ferulic acid are partially cleaved by hydrothermal treatment at 180 °C [213]. As a further repolymerization reaction, the formation of new lignin–carbohydrate complex linkages was observed during hydrothermal treatment [224].

Key findings and implications for technical lignin valorization by depolymerization:

- Ether bonds within lignin as well as lignin–carbohydrate complexes (LCCs) are cleavable under acidic conditions with benzylic carbocations as typical intermediates. However, lignin fragments are only removed when they are sufficiently soluble in the solvent used. Repolymerization reactions, e.g., through the formation of reactive carbocations, can easily occur under acidic conditions.
- Besides these reactions on lignin, carbohydrates (especially hemicellulose) are significantly hydrolyzed under acidic conditions.

4.3.4. Effect of Alkaline Environments

Alkaline conditions are usually applied to achieve delignification by lignin solubilization while offering the possibility of maintaining the majority of the carbohydrates, especially cellulose, as polymers. Depending on the biomass feedstock and process conditions, hemicellulose is furthermore solubilized and eventually degraded to a large extent [225]. Kraft pulping, the most used form of chemical pulping, is an example for an alkaline process applying sodium hydroxide and additionally sulfides, which further enhance delignification due to their high nucleophilicity [226,227] (pp. 91–119).

For delignification, the fragmentation and dissolution of lignin is required, which is essentially achieved by cleaving β-O-4 structures. In one proposed pathway, cations polarize β-O-4 ether bonds by forming an adduct with the oxygen atom, thus reducing the energy required for heterolytic cleavage [228]. Another proposed mechanism depends on the ionization of either the α- or γ-hydroxyl group and its nucleophilic attack at the β-atom, leading to bond cleavage, an epoxide structure (Scheme 2c) and a new free phenolic lignin end group (Scheme 2d), which is responsible for better solubility in alkali due to the conversion to a phenolic anion [227] (pp. 91–119). Phenolic β-O-4 structures (i.e., involving a free phenolic hydroxyl group) form an equilibrium with the corresponding quinone methides under alkaline conditions accompanied by the cleavage of α-O bonds (Scheme 2e); such a structure might be converted to an alkali-stable enol ether by γ–OH elimination leading to the release of formaldehyde [227] (pp. 91–119). In the presence of strong nucleophilic anions such as sulfides, further cleavage of the quinone methide ether structure can be achieved by initial nucleophilic attack on the α-carbon, so that further free phenolic end groups are formed [78,227]. Similarly to acidic cleavage, the cleavage of non-phenolic ethers occurs much more slowly than the cleavage of non-phenolic ethers; thus, it is regarded as the rate-limiting step [229]. Reactive intermediates and products, such as quinone methides in particular, but also epoxide structures, enol ethers and the formaldehyde released, are prone to repolymerization reactions, eventually leading to the formation of new, stable carbon–carbon bonds [210,227,230] (pp. 91–119).

Lignin–carbohydrate complexes (LCCs) apparently survive the alkaline Kraft cooking conditions to a large extent [231]. Especially, phenyl glycosidic bonds and benzyl ether bonds are believed to be alkali-stable to a certain extent [223,232–234]. On the contrary, ester bonds are alkali-labile (e.g., they are cleaved in 1 M NaOH at 30 °C), which explains the higher lignin dissolution from grasses under alkaline conditions, as ester bonds involving ferulic acids play an important role in grasses [63,209,234–237].

Key findings and implications for technical lignin valorization by depolymerization:

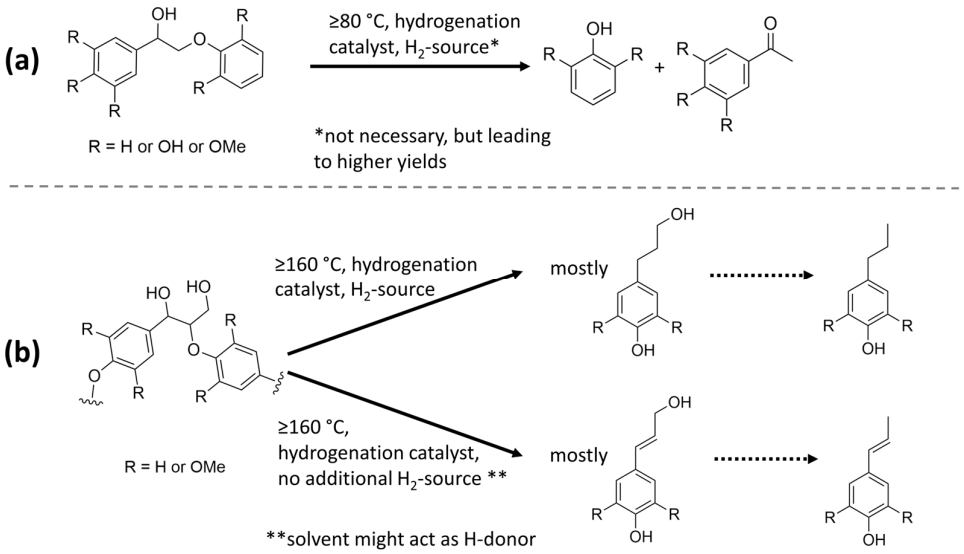
- Under alkaline conditions, ether bonds can be cleaved with quinone methide structures as typical intermediates and released fragments are typically soluble, so a delignification can be achieved. However, different intermediates are prone to repolymerization reactions.
- Among the lignin–carbohydrate complexes (LCCs), ester bonds in particular are easily cleavable by alkali, leading to the high solubilization of ester-bound fragments, whereas other LCCs appear to be more challenging to cleave.
- Alkaline treatment removes lignin and hemicellulose and leaves cellulose more or less intact.

