Review Article

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Insights into Production of Hydroxybenzaldehydes via Lignin Oxidation

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Abstract
Hydroxybenzaldehydes (HBAs) are ubiquitous in reaction mixtures obtained from various types of lignin degradation, particularly oxidative degradation. This article reviews the formation behaviors, pathways, and mechanisms of HBAs during alkaline nitrobenzene and alkaline aerobic oxidations of lignin. The former is a well-known analytical method for lignin, while the latter is of industrial importance from the viewpoint of the production of bio-based aromatics.

Keywords: *Nitrobenzene; Mechanism; Molecular oxygen; Oxidation; Vanillin*

INTRODUCTION

Hydroxybenzaldehydes (HBAs) are a group of ubiquitous compounds found in reaction mixtures obtained from many types of lignin degradation. These compounds reflect the substitution patterns of the aromatic nuclei in lignin and mainly include vanillin, syringaldehyde, and *p*-hydroxybenzaldehyde. The formation of HBAs is particularly prominent in oxidative degradation reactions of lignin, as expected from their structures [1-8)]. For instance, in the alkaline nitrobenzene (AN) oxidation method for lignin analysis, the yield of HBAs can reach 30–50% depending on the lignin sample used [7,8)]. Apart from AN oxidation, HBAs are also produced as major products in oxidation reactions using other oxidants, such as molecular oxygen, sometimes accompanied by the formation of relatively minor amounts of carboxylic acids and *p*-hydroxyacetophenone derivatives [1-6)]. These facts suggest that HBAs are present at major energy minima in the potential energy maps of various oxidative degradation reactions of lignin. It therefore becomes obvious that gaining an accurate understanding of the principles underlying this phenomenon holds immense significance in lignin chemistry.

The oxidative degradation of lignin to produce HBAs, such as vanillin (4-hydroxy-3-methoxybenzaldehyde), has significant industrial importance. Vanillin is not only well-known as a flavoring agent but also serves as a raw material for pharmaceuticals and polymers, and has established itself as one of the platform chemicals in the chemical industry [6,9,10)]. Moreover, syringaldehyde obtained from hardwood lignin has high potential as a chemical product and is expected to be utilized as a raw material for pharmaceuticals [9)]. One of the methods for producing vanillin involves converting lignosulfonate, which is a byproduct of sulfite pulping, into vanillin through aerobic oxidation. This was the major vanillin production method in the world until the 1990s [6,10)].

Despite the academic and industrial significance of generating HBAs through the oxidation of lignin, the mechanism underlying HBA production from lignin remains incompletely understood. For example, although AN oxidation has long been a vital method for lignin analysis, few studies have investigated the detailed reaction pathways and mechanisms of AN oxidation. Also, mechanistic insights into the aerobic oxidation for vanillin production would be useful for the development and improvement of chemical processes. However, studies in related fields are more on the application side, focusing mostly on the development of catalysts and elucidating the relationship between various reaction conditions and vanillin yield [11-15]. There are only a few instances of extensive investigations into the reaction mechanism of aerobic oxidation from the viewpoint of vanillin production.

Our research group is primarily focused on generating vanillin from softwood lignin, and we are currently conducting studies to elucidate the molecular mechanisms of the oxidation process. As previously mentioned, the crucial oxidants for vanillin production are nitrobenzene and molecular oxygen, which have different academic and industrial perspectives. In this review, we survey the reported mechanisms of vanillin production using these oxidants and introduce our research results on elucidating the vanillin production reaction using molecular oxygen, in particular.

Alkaline nitrobenzene (AN) oxidation

AN oxidation is typically carried out by reacting lignin-containing samples (such as wood flour or isolated lignin) with an excess of nitrobenzene in 2 M NaOH aqueous solution (aq.) at 170-180℃ for 2.0-2.5 h. The AN oxidation method is advantageous in that it can be relatively easily performed by adapting the reaction system to the high pressure required, and can be applied to solid samples such as wood flour. Additionally, the produced HBAs can be accurately analyzed by various chromatography techniques. Despite the recent development of direct analysis methods for lignin samples such as two-dimensional (2D) nuclear magnetic resonance (NMR), AN oxidation retains its position as a major lignin analysis method due to those advantages. As we will discuss below, ether linkages in lignin are a major source of HBAs generated in AN oxidation with the other types of linkages in lignin, mainly C-C linkages, having relatively minor contribution.

