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Oxidation-Reduction Characteristics of Chlorophenols in an Aprotic Medium

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Abstract

Eighteen chlorophenols, containing from one to five chlorine atoms on the benzene ring at various positions, have been studied by cyclic voltammetric methods to evaluate their oxidation-reduction characteristics in an aprotic medium. The compounds were dissolved in dimethylsulfoxide containing 0.10 M tetrabutylammonium perchlorate as the supporting electrolyte and were then both oxidized and reduced on a glassy carbon electrode. The results indicate that phenols oxidize in a one-step process to phenoxium ion which dimerizes to quinone ether. The ether can be reduced back to phenol in a two-step reduction process. The oxidation potential of the chlorophenols varies with the number and the position of the chlorine substitution. It may also have a relationship with the toxicity of the compound. The main purpose of this study is to understand how chlorophenols, classified as environmental pollutants for their toxicity and carcinogenicity, are oxidized by cytochrome P450 in the metabolic activation process in living systems.

Introduction

Chlorophenols are classified as environmental pollutants by the Environmental Protection Agency (USEPA, 1979) since many of them are toxic, and some of them are carcinogenic (Lewis, 2000). The major sources of these compounds are pulp and paper mills (Kristiansen et al., 1994), petrochemical refineries (Rogers et al., 1996), plastic and glue manufacturers (Pavlov and Terentyev, 1965), coke plants and leachate from municipal waste dumps (Gilman et al., 1982). Many chlorophenols are produced in the environment by reactions between phenol and chlorine during municipal water treatment (NTP, 1985). Significant *in vivo* generation of some chlorophenols, such as pentachlorophenol, in living systems occurs through metabolism of hexachlorobenzene (Stewart and Smith, 1986) or hexachlorocyclohexane (Munir et al., 1984), which are ubiquitous environmental pollutants.

Because of the acute toxicity and carcinogenicity of chlorophenols, considerable research has been conducted to detect these compounds in aqueous environments (Terashima et al., 2002). Among them, photochemical, chemical and enzymatic methods are not very successful due to their lack of sensitivity, complexity, and limitation to only a few chlorophenols. More successful methods are gas chromatography (G.C.) and gas chromatography-mass spectrometry (GC/MS), high performance liquid chromatography (HPLC), and electrochemical methods coupled with HPLC.

In aqueous solution of pH 5 and above, most chlorophenols exist in the ionic form. In living systems, however, chlorophenols tend to be absorbed primarily in the adipose tissues in the molecular form because of their low solubility in water. The major target organs for pentachlorophenol toxicity and carcinogenicity include the liver, kidney, hematopoietic tissues, pulmonary system, and central nervous system. It is a general cytotoxic agent because of its ability to uncouple mitochondrial oxidative phosphorylation (Weinbach, 1954). In addition, pentachlorophenol undergoes cytochrome P450–dependent metabolic oxidation *in vitro* and *in vivo* to genotoxic tetrachlorobenzenediols and tetrachlorobenzoquinones, which have been shown to react with protein and DNA-derived nucleophiles (Juhl et al., 1985; Ehrlich, 1990). Some chlorophenols, such as 2,4,6-trichlorophenol and pentachlorophenol, undergo oxidative metabolic activation and partial dechlorination by mammalian peroxidases to 2,6-dichloro-1, 4-benzoquinone and tetrachloro-1, 4-benzoquinone, respectively (Samokyszyn, et al., 1995, Weise et al., 1999). It is expected that all chlorophenols will act in a similar manner in living systems. Since chlorophenols differ significantly in their toxicity (Lewis, 2000.), it is important that their general oxidation-reduction characteristics be investigated in order to understand any relation between their relative ease of oxidation by enzymes and toxicity.

Eighteen chlorophenols, containing chlorine substitution of one to five in various positions on the benzene ring, have been studied in an aprotic medium to mimic the hydrophobic situation in various organs of living systems. The chlorophenols chosen have one to five chlorine substitutions, as listed in Table 1. Cyclic

Table 1. List of chlorophenols used for the present study.

Compound Name
Phenol
2-chlorophenol
3-chlorophenol
4-chlorophenol
2,3-dichlorophenol
2,4-dichlorophenol
2,5-dichlorophenol
2,6-dichlorophenol
3,4-dichlorophenol
3,5-dichlorophenol
2,4,5-trichlorophenol
2,3,5-trichlorophenol
3,4,5-trichlorophenol
2,3,4-trichlorophenol
2,3,6-trichlorophenol
2,4,6-trichlorophenol
2,3,5,6-tetrachlorophenol
2,3,4,5-tetrachlorophenol
Pentachlorophenol

voltammetry was used to determine the oxidation potentials of phenols, as well as the reduction potentials of the oxidized products to elucidate the mechanism of oxidation-reduction processes. The aprotic medium was anhydrous dimethylsulfoxide (DMSO). Tetrabutylammonium perchlorate (TBAP) was used as the supporting electrolyte to make the solution conducting for voltammetric measurements of Faradaic current as a function of applied voltage.

Materials and Methods

All 19 chlorophenols were purchased from Supelco (Bellafontaine, PA) with 98% or greater purity and were used without further purification. DMSO (spectroscopic quality) and TBAP (99.9% purity) were obtained from Fisher Scientific. Glassy carbon electrodes (GCE), saturated calomel electrodes (SCE) and platinum electrodes were obtained from Bioanalytical Systems (Lafayette, IN). A Bioanalytical Systems Model 100-A Electrochemical Analyzer was used to record all cyclic voltammograms in conjuction with a Model DMP-40 (Houston Instruments) plotter. Prior to use, the GCE was polished with alumina sol (Buehler, IL) followed by rinsing with distilled water to assure a clean surface.