4.3.5. Effect of Reductive Environments

Adding a hydrogenation catalyst to a lignocellulose fractionation system with available hydrogen and a good lignin solvent typically leads to significantly increased monomer yields, achieved supposedly by two effects: (1) stabilization of reactive fragments like unsaturated side chains by hydrogenation and (2) further ether bond cleavage by hydrogenolysis [185,186]. Besides the external addition of hydrogen gas, alcohols, hemicellulose components or even the α-OH group within the lignin might act as hydrogen donors making hydrogen available [185,238–241].

Regarding hydrogenolysis, different reaction mechanisms have been proposed, depending on the lignin models used and especially the reaction system applied, whose influences might be difficult to differentiate from the reductive environment. For different lignin model compounds all lacking the γ-carbon, ether bond cleavage already occurred at temperatures as low as 80 °C in the presence of a hydrogenation catalyst (Pd/C or Ru/C), even without the addition of an external hydrogen source (Scheme 3a) [239,240]. Based on

the achieved products, it was assumed that the cleavage was initiated by the dehydrogenation of α-OH, leading to the formation of an α=O ketone, which was further supported by computer simulations, suggesting the subsequent keto-enol-tautomerization and dehydrogenation prior to ether bond cleavage, enhanced by the addition of a base [240,242]. The α-OH group appears to be essential, as no conversion of the model ethers was observed when the α-OH group was absent [239].



Scheme 3. Reductive cleavage of β-O-4 ether bond structures in (**a**) model compounds lacking the γ-carbon and (**b**) native lignin and respective model compounds carrying the γ-carbon.

Using lignin models involving the γ-carbon, applying higher temperatures (≥160 °C) and adding hydrogen gas, the important role of the α-OH group was confirmed, and furthermore, the important role of oxygenated moieties at the aromatic ring was revealed, as model compounds lacking these functionalities were hardly converted at all under similar conditions [243]. However, during these experiments, monomers without any α-oxygen functionality were released, indicating that different or further reactions occur under these conditions [243]. Also, during reductive catalytic fractionation of native lignocellulose under comparable conditions (organic solvent possibly mixed with water, hydrogenation catalyst and eventually hydrogen gas; temperatures typically around 160 to 260 °C), lignin monomers with neither α-OH nor α=O group are typically obtained (Scheme 3b) [78,128,186,193,209,244]. Fast subsequent reactions like subsequent dehydration or direct hydrogenolysis might lead to the loss of any α-oxygen functionality [245]. As a different reaction pathway, the loss of α-OH by dehydration and thus the formation of an enol ether intermediate was suggested to occur through the action of acidic sites before ether bond cleavage by hydrogenolysis of the β–O bonds [246,247]. However, in reductive environments, the enol ether intermediate might be easily hydrogenated and the resulting ether structure without α-oxygen functionality can apparently hardly be further depolymerized under the same reductive conditions [200,243]. Recent experiments with deuteriated lignin do not support the reaction mechanisms mentioned so far, but indicate a concerted hydrogenolysis/elimination process with α–O and β–O bonds in β-O-4 structures being concurrently cleaved, which is the same mechanism that was already described for the alcoholysis process in Section 4.3.2 (Scheme 1) [184,185,200,243].

It is still under debate whether ether bond cleavage occurs mostly by alcoholysis or is strongly enhanced by reductive catalysis during reductive catalytic fractionation [248]. Experiments with catalysts enclosed in porous nanospheres only accessible by monomers indicate that the hydrogenation catalyst is not necessary for ether bond cleavage; however,

it is essential for the reductive stabilization of reactive intermediates (e.g., carbon–carbon double bonds), and thus prevents recondensation reactions [248]. Generally, there is an agreement on this essential stabilizing effect within reductive environments [13,78,186,210]. Still, by regenerating dehydrogenated alcohols from the solvent, hydrogenation catalysts might also influence the kinetics of ether bond alcoholysis. As a further possible reaction mechanism within reductive environments, the γ-OH group can be cleaved by hydrogenolysis [184]. Under stronger reductive conditions (e.g., using highly active hydrogenation catalysts like Raney nickel), full saturation of the aromatic rings can furthermore occur [194].

Key findings and implications for technical lignin valorization by depolymerization:

- As essential effect, reductive environments stabilize reactive fragments released during lignin fragmentation and depolymerization and thereby reduce repolymerization reactions and increase monomer yields.
- It is uncertain, and depends on the process conditions and lignin structure, how and to what extent reductive environments furthermore induce ether bond cleavage by hydrogenolysis reactions. For such reactions, the existence of an oxygen functionality at the α-carbon appears to be essential, under the reaction conditions considered.