The reaction mechanism of AN oxidation has been studied using model compounds since the method was first reported. In 1971, Chan and Allan conducted a review of previous reports up to that time [16]. The presence of a phenolic OH group at the *p*-position to the alkyl side-chain and/or α-OH or $C_\alpha=C_\beta$ moieties in the side-chain play important roles in the efficient generation of C_α-aldehyde structures by AN oxidation. Based on these phenomena, they proposed that nitrobenzene ionically (2-electronically) oxidizes the reactant and intermediates to produce vanillin, as shown in Figure 1A using isoeugenol (2-methoxy-4-(2-propenyl)phenol) as an example. Isoeugenol is known to give vanillin in a yield of more than 90 mol% by AN oxidation [16]. Although not discussed in detail, it is considered that nitrobenzene attacks the negatively charged site (phenolic OH groups, β-position in the side-chain, etc.) of the deprotonated isoeugenol molecule.

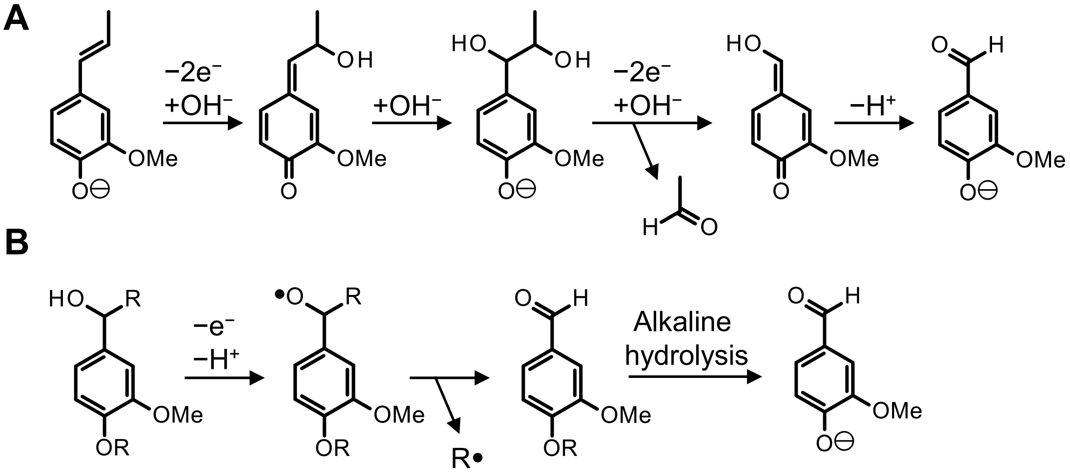

Fig. 1. The ionic oxidation of isoeugenol by nitrobenzene proposed by Chan and Allan (A) [16] and the oxidation of a middle non-phenolic unit by nitrobenzene through the radical mechanism proposed by Schultz and Templeton (B) [17].

On the other hand, Schulz and co-workers have proposed an AN oxidation mechanism based on a radical mechanism (1-electron mechanism), as shown in Figure 1B [17-20]. A plausible initial step of this mechanism is the formation of a complex between the α-OH of the side-chain and nitrobenzene. The N-O bond in this complex is then homolytically cleaved, resulting in the formation of an α-oxyl radical. An α-aldehyde structure is generated by the further progress of β-elimination reaction from this radical [17,20]. The experimental results supporting this mechanism include: 1) a significant decrease in reactivity in AN oxidation for model compounds without the α-OH group in the side-chain, and 2) electron spin resonance (ESR) analysis of the reaction solution suggesting the generation of radical species.

While there are various chemical phenomena that support both the ionic and the radical mechanisms, definitive evidence to confirm their existence has not yet been reported. Additionally, many of the model compounds used in the mechanistic studies, such as those observed in isoeugenol, contain structures that are not present in native lignin. Chan and Allan have deduced the pathway for vanillin production from the phenolic β-O-4 structure shown in Figure 2, based on the reaction mechanisms reported in studies on the above ionic AN oxidation mechanism and alkaline degradation under soda cooking [16]. In this pathway, the non-oxidative alkaline decomposition of the β-ether in lignin generates an enol ether intermediate, which is gradually oxidized by nitrobenzene in a manner similar to that in Figure 1A, resulting in the formation of a HBA. However, the existence of this pathway has not been experimentally confirmed, for example by subjecting the isolated enol ether to AN oxidation.

