Kinetics and Process Parameter Studies in Oxidative Chlorination of 4-Methylphenol under Phase-Transfer Conditions

Sudip Mukhopadhyay,*,† Jayanta K. Mukhopadhyaya,*,‡ Datta E. Ponde,§ Shlomo Cohen,† and Basan G. S. Kurkalli§

Casali Institute of Applied Chemistry, The Hebrew University of Jerusalem, Givat Ram Campus, Jerusalem 91904, Israel

Abstract:

The effect of phase-transfer catalysts on the rate and selectivity of oxidative chlorination of 4-methylphenol was studied in ethylenedichloride with HCl−H₂O₂. Under identical reaction conditions, the rate of oxidative chlorination increased 6−7-fold in the presence of a phase-transfer catalyst (PTC) like tetraheptylammonium chloride in comparison to an ordinary two-phase system with no PTC. The activation energy was found to be 78 kJ/mol, and the reaction was found to be first-order on 4-methylphenol. An appropriate mechanism has been proposed.

Introduction

Oxidative chlorination[1−4] appears to be a better means to synthesize chloro-substituted organic intermediates for fine chemicals and pharmaceuticals with very high selectivity. Oxidative halogenation of 4-methylphenol by using HCl or HBr and H_2O_2 has been reported.[5−7] The liquid−liquid heterogeneous systems are always preferable due to the ease of separation of the desired product from the highly corrosive aqueous hydrochloric acid solution. However, the lower rate of reaction in heterogeneous systems and less than 100% utilization of chlorine may cause an increase in operation cost. The use of phase-transfer catalysts may provide an aid to solve this problem from the process development point of view. In this work, oxidative chlorination of 4-methylphenol was performed in a liquid−liquid two-phase system under phase-transfer conditions to achieve faster rate of reaction, very high selectivity to the product, and an easy separation of the desired product from the reaction mixture. A kinetic interpretation has been made to provide a detailed know-how of this process.

4-methylphenol → (Oxidative chlorination, HCl-H₂O₂ /Phase transfer catalyst (PTC)) → 2-chloro-4-methylphenol
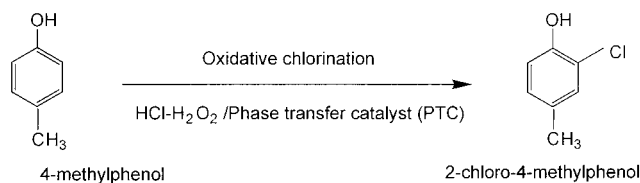
Experimental Procedures

The experiments were carried out in a 250-mL borosilicate glass reactor equipped with six-blade turbine impeller, four

Table 1. Oxidative chlorination of *4*-methylphenol under phase-transfer conditions: effect of addition time of hydrogen peroxide[a]

addition time, h	% overall conversion	% selectivity to monochloro compound
0.5	63	87
0.75	76	91
1.0	87	95
1.5	100	99.8
2.0	100	99.8

[a] Reaction conditions: reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; hydrogen peroxide, 1.926 mol/L of aqueous phase; PTC, 1.9 mol % of the substrate; organic phase, 25 mL; aqueous phase, 30 mL; temperature, 45 °C; reaction time including addition time, 2 h.

baffles, a dropping funnel, and a water condenser. The outgoing gases were passed through a caustic scrubber. The assembly was kept in a constant temperature water bath.

In a typical reaction, 0.0575 mol of 4-methylphenol, total aqueous phase with water, 30 mL, 0.0011 mol of tetraheptylammonium chloride, total organic phase with ethylenedichloride (EDC), 25 mL, and 0.1155 mol of 32% hydrochloric acid, were taken in the reactor, and the reaction mixture was heated to 45 °C. Then 0.05778 mol of 30% hydrogen peroxide was added dropwise to the reaction mixture over 1.5 h, maintaining the desired temperature at 45 °C throughout the reaction period. Then the reaction mixture was stirred for another 0.5 h to complete the reaction. After the reaction, the organic layer was separated. The separation of layers with PTC reaction was 5 times faster in comparison to no PTC reaction. No attempts have been made to recycle the PTC.

