Chapter

Depolymerization of Native Lignin into Vanillin, Vanillic Acid, and Other Related Compounds via Alkaline Aerobic Oxidation: Reaction Mechanisms and Process Control Using Organic Cations

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Abstract

Vanillin is one of the platform chemicals in industry, which is used not only as a traditional fragrance but also as a raw material for medicines and polymer materials. Industrial vanillin production by alkaline aerobic oxidation of lignin is carried out with degradation of lignosulfonate at temperatures around 170°C under pressurized air in the presence of Cu^{2+} as a catalyst. However, this method has problems such as low vanillin yields and by production of sulfur-containing wastewater, and various studies have been conducted to solve them. Research on the mechanism of the vanillin formation reaction by aerobic oxidation of lignin and the search for a method to control this reaction has also been conducted. In this chapter, we review relevant studies from the above perspective, mainly those conducted by the authors' research group.

Keywords: tetrabutylammonium ion, cyclic polyether, bio-based aromatics, model compound, organic cation

1. Introduction

Currently, environmental issues, such as the depletion of fossil resources and global warming, are of worldwide concern, which has raised growing interest in renewable and environmentally friendly biomass resources as an alternative to fossil resources. Among the various types of biomasses, wood is a promising resource because of its huge stocks and inedibility. Wood is composed mainly of three components: cellulose, hemicellulose, and lignin. Among these, lignin constitutes 20–35% of the wood [1]. Because of its aromatic nature, lignin is expected as bio-based source of low molecular weight (MW) aromatics that are indispensable in the chemical industry [2–8].

The production of low MW aromatics from lignin requires conversion methods that facilitate effective cleavage of interunit linkages in lignin polymer. Among many methods currently suggested, alkaline aerobic oxidation is a promising way from the viewpoint that lignin is effectively degraded by nontoxic molecular oxygen [9–21]. Aerobic oxidation of lignosulfonate in waste liquor from sulfite pulping of softwood has been put into practical use as industrial vanillin (4-hydroxy-3-methoxybenzaldehyde) production [22–27].

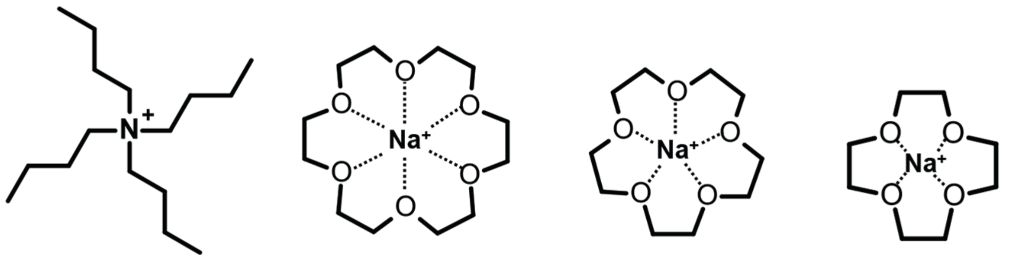
Vanillin is a versatile compound that is useful as a source of medicines and polymer materials, as well as a traditional fragrance [24–30]. The vanillin production from lignosulfonate is usually carried out in aqueous alkali, that is, aqueous NaOH solution, under compressed air in the presence of a Cu^{2+}-based catalyst. This method was a major industrial vanillin production method until 1990s. However, the yield of vanillin is usually less than 10% based on the original sodium lignosulfonate [25, 31]. In addition to this relatively low yield of the target compound, high temperature and air pressure, typically 160–200°C/0.5–2.0 MPa, required for the process and management of wastewater containing sulfur compounds are drawbacks of this biomass-based vanillin production [25]. Recent vanillin production is, therefore, substituted almost with petrol-based ones, that is, formylation of guaiacol [27].

In light of recent environmental concerns, however, the production method of vanillin derived from biomass should be continuously studied and improved as it could be a breakthrough in establishing a method to produce low MW aromatic compounds from wood. To promote the adoption of the lignin-based vanillin production method in the chemical industry, it is necessary to address some of the shortcomings of this method described above. One solution to the sulfur-containing waste problem is to use native lignin in wood, as well as lignosulfonate as raw material for vanillin. Developing methods that provide the target product in good yield without the use of transition metals or high-temperature and high-pressure conditions would be another issue to tackle. Furthermore, mechanistic knowledge of alkaline aerobic oxidation as the foundation of the process development is essential for realizing these goals.

This chapter presents the results of fundamental and applied studies on vanillin production from lignin, conducted mainly in the authors' research group, from the above perspective. In addition to vanillin, other related oxidation products, for example, vanillic acid, are also produced in the aerobic oxidation of lignin. The formation of these compounds will also be briefly summarized.

2. Alkaline aerobic oxidation of lignin in the presence of organic cations

In vanillin production via alkaline aerobic oxidation of lignin, simple alkaline solution, such as aqueous NaOH solution, is generally employed as a reaction medium. Alternatively, our research group developed a new alkaline medium, that is, tetrabutylammonium hydroxide (TBAH) for lignin degradation. The chemical structure of tetrabutylammonium ion, Bu_4N^+, is presented in **Figure 1**. TBAH is a salt of Bu_4N^+ and OH^- and its aqueous solution exhibits strongly alkaline nature, as aqueous NaOH solution does. In this respect, TBAH is similar to NaOH, but a distinguishing characteristic of TBAH is that it possesses the bulky organic cation.



