# Determining Factors for the Product Para/Ortho Ratio and Reaction Rate in the Formation of (Hydroxymethyl)phenols from Phenol and Formaldehyde

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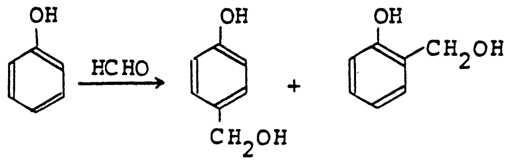
Formations of 2- and 4-(hydroxymethyl)phenols from phenol and formaldehyde in aqueous alkaline solutions were kinetically investigated by the use of HPLC. The para/ortho ratio for the products sigmoidally increased with increasing concentration of sodium hydroxide, whereas the total yield of the (hydroxymethyl)phenols showed a steep maximum at the charged molar ratio unity of sodium hydroxide to phenol. Use of lithium hydroxide and potassium hydroxide, in place of sodium hydroxide, as alkaline catalysts results in almost the same para/ortho ratios. The addition of potassium chloride and magnesium sulfate decreased both the para/ortho ratio and the yield. These results indicate that the reactions proceed via an electrophilic attack of formaldehyde, which is free from the adduct formation with hydroxide ion, at phenolate ion. Electrostatic interactions between the phenoxide oxygen atom of the phenol and the incoming hydroxymethyl residues in the transition state exhibit a predominant role in the determination of the para/ortho ratio.

Preparations of (hydroxymethyl)phenols by the reactions of phenol and formaldehyde in alkaline solutions (Eq. 1) are important in industry, since both of the products, 2- and 4-(hydroxymethyl)phenols, are valuable intermediates for the syntheses of various fine chemicals.



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Previously, these reactions were kinetically examined by several authors.[1-7] However, the reported results are not necessarily consistent with each other. For example, the para/ortho ratios in the products for the sodium hydroxide-catalyzed reactions were 0.61, 1.0, and 1.4, according to Freeman,[1] Minami,[2] and Peer,[5] respectively. For all the reactions, the molar ratio of sodium hydroxide to phenol was unity. These discrepancies are, at least partly, associated with the fact that the reactions were followed by paper chromatography; thus, quantitative analyses were rather difficult. The reaction mechanism has not been sufficiently clarified yet.

Quite recently, the present author found that 4-(hydroxymethyl)phenol can be selectively prepared by the use of cyclodextrin as a catalyst for the reaction of Eq. 1.[8] This finding has prompted the author to study in more detail the effects of the reaction conditions on the selectivity and the rate for the reaction in the absence of cyclodextrin. The reactions have been precisely followed by HPLC.

This paper reports on the effects of kinds and concentrations of alkaline catalysts on the para/ortho ratio in the products and the rate for the formation of (hydroxymethyl)phenols from phenol and formaldehyde in water. Furthermore, results for the reactions in various organic solvents are described. Factors determining the para/ortho ratio and the reaction rate are shown.

## Experimental

The reactions between phenol and formaldehyde were carried out at 30 °C under nitrogen. The product analyses were made by HPLC (JASCO $C_{18}S$ column, 10 cm; eluent, 2:1 water-ethanol mixture). All the reactions in the present study satisfactorily followed pseudo-first-order kinetics, and the reaction rates were expressed in terms of the yields with respect to the charged phenol in 1 h or 1 day. The formation of phenols having two or more hydroxymethyl groups was not detected.

## Results

**Effect of Concentration of Sodium Hydroxide on the Para/Ortho Ratio and the Reaction Rate.** Figure 1 shows plots of the para/ortho ratio (4-(hydroxymeth-