The organic layer then fractionated under reduced pressure to isolate desired 2-chloro-4-methylphenol, bp, 93−97 °C at 30−31 mm (lit. bp 195−196 °C).

Analytical Procedures

Samples (1−2 mL) were withdrawn after regular intervals of time and were analyzed by GC

* Corresponding author.
† The Casali Institute of Applied Chemistry, The Hebrew University of Jerusalem, Givat Ram Campus, Jerusalem 91904, Israel.
‡ Georgetown University Medical Center, Drug Discovery Program, Institute for Cognitive and Computational Sciences, 3970 Reservoir Road, NW, Washington, DC-20007-2197.
§ School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, Israel.

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Table 2. Effect of different PTC on the rate and selectivity[a]

PTC	% conversion	% selectivity
tetraheptylammonium chloride	100	99.8
tetrahexylammonium chloride	98	99.7
tetrabutylammonium chloride	97	99.8

[a] Reaction conditions: reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; hydrogen peroxide, 1.926 mol/L of aqueous phase; PTC, 1.9 mol % of the substrate; organic phase, 25 mL; aqueous phase, 30 mL; temperature, 45 °C; reaction time including addition time, 2 h.

Table 3. Oxidative chlorination of 4-methylphenol in different organic solvents[a]

solvent	% overall conversion	% selectivity
ethylenedichloride	100	99.8
carbontetrachloride	98	99.5
chloroform	100	100
1,1,1-trichloroethane	96	99

[a] Reaction conditions: reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; hydrogen peroxide, 1.926 mol/L of aqueous phase; PTC, 1.9 mol % of the substrate; organic phase, 25 mL; aqueous phase, 30 mL; temperature, 45 °C; reaction time including addition time, 2 h.

Conditions. Column used, 30-m Crossbond 5% di-phenyl−95% dimethylpolysiloxane; ID, 0.53 mm; supplier, Restek Corp; carrier gas, helium; flow rate, 15 mL/min; injector temperature, 300 °C; detector temperature, 300 °C; oven temperature, 120 °C, 2 min, 8 °C/min, 200 °C, 5 min.

Results and Discussion

Definitions. *Conversion.* The conversion is defined as the ratio of the moles of the reactant reacted to the moles of the reactant taken.

Selectivity. The selectivity to a particular product is defined as the ratio of the moles of the reactant reacted for the formation of that particular product to the moles of reactant reacted.

Process Parameter Studies. Different important process parameters were studied to develop the most suitable reaction conditions for obtaining the maximum selectivity to the desired product under the reaction conditions. All of the reactions for process parameter studies were performed in semi-batch manner where hydrogen peroxide was added dropwise to the reaction mixture.

With an increase in addition time, the overall conversion of 4-methylphenol increased as usual but the selectivity also increased (Table 1). This is due to the increase in rate of formation of dichloro compund at a faster hydrogen peroxide addition. It was observed that a 1.5 h addition time was preferred under these reaction conditions to obtain maximum selectivity and H_2O_2 utilization.

Different PTC like, tetraheptylammonium chloride, tetra-hexylammonium chloride, and tetrabutylammonium chloride were used, and it was observed that any one of these PTC could be used as the conversion and selectivity obtained was almost the same, (Table 2).

The rate of oxidative chlorination of 4-methylphenol was examined in different solvents, for example, EDC, carbon-

Table 4. Effect of temperature on the rate and selectivity of oxidative chlorination of *4*-methylphenol under phase-transfer conditions[a]

temperature (°C)	% overall conversion	% selectivity
35	57	100
45	100	99.8
55	100	89

[a] Reaction conditions: reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; hydrogen peroxide, 1.926 mol/L of aqueous phase; PTC, 1.9 mol % of the substrate; organic phase, 25 mL; aqueous phase, 30 mL; reaction time including addition time, 2 h.