A 100.0 mL of 0.10 M TBAP in DMSO solution was dehydrated by stirring with about 5 g of molecular sieve (Union Carbide, Plainfield, NJ) for an hour. The solution was filtered quickly into a 100 mL volumetric flask and sealed tightly. Exactly 10.0 mL of the solution was taken in a cell in which the electrodes (GCE –working electrode, SCE-reference electrode, platinum wire – counter electrode) were assembled. A cyclic voltammogram was taken between +1.00 volt and –2.00 volts versus SCE (the entire potential range of the GCE) to determine the response of the electrode in terms of dissolved oxygen. The solution was then deoxygenated by bubbling high purity nitrogen for 15 minutes to obtain a clean background response (with no visible peak in the entire potential range). About 10 mg of a chlorophenol was added to the solution and dissolved completely by bubbling nitrogen for five minutes. The nitrogen flow was then diverted and held to just above the solution as a cyclic voltammogram was taken throughout the entire potential range to observe the electrochemical response of the chlorophenol. A series of cyclic voltammograms was taken for each chlorophenol at the potential scan rates varying from 10 mV/sec to 1.0 V/sec. GCE was polished periodically as needed in order to ensure reproducibility of the peaks as well as to minimize electrode contamination prior to using another chlorophenol. The oxidation and reduction potentials were estimated at 85% of the peaks due to oxidation of phenol and the reduction of the oxidized products of phenol.

Results and Discussion

A typical cyclic voltammogram of chlorophenols, using 2,6-dichlorophenol as the representative, is shown in Figure

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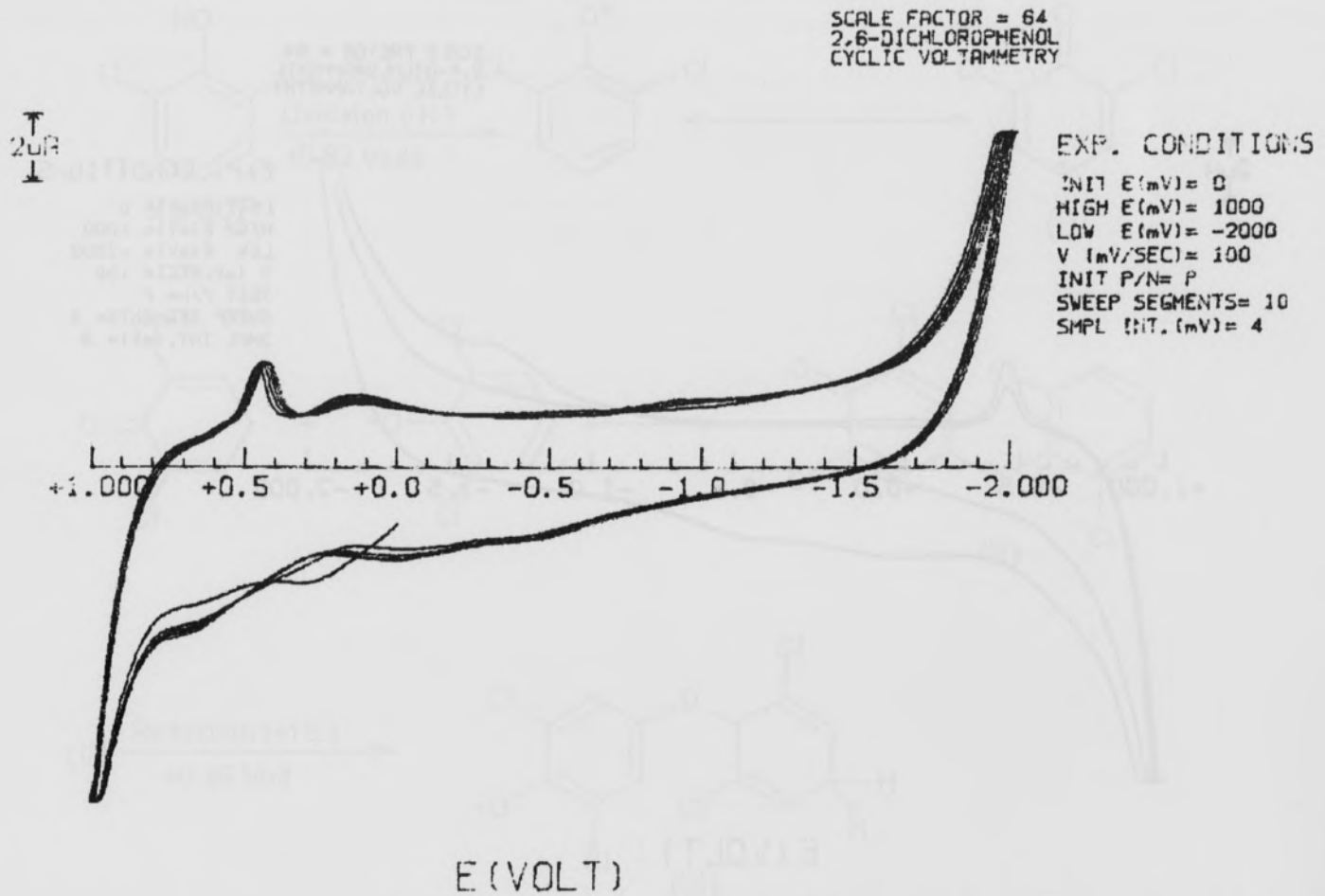

Fig. 1. Cyclic voltammogram of 2,6-dichlorophenol in 0.10 M tetrabutylammonium perchlorate in dimethylsulfoxide performed at a scan rate of 0.10 volt/sec. Five repeated scans were performed without renewing the GCE surface between 1.00 volt and –2.00 volt versus SCE.

1. The starting potential is 0.00 volt vs. SCE, which is close to