Bu_4N^+ **18C6**-Na^+ **15C5**-Na^+ **12C4**-$Na^{+\,a)}$

Figure 1.
Organic cations employed in our studies [32, 33]. $^{a)}$ *In the case of* **12C4**-*Na*$^+$*, a complex cation in which Na*$^+$ *is bound by two molecules of* **12C4** *is also reported [34].*

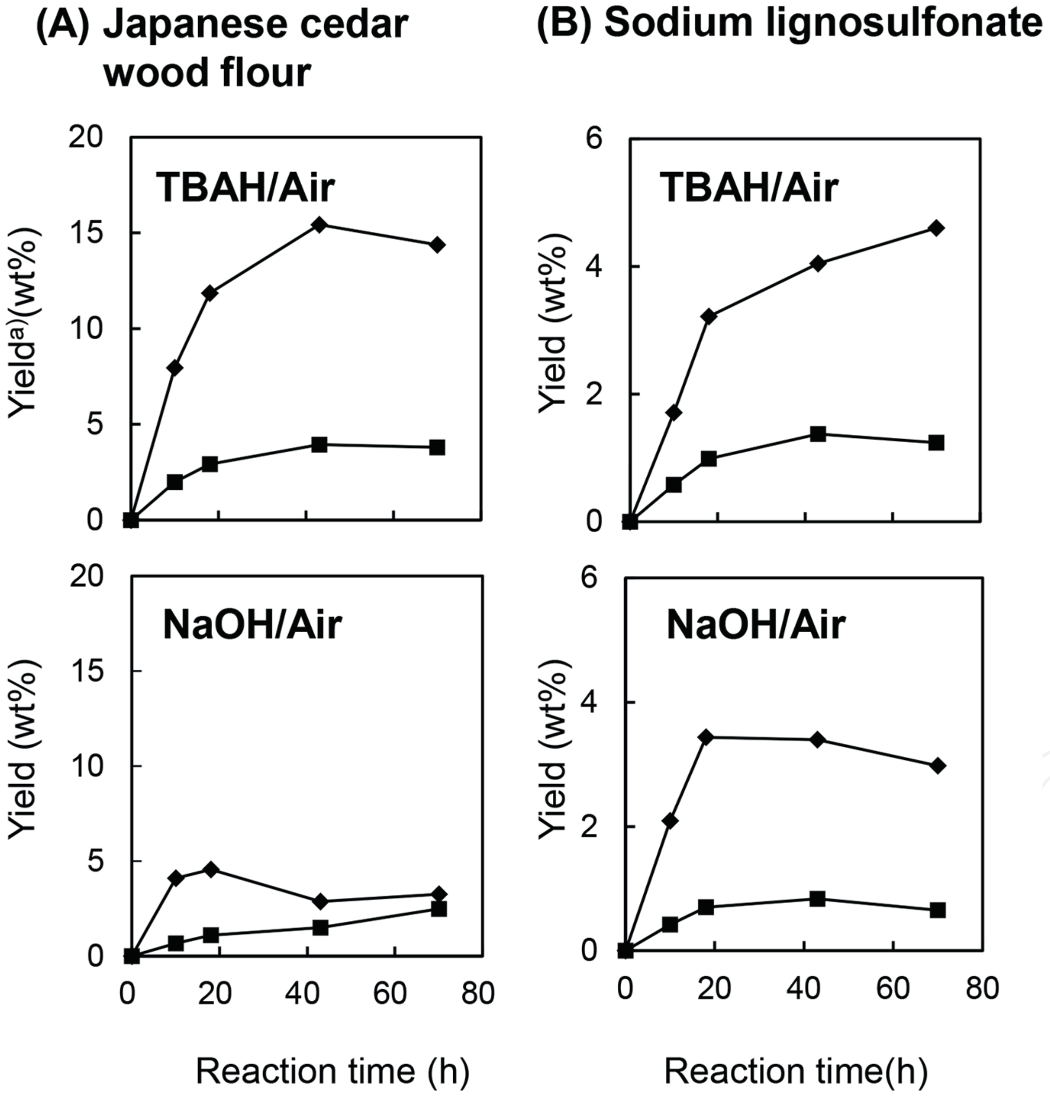


Figure 2.
Formation behavior of vanillin (♦) and vanillic acid (■) from Japanese cedar wood flour (A) and sodium lignosulfonate (B), during their alkaline aerobic oxidation under air in a sealed system (volume of the gas phase: 8 mL). Reaction conditions: sample 14 mg/ reaction solution (1.25 mol/L aqueous TBAH solution or aqueous NaOH solution 2.0 mL)/ 120°C. $^{a)}$ *Yield from the wood flour is based on its Klason lignin amount [33].*

Figure 2 shows the changes with time in yields of vanillin and its related substance, vanillic acid (4-hydroxy-3-methoxybenzoic acid); when sodium lignosulfonate or Japanese cedar (*Cryptomeria japonica*) wood flour is oxidatively degraded at 120°C under air in the aqueous NaOH solution or aqueous TBAH solution with their concentration being 1.25 mol/L. In the vanillin production from the sodium lignosulfonate, the raw material for current lignin-based vanillin production [33], it has been indicated that the -SO_3^- moieties in the raw material play important roles in the vanillin formation [35, 36]. This point can be confirmed by comparing the yield of vanillin in the NaOH medium in **Figure 2** between wood flour and sodium lignosulfonate. In other words, in the case of the NaOH medium, the yields of vanillin and vanillic acid are comparable between sodium lignosulfonate and the wood flour (vanillin yield: 3–5 wt%; vanillic acid yield: 1–3 wt%). Considering significant degradation of the original lignin structures during its isolation process, it can be concluded that sodium lignosulfonate gives the target compounds in relatively high yields. This result would be attributed to the presence and the positive effect of the -SO_3^- moiety.