Table 5. Effect of mole ratio of reactant to hydrogen peroxide in the oxidative chlorination of *4*-methylphenol[a]

reactant: H_2O_{2n}	% overall conversion	% selectivity to monochloro compound	% selectivity to dichloro compound
1:0.5	50	100	0
1:0.9	90	100	0
1:1	100	99.8	0.1
1:1.5	100	54	45

[a] Reaction conditions: Reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; tetraheptylammonium chloride, 1.9 mol % of the substrate; organic phese, 25 mL; aquous phase, 30 mL; temperature, 45 °C; reaction time including addition time, 2 h.

Table 6. Optimum conditions and isolated yield with 100% material balance for the oxidative chlorination of 4-methylphenol[a]

overall conversion of *4*-methylphenol	100%
selectivity with respect to monochloro compound	99.8%
conversion to dichloro compound	0.12%
tarry material	0.08%
isolated yield	96%

[a] Reaction conditions: reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; hydrogen peroxide, 1.926 mol/L of aqueous phase; PTC, 1.9 mol % of the substrate; organic phase, 25 mL; aqueous phase, 30 mL; temperature, 45 °C; reaction time including addition time, 2 h.

tetrachloride, chloroform, and 1,1,1,-trichloroethane. It was observed that the rate and selectivity was maximum in chloroform, but the same selectivity was achieved in almost each of these solvents (Table 3).

The oxidative chlorination of 4-methyphenol was studied by using HCl−H_2O_2 over a wide range of temperature. At 35 °C, only 57% conversion was obtained in 2 h (Table 4). When the temperature was increased to 45 °C the conversion of 4-methylphenol increased to 100%. However, with a further increase in temperature from 45 to 55 °C, the selectivity decreased from 100 to 89%. This is due to the faster rate of side reactions leading to the dichloro and isomer formations at the higher temperature.

From stoichiometry, to form one mole of monochloro compound, one mole of hydrogen peroxide and one mole of hydrochloric acid are needed for one mole of reactant. Different molar ratios, 1:1.5, 1:1.75, and 1:2 of HCl to substrate have been used, and in 2 h, the conversions were 65, 84, and 100, respectively. In all of the reactions carried out, hydrochloric acid was used at 2 mol/mol of reactant to
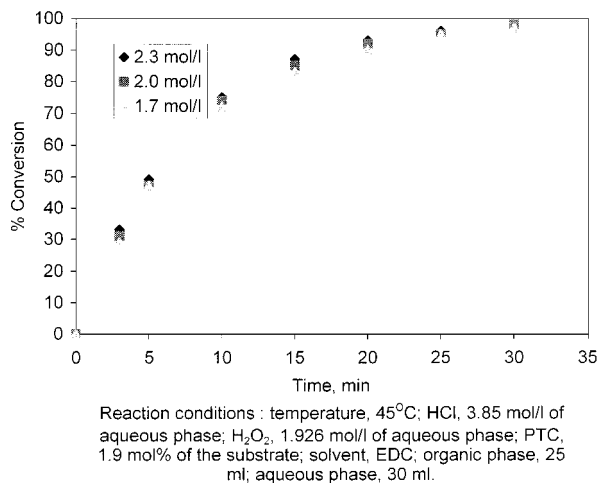
Reaction conditions : temperature, 45°C; HCl, 3.85 mol/l of aqueous phase; H_2O_2, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 ml; aqueous phase, 30 ml.

Figure 1. Effect of initial concentration on the rate of reaction.