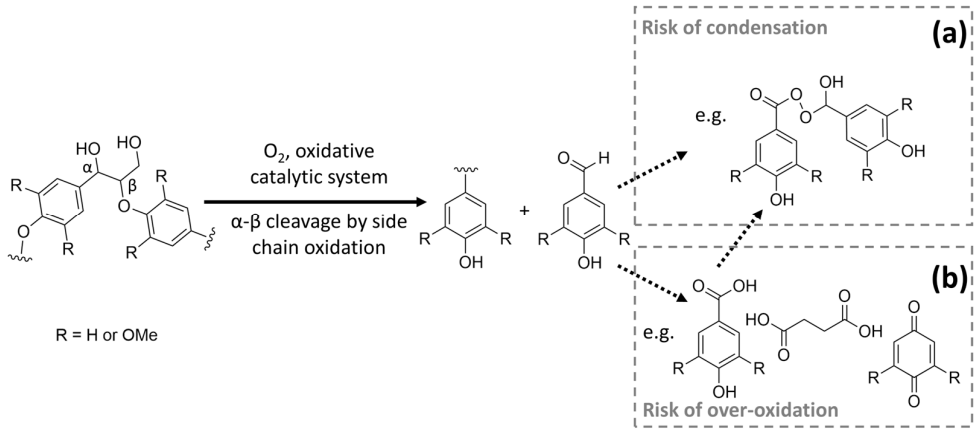
4.3.6. Effect of Oxidative Environments

Oxidative lignin depolymerization often proceeds via carbon–carbon bond cleavage and not via ether-bond cleavage, even under relatively mild conditions in terms of temperature and pH [78,249]. Consequently, oxidative methods are also able to release condensed lignin units, which is one reason why they are often applied as analytical methods (e.g., nitrobenzene or cupric oxide oxidation) [250]. Oxidative methods are also used to remove lignin for pulp bleaching. However, processes resulting in an unselective, radical lignin degradation are typically applied for this purpose [227] (pp. 201–238), [249]. Many different oxidative systems and reaction pathways have been established and are reviewed elsewhere; such systems typically comprise an appropriate catalyst (e.g., copper salts, oxovanadium complexes, cobalt salen complexes or metalloporphyrins) and an oxygen-rich atmosphere or directly apply reactive oxidant species (e.g., H_2O_2) [78,249,251]. They can lead to phenolic aldehydes, ketones or acids if the oxidation reactions are limited to the side chains of the aromatic ring and to benzoquinones and aliphatic carboxylic acids if the aromatic ring is also affected by oxidation [249]. The latter may be a valid goal, but is considered undesirable in the following, as this review focusses on the recovery of aromatics.

Regarding the most prominent β-O-4 structure, the oxidation of α-OH and/or γ-OH theoretically reduces the homolytic bond dissociation enthalpy (BDE) of the β-O-4 ether bond (Section 4.2). Consequently, some methods apply a two-step approach, starting with selective oxidations of these side groups without cleaving any inter-unit linkages, followed by a subsequent, not necessarily oxidative lignin depolymerization step [252,253]. Indeed, an increase in depolymerization yield after selective lignin oxidation has been reported [254–256]. However, some investigations have documented a decrease, indicating that there is a strong dependence on the methods applied for oxidation and depolymerization (e.g., condensation reactions have to be avoided during oxidation) [257].

As a parallel approach, many different methods for direct oxidative cleavage of inter-unit bonds were investigated. The application of oxovanadium complexes or copper-based catalysts to model β-O-4 dimers mostly led to monomeric, aromatic ketones or aldehydes from non-phenolic dimers but to p-quinones from phenolic dimers [251]. Despite the reduction in homolytic bond dissociation enthalpy of β-O achievable by α- or γ- oxidation and in contrast to the previously presented acidic, alkaline, reductive or alcoholysis procedures, a splitting of the α-β-bond and not the β-O-bond within the β-O-4 ether structure is often

observed in such oxidative processes [249]. According to theory, α-oxidation even increases the homolytic bond dissociation enthalpy of the α-β bond, but the degradation products like vanillin or vanillic acid still indicate a cleavage of the α-β bond (Scheme 4) [149,258]. In the case of a process using a copper-based catalyst, a further oxidation of the β-carbon was assumed to occur, leading to a further significant reduction in the binding energy of the α-β bond [258]. Other authors reported the cleavage of the α−β bond through a retro-aldol reaction induced by the oxidation of γ-OH [259–261]. At mild conditions, the aromatic rings are preserved, whereas harsher conditions lead to ring opening and the formation of aliphatic (di-) carboxylic acids [78,249]. Often, oxidative depolymerization is combined with alkaline conditions, where the formed enol ether intermediate (Section 4.3.4) can be cleaved under vanillin formation, while further, not yet fully understood cleavage mechanisms occur [262,263].



Scheme 4. Reaction scheme for the oxidative cleavage of β-O-4 ether bonds and possible side-reactions like (**a**) condensation reactions or (**b**) over-oxidation.