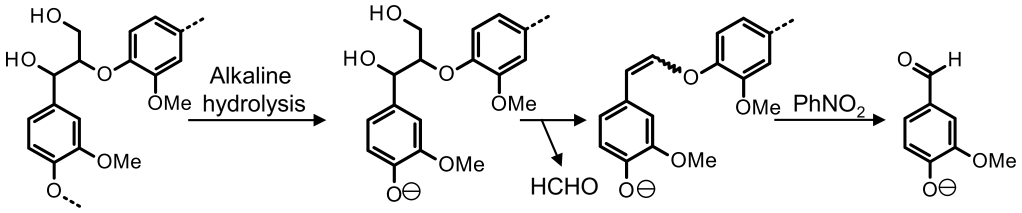

Fig. 2. Production of HBA (vanillin in this case) through the oxidation of an enol ether intermediate [16].

Despite the limited knowledge regarding the reaction mechanism, there are several systematic reports on the relationship between the partial structures in lignin and HBAs yield [21,22]. In these cases, models that relatively well reflect the structures in lignin are often used. For example, the yield of vanillin produced from guaiacylglycerol-β-guaiacyl ether **GG**, a model compound that represents the lignin structure, under typical AN oxidation conditions was 60-90 mol% [21,22]. On the other hand, the yield of vanillin from a model compound of a phenolic β-5 structure is lower, around 55 mol% [21]. Somewhat lower HBA yield of 31 mol% is reported for a phenolic β-β type model [16]. The high stability of the 5-5' linkage under the AN oxidation conditions has been demonstrated [16,23]. Furthermore, protecting the phenolic OH group significantly reduces the reactivity of these model compounds towards AN oxidation [21,22]. The reactivity of condensed structures, such as α-5, which are generated during the denaturation process of lignin under high-temperature alkaline conditions, such as those in soda cooking, is known to be significantly low [22,24]. These experimental facts make it plausible that HBAs production under AN oxidation mainly proceeds from the phenolic β-O-4 structure, while HBAs production from condensed structures and non-phenolic ether units is less efficient.

Alkaline aerobic oxidation oriented to chemical production

The AN oxidation method is the most efficient among many lignin oxidation methods for producing HBAs. However, if this method is to be utilized industrially, the coexistence of unreacted nitrobenzene and its reduced products with HBAs in the reaction mixture can cause separation and removal problems [6,10]. The toxicity of nitrobenzene is another factor that impedes its industrial application. Against this background, the production of vanillin from softwood lignin (specifically, softwood-derived lignosulfonate), which has long been industrialized, adopts similar high-temperature alkaline conditions to those of AN oxidation. Nevertheless, inexpensive and non-toxic molecular oxygen is utilized as the oxidizing agent. In other words, the production of vanillin involves the reaction of lignosulfonate with a copper (II) oxide catalyst in a sodium hydroxide solution at a temperature of approximately 170°C under pressurized air [6,10, 25-27].

The production of vanillin from lignin has been mostly replaced by the formylation of guaiacol (2-methoxyphenol), a fossil fuel-based method, due to difficulties in treating waste liquids containing sulfur compounds from the raw materials, the need for complex purification processes resulting from low product yields, and harsh reaction conditions [6,10]. However, in today's society, where the transition to non-fossil resources is being encouraged, the production of vanillin from lignin is once again gaining attention as an industrialized method of lignin conversion. Among the aforementioned issues, the problem of waste liquids containing sulfur compounds has become a bottleneck in this method, and process improvements are required to solve this problem. One of the various solutions is to use lignin raw materials that do not contain sulfur. Utilizing native lignin in sawdust generated during the lumbering process, for instance, would be an effective solution.

Few studies have investigated the reaction mechanism of vanillin production from native lignin, which should be useful for the development and improvement of vanillin production processes, except for several examples proposing vanillin production through retro-aldol reactions using simple model compounds [28,29]. On the other hand, although the reaction conditions are quite different (lower temperatures and thinner alkaline concentrations are employed), several detailed reports using model compounds exist in studies related to pulp bleaching using molecular oxygen [30-32]. A mechanism has been proposed in which vanillin is produced by homolysis of a dioxirane intermediate generated by the attack of O_2 on the C_α=C_β structure of the enol ether generated from **GG** as shown in Figure 3 [30]. This mechanism is interesting in that vanillin is generated via the enol ether formed by the alkaline decomposition of **GG**, similar to the reaction pathway in AN oxidation shown in Figure 2. It is known that fragmentation reactions to produce various carboxylic acids, aldehydes, etc. other than vanillin production occur under pulp bleaching conditions [30,31,33]. It has been also shown that powerful oxidants such as OH radical are generated from superoxide ions produced by one-electron transfer between molecular oxygen and phenolate ions, and these active oxygen species play important roles [34-37]. However, further investigation is necessary to determine whether these complex reactions in pulp bleaching are also functioning similarly under vanillin production conditions.