Reaction conditions : temperature, 45°C; HCl, 3.85 mol/l of aqueous phase; H_2O_2, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 ml; aqueous phase, 30 ml.
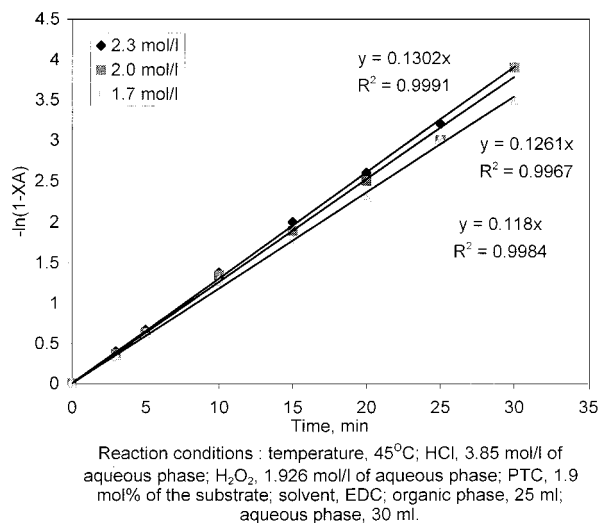
Figure 2. $-\ln(1 - \mathrm{XA})$ vs t at different initial concentrations.

Reaction conditions : temperature, 45°C; 4-methylphenol, 2.3 mol/L of organic phase; HCl, 3.85 mol/L of aqueous phase; H_2O_2, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 mL; aqueous phase, 30 mL.
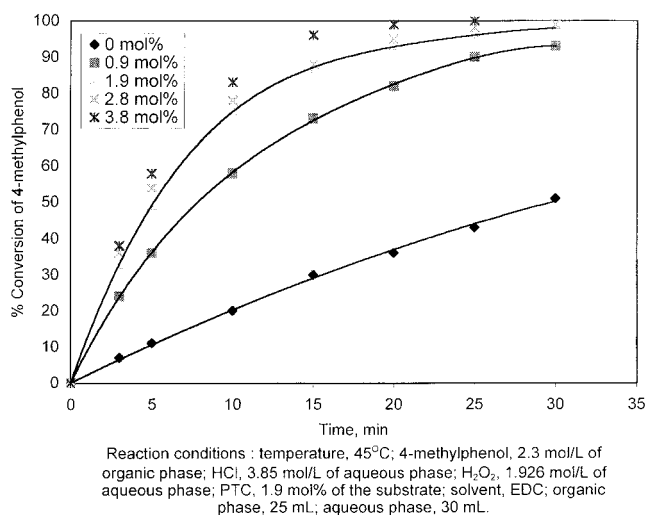
Figure 3. Effect of PTC loading on the rate of reaction.

ensure maximum utilization of hydrogen peroxide to form chlorine. The mole ratio of *4*-methylphenol to hydrogen peroxide was varied from 1.0**:**0.5 to 1.0**:**1.5 (Table 5). It was observed that when exactly 100% of the theoretical amount of hydrogen peroxide was used, 100% conversion of 4-methylphenol was achieved.
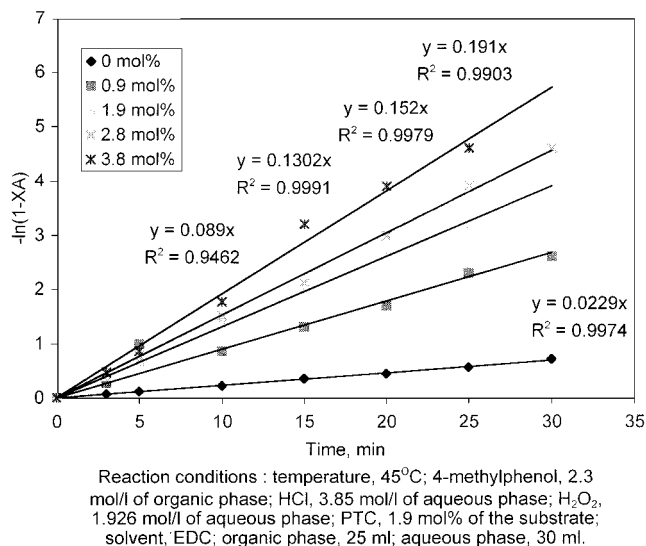

Reaction conditions : temperature, 45°C; 4-methylphenol, 2.3 mol/l of organic phase; HCl, 3.85 mol/l of aqueous phase; H_2O_2, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 ml; aqueous phase, 30 ml.