Whereas reductive environments induce the stabilization of monomers and might be applied as a strategy for preventing condensation reactions, oxidative environments, and especially the presence of molecular oxygen, might increase the risk of condensation reactions [264]. α-oxidation by transformation of α-OH to a carbonyl group or an alcohol ether might reduce the risk of repolymerization reactions by avoiding the formation of reactive sites at the α-position [255,265]. However, as a huge possible drawback due to the resulting reduction in yield, obtained oxidized products appear not to be stable in oxidative environments due to easily occurring over-oxidations to aliphatic carboxylic acids (Scheme 4b) or condensation reactions like phenolic oxidative coupling or carbonylic oxidative coupling under typical reaction conditions (Scheme 4a) [261,264].

Key findings and implications for technical lignin valorization by depolymerization:

- Oxidative cleavage apparently rather occurs at carbon–carbon bonds than at ether bonds. Thus, a larger lignin fraction might be depolymerizable by oxidative methods.
- There seems to be an increased risk of side and repolymerization reactions under oxidative conditions.

5. Biodegradation of Lignocellulose

In the following, the biodegradation of lignocellulose will be reviewed in more detail to examine which lessons can be learned from nature and which implications for technical degradation (with the aim of producing aromatic monomers) can be derived.

Nature developed the ability to deconstruct lignocellulose to smaller molecules and ultimately back to CO_2 and thereby closed the loop of carbon uptake and release from land-based plant biomass, this being an important part of the earth's fast carbon cycle [266,267].

However, this is an intricate process and apparently, only a few microorganisms (fungi and bacteria) are able to conduct it [266]. Some fungi in particular appear to be effective in lignin degradation [266]. These fungi can be divided into the two groups of white-rot fungi and brown-rot fungi (Figure 1c,d). Whereas white-rot fungi and also some bacteria are able to perform lignolysis and degrade lignin, brown-rot fungi, which evolved from white-rot fungi, only modify lignin in a way to make the carbohydrates more accessible [268].

Special challenges regarding the biodegradation of lignocellulose are the insolubility, high molecule sizes, heterogeneity, bond stability, possible toxicity of degradation products and the high carbon-to-nitrogen ratio of lignocellulose [266]. Consequently, the lignin content and especially the cellulose–lignin–nitrogen ratio of plant material are considered important parameters determining its biodegradability [269–271]. Partly, lignin appears to be stabilized and accumulated in soils and seems to play a role in humus formation; however, high variations in lignin degradation kinetics are observed and many knowledge gaps still exist regarding the fate of lignin in soils [272–275]. In order to form an impression of the solutions nature has at hand for lignocellulose degradation, lignin biodegradation is briefly summarized here.

As cells cannot take up large lignocellulose fragments, the primary deconstruction has to take place extracellularly. Therefore, microorganisms secrete a broad variety of different enzymes and reactive molecules for lignocellulose degradation. Both white-rot and brown-rot fungi secrete non-enzymatic, reactive, low molecular weight compounds that react with lignin and initiate its decay [276]. White-rot fungi furthermore extensively secrete oxidative enzymes such as peroxidases and laccases, which further act on lignin degradation [277,278]. As a typical pathway, these enzymes induce the oxidation of aromatic nuclei by single-electron transfer, leading to unstable radicals, which consequently undergo a variety of non-enzymatic reactions, e.g., cleavage of α-β bonds, demethylation or even ring cleavage [267,279,280]. In this way, these enzymes lead to the non-selective oxidative bleaching process, known as white rot, releasing oxidized aromatic molecules like vanillin [266,280]. The enzymes typically released are non-specific; they can also be used to degrade components similar to lignin like dyes or pesticides [276].

By applying such lignolytic enzymes for lignin cleavage in vitro, repolymerization (condensation) reactions are observed in addition to depolymerization reactions. However, these repolymerization reactions are not observed in microbial lignin conversion, indicating that microorganisms have developed mechanisms to avoid condensation, e.g., by the release of accessory, reductive enzymes [280]. It is believed that enzymatic white-rot degradation can only take place at the surface of the wood cell wall, as enzymes cannot diffuse through the cell wall [144,281]. Compared to lignolytic bacteria and white-rot fungi, brown-rot fungi lack different oxidative enzymes and seem to apply non-enzymatic lignin degradation to a larger extent [268,282]. This non-enzymatic brown-rot degradation is based on the release and action of small reactive, oxidative molecules, e.g., hydroxyl radicals, presumably produced by the reaction of reduced metals (e.g., iron) with hydrogen peroxide (Fenton chemistry) that attack the lignocellulose matrix [268,281,282]. The reduced metals (e.g., iron) might be released from the biomass and generated via low molecular weight compounds (e.g., phenolates, peptides, organic acids) released from the cell, and the hydrogen peroxide might be produced by oxidative enzymes. However, the exact mechanisms have not yet been conclusively clarified [268,276,282,283]. Oxidative demethylation of aromatic rings, side chain oxidations (e.g., to aldehydes or carboxylic acids), combined with depolymerization and repolymerization reactions, are thus effected during brown-rot, leading to a structurally highly modified, but still polymeric, lignin [281,282,284]. Through this mechanism relying on small molecular weight compounds as degradation reagents,

brown-rot degradation is not limited to the lignocellulose surface but can directly attack the cellulose-rich S2 layer, which leads to a faster destabilization of the wood structure [281].