On the other hand, higher yields of vanillin and vanillic acid are obtained in the TBAH medium, regardless of the presence of the -SO_3^- moiety, as shown in **Figure 2**. Also, the wood flour exhibited much higher vanillin yield in TBAH than sodium lignosulfonate did in the same medium. This result is interesting from the perspective of reducing sulfur-containing waste during the vanillin production; efficient vanillin production from the wood flour, an originally sulfur-free material, was achieved in TBAH, which leads to the establishment of processes that are not bothered by the sulfur-containing waste. It should be also emphasized that the vanillin production was carried out without any transition metal additives. The employed reaction temperature, 120°C, was much lower than those generally adapted in current vanillin production processes.

The vanillin production shown in **Figure 2** takes a long reaction time, over 43 h, to reach the maximum product yield. The current process solves this problem by using pressurized air and high temperatures to promote the oxidation. **Table 1** summarizes the maximum yields of vanillin and vanillic acid and the time to reach them for the oxidation of Japanese cedar wood flour in various reaction media. It becomes clear that the addition of NaOH(s) to the reaction system and replacing the air in the reaction system with pure O_2 significantly shortens the reaction time and increases the yields of the products [16, 20]. Finally, the yields of vanillin and vanillic acid under optimum conditions are 23.2, 1.2 wt%, respectively, and the time to reach of this yield is 4.0 h. Thus, in the TBAH media, it is possible to improve the reaction efficiency at low temperature of 120°C without pressurizing the reaction system, which is advantageous compared to the current process with harsh reaction conditions. For vanillic acid, on the other hand, the compound tends to form in relatively low yields under the conditions in which vanillin production is facilitated. This may suggest that the production pathways of vanillin and vanillic acid are in trade-off relationship.

The above yields of vanillin and vanillic acid are remarkable in the history of lignin chemistry. One of the most important reactions in lignin chemistry is alkaline nitrobenzene oxidation (AN oxidation). This is an oxidative degradation of a lignin-containing sample such as wood and isolated lignin by nitrobenzene to give *p*-hydroxybenzaldehydes reflecting the substitution pattern of the lignin sample, mostly vanillin in the case of softwood lignin. Despite its more than 60-year history, AN oxidation has been one of the most efficient lignin degradation methods in use today and the product yield in the AN oxidation has been employed as a benchmark to measure the efficiency of other oxidation methods. **Table 1** shows that the yields of vanillin and vanillic acid in the TBAH+NaOH/O_2 system are comparable to those of

Medium/oxidant	**[OH$^-$] (mol/L)**	**Time (h)**[b]	**Temperature (°C)**	**Yield (wt %)**[a]		
				Vanillin	**Vanillic acid**	**Total**
NaOH/air	4.0	96	120	6.2	2.4	8.6
NaOH/nitrobenzene[c]	2.0	2.5	170	27.2	1.2	28.4
TBAH/air	1.25	43	120	15.4	3.9	19.3
TBAH+NaOH[d]/air	3.75	20	120	18.9	2.2	21.1
TBAH+NaOH/oxygen[e]	3.75	4.0	120	23.2	1.2	24.4
NaOH +**18C6**[f]/air	4.0	96	120	16.1	2.3	18.4
NaOH +**15C5**[f]/air	4.0	96	120	15.2	2.3	17.5
NaOH +**12C4**[f]/air	4.0	72	120	16.1	2.3	18.4
NaOH +1,4-dioxane[f]/air	4.0	96	120	5.5	3.4	8.9
NaOH + **TEG**[f]/air	4.0	96	120	8.9	5.0	13.9
NaOH + **TRG**[f]/air	4.0	96	120	5.4	9.2	14.6

[a] *The yield is based on the Klason lignin content of the wood flour.*
[b] *The reaction time is the one in which the yield of vanillin becomes maximum.*
[c] *The alkaline nitrobenzene oxidation (AN oxidation) was carried out under the established conditions.*
[d] *In the TBAH+NaOH medium, [Bu$_4$N$^+$] is set to 1.25 mol/L with [OH$^-$] being adjusted to the presented value by adding NaOH(s) to the TBAH solution.*
[e] *"Oxygen" means the experiment is carried out under pure O$_2$.*
[f] *The reaction medium is prepared by adding the ether compounds to the NaOH solution, where* **18C6**, **15C5**, *and* **12C4** *are the polycyclic ethers with different cavity sizes (see* **Figure 1**), *and* **TEG** *and* **TRG** *are tetraglyme and triglyme (non-cyclic polyethers with different chain lengths), respectively.*

Table 1.
The yield of vanillin and vanillic acid from Japanese cedar wood flour after its oxidation in several oxidation systems [16, 32, 33].

AN oxidation. These results indicate that the TBAH-based alkaline aerobic oxidation is a highly efficient oxidation method and exploit the potential of the raw material to produce the target compounds.

