Role of alkali in catalytic oxidation of *p*-cresols

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ABSTRACT

The investigation of alkali acting as the key component during the liquid-phase catalytic oxidation of *p*-cresols to *p*-hydroxyl aromatic aldehydes is far from satisfied, thus a detailed exploration is presented. It was observed that the *p*-cresols were activated by alkali to form phenolate salt to ensure mild reaction conditions demonstrated by comparing the oxidation of *p*-cresol and its phenolate sodium. It was also found that excess alkali improved the selectivity of aldehyde by inhibiting the formation of dimeric side products in view of an analysis of the side products distribution. The alkaline alcoholic anion facilitates the 1,6-addition reaction between *p*-benzoquinone methide and solvent. Thus, more alkali was needed in solvents with high pKa values and high water content. The detection of trace acid during the oxidation of *p*-cresols suggested the phenoxy radical mechanism rather than the classic benzyl radical mechanism proposed for interpreting the oxidation of non-hydroxyl aromatic hydrocarbons. These conclusions contribute significantly to both the understanding of role of alkali during the reaction process and the mechanism study for the catalytic oxidation of cresols and non-hydroxyl aromatic hydrocarbons.

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1. Introduction

p-Hydroxyl aldehyde is an important intermediate for the industrial synthesis of a wide variety of special chemicals, such as pharmaceutical, perfumes, dyes, and polymers [1–13]. Among many synthetic methods, liquid-phase catalytic oxidation of *p*-cresols with molecular oxygen could be most promising [1–13]. Alkali was normally needed during the liquid-phase oxidation of *p*-cresol and mono-substituted *p*-cresols [1–3,14–21]. To the best of our knowledge, no reports on the liquid-phase oxidation of *p*-cresols to *p*-hydroxyl aromatic aldehydes under base-free conditions have been presented. It is also interesting that trace *p*-hydroxyl aromatic acids are detected during the oxidation of *p*-cresols, which is very different from that of non-hydroxyl aromatic hydrocarbons [1–3]. The alkali was used to improve the selectivity of aldehyde by inhibiting the side reactions, which were mentioned by many references without in-depth interpretations [2,3,16–22]. For example, Ji and co-workers proposed three possible roles of

NaOH: (i) facilitating phenoxy radical formation *via* phenolate anion; (ii) inhibiting free radical-based coupling side-reactions; (iii) protecting in situ the formed aldehyde group *via* dearomatization-enolization [3]. Unfortunately, no solid evidence was shown in this reference. Our preliminary experiments also showed that no vanillic acid was detected when 3-methoxyl-4-hydroxyl-benzaldehyde (vanillin) was oxidized under base-free conditions, which are contradictory with the above explanation (iii). Despite Xu et al. believed that sodium hydroxide is essential for preventing oxidation on the benzene ring and benefiting for selective oxidation [17] and Chandalia et al. also held that a large amount of alkali was necessary to ensure a high selectivity [22], the origin of role of alkali has not yet been clearly understood. Moreover, the amount of alkali used are also varied in different alcoholic solvents [1–6,14–22], and the reason of which is still unknown. Therefore, a systematic study on the important roles of alkali is urgently needed.

The mechanism for the liquid-phase catalytic oxidation of *p*-cresols has been discussed for several decades [1–30]. The formation of *p*-benzoquinone methide through phenoxy radical is considered as the main viewpoint [1–30]. Although the mechanism is still under discussion, many evidences have been provided. In our previous studies, *p*-benzoquinone methide, aromatic ether, and dimers were found during the catalytic oxidation of 4-methyl

guaiacol to vanillin. Therefore, the evidence above shows that phenoxy radical mechanism would be reasonable for oxidation of *p*-cresols. Traditional classic benzyl radical mechanism is usually applied into non-hydroxyl aromatic hydrocarbons, such as toluene, *p*-chlorotoluene, and *p*-methoxytoluene [31–35].

The main goal of this work is to study the roles of alkali during the liquid-phase oxidation of *p*-cresols. The necessity of alkali to activate the substrate is demonstrated. The role of alkali to improve the selectivity of aldehydes was explained in terms of the mechanistic study and experimental results. It was also found that the amount of alkali needed is closely related with the water content and the *p*Ka values of solvents. The mechanistic explanations are given to explain why *p*-hydroxyl aromatic aldehydes are hard to be oxidized to form the corresponding acids.

2. Materials and methods

2.1. Materials

Reagent-grade 4-methyl guaiacol, *p*-cresol, 2-bromo-4-cresol, and vanillyl alcohol with mass fraction purity ≥99.0% were obtained from Sahn Chemical Technology Co., Ltd and used without further purification. The ethylene glycol monomethyl ether (EGME), employed as the solvent with mass fraction purity ≥99.5%, was obtained from Sinopharm Chemical Technology Co., Ltd. The vanillin and vanillyl alcohol used as external standard in HPLC with mass fraction purity ≥99.5% were also obtained from Sinopharm Chemical Technology Co., Ltd. The O_2 with purity of ≥99.99 mol% and N_2 with purity of ≥99.999 mol% were used in the reaction.

N,N′-ethylenebis(acetylacetoniminato)-cobalt(II) hexafluorophosphoric pyridinium (Co-[Salen-Py][PF_6]$_2$) was used as the catalyst in the experiment. Detailed information about the synthesis route is shown in the reference [2].

