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Selective Degradation of Technically Relevant Lignin to Vanillic Acid and Protocatechuic Acid

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A new and practical method for the thermal degradation of technically relevant bio-based lignin is presented. By heating a solution of lignin in highly concentrated caustic potash, vanillic acid is almost exclusively obtained in yields up to 10.6 wt%. By altering the reaction parameters, the selectivity of the reaction can be shifted towards the demethylation product, protocatechuic acid, which is obtained in a yield of 6.9 wt%. Furthermore, the procedure was applicable to different types of Kraft and organosolv lignin. To create an economically feasible process, ion exchange resins were used for the work-up of the highly caustic reaction media without neutralizing the complete mixture. By the selective removal of the desired vanillic acid from the caustic potash, this alkaline media could directly be reused for at least 5 further lignin degradations without significant loss of yield.

Introduction

For the production of fine chemicals and monomers, the chemical industry still relies on crude oil as the primary feedstock.[1] Due to its diminishing availability, renewable feedstocks need to be investigated. Lignin, a biobased phenolic polymer, presents a promising alternative for the production of aromatic fine chemicals.[2] It can make up to 35 wt% of woody biomass and does not compete with the globally rising demand in food.[3,4] Industrially, lignin is processed during pulping, in which cellulose is separated from lignin and lignocellulose (delignification), resulting in the accumulation of processed lignin as a byproduct.[5] The Kraft process is the dominating method for delignification with an annual volume of 130 million tons of pulp in 2012.[6] During this process the wood is heated with Na_2S and NaOH under harsh conditions, leading to significant structural changes, like C—O bond fission and C—C bond formation.[4,7] On a smaller scale, lignosulfonate (LS) is produced by pulping with sulfite, which adds sulfonate groups, leading to an improved water solubility, but additionally condensation reactions occur, altering the lignin structure.[8] Predominantly, the processed lignin is then burned on site for recovery of inorganic process chemicals and energy production, not utilizing its aromatic substructures. The depolymerization of lignin is considered challenging, due to the large structural changes associated with the harsh reaction conditions during pulping.[9] Nevertheless, different strategies for the depolymerization have been developed: thermal,[10] oxidative,[11] and catalytic treatment.[12] A different approach was found in the 'lignin first' strategy, which puts the focus on the direct utilization of native lignin and not as an industrial side stream. By hydrogenation reaction, monomeric phenols can be accessed in high yields and be used as platform chemicals for further transformations.[4,13]

Our previous reports enabled access to vanillin (1) and derivatives from industrially relevant lignosulfonate (LS),[14] organosolv lignin[15] and Kraft lignin.[16,17] Among these, vanillic acid (2) was produced in 7.2 wt% yield by treatment of LS with electrochemically generated ferrate in highly concentrated caustic soda.[18] The interest and demand of 2 have been increasing in recent years, due to its interesting biological activity profile. It has been found to have anti-inflammatory, anti-bacterial, antioxidant and anticancer activities and is the active compound of herbs used in traditional medicine.[19,20] Furthermore, it can serve as a building block for the synthesis of pharmaceutically active ingredients and polyesters.[19,21] Meanwhile 2 is found in many plants, the extraction is very low yielding, therefore, it is synthesized industrially by oxidation of vanillin (1), which is still predominantly produced from petrochemicals.[22]

The demethylation of 2 yields protocatechuic acid (3), which also shows promising biological properties and has been studied intensively in the recent years.[23] Furthermore, it has already been applied as a monomer for grafted chitosan co-polymers, which could be used as anti-microbial, biobased packaging materials.[24] It also found application in the electrochemical co-polymerization with aniline on gold microdisk electrodes, enhancing their electrochemical properties.[25] Mean-