The high yield of vanillin achieved in the aforementioned TBAH is clearly due to the presence of the bulky tetrabutylammonium ion, compared to Na$^+$. This led us to the idea of producing vanillin under the presence of various bulky organic cations. Namely, we added polycyclic ethers, that is, 18-Crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane, **18C6**), 15-Crown-5 (1,4,7,10,13-pentaoxacyclopentadecane, **15C5**), and 12-Crown-4 (1,4,7,10-tetraoxacyclododecane, **12C4**) to an aqueous NaOH solution and studied the alkaline aerobic oxidation behaviors of Japanese cedar wood flour in these reaction media. These crown ethers capture Na$^+$ in the aqueous NaOH solution, forming three types of complex cations **18C6**-Na$^+$, **15C5**-Na$^+$, and **12C4**-Na$^+$ as shown in **Figure 1** [37]. It is expected that these organic cations would exhibit enhancing effects on the vanillin production, which is similar to those observed for Bu$_4$N$^+$.

The aerobic oxidation of Japanese cedar wood flour was conducted in a 4.0 mol/L aqueous NaOH solution in the presence of 2.0 mol/L of the three crown ethers. As shown in **Table 1**, the vanillin yield under the three crown ethers (**18C6**, **15C5**, **12C4**) is 15.2–16.1 wt%, which is clearly higher than that in the pure NaOH system. In contrast, in the aerobic oxidation using equimolar amounts of tetraglyme (**TEG**) and triglyme (**TRG**) and non-cyclic analogs of **15C5** and **12C4** respectively, the vanillin yields are 8.9 and 5.4 wt%, nearly the same as that obtained in the pure NaOH system. This can be explained by the fact that cyclic polyethers generally exhibit much stronger complexing ability toward metal cations than their corresponding non-cyclic polyethers [38], suggesting that the increased vanillin yield due to the addition of the crown ethers results from the formation of the complex cations in **Figure 1**. Moreover, the increase in vanillin yield by cyclic polyethers seems to depend highly on their Na^+ accommodation ability. For instance, the addition of 1,4-dioxane, which has a considerably smaller ring size than the three crown ethers, results in a vanillin yield of 5.5 wt% (**Table 1**). This is likely because the cavity size of 1,4-dioxane is too small to accommodate Na^+.

For vanillic acid, another major product, the yield from Japanese cedar wood flour in the presence of complex cations is 2.3 wt%, regardless of the types of the crown ethers. This value is nearly identical to that obtained in the absence of the complex cations (2.4 wt%). This phenomenon of minimal influence of the complex cations on the production of vanillic acid is also observed in the aforementioned aerobic oxidation of Japanese cedar wood flour in the presence of Bu_4N^+. Thus, it can be stated that the complex cations formed from Na^+ and the crown ethers and Bu_4N^+ exert quite similar effects, significantly increasing the yield of vanillin while having little impact on the formation of vanillic acid. In the following section, we will elaborate on this issue from the perspective of reaction mechanisms. Moreover, the addition of **TEG** and **TRG**, which are non-cyclic polyethers, does not substantially increase the vanillin yield, but it increases the yield of vanillic acid. For instance, the addition of **TRG** significantly increases the yield of vanillic acid from 2.4 to 9.2 wt% (**Table 1**). Although there are few clues to explain these results rationally at this point, they represent intriguing phenomena when considering the potential for further reaction control by complex cations.

3. Mechanism of vanillin formation from lignin and the roles of organic cations

Bu_4N^+ and the complex cations between Na^+ and the polycyclic ethers are found to facilitate the vanillin production by alkaline aerobic oxidation of lignin. However, the mechanisms underlying the improved vanillin yield caused by the presence of the organic cations are not clear. We, thus, investigated the role of organic cations (Bu_4N^+ and the crown ether-based complex cations) in the vanillin formation mechanisms, by analyzing the behaviors of lignin model compounds **LM1** and **LM2** shown in **Figure 3** under the alkaline aerobic oxidation conditions. These models carry a β-O-4 linkage, which is the most abundant linkage in lignin, but are different in that **LM1** has the phenolic OH group, while **LM2** does not.

LM1 with the phenolic OH group was examined as a model for the phenolic end group of lignin [16]. As shown in **Figure 3**, an enol ether intermediate **EE** is formed in the initial stage of the oxidation via the formation of a quinone methide **QM** structure from **LM1** and the following elimination of C_γ position as HCHO (Pathway A1 and A2). The second step involves the oxidation of the $C_\alpha = C_\beta$ moiety of **EE** finally leading to vanillin (Pathway A3). The mechanisms in the oxidation of **EE** are not clear at the moment, but vanillin formation from **EE** via a dioxetane intermediate was suggested in several studies on O_2 pulp bleaching conditions [40, 41]. For the effect of Bu_4N^+ in the TBAH medium, Bu_4N^+ stabilizes **EE** probably by coordinating with the side chain of **EE**, which results in slower vanillin formation from **LM1** in TBAH