2.1.1. Experimental and analytical procedure

The experimental apparatus employed is the agitator bubbling reactor comprising a 100 ml volume, four-neck, and round-bottom reactor with a stirring device above. The reactor was placed in a water bath providing isothermal operating conditions with an accuracy of ±0.1 K. The gas reactant flowed into the reactor through an inlet needle. The reagent NaOH, solvent, substrate and catalyst were fed into the reactor in sequence. The temperature of the water bath was set at 353.2 K before the reaction occurred. Oxygen was introduced into the reactor continuously after the reactants dissolved under nitrogen atmosphere. The reactant solution was acidified by aqueous HCl before being measured.

The substrate (4-methyl guaiacol), intermediates (vanillyl alcohol, ether intermediate) and desired products (vanillin, vanillic acid) were confirmed by comparing with standard chemicals by HPLC and HPLC–MS. Specifically, the mobile phase consisted of three eluents: buffer liquid (1.2 vol% phosphoric acid), 30 vol% methanol and 70 vol% distilled water. The reactant was diluted by solutions consisting of 50 vol% methanol and 50 vol% distilled water. The wave number of UV detector of HPLC was set as 279 nm and the flow rate of mobile phase was 1 mL min⁻¹ with a C18 reversal pillar (size: 150 × 4.6 mm).

To isolate the pure products, the reaction mixtures were stirred for 0.5 h in an open system with H_2O (20 ml) added, and then concentrated to recover the mixtures of EGME and water. MTBE (50 ml) was added to the residue and diluted hydrochloric acid (1.0 M) was used to adjust the pH to the range of 2.0–3.0. Furthermore, the solution was partitioned into two layers, and the aqueous phase was extracted with MTBE by three times. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a solid. The purified vanillin was obtained by recrystallization

Table 1
The liquid-phase oxidation of *p*-cresols under base-free/base conditions.[a]

Entry	Substrate	Time/h	Conv./%	TOF[b]
1	*p*-cresol	8	0 (99.9)	0 (30.2)
2	2-bromo-cresol	8	0 (99.9)	0 (30.2)
3	4-methyl guaiacol	8	0 (99.9)	0 (30.2)
4	Vanillyl alcohol	8	0 (99.9)	0 (30.2)
5	4-methyl guaiacol sodium salt	8	99.9	30.2

[a] Reaction conditions: temp, 353.2 K; substrate, 50 mmol; catalyst, 0.15 g; solvent, EGME 20.5 g; 500 rpm; oxygen, 25 ml min⁻¹. The values in parentheses were obtained by addition of 50 mmol NaOH.
[b] Turnover frequency (TOF) = number of moles of substrate converted per mole of catalyst per hour.

Table 2
The liquid-phase oxidation of 4-methyl guaiacol under different base/substrate ratio.[a]

Entry	Base/Substrate (molar ratio)	Time/h	Conv./%	Sel./%	TOF
1	1.0	8	99.9	5.0	30.2
2	2.0	8	99.9	81.1	30.2
3	2.7	8	99.9	90.0	30.2
4	4.0	8	99.9	90.8	30.2
5[b]	0	8	99.9	4.4	30.2
6[b]	1.7	8	99.9	90.2	30.2
7[b]	3.0	8	99.9	89.5	30.2

[a] Reaction conditions: temp, 353.2 K; 4-methyl guaiacol, 50 mmol; NaOH; catalyst, 0.15 g; solvent, EGME 20.5 g; 500 rpm; oxygen, 25 ml min⁻¹.
[b] 4-methyl guaiacol sodium salt was used as the substrate.

in alcohol-water solution (25 vol% enthaol and 75 vol% distilled water) under 278.15 K for 5 h. The mixtures of EGME and water were separated by rectification.

3. Results and discussion

3.1. The substrates were activated by NaOH

The importance of NaOH to activate the substrate was confirmed by control experiments. No reaction occurred when no alkali was added (Entries 1–4 in Table 1). However, when equivalent molar of NaOH was added, the reaction proceeded smoothly. The phenomenon was reinforced when the 4-methyl guaiacol sodium salt was used as the substrate. We concluded that the *p*-cresol sodium salt was much easier to be oxidized than 4-methyl guaiacol, which could be explained by the higher electron-donating ability of the phenolate anion than that of hydroxyl group. Namely, the abstraction of proton from the hydroxyl group by alkali was a key step during the oxidation of *p*-cresols.

3.2. The promotion effect of NaOH on the selectivity of vanillin

The addition of alkali improved the selectivity of aldehyde during the oxidation of 4-methyl guaiacol, which was also confirmed by many studies [2–6,16,22]. As shown in Table 2, the selectivity of vanillin could be greatly improved by increasing the amount of base. Only selectivity of 5% was obtained when 1.0 molar equivalent of base was added. However, selectivity of 90.0% was achieved when 2.7 molar equivalents of NaOH were used. More excess alkali has minor effect on the reactions (Table 2). The same result was also found when 4-methyl guaiacol sodium salt was used as the substrate. This experiment also demonstrated that 1.0 molar equivalent of NaOH was utilized to activate the substrate. The side products under insufficient alkaline conditions were analyzed (see supporting information). Analysis indicated that the dimers of vanillin and 4-methyl guaiacol were the main side products.

To explain the above results, the mechanism was proposed. The detailed reaction scheme for the liquid-phase oxidation of 4-methyl