Figure 4. $-\ln(1 - \mathrm{XA})$ vs t at different catalyst loadings.

Reaction conditions : 4-methylphenol, 2.3 mol/l of organic phase; HCl, 3.85 mol/l of aqueous phase; H_2O_2, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 ml; aqueous phase, 30 ml.
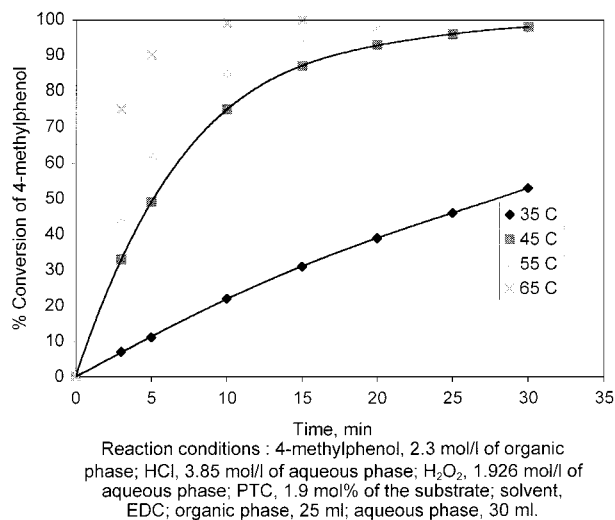
Figure 5. Effect of temperature on the rate of reaction.

Optimum Conditions. The optimum conditions with 100% material balance are given in Table 6.

Kinetics of the Oxidative Chlorination under Phase-Transfer Conditions

For kinetic studies the reactions were performed in a batch-mode fashion. In a typical reaction, 4-methylphenol, 2.3 mol/L of organic phase, HCl, 3.85 mol/L of aqueous phase, PTC, 1.9 mol % of the substrate; H_2O_2, 1.926 mol/L of aqueous phase, EDC (total organic phase with EDC), 25 mL, and water (total aqueous phase), 30 mL were charged to the reactor and heated to 45 °C. The reaction progress was monitored by gas chromatography.
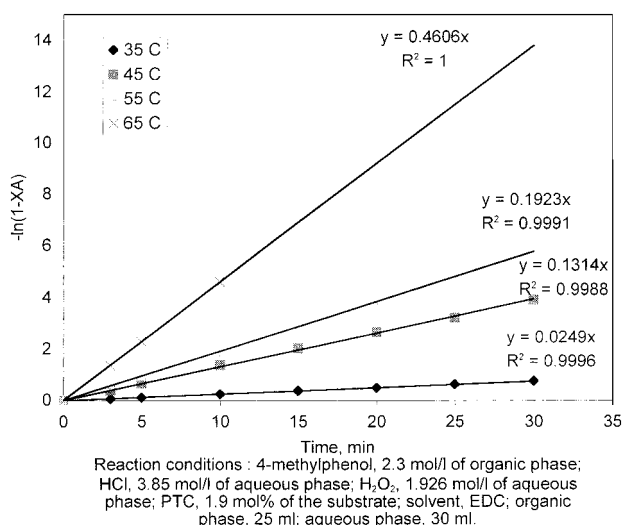
The effect of substrate concentration was studied under phase-transfer conditions (Figure 1), and it was observed that the reaction is a first-order on 4-methylphenol for a specific concentration of HCl, H_2O_2, and PTC (Figure 2).