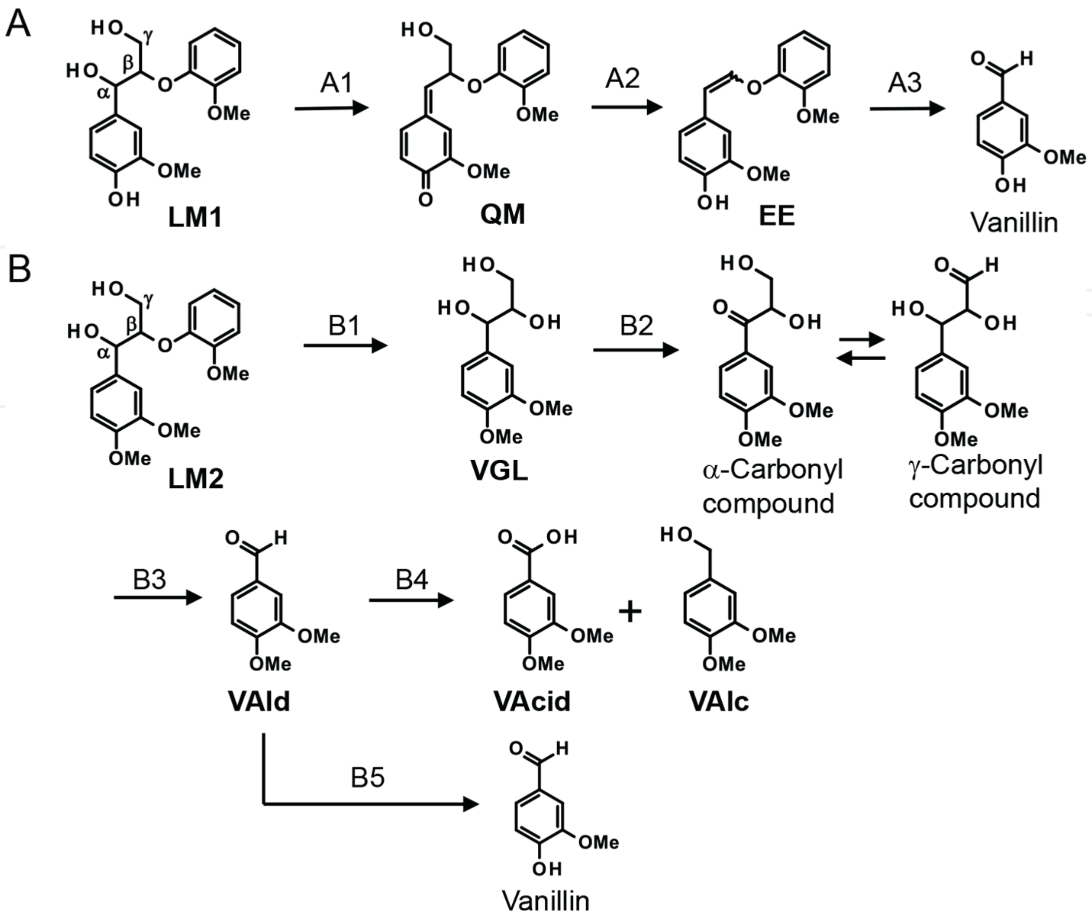


Figure 3.
Reaction pathways involved in alkaline aerobic oxidation of **LM1** *(A) and* **LM2** *(B) [16, 33, 39].*

compared to that in NaOH. It is, therefore, likely that Bu_4N^+ does not have positive effects on the vanillin production from the phenolic end of lignin.

Experiments using **LM2**, a model for the middle β-O-4 phenylpropane unit of lignin, have suggested the following reaction mechanisms [16, 39]. First, the cleavage of the β-ether of **LM2** via the neighboring group participation of C_α-OH occurs to give a veratryl glycerol intermediate **VGL** (Pathway B1). This intermediate is then oxidized to an α-carbonyl compound, which is in equilibrium with the corresponding γ-carbonyl compound through the keto-enol tautomerization (Pathway B2). A retro-aldol reaction proceeds from the γ-carbonyl compound, leading to the formation of veratraldehyde (**VAld**) via Pathway B3. On the other hand, another retro-aldol pathway starting from the α-carbonyl is less significant [39]. There are two possible fates of **VAld** with one being disproportionation to produce veratric acid (**VAcid**) and veratryl alcohol (**VAlc**) (Pathway B4) and the other being conversion of the 4-OMe group to OH to produce vanillin (Pathway B5).

Comparison of the degradation behaviors of **LM2** in the TBAH and NaOH system revealed that TBAH promoted the cleavage of the β-ether in the initial stage of the reaction (Pathway B1) and increased the selectivity of the vanillin production from **VAld** in the final stage (Pathway B5). The former promotion of the β-ether cleavage can be explained by the fact that the OH^- activity in the aqueous TBAH solution is higher than that of the aqueous NaOH solution, even when their OH^- concentration is the same. On the other hand, the latter promotion of vanillin formation from **VAld** is due to the interaction of Bu_4N^+ with **VAld** in the aqueous TBAH solution, as indicated by the ^{1}H NMR analysis of **VAld** in the presence of Bu_4N^+ salt [16]. In other words, **VAld** is in the cage made of Bu$_4$N$^+$ in the aqueous TBAH solution, which inhibits the progress of the disproportionation (Pathway B4). This results in relative increase in the selectivity of the vanillin forming pathway B5.