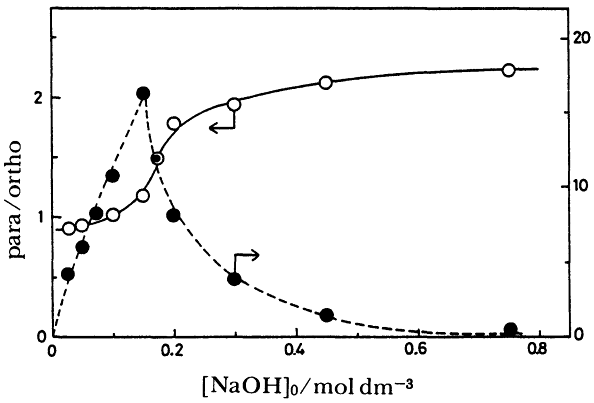


Fig. 1. Plots of the para/ortho ratio (○) and the total yield of 2- and 4-(hydroxymethyl)phenols (●) vs. the charged concentration of sodium hydroxide for the reactions of phenol and formaldehyde in water: $[\mathrm{phenol}]_0=0.15$ and $[\mathrm{HCHO}]_0=0.58\,\mathrm{mol\,dm^{-3}}$; at 30 °C for 1 h.

yl)phenol/2-(hydroxymethyl)phenol) and the total yield of 2- and 4-(hydroxymethyl)phenols as functions of the charged concentration of sodium hydroxide for reactions in water. The initial concentrations of phenol and formaldehyde were kept constant at 0.15 and 0.58 mol dm$^{-3}$, respectively.

As shown by the open circles, the para/ortho ratio sigmoidally increases with an increase in the charged concentration of sodium hydroxide, showing a gradual saturation at large concentrations of sodium hydroxide.

The total yield (the closed circles) significantly increases with increasing concentration of sodium hydroxide up to the concentration 0.15 mol dm$^{-3}$, and then rapidly decreases. Thus, it shows a steep maximum at the charged molar ratio unity of sodium hydroxide to phenol.

**Effects of Kinds of Alkaline Catalysts on the Para/Ortho Ratio and the Reaction Rate.** Table 1 shows the para/ortho ratios and the yields for the reactions using various alkali metal hydroxides as catalysts. The concentrations of the catalysts are 0.75 mol dm$^{-3}$. The yields for the reaction with sodium hydroxide are larger than the values for the reactions with lithium hydroxide and potassium hydroxide. However, the para/ortho ratio is not significantly affected by the kinds of alkali metal hydroxide.

Table 1. Yields and Para/Ortho Ratios for the Reactions of Phenol and Formaldehyde Using Various Alkali Metal Hydroxides as Catalysts[a]

| Catalyst | Yield/mol% | | para/ortho |
|---|---|---|---|
| | *p* | *o* | |
| LiOH | 0.33 | 0.15 | 2.2 |
| NaOH | 0.44 | 0.20 | 2.2 |
| KOH | 0.24 | 0.11 | 2.2 |
| NaOH+LiOH[b] | 0.35 | 0.15 | 2.3 |
| NaOH+KOH[c] | 0.38 | 0.17 | 2.2 |

a) [phenol]$_0$=0.15 mol dm$^{-3}$; [alkali metal hydroxide]$_0$=0.75 mol dm$^{-3}$; [HCHO]$_0$=0.58 mol dm$^{-3}$; at 30 °C for 1 d. b) [NaOH]$_0$=0.15 and [LiOH]$_0$=0.60 mol dm$^{-3}$. c) [NaOH]$_0$=0.15 and [KOH]$_0$=0.60 mol dm$^{-3}$.

Table 2. Effects of Additive Salts on the Yields and the Para/Ortho Ratios for the Reactions of Phenol and Formaldehyde Using Sodium Hydroxide as Catalyst[a]

| Additive salt | Concentration of NaOH/mol dm$^{-3}$ | Yield/mol% | | para/ortho |
|---|---|---|---|---|
| | | *p* | *o* | |
| KCl | 0.75[b] | 0.23 | 0.12 | 1.9 |
| KCl[c] | | 0.22 | 0.13 | 1.7 |
| None | | 0.44 | 0.20 | 2.2 |
| KCl | 0.15[b] | 5.0 | 4.4 | 1.1 |
| CaCl$_2$ | | 5.9 | 5.4 | 1.1 |
| MgSO$_4$ | | 5.0 | 5.3 | 0.94 |
| None | | 8.8 | 7.7 | 1.1 |

a) [phenol]$_0$=0.15 mol dm$^{-3}$; [HCHO]$_0$=0.58 mol dm$^{-3}$; a) [Additive Salt]$_0$=0.6 mol dm$^{-3}$ unless otherwise noted; at 30 °C. b) Reaction time, 1 d. c) [KCl]$_0$=2.0 mol dm$^{-3}$. d) Reaction time, 1 h.