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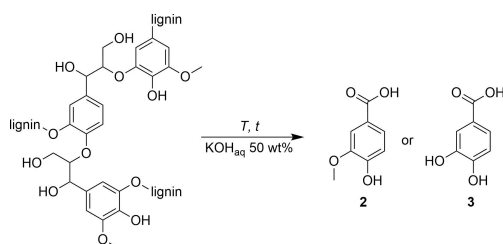European Chemical
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while, the industrial synthesis also relies on petrochemically produced vanillin (**1**), efforts have been made to synthesize it through fermentation of glucose by genetic engineering of bacteria.[26]

In the scope of this contribution, a novel process for the selective production of either vanillic acid (**2**) or protocatechuic acid (**3**) was developed and paired with a work-up on ion exchange resins, that allowed the repeated use of the caustic reaction mixture, providing attractive pre-requisites for technical use (Scheme 1).

Results and Discussion

Waldvogel et al. published the degradation of various types of processed lignin with the green oxidant ferrate to selectively generate **2**.[18] However, vast amounts of energy were needed for the production of the oxidant from sacrificial iron anodes, which also suffer from passivation, making a long term use of the process challenging. Additionally, the highly caustic mixture had to be acidified during work-up, causing large amounts of salt waste. Therefore, it is of high interest to develop an alternative strategy to generate **2** with a purely thermal treatment of lignin in caustic medium and to develop an efficient and viable work-up, that does not rely on complete acidification. Previous studies indicated that the highly caustic medium plays a central role in the degradation of lignin. According to literature, the oxidation of pure vanillin (**1**) to vanillic acid (**2**) gives better yields in KOH_{aq} than in $NaOH_{aq}$, so first caustic potash in different concentrations was tested as shown in Table 1.[27,28] Other alkaline hydroxides are less soluble in water or have tremendously higher costs and were therefore not tested.

Thermal treatment of lignin in 50 wt% KOH_{aq} resulted in the highest yield of **2** with 8.3 wt%. Following this, a Design of Experiments (DoE) with a response surface plan was developed, focusing on the interaction of temperature and time, keeping the lignosulfonate and potassium hydroxide concentration constant at 5 g/L and 50 wt%, respectively. The DoE revealed that lower temperatures in combination with prolonged reaction times result in higher yields of **2**. At increased temperatures demethylation of in-situ generated **2** to **3** occurs, which was also reported for the oxidation of vanillin (**1**) under highly caustic conditions.[27,28] The optimal parameters were found to be a degradation temperature of 139 °C for 36 h, which resulted in a yield of 9.0 wt% of **2**.

Finally, the influence of the lignosulfonate concentration on the yield was screened and the results are depicted in Table 2.

The relative yield of **2** strongly decreases with higher LS concentrations, while the highest yield was observed with a lignosulfonate concentration of 1.7 g(LS)/L resulting in 10.6 wt% of vanillic acid (**2**). The optimized reaction also showed a very high selectivity for **2**, as it was the sole detected product via HPLC as shown in Figure 1.

The optimized procedure was then applied to other technical types of Kraft lignin and organosolv lignin. To compare the individual feedstock, nitrobenzene oxidation (NBO) was performed.[29] The reaction shows a high selectivity for vanillin (**1**) and is used as a benchmark reaction to compare different lignin feedstocks. The yields are depicted in Table 3.

These results show that the protocol is suitable for different kinds and grades of processed lignin, obtaining **2** in yields close to those obtained by nitrobenzene oxidation.

After optimizing the yield of **2**, it was tried to achieve selective and complete conversion of in-situ generated **2** to protocatechuic acid (**3**), which is favoured by higher temperatures and prolonged reaction times. A study of the time dependency of the reaction was performed at 190 °C and a LS concentration of 5 g/L. The results are depicted in Figure 2.

The diagram displays a drop in the combined yield of **2** and **3** after 24 h and a direct drop of yield of **3** after 48 h, which

Scheme 1. Thermal degradation of lignin in aqueous potassium hydroxide for a selective production of vanillic acid (2) or protocatechuic acid (3).