The influence of the complex cations on the reactivity of **LM2** is confirmed by evaluating the additive effect of crown ethers (**18C6**, **15C5**, and **12C4**) on the reactivity of **LM2** in the aqueous NaOH solution. When the complex cations are present in the reaction system, a decrease in the yields of **VAcid** and **VAlc** is observed, along with an increase in vanillin yield, similar to the previously confirmed Bu$_4$N$^+$ system. Thus, it is inferred that both complex cations and Bu$_4$N$^+$ essentially increase the vanillin yield through the same mechanism, namely, the suppression of the disproportionation pathway of **VAld** due to the cage effect. Interestingly, in the case of the non-cyclic ethers such as **TEG** and **TRG**, and 1,4-dioxane, a cyclic ether with a much smaller ring size, no significant increase in vanillin yield is observed in the model experiments using **LM2**. This suggests that the formation of complex cations shown in **Figure 1**, and the suppression of the disproportionation pathway (Pathway B4) are closely related. In addition to the similar effects of Bu$_4$N$^+$ and the complex cations as mentioned above, the complex cations exhibit several specific effects that are not observed with Bu$_4$N$^+$ [32]. For instance, in the case of the complex cation systems, the inhibition of the oxidative degradation of the **VGL** side chain to the aldehyde group is observed probably by the stabilization of **VGL** by its interaction with the complex cation.

The above phenomena observed for **LM1** and **LM2** suggest that vanillin formation from middle phenylpropane units in lignin is promoted in the presence of the organic cations, with the reaction at the phenolic end being rather suppressed. In other words, the formation of vanillin from the middle unit plays an important role in the formation of vanillin under the alkaline aerobic oxidation conditions. **Figure 4** shows a possible pathway for vanillin formation from the middle unit of lignin based on the study of the reaction mechanisms of **LM2**. First, the β-ether of the middle β-O-4 unit undergoes alkaline hydrolysis to form the glycerol end (pathway I). The glycerol end is oxidized to a C$_\alpha$-aldehyde end (pathway Π), and finally, vanillin is released from this end (pathway Ш). In an actual lignin molecule, the middle units are considered to be more abundant than the phenolic ends. It is, thus, likely that the suppressing effect of Bu$_4$N$^+$ on the vanillin production from the phenolic end is canceled out, and the overall vanillin yield was increased in the organic cation-containing media.

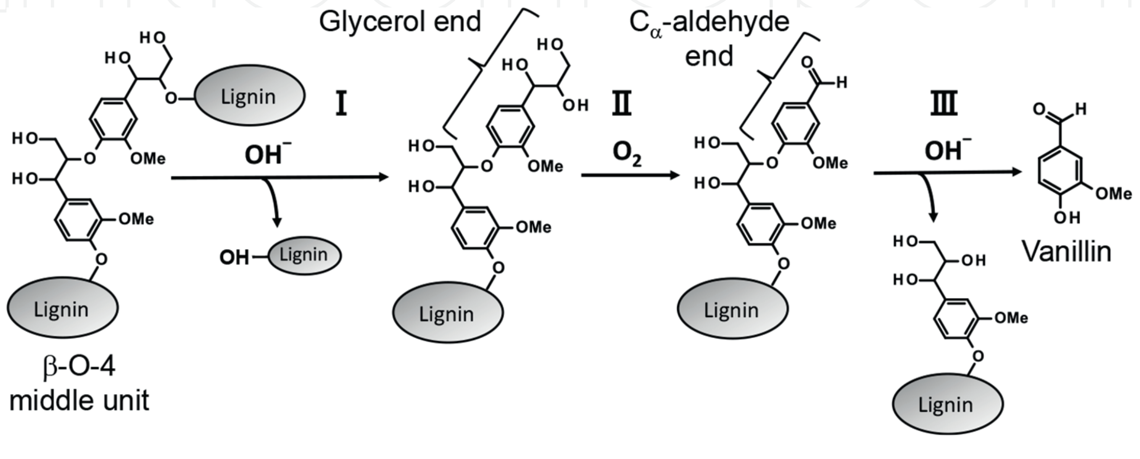


Figure 4.
Vanillin formation from a β-O-4 middle unit of lignin polymer [16].

The model compounds **LM1** and **LM2** discussed so far are designed to mimic the β-O-4 structure in lignin. However, the compound has a much more simplified structure than the actual lignin. Therefore, when applying the reaction pathway based on the degradation behavior of **LM2** (**Figure 3**) to actual lignin molecules, careful consideration is required. When comparing the vanillin production behavior from **LM2** and wood flour, a certain correspondence can be recognized between the oxidation behaviors of actual lignin and the model compounds in that the increase in vanillin yield from the wood flour observed in the presence of organic cations is reproduced even in the case of the model compound. Thus, it is likely that the suppression of the disproportionation by the cage effect of the organic cations plays a certain role also in the vanillin production from actual lignin. In the case of actual lignin, however, **VAld**, which was produced from **LM2**, never forms, and instead the C_α-aldehyde end group shown in **Figure 4** is formed as a vanillin precursor. The rates of vanillin elimination from this C_α-aldehyde end and the conversion reaction of **VAld** to vanillin (conversion of the 4-position methoxy group to a hydroxy group) are expected to differ significantly, which may affect the degree of suppression of disproportionation by the cage effect. Also, in the C_α-aldehyde end linked to the actual lignin side chain, more complex side reactions not observed with **VAld** might proceed. According to these ideas, future studies using model compounds that more accurately mimic the actual C_α-aldehyde end are needed to more precisely elucidate the mechanism of increased vanillin yield by the cage effect.