The reaction involving mixture of sodium hydroxide and either lithium hydroxide or potassium hydroxide at the total concentration 0.75 mol dm$^{-3}$ gives a similar para/ortho ratio.

**Effects of Additive Salts.** The effects of the addition of neutral salts on the para/ortho ratio and the yields for the formation of (hydroxymethyl)phenols are listed in Table 2. The charged concentration of phenol is 0.15 mol dm$^{-3}$.

When the charged concentration of sodium hydroxide is 0.75 mol dm$^{-3}$, the addition of potassium chloride exhibits a small but definite decrease in the para/ortho ratio. At a concentration 0.15 mol dm$^{-3}$ of sodium hydroxide, magnesium sulfate also decreases the para/ortho ratio. However, potassium chloride and calcium chloride show no significant effects at concentration 0.6 mol dm$^{-3}$.

All the metal salts examined decreased the yields of both 2- and 4-(hydroxymethyl)phenols.

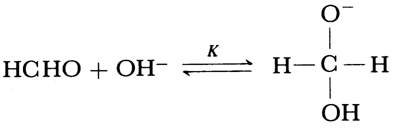
**Reactions in Various Organic Solvents.** The para/ortho ratios and the yields for the reactions in various organic solvents are presented in Table 3. The para/ortho ratio decreases in the following order:

ethanol $>$ 2-propanol $\gg$ water $\approx$ methanol $\approx$ *N,N*-dimethylformamide $\gg$ 1,4-dioxane.

## Discussion

**Factors Determining the Reaction Rate.** A plot of the yield vs. the concentration of sodium hydroxide (the closed circles in Fig. 1) satisfactorily fits the theoretical line (the dotted line) calculated in terms of the following scheme:

$$C_6H_5OH \xrightleftharpoons{K_a} C_6H_5O^- + H^+ \qquad (2)$$



$$HCHO + OH^- \xrightleftharpoons{K} H-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-H \qquad (3)$$

$$\text{Rate} = k[C_6H_5O^-][HCHO_{\text{free}}] \qquad (4)$$

Here, the activation of phenol for the reaction by deprotonation (Eq. 2) and the deactivation of formaldehyde by the addition of hydroxide ion (Eq. 3) are taken into consideration. The reaction rate is proportional to the product of the concentrations of phenolate ion and free formaldehyde, as shown by Eq. 4. The equilibrium constant $K_a$ for Eq. 2 is taken as $10^{-9.998}$,[9] and the value $K$ for Eq. 3 has been determined as 13 mol$^{-1}$ dm$^3$ by best-fitting method.

The concentration of phenolate ion significantly increases with an increase in the charged concentration of sodium hydroxide, when the charged molar ratio of sodium hydroxide to phenol is smaller than unity. Here, the concentration of free formaldehyde is almost identical with the charged concentration, since the equilibrium concentration of hydroxide ion is minimal. When the charged molar ratio of sodium hydroxide to phenol is larger than unity, however, the concentration of phenolate ion shows a gradual saturation, and the concentration of free formaldehyde decreases in a hyperbolic manner with increase in the equilibrium concentration of hydroxide ion. Thus the rate shows a steep maximum at a charged molar ratio unity of sodium hydroxide to phenol, as clearly shown in Fig. 1.

Similar kinetic analysis was attempted by Peer.[5] However, the analysis was qualitative due to insufficient accuracy of the data, especially at the large concentration of sodium hydroxide, as described by the author.

**Factors Determining the Para/Ortho Ratio.** The sigmoidal increase of the para/ortho ratio with increase in the charged concentration of sodium hydroxide, depicted by the open circles in Fig. 1, indicates that the electrostatic interactions between the incoming hydroxymethyl residues and the phenoxide oxygen atoms of phenol in the transition states predominantly determine the para/ortho ratio. In the highly alkaline media containing sufficient amounts of sodium hydroxide, the protonation of the hydroxymethyl groups prior to the transition state can not proceed efficiently; these groups are present mostly in anionic forms in the transition state. As a result, the electrophilic attack by formaldehyde at the ortho positions of phenolate is suppressed with respect to the reaction at the para position, since the magnitude of the electrostatic repulsion between the negative charge at the phenoxide oxygen atom and the negative charge at the hydroxymethyl residue is larger for the ortho-reaction.