Table 1. Yield of **2** in KOH_{aq} in different mass concentrations. Cond.: 170 °C, 18 h, 5 g(LS)/L. Yields were determined by HPLC with 1,3-dimethoxybenzene as internal standard.

Alkaline media	Yield of **2**
40 wt% KOH_{aq}	6.6 wt%
45 wt% KOH_{aq}	7.3 wt%
50 wt% KOH_{aq}	8.3 wt%
55 wt% KOH_{aq}	6.1 wt%

Table 2. Dependence of the yield of **2** from the lignosulfonate concentration. Cond.: 139 °C, 36 h, 50 wt% KOH_{aq}. Yields were determined by HPLC with 1,3-dimethoxybenzene as internal standard.

Lignosulfonate concentration	Yield of **2**
1.8 g/L	10.6 wt%
5.0 g/L	9.0 wt%
15 g/L	5.6 wt%
30 g/L	4.3 wt%
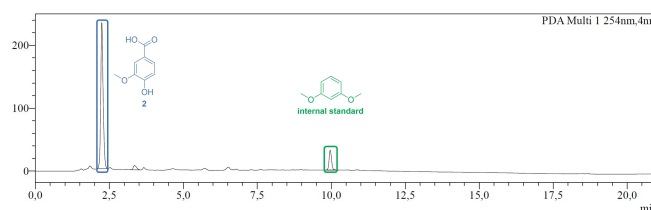
Figure 1. Exemplary HPLC of the depolymerized lignin after extractive work-up, with the optimized conditions.

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Table 3. Degradation of various types of lignin by thermal treatment in KOH_{aq} and the yield of the nitrobenzene oxidation as reference reaction. Cond.: 139 °C, 36 h, 1.7 g(LS)/L, 50 wt% KOH_{aq}. Yields were determined by HPLC with 1,3-dimethoxybenzene as internal standard. [a] reaction time was 42 h.

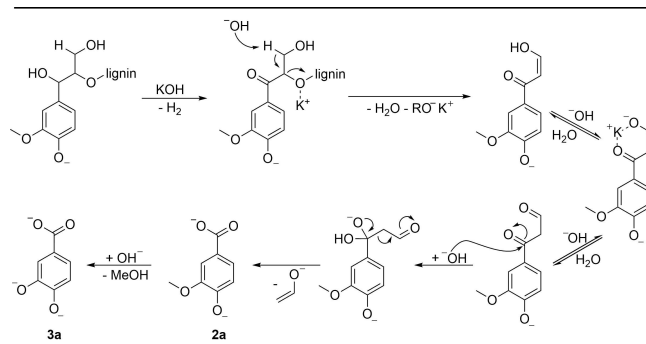| Lignin	Yield of **2**	Yield of **1** (NBO)
Lignosulfonate (Borregaard)	10.6 wt%	10.6 wt%
Kraft Lignin, Indulin AT (WestRock) [a]	9.5 wt%	9.5 wt%
Kraft Lignin (MeadWestvaco) [a]	6.6 wt%	6.5 wt%
Organosolv Lignin (Fraunhofer) [a]	4.1 wt%	4.2 wt%
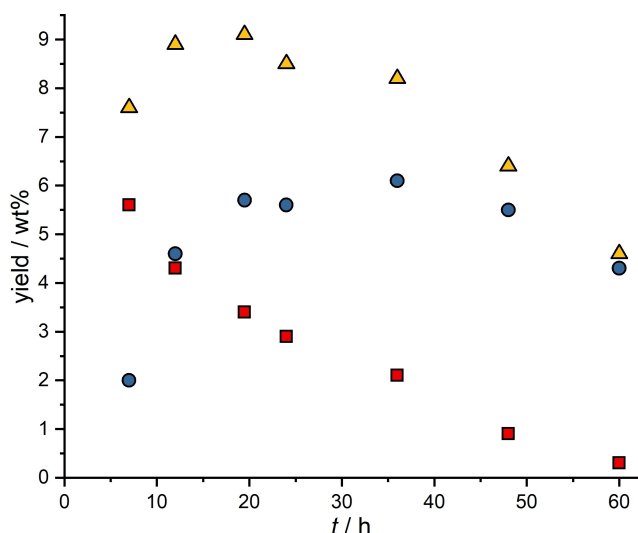
Figure 2. Yield of **2** [■], **3** [●] and the combined yield [▲] in dependency of time. Cond.: 190 °C, 5 g(LS)/L, 50 wt% KOH_{aq}. Yields were determined by HPLC with 1,3-dimethoxybenzene as internal standard.