A certain extent of unselective oxidation already takes place extracellularly, and also, the release of CO_2 is already observed from extracellular enzymatic reactions resulting in no direct metabolic gain for the microorganisms. Consequently, lignin degradation is also designated as an "enzymatic combustion" process [267,285,286]. However, smaller lignin fragments released by the extracellular treatment can be taken up by microorganisms and degraded intracellularly. As an example, with the combination of non-radical and selective intracellular β-etherases with further enzymes and necessary co-factors, ether bonds in lignin dimers and oligomers could be selectively cleaved to release monomers [287,288]. The fact that lignin is racemic and contains many chiral centers makes selective enzymatic degradation more complicated, as many enzymes are stereospecific and therefore different enzyme variants might be required [287]. However, in this way, lignin components can be processed within the cells of white-rot fungi, whereby they are biologically funneled into central intermediates and thus incorporated into the metabolism, so that ultimately, white-rot fungi pave the way for the conversion of carbon sequestered in lignin back to CO_2 [289–291].

However, the main metabolic benefit in lignin degradation probably lies in increasing the accessibility of carbohydrates, which are also degraded by white-rot fungi either simultaneously or, for some species, following the lignin removal [292]. Brown-rot fungi evolved from white-rot fungi; however, this was not accompanied by a further refinement of enzymatic lignin degradation. Instead, the enzymatic apparatus was reduced and brown-rot fungi predominantly apply non-enzymatic lignin degradation [268]. This pathway is regarded as less energetically expensive than the white-rot pathway requiring the synthesis and export of many different enzymes [281]. Overall, lignin is not fully degraded during brown-rot degradation, and a large chemically modified part is left. Consequently, the metabolic gain for brown-rot fungi definitely mainly results from the increased accessibility of the carbohydrates [268].

For carbohydrate degradation, different types of enzymes are abundantly found in fungi and bacteria. However, their action is constricted by the lignin groups attached, so that an efficient conversion requires the removal of lignin [293]. One important class of enzymes are glycoside hydrolases cleaving glycosidic linkages in hemicellulose and cellulose [277]. These are further supported by other enzymes like esterases cleaving ester-bound side groups of hemicellulose and lignin–carbohydrate complexes (LCCs) [294,295]. Additionally, lytic polysaccharide monooxygenases (LPMOs) act on both hemicellulose and cellulose [296,297].

As is evident from the presented main pathways of lignin biodegradation, oxygen plays a major role in lignin biodegradation. For both white-rot and brown-rot degradation, oxidative enzymes or oxidative molecules were involved inserting oxygen functionalities like carboxyl groups during degradation. Indeed, lignin biodegradation rates increase with increasing oxygen concentration [298–300]. This finding leads to the question as to whether any lignin degradation is possible under anaerobic conditions; and this question is still under debate. Lignin monomers, dimers or smaller oligomers are anaerobically degradable [301,302]. However, many studies report a very limited degradation of native, polymeric lignin under anaerobic conditions, and typically, the relative accumulation of lignin is observed during anaerobic digestion [209,267,271]. Reports about the reduction in acid-soluble lignin, the reduction in purely ester-bound aromatics and the release of aromatic acids like p-coumaric acid or p-hydroxybenzoic acid during anaerobic digestion indicate that ester-bonds are cleaved under anaerobic conditions; which is not surprising, as ester cleavage does not require

oxygen [209,303,304]. Different studies indicate a reduction in syringyl to guaiacyl ratios in lignin after anaerobic digestion of native biomass [209,284,304]. This might have been caused by the conversion of syringyl to guaiacyl units by redox-neutral O-demethylation reactions observed under anaerobic conditions [280,305,306]. The loss in ether bonds and phenylcoumarans and changes in molecular weight were observed during NMR-based investigations of lignin deconstruction by anaerobic fungi, indicating some structural remodeling under anaerobic conditions [303]. Even under anaerobic conditions, traces of oxidative cleavage of ether and carbon–carbon bonds in peripheral lignin were found, indicated, e.g., by new α- and γ-oxidized end units [304]. However, no significant change in ether bond content was observed for lignin obtained after the anaerobic digestion of straw [209,304]. Consequently, there are apparently some lignin degradation reactions that also take place under anaerobic conditions. Nevertheless, they appear to be slower than under aerobic conditions and they are so far not sufficiently understood.

Key findings and implications for technical lignin valorization by depolymerization:

- Nature's response to the complex lignin structure is an oxidative and nonspecific lignin degradation mediated by an extracellular system [267]. Similarly to its role during lignin synthesis, enzymatic action is rather indirect during lignin degradation, which is instead largely based on radical formation as well. There is no recycling to the original lignin monomers, which would require selective, reductive cleavage. Instead, further oxidation is the main pathway for lignin degradation in nature, leading to either degraded lignin (brown-rot) or a variety of lignin fragments, which are biologically funneled and incorporated in metabolism (white-rot). Can these natural mechanisms be utilized or copied?
    - Copying this mechanism in vitro would presumably require a complex set of enzymes, co-factors and auxiliary molecules and finally end up in a complex, heterogeneous mixture of possibly condensed lignin fragments. This process appears to be much more complex than the in vitro enzymatic cleavage of cellulose, which requires a small subset of enzymes selectively leading to the original glucose monomers, which nevertheless already poses some challenges in terms of costs and reaction rates [307].
    - Adapting the use of redox-active molecules for lignin degradation from brown-rot fungi, but generating these chemically is a nature-mimicking strategy currently being investigated [308–311]. However, condensation reactions in the lignin can be expected due to the non-selective, radical-based procedure.
    - Applying lignin-degrading microorganisms is generally regarded as one possibility of biological pre-treatment of lignocellulose. However, biological degradation is a slow process and microorganisms will degrade both lignin and carbohydrates so that pre-treatment comes along with a loss in both [312].
    - Applying genetically modified microorganisms to conduct lignolysis as well as biological funneling to specific reactive intermediates could be used to avoid the expense of enzyme production and achieve a high selectivity (even single products) [280]. However, the challenges of slow reaction rates remain and the challenges of handling fermentations with genetically modified organisms are added.
- Biological processes typically have the advantage of high selectivity and specificity, but these do not appear to be provided in the case of lignin biodegradation. Instead, there are some challenges and disadvantages for biodegradation that do not exist or could be overcome in thermo-chemical processes (among them are the insolubility, high molecule sizes, possible toxicity of degradation products, the high carbon-to-nitrogen ratio of lignocellulose and the slow apparent reaction rates in

the case of biodegradation). What remains are the challenges of heterogeneity and bond stability, and the disadvantage of reactivity is even more severe in the case of thermo-chemical processes.

6. Discussion of the Derived Implications

In the following, the derived implications for lignin valorization by depolymerization will be arranged and discussed from a technological process, economic and environmental point of view and compared with the current scientific and technical status of lignocellulose fractionation. The points discussed apply generally to native, lignocellulosic biomass, although it should not be forgotten that each type of biomass entails its own specific challenges. In contrast to the chemical, physical and/or biological correlations presented above, this interpretation is not completely conclusive; obviously, different conclusions might be drawn from the same theoretical basis.

What products can be made from lignin?

The possible products that can in principle be made from lignin seem endless in a range from carbon nanotubes to small organic acids. This paper is limited to the aim of obtaining phenolic monomers and oligomers from native lignin. Based on its structure, phenylpropanoids and thereof derived phenolic structures can be obtained from lignin by depolymerization, whereby the selectivity is very limited by the fact that lignin consists of several different alcoholic or carboxylic phenylpropanoids and, to a lesser extent, other phenolic components. The monomeric composition and thus the composition of the possible product mixture largely depend on the biomass type applied.

How to proceed for valorizing native lignin by depolymerization?

Native lignin cannot be viewed in isolation without considering lignocellulose. If the depolymerization of native lignin is envisaged, the treatment of an entire native lignocellulose complex is to be considered. Lignin is added as the last component during the biosynthesis of lignocellulose and its function is often compared to that of a glue. Furthermore, it has to be biodegraded before carbohydrates can be extensively valorized by fungi and bacteria, it shows the highest mobility among the lignocellulose constituents and it has reactive side groups prone to side-reactions under harsh conditions. All these arguments speak in favor of carefully removing lignin first during lignocellulose fractionation with the aim of lignin depolymerization. However, some studies attribute the effect of a glue not to lignin but to hemicellulose, which is also plausible due to its compatibility with both constituents of cellulose and lignin and its position between them [313]. So, bringing these two points of view together, the combination of lignin and hemicellulose could be described as a two-component glue. Hemicellulose also has reactive parts solubilizing readily under mild conditions, e.g., in hot water or steam [217]. Thus, in order to achieve high carbon efficiency, both fractions of lignin and hemicellulose should be regarded with special focus at the beginning of a process and removed at least to a certain extent, whereas cellulose is the most stable fraction within the overall lignocellulosic material.

In view of the nature of native lignin, what should a lignocellulose fractionation process involving lignin depolymerization look like?

As concluded by the end of Section 5, biology is successful in depolymerizing lignin but faces some challenges, especially with regard to the requirements of industrial processes that might be overcome by thermo-chemical processes. Cleaving β-O-4 ether bonds and lignin–carbohydrate complexes (LCCs) (which are also carbon–oxygen bonds and have a comparable stability) is the most effective way to release lignin and depolymerize it into monomers and oligomers, whereas for further depolymerization of the oligomers, the cleavage of more stable bonds would be necessary (i.e., the cleavage of carbon–carbon bonds and especially those bonds directly involving an aromatic ring).

Ether bond cleavage can be achieved by many different approaches, e.g., the application of heat at high temperatures above 300 °C or of heat at lower temperatures in combination with neutral solvents or acidic, alkaline, reductive or oxidative environments, as outlined above. In oxidative environments, however, carbon–carbon bonds tend to be cleaved, also within an ether bond structure. Less is known regarding the fate of lignin–carbohydrate complexes under these treatments; however, as they do not contain bonds directly involving the aromatic ring according to the current state of knowledge, they can be assumed to be among the bond types with rather low stability. Whereas acidic conditions appear to cleave most of the lignin–carbohydrate complexes (LLCs), the cleavage of LCCs might be limited to ester bonds under alkaline conditions.