The effect of phase-transfer catalyst loading has a significant role on the rate of reaction. It was observed that the rate of oxidative chlorination under phase-transfer conditions was almost 6−7 times faster than that of ordinary

Table 7. k values at different PTC loading[a]

PTC loading, mol % of the starting material	k, s^{-1}
0	3.8×10^{-4}
0.9	1.4×10^{-3}
1.9	2.19×10^{-3}
2.8	2.53×10^{-3}
3.8	3.18×10^{-3}

[a] Reaction conditions: reactant concentration, 2.3 mol/L of organic phase; hydrochloric acid, 3.85 mol/L of aqueous phase; hydrogen peroxide, 1.926 mol/L of aqueous phase; temperature, 45 °C; organic phase, 25 mL; aquous phase, 30 mL; reaction time including addition time, 2 h.

Reaction conditions : 4-methylphenol, 2.3 mol/l of organic phase; HCl, 3.85 mol/l of aqueous phase; H$_2$O$_2$, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 ml; aqueous phase, 30 ml.

Figure 7. Arrhenius plot.

(b) The rate of oxidative chlorination increased 6−7-fold in the presence of a phase-transfer catalyst in comparison to the ordinary two-phase system with no PTC.

It is believed that hydrogen peroxide oxidizes hydrochloric acid to molecular chlorine which forms an adduct initially with the phase-transfer catalyst, having a general structure R$_4$NCl$_n$ ($n = 3$ or 5), as explained by Sasson et al..[8] This complex is being expected as a mild aromatic chlorinating agent.[9]

Thus, PTC plays a vital role in this type of oxidative halogenation reaction in the presence of hydrogen peroxide.

Conclusions

The incorporation of a phase-transfer catalyst in a liquid−liquid two-phase system in the oxidative chlorination is an added advantage to this process-scheme. PTC acts as a multifunctional catalyst in this type of reaction, and thus, the rate was increased significantly, and the separation of the desired product was much easier and environmentally friendly. It is worth considering to use glass-lined or titanium-lined reactors in the case of plant-scale productions.

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Reaction conditions : 4-methylphenol, 2.3 mol/l of organic phase; HCl, 3.85 mol/l of aqueous phase; H$_2$O$_2$, 1.926 mol/l of aqueous phase; PTC, 1.9 mol% of the substrate; solvent, EDC; organic phase, 25 ml; aqueous phase, 30 ml.

Figure 6. $-\ln(1 - XA)$ vs t at different temperatures.

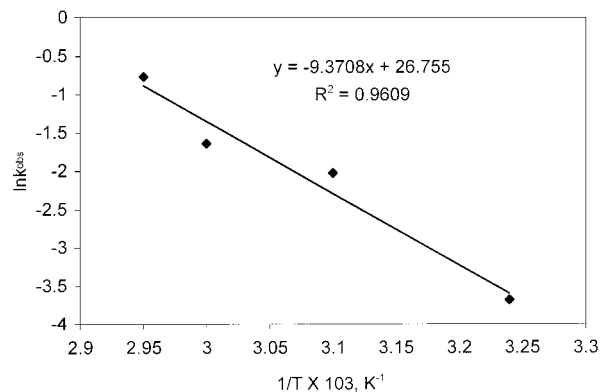two-phase reaction (Figure 3). The k values obtained from Figure 4 are tabulated in Table 7.

The effect of temperature was studied (Figure 5), and the rate constants were found to be 4.15×10^{-4}, 2.19×10^{-3}, 3.2×10^{-3}, 7.6×10^{-3} s^{-1} at 35, 45, 55, and 65 °C, respectively, from Figure 6. From the Arrhenius plot (Figure 7) the activation energy was found to be 78 kJ/mol.

Oxidative Chlorination and Role of PTC. Oxidative chlorination of an aromatic compound in the presence of hydrogen peroxide proceeds according to the stoichiometry of eq 1.

$$\text{ArH} + \text{H}_2\text{O}_2 + \text{HCl} = \text{ArCl} + 2\text{H}_2\text{O} \qquad (1)$$

The following important observations from our studies could easily help us to draw some light on the mechanism.

(a) With increase in molar proportion of hydrogen peroxide, selectivity to monochlorination decreased and that of the dichlorination increased.