Scheme 2. Postulated mechanism for the depolymerization of lignin to form vanillic acid (**2**) and protocatechuic acid (**3**).

acid and potassium hydroxide are consumed in the process, which renders it uneconomic. Therefore, an ion exchange resin, which has already been used in previous publications by the Waldvogel group for the separation of monomeric lignin degradation products such as vanillin (**1**) or stilbenes, was tested as an alternative work-up to enable the reusage of the caustic solution.[16,32] The resin consists of a polystyrene backbone that is modified by cationic alkylammonium groups, thus a combination of Coulomb and π–π dispersions/interactions are involved in binding the anionic monomer, as depicted in Figure 3. The dispersion interactions become more dominant with the high ionic strength of the media.

In screening experiments, glacial acetic acid proved to be the best desorbant, acting as an acid and a solvent, and can theoretically be reused after distillation and was thus used for further experiments. To validate the reusability of the reaction mixture, 6 consecutive runs were conducted. The results are summarized in Figure 4.

shows that degradation of **3** is also taking place at higher temperatures, although no degradation products were observed. Thus, lower temperatures and longer reaction times were tested, which lead to no significant improvement. Additionally, it was tested, if higher conversions could be achieved, when optimal conditions for the conversion to **2** were applied first, and afterwards the reaction continued at elevated temperatures. With this approach the yield was increased to 6.9 wt% of **3** with a second treatment at 170 °C for 55 h.

In Scheme 2 a mechanism for the depolymerization is proposed, starting with the oxidation of the benzylic alcohol to the corresponding ketone under hydrogen evolution, which is reported to occur under highly caustic conditions with electron-rich benzylic alcohols and aldehydes.[27,30] This is followed by elimination of a beta-aryl ether moiety, to yield a 1,3-dicarbonyl compound.[31] In the next step, acetaldehyde and **2** are formed in a retro aldol reaction. Following this, the remaining ether bond can be cleaved in an S_N2 reaction, yielding protocatechuic acid (**3**) and methanol. The high concentrations of potassium will stabilize such molecules as **3a**.
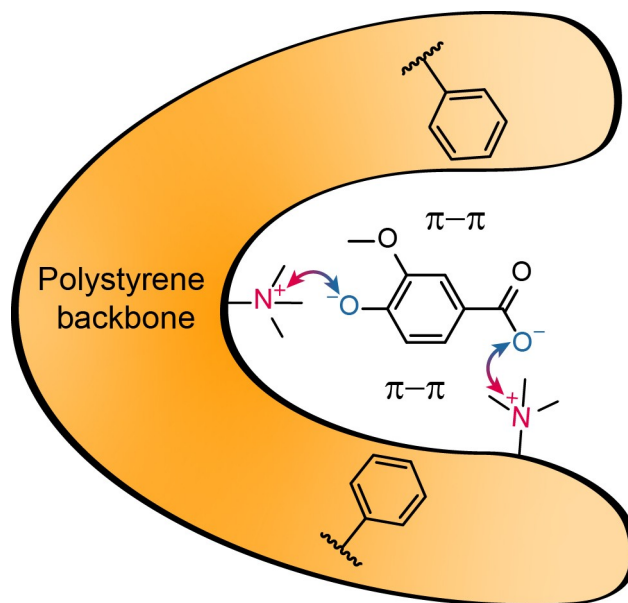
Since the work-up consists of acidification of the highly concentrated caustic solution, large amounts of hydrochloric
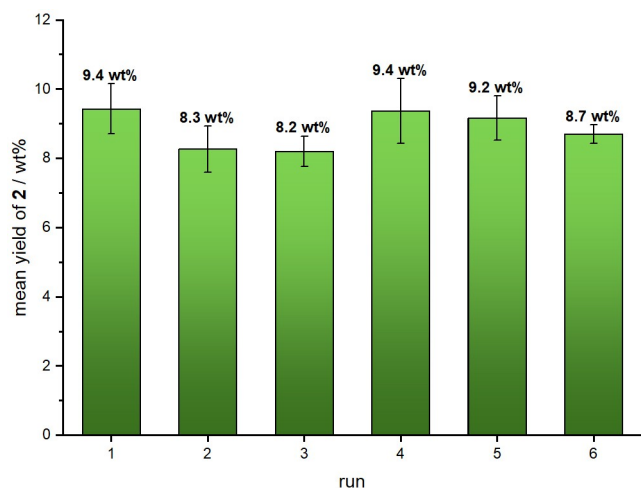