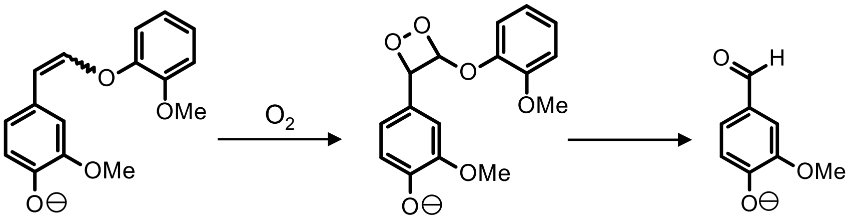

Fig. 3. Vanillin formation via the dioxirane intermediate generated by the oxidation of the enol ether, reported as one of the reaction pathways involved in the degradation of **GG** under the condition for O_2 pulp bleaching [30].

The vanillin-forming reaction shown in Figure 3 proceeds in the phenolic β-O-4 structure. When this reaction is applied to actual lignin molecules, vanillin production occurs from phenolic structures that already exist in the lignin molecule or those generated by alkaline hydrolysis of middle β-ether units. Meanwhile, in our laboratory, a vanillin production pathway based on non-phenolic structures has been proposed under catalyst-free conditions with $[OH^-]$ = 1.25−4.0 mol/L, 120°C, and under O_2 or air atmosphere, as shown in Figure 4 [38,39]. In this pathway, the C_3 side-chain of the arylglycerol structure formed by alkaline hydrolysis of the β-ether undergoes oxidation to form a vanillin precursor with a C_α-aldehyde structure. The final vanillin is produced by further alkaline hydrolysis of this precursor structure.

The vanillin production pathway depicted in Figure 4 is supported by experimental results that systematically examine the effects of organic cations on vanillin yields during the alkaline aerobic oxidation of various lignin samples and model compounds [38,39)]. The yield of vanillin from native lignin in Japanese cedar (*Cryptomeria japonica*) wood during its alkaline aerobic oxidation significantly increased in the presence of organic cations, such as complex cations between Na^+ and polycyclic ethers and quaternary ammonium ions [38-42)]. In particular, when the wood flour was reacted with Bu_4NOH aq. as a reaction medium under O_2 at 120°C, vanillin was generated in a yield (23.2 weight percent (wt%) on a Klason lignin basis) similar to that obtained by AN oxidation (27.2 wt%) [39)]. To investigate the reason for the increased vanillin yield in the presence of the organic cations, the effects of Bu_4N^+ were compared for the generation of C_α-aldehydes from the phenolic model **GG** and the non-phenolic model (*erythro*-veratrylglycerol β-guaiacyl ether, **VG**) shown in Figure 5 [39)]. The presence of Bu_4N^+ in the reaction solution increased the yield of vanillin and veratraldehyde from **VG**, whereas it had an inhibitory effect on vanillin production from **GG**. These results clarify that the positive effects of the organic cation on the vanillin production cannot be explained without considering the vanillin production pathway from the non-phenolic structure shown in Figure 4.

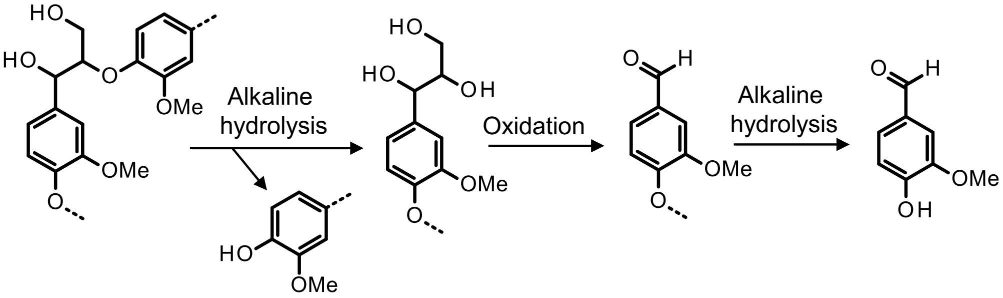

Fig. 4. Vanillin production from a β-O-4 middle unit of lignin [39)].