However, much more important than bond cleavage seems to be that subsequent repolymerization and redeposition reactions are avoided. Therefore, it is firstly important to achieve a good removal of dissolved lignin fragments and for this, in turn, a high solubility of these fragments in the solvent used is important. Solubility properties depend on the properties of the lignin fragments released by a specific process; however, in general, solvent mixtures with medium polarity, such as alcohol–water mixtures, have proven to be suitable with regard to the heterogeneous lignin structure, while non-polar solvents are rather unsuitable. For a process rapidly leading to lignin depolymerization to small fragment sizes (monomers and oligomers), a broader range of solvents might be suitable. Flow-through reactors enable faster removal in order to further shorten the time span for side reactions [210]. Furthermore, the reaction conditions should be chosen to be as mild as possible so that the desired cleavage reactions still take place and the undesired side reactions are minimized [198,210]. This is an argument for initially limiting the process severity to achieve cleavage of only the dominant, less stable ether and ester bonds within lignin. In addition, active measures should be taken to stabilize reactive side groups; for example, reductive conditions or the use of alcohols as solvents have proven to have a stabilizing effect. There are further approaches for minimizing side reactions with the help of protective groups, introduced, for example, by using diols or aldehydes that form cyclic acetals with lignin side groups [13,210,314,315].

What technical, economic and environmental restrictions exist with regard to the derived implications for technical lignin valorization by depolymerization?

Until now, there has been "very low commercial success" [316] regarding the implementation of lignocellulosic biorefineries at industrial production levels. Process complexity was identified as a main obstacle [316,317]. Lignocellulose always entails unavoidable complexity due to its heterogeneity, the associated handling of solids and the challenge of irregular and decentralized availability. However, the subsequent fractionation process should be as simple as possible. Furthermore, chemical, solvent and energy input as well as waste generation are to be minimized due to economic reasons and to provide environmental benefits. Ultimately, the process must be technologically feasible and profitable, for which high value final products and a high overall carbon efficiency are beneficial. Typically, the utilization of lignin as a value-added co-product in addition to carbohydrate valorization is regarded as essential for the viability of lignocellulosic biorefinieries [318].

However, additional lignin valorization by depolymerization appears to necessarily complicate the biorefining process, as indicated by the implications derived from the nature of lignin outlined above. In particular, the need to process native lignocellulose instead of isolated, but condensed fractions and applying active stabilization to avoid side reactions entails further complexity (e.g., the intermixing of a catalyst with biomass solids, addition of further chemicals or implementation of a hydrogen atmosphere). Catalysts need to be separated from biomass remnants and recycled; further chemical input implies higher costs, and the work with hydrogen gas entails expensive safety measures. Furthermore,

the degree of milling required for a stabilization measure to be effective (e.g., to ensure sufficient diffusion) is critical, as small particle sizes that can be easily produced in the laboratory can make a process uneconomic and/or technically unfeasible on an industrial scale [109,210,319].

The need for solvents, preferably small-molecule solvent mixtures containing an organic fraction, comes with the need for a presumably energy-intensive solvent recuperation, high reaction pressures and possibly explosive atmospheres and thus, safety and environmental risks. Water alone, as an abundant, environmentally friendly and cheap solvent, is only suitable for lignin depolymerization under very specific conditions (i.e., quick depolymerization, Section 4.3.2). Small organic molecules like methanol or ethanol are available as bio-based. However, they are more expensive and thus require a high degree of recuperation, which might be energy intensive. As an example, for a certain reductive catalytic fractionation process using a solvent mixture of methanol and water, solvent recycling and water removal via distillation alone required an energy demand corresponding to 73% of the input biomass energy content [318]. The related study identified the reduction in reaction pressures and the minimization of solvent loading and energy requirements for solvent recycling as key adjustment parameters for increasing economic profitability and decreasing environmental impacts [318]. Solvents with high vapor pressures (e.g., ethylene glycol) can be used to avoid high reaction pressures; however, such solvents are typically more expensive and product separation might be more complicated and energy intensive [197,320,321]. Using membrane separation or the partial direct reuse of reaction liquor without separation are possible ideas for the reduction in the energy requirement related to solvent recovery [322–324]. The issue of solvent recovery is also associated with the topic of product separation, where different lignin and sugar products are to be separated.

Processes including the depolymerization of native lignin offer the possibility to recover bio-based aromatic chemicals and carbohydrate-based products at the same time, thus enabling a high carbon efficiency and value creation. In particular, oxidized monomers like vanillin, obtained, for example, by oxidative treatments, are regarded as valuable due to their high degree of functionalization [251,325]. However, also for monomers obtained by reductive treatments, valuable applications, like the use for plasticizer generation or further conversion to phenols, are proposed [326,327].

In summary, increased value creation in a lignocellulosic biorefinery by using lignin by depolymerization is accompanied by an increase in process complexity and typically also energy and material input. Specific process development and research have to be conducted to minimize these constraints and achieve a final net economic and environmental benefit, which has to be assessed by appropriate analyses.

To what extent do established or recently developed processes fulfill the developed criteria?