Figure 3. Adsorption of vanillic acid (**2**) by cationic ion exchange resins.

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Figure 4. Trend of yield of **2** with direct reusage of the reaction media after work-up on ion exchange resins. Experiments were conducted in triplicates and the mean yield calculated. Cond.: 139 °C, 36 h, 1.7 g(LS)/L, 50 wt% KOH_{aq}. Yields were determined by HPLC with 1,3-dimethoxybenzene as internal standard.

After the first run, a drop in the yield of 1.1 wt% is observed, but the yield stabilises in the next couple of runs. Additionally, the error bars of all runs show overlap. Consequently, the filtrate can be directly reused as media for multiple times, without significant loss of yield.

Conclusions

We established the oxidant-free synthesis of vanillic acid (**2**) and protocatechuic acid (**3**) from industrially relevant lignin by thermal treatment in highly concentrated caustic potash. After optimization of the reaction parameters the yield of **2** was increased to 10.6 wt%. By increasing the reaction temperature **3** was obtained selectively in 6.9 wt% yield. To circumvent a work-up with acidification, which would destroy the large amounts of potassium hydroxide used, ion exchange resins were employed. Through this, the reaction mixture was depleted of the product and used directly again for at least 5 further times without a significant loss of yield.

Experimental Section

Lignin Depolymerization

85 mg of lignosulfonate and 50 mL of 50 wt% KOH_{aq} were added to an autoclave equipped with a stirring bar. The autoclave was sealed and placed in an oil bath and heated for 36 h at 139 °C with stirring.

Acidic Work-Up

After the autoclave cooled down, the reaction mixture was transferred to an Erlenmeyer flask and the solution acidified to pH 1 with conc. hydrochloric acid, followed by threefold extraction with 200 mL ethyl acetate. The combined organic fractions were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. 20 μL of 1,3-dimethoxybenzene were added and the crude product dissolved in 9 mL acetonitrile and analyzed by HPLC.

Work-Up on Ion Exchange Resins

After the autoclave cooled down, the reaction mixture was transferred to an Erlenmeyer flask and 6 g of ion exchange resin added and mechanically shaken at 300 rpm for 1.5 h. Afterwards the mixture was filtered under reduced pressure and the resin washed with 10 mL of deionized water. The resin was placed in an Erlenmeyer flask, 70 mL glacial acetic acid added and the flask mechanically shaken at 300 rpm for 1.5 h. The mixture was filtered under reduced pressure and the resin washed with 10 mL ethyl acetate. The solvents of the filtrate were removed under reduced pressure. 20 μL of 1,3-dimethoxybenzene were added and the crude product dissolved in 9 mL acetonitrile and analyzed by HPLC.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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