One of the proposed mechanisms for the effect of organic cations on the generation of the C_α-aldehydes from **VG** involves a cage effect caused by the organic cations that suppresses the disproportionation reaction of veratraldehyde to the corresponding alcohol and acid in Figure 5 [38,39)]. However, since the chemical structure of veratraldehyde differs considerably from that of the C_α-aldehyde end unit formed in actual lignin (Figure 4), further investigation using model compounds that are more representative of actual lignin is necessary. In the alkaline degradation of a β-O-4 model compound with a vanillin residue introduced at the β-position of the side-chain (2-(4-formyl-2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)ethanol), migration reactions of the vanillin residues to other positions of the side-chain have been reported [43,44)]. The effects of the organic cations are of interest in relation to these migration reactions.

The oxidative process depicted in Figure 4 involves the conversion of the C_3 side-chain of the arylglycerol structure to the C_α-aldehyde. It is therefore acknowledged that alkaline aerobic oxidation is a complex process that comprises both oxidative and non-oxidative processes. The oxidative degradation mechanism of the glycerol side-chain to the C_α-aldehyde has been studied by analyzing the detailed reaction behaviors of several model compounds, including **VG** and veratrylglycerol. Three oxidative pathways have been proposed, as shown in Figure 5: 1) oxidation of the α-OH group to a carbonyl group; 2) generation of the C_γ-aldehyde intermediate from the C_α=O via keto-enol tautomerization; 3) generation of the C_α-aldehyde via a retro-aldol reaction [45)]. However, the detailed elementary reaction mechanisms involved in this oxidative process, including the identity of the oxidants responsible for the oxidation of the α-OH group, remain unclear. Furthermore, the role of this mechanism under conditions other than those employed in the model experiment, which employs a relatively low-temperature, catalyst-free reaction condition (4.0 mol/L NaOH aq./120°C/air), requires further extensive investigation.

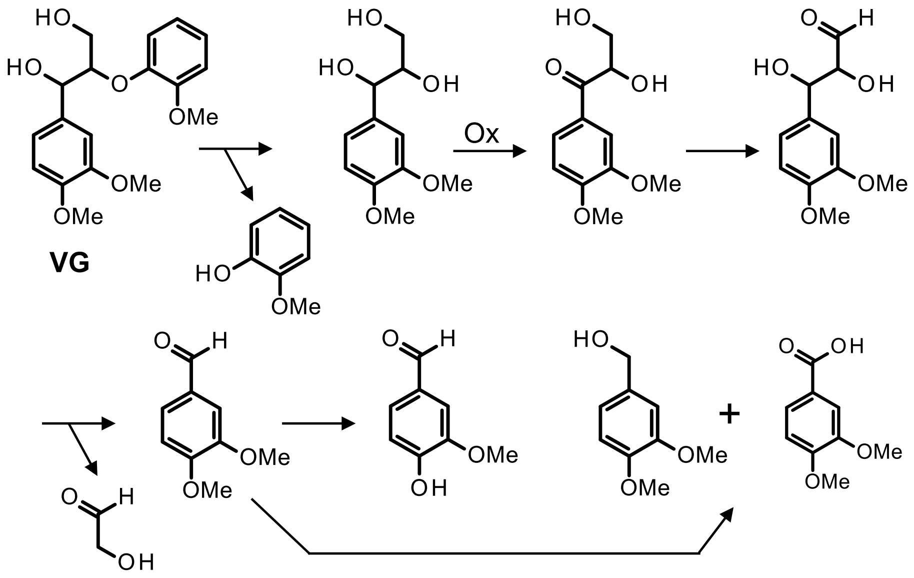

Fig. 5. Pathways involved in the aerobic oxidation of a non-phenolic mode compound, veratrylglycerol β-guaiacyl ether **VG** [38,39,45)].

CONCLUSIONS

1. The production of HBAs in AN oxidation seems to occur mainly from phenolic β-O-4 units via the enol ether intermediate, according to studies with lignin model compounds.
2. Detailed molecular mechanisms involved in AN oxidation currently remains unclear.
3. The formation of HBAs, especially vanillin from guaiacyl lignin, by alkaline aerobic oxidation involves reactions occurring in both phenolic and non-phenolic structures.
4. It is possible to modify the reactions involved in the vanillin production from the non-phenolic unit to achieve higher yields of vanillin.

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