The main criteria for an efficient fractionation of native lignocellulose with the aim of enabling lignin depolymerization were found to be as follows:

1. The primary focus should be on the gentle removal of lignin and possibly hemicellulose, enabling the utilization of all fractions;
2. Lignin–carbohydrate complexes (LCCs) and β-O-4 ether bonds should be cleaved;
3. Liberated lignin fragments must be soluble;
4. Reactive lignin fragments should be actively stabilized.

Table 3 shows to what extent different processes fulfill these criteria. Compared are the industrially established Kraft and sulfite processes, the organosolv and hydrothermal treatment processes already implemented on a pilot scale in the research area and two different lignin-first processes still under research on a laboratory scale: reductive catalytic fractionation (RCF) and aldehyde-assisted fractionation (AAF). It turns out that all these

processes fulfill most of the criteria, but that the processes established on industrial scale lack an active stabilization strategy and thus end up with condensed lignin that is hard to depolymerize. The key for a higher-value lignin valorization by its depolymerization will thus be to develop a lignin stabilization strategy that can be combined with a lignocellulose fractionation process and is practically realizable and economically viable as well as environmentally sound. Many different successful strategies of lignocellulose fractionation with lignin stabilization such as RCF and AAF, generally grouped as lignin-first processes, have already been developed, but their scalability still needs to be demonstrated [13].

Table 3. Comparison of how different lignocellulosic treatment processes with different technology readiness levels (TRLs) meet the criteria for an efficient fractionation of native lignocellulose with the aim of enabling lignin depolymerization elaborated in this review.

	Established Processes		**Under Research at TRL ≥ 7**		**Under Research at TRL ≤ 7**	
	Kraft pulping (pp. 91–119), [227,328]	Sulfite pulping [227] (pp. 91–119)	Organosolv pulping [188,195,212]	Hydrothermal treatment [213,217,220]	Reductive catalytic fractionation (RCF) [128,186,209]	Aldehyde-assisted fractionation (AAF) [314]
Primary focus	Removal of lignin	Removal of lignin	Removal of lignin	Removal of hemicellulose	Removal of lignin	Removal of lignin and hemicellulose
β-O-4 ether bond cleavage	Largely by alkaline conditions and application of strong nucleophiles	Largely by acidic or alkaline conditions and application of strong nucleophiles	To a certain extent, by solvolysis and often acidolysis	Slightly by (auto-)hydrolysis	Largely by solvolysis and hydrogenolysis	Not in first step due to stabilization strategy. Possible, e.g., by hydrogenolysis in second step.
Lignin solubility	Yes, in aqueous alkali	Yes, in water due to sulfonation	Yes, in organic solvent	No	Yes, typically in organic solvent	Yes, in organic solvent
Active lignin stabilization	None	None, but sulfonation leads to certain stabilization	None, but attachment of alcohols leads to certain stabilization	None	Yes, by hydrogenation	Yes, reactions with aldehydes lead to blocking of reactive positions and hinder ether cleavage
Modifications to lignin	Fragmentation, condensation, addition of thiol groups	Fragmentation, condensation, sulfonation	Fragmentation, condensation	Fragmentation, redeposition, condensation	Depolymerization to oligomers and monomers. Hydrogenation. Partial loss of aliphatic OH groups	Acetal formation and reaction of aldehydes with aromatic rings in first step.
Utilization of all fractions	Lignin typically burned. Hemicellulose partly retained in pulp, partly burned. Cellulose as pulp.	Lignin burned or low-value material use (e.g., as dispersant). Hemicellulose partly retained in pulp, partly burned. Cellulose as pulp.	Solid lignin recovered, potential use, e.g., for phenolic resins. Hemicellulose partly solubilized, partly retained together with cellulose as pulp.	Hemicellulose oligomers solubilized in water. Cellulose enzymatically hydrolysable. Solid lignin potentially usable, e.g., as filling material.	Lignin as oil with diverse potential uses as aromatic chemicals. Hemicellulose partly solubilized, partly retained together with cellulose as pulp.	Potential use of functionalized hemicellulose sugars and depolymerized lignin as chemicals. Cellulose as pulp.

7. Conclusions

The nature of lignin and lignocellulose is extremely complex and still not fully understood. Nevertheless, a huge variety of research results provides a fundamental understanding, which this review article attempts to consolidate in order to derive consequences for the technical implementation of native lignin depolymerization.

It becomes clear that special attention should be paid to lignin when developing valorization strategies due to its high reactivity and the associated risk of condensation reactions (repolymerization with the formation of very stable bonds). To avoid condensation reactions, process conditions during fractionation should be as mild as possible so that only the predominantly present and less stable ether and ester bonds are cleaved. However, even under such conditions, repolymerization reactions typically occur, so active measures should be taken to stabilize reactive side groups.

Currently established lignocellulose valorization processes do not include such active stabilization measures and thus end up with condensed lignin that is hard to depolymerize. However, requirements such as the implementation of active stabilization measures conflict

with the technical and economic necessity of keeping the process as simple as possible and minimizing energy and material input. Consequently, there has to be a tradeoff between these requirements to find viable process options. Further research should focus on the development of simple, efficient stabilization strategies.

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