4. Conclusions

This chapter presented high-yield vanillin production from lignin (mainly native softwood lignin) by the alkaline aerobic oxidation in the presence of organic cations. When conducting alkaline aerobic oxidation of lignin in the presence of bulky organic cations such as Bu_4N^+ and the complex cations formed between the crown ethers and Na^+, a significant increase in the yield of vanillin from the lignin samples is observed. In this organic cation-containing system, the alkaline aerobic oxidation allows for the efficient production of vanillin at a temperature of 120°C, employing native lignin in the wood flour as the starting material. This vanillin production process is more advantageous than the current process using lignosulfonate in that it can achieve a high vanillin yield comparable to that of AN oxidation and does not produce sulfur-containing effluent.

One of the vanillin production pathways in the alkaline aerobic oxidation of lignin involves the elimination of vanillin from the C_α-aldehyde structure, which is produced by the oxidative degradation of non-phenolic intermediate units in lignin. It has been found that the aforementioned organic cations improve the selectivity of this vanillin elimination reaction. Research on such reaction mechanisms and further mechanistic insights into the function of the organic cations are expected to lead to the development of more rational reaction control methods to improve the efficiency of the vanillin production processes.

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References

[1] Ralph J, Brunow G, Boerjan W. Lignins. Encyclopedia of Life Science. 2007:1-10

[2] Liu X, Bouxin FP, Fan J, Budarin VL, Hu C, Clark JH. Recent advances in the catalytic depolymerization of lignin towards phenolic chemicals: A review. ChemSusChem. 2020;**13**:4296-4317

[3] Jing Y, Dong L, Guo Y, Liu X, Wang Y. Chemicals from lignin: A review of catalytic conversion involving hydrogen. ChemSusChem. 2020;**13**:4181-4198

[4] Sun Z, Fridrich B, de Santi A, Elangovan S, Barta K. Bright side of lignin depolymerization: Toward new platform chemicals. Chemical Reviews. 2018;**118**:614-678

[5] Schutyser W, Renders T, Van den Bosch S, Koelewijn SF, Beckham GT, Sels BF. Chemicals from lignin: An interplay of lignocellulose fractionation, depolymerisation, and upgrading. Chemical Society Reviews. 2018;**47**:852-908

[6] Tarabanko VE, Tarabanko N. Catalytic oxidation of lignins into the aromatic aldehydes: General process trends and development prospects. IJMS. 2017;**18**:2421

[7] Gillet S, Aguedo M, Petitjean L, Morais ARC, da Costa Lopes AM, Łukasik RM, et al. Lignin transformations for high value applications: Towards targeted modifications using green chemistry. Green Chemistry. 2017;**19**:4200-4233

[8] Rinaldi R, Jastrzebski R, Clough MT, Ralph J, Kennema M, Bruijnincx PCA, et al. Paving the way for lignin valorisation: Recent advances in bioengineering, biorefining and catalysis. Angewandte Chemie (International Ed. in English). 2016;**55**:8164-8215

[9] More A, Elder T, Jiang Z. Towards a new understanding of the retro-aldol reaction for oxidative conversion of lignin to aromatic aldehydes and acids. International Journal of Biological Macromolecules. 2021;**183**:1505-1513

[10] Zhu Y, Liao Y, Lv W, Liu J, Song X, Chen L, et al. Complementing vanillin and cellulose production by oxidation of lignocellulose with stirring control. ACS Sustainable Chemistry & Engineering. 2020;**8**:2361-2374

[11] Wang J-X, Asano S, Kudo S, Hayashi J. Deep delignification of Woody biomass by repeated mild alkaline treatments with pressurized O2. ACS Omega. 2020;**5**:29168-29176

[12] Tarabanko VE, Kaygorodov KL, Vigul DO, Tarabanko N, Chelbina YV, Smirnova MA. Influence of acid prehydrolysis on the process of wood oxidation into vanillin and pulp. Journal of Wood Chemistry and Technology. 2020;**40**:421-433

[13] Rawat S, Gupta P, Singh B, Bhaskar T, Natte K, Narani A. Molybdenum-catalyzed oxidative depolymerization of alkali lignin: Selective production of vanillin. Applied Catalysis A: General. 2020;**598**:117567

[14] Paananen H, Eronen E, Mäkinen M, Jänis J, Suvanto M, Pakkanen TT. Base-catalyzed oxidative depolymerization of softwood Kraft lignin. Industrial Crops and Products. 2020;**152**:112473

[15] Jeon W, Choi I-H, Park J-Y, Lee J-S, Hwang K-R. Alkaline wet oxidation of

lignin over Cu-Mn mixed oxide catalysts for production of vanillin. Catalysis Today. 2020;**352**:95-103

[16] Hosoya T, Yamamoto K, Miyafuji H, Yamada T. Selective production of bio-based aromatics by aerobic oxidation of native softwood lignin in tetrabutylammonium hydroxide. RSC Advances. 2020;**10**:19199-19210

[17] Cabral Almada C, Kazachenko A, Fongarland P, Da Silva Perez D, Kuznetsov BN, Djakovitch L. Oxidative depolymerization of lignins for producing aromatics: Variation of botanical origin and extraction methods. Biomass Conversion and Biorefinery. 2020;**12**:3795-3808

[18] Abdelaziz OY, Ravi K, Mittermeier F, Meier S, Riisager A, Lidén G, et al. Oxidative depolymerization of Kraft lignin for microbial conversion. ACS Sustainable Chemistry & Engineering. 2019;**7**:11640-11652