On the other hand, the hydroxymethyl groups are effectively protonated to neutral species prior to the transition state, when the charged molar ratio of sodium hydroxide to phenol is smaller than unity and, thus, the media are less alkaline. The electrostatic repulsion is less important, and a reaction at the ortho positions takes place rather smoothly.

These arguments are definitely confirmed by the fact that the para/ortho ratio largely changes around the charged concentration 0.15 mol dm$^{-3}$ of sodium hydroxide, where the equilibrium concentration of hydroxide ion significantly increases with increase in the charged concentration of sodium hydroxide (see Fig. 1). The charged concentration of phenol is 0.15 mol dm$^{-3}$.

The significance of the electrostatic interaction between the phenoxide oxygen atom and the incoming hydroxymethyl residues in the determination of the para/ortho ratio is further supported by the results for the reactions in organic solvents, shown in Table 3. The para/ortho ratios (2.1 and 1.7) for the reactions in ethanol and 2-propanol are larger than the values (1.1, 1.0, and 0.96) in water, methanol, and *N,N*-dimethylformamide, since the electrostatic interaction is stronger due to smaller dielectric constants (24.55 and 19.92); the dielectric constants for water, methanol, and *N,N*-dimethylformamide are 80.2, 32.7, and 36.71.[10] Quite a small para/ortho ratio (0.43) in 1,4-dioxane is ascribed to the fact that sodium phenoxide is present as an intimate ion pair, rather than as dissociated ions, in the solvent of small dielectric constant (2.209).[10]

Table 3. Yields and Para/Ortho Ratios for the Reactions of Phenol and Formaldehyde Using Sodium Hydroxide as Catalyst in Various Solvents[a)]

| Solvent | Yield/mol% | | para/ortho |
|---|---|---|---|
| | *p* | *o* | |
| Ethanol | 0.30 | 0.14 | 2.1 |
| 2-Propanol | 1.4 | 0.81 | 1.7 |
| Water | 8.8 | 7.7 | 1.1 |
| Methanol | 0.05 | 0.05 | 1.0 |
| *N,N*-Dimethylformamide | 0.26 | 0.27 | 0.96 |
| 1,4-Dioxane | 1.2 | 2.8 | 0.43 |

a) $[\text{phenol}]_0=[\text{NaOH}]_0=0.15$ mol dm$^{-3}$; $[\text{HCHO}]_0=0.58$ mol dm$^{-3}$; at 30 °C for 1 h.

A decrease of the para/ortho ratio upon the addition of potassium chloride (Table 2) is also consistent with the above arguments. The electrostatic repulsion is reduced by the increase in the ionic strength, promoting the ortho-reaction more than the para-reaction. The smaller effect of potassium chloride on the para/ortho ratio at the concentration 0.15 mol dm$^{-3}$ of sodium hydroxide than that at the concentration 0.75 mol dm$^{-3}$ is associated with the minor importance of the electrostatic repulsion here due to a smaller magnitude of the ionization of the hydroxymethyl residues.

The decrease in the para/ortho ratio by the addition of magnesium sulfate is consistent with the previous results[3,5] that the ratio for the magnesium hydroxide-catalyzed reaction is smaller than the value for the sodium hydroxide-catalyzed reaction.

Of the previously reported para/ortho ratios at the charged molar ratio unity of sodium hydroxide to phenol, Minami's value (1.0)[2] is close to the value (1.1) determined in the present study. Freeman's value (0.61)[1] is considerably smaller than the present one, whereas Peer's one (1.4)[5] is larger.

In conclusion, the present kinetic study shows that the rate of the formation of (hydroxymethyl)phenols from phenol and formaldehyde is governed by the concentration of hydroxide ion. The para/ortho ratio in the products is determined by factors affecting the magnitude of the electrostatic interaction between the phenoxide oxygen atom and the incoming hydroxymethyl residue in the transition state.

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