[19] Schutyser W, Kruger JS, Robinson AM, Katahira R, Brandner DG, Cleveland NS, et al. Revisiting alkaline aerobic lignin oxidation. Green Chemistry. 2018;**20**:3828-3844

[20] Maeda M, Hosoya T, Yoshioka K, Miyafuji H, Ohno H, Yamada T. Vanillin production from native softwood lignin in the presence of tetrabutylammonium ion. Journal of Wood Science. 2018;**64**:810-815

[21] Hosoya T, Okamoto D, Miyafuji H, Yamada T. Production of vanillin and vanillic acid by aerobic oxidation of polyethylene glycol (PEG)-modified glycol lignin in tetrabutylammonium hydroxide. Lignin. 2021;**2**:9-18

[22] Pacek AW, Ding P, Garrett M, Sheldrake G, Nienow AW. Catalytic conversion of sodium lignosulfonate to vanillin: Engineering aspects. Part 1. Effects of processing conditions on vanillin yield and selectivity. Industrial and Engineering Chemistry Research. 2013;**52**:8361-8372

[23] Ding P, Garrett M, Loe Ø, Nienow AW, Pacek AW. Generation of hydrogen gas during the catalytic oxidation of sodium lignosulfonate to vanillin: Initial results. Industrial and Engineering Chemistry Research. 2012;**51**:184-188

[24] Fache M, Boutevin B, Caillol S. Vanillin production from lignin and its use as a renewable chemical. ACS Sustainable Chemistry & Engineering. 2016;**4**:35-46

[25] Hocking MB. Vanillin: Synthetic flavoring from spent sulfite liquor. Journal of Chemical Education. 1997;**74**:1055

[26] Vu TT, Lim Y-I, Song D, Hwang K-R, Kim D-K. Economic analysis of vanillin production from kraft lignin using alkaline oxidation and regeneration. Biomass Conversion and Biorefinery. 2023;**13**:1819-1829

[27] Havkin-Frenkel DV. In Kirk-Othmer Encyclopedia of Chemical Technology. New York: Wiley; 2018. pp. 1-12

[28] Zhang H, Yong X, Zhou J, Deng J, Wu Y. Biomass vanillin-derived polymeric microspheres containing functional aldehyde groups: Preparation, characterization, and application as adsorbent. ACS Applied Materials & Interfaces. 2016;**8**:2753-2763

[29] Llevot A, Grau E, Carlotti S, Grelier S, Cramail H. From lignin-derived aromatic compounds to novel biobased polymers. Macromolecular Rapid Communications. 2016;**37**:9-28

[30] Bjørsvik H-R, Liguori L. Organic processes to pharmaceutical chemicals based on fine chemicals from Lignosulfonates. Organic Process Research and Development. 2002;**6**:279-290

[31] Vidal JP. Vanillin. In: Kirk-Othmer Encyclopedia of Chemical Technology. Hoboken: Wiley; 2006. DOI: doi.org/10.1002/0471238961

[32] Hosoya T, Kawase K, Hirano Y, Ikeuchi M, Miyafuji H. Alkaline aerobic oxidation of native softwood lignin in the presence of Na^+-cyclic polyether complexes. Journal of Wood Chemistry and Technology. 2022;**42**(1):1-14

[33] Yamamoto K, Hosoya T, Yoshioka K, Miyafuji H, Ohno H, Yamada T. Tetrabutylammonium hydroxide 30-hydrate as novel reaction medium for lignin conversion. ACS Sustainable Chemistry & Engineering. 2017;**5**:10111-10115

[34] Buschmann H-J. Stability constants and thermodynamic data for complexes of 12-Crown-4 with alkali metal and alkaline-earth cations in methanol solutions. Journal of Solution Chemistry. 1987;**16**:181-190

[35] Tomlinson GH, Hibbert H. Studies on lignin and related compounds. XXIV. The formation of vanillin from waste sulfite liquor. Journal of the American Chemical Society. 1936;**58**:345-348

[36] Tomlinson GH, Hibbert H. Studies on lignin and related compounds. XXV. Mechanism of vanillin formation from spruce lignin sulfonic acids in relation to lignin structure. Journal of the American Chemical Society. 1936;**58**:348-353

[37] Izatt RM, Pawlak K, Bradshaw JS, Bruening RL. Thermodynamic and kinetic data for macrocycle interactions with cations and anions. Chemical Reviews. 1991;**91**:1721-2085

[38] Tuemmler B, Maass G, Voegtle F, Sieger H, Heimann U, Weber E. Open-Chain Polyethers. Influence of aromatic donor end groups on thermodynamics and kinetics of alkali metal ion complex formation. Journal of the American Chemical Society. 1979;**101**:2588-2598

[39] Hirano Y, Izawa A, Hosoya T, Miyafuji H. Degradation mechanism of lignin model compound during alkaline aerobic oxidation: Formation of vanillin precursor from β-O-4 middle unit of softwood lignin. Reaction Chemistry & Engineering. 2022;**7**:1603-1616

[40] Imai A, Yokoyama T, Matsumoto Y, Meshitsuka G. Significant lability of Guaiacylglycerol β-Phenacyl ether under alkaline conditions. Journal of Agricultural and Food Chemistry. 2007;**55**:9043-9046

[41] Gierer J. Chemistry of delignification part 2: Reactions of lignins during bleaching. Wood Science and Technology. 1986;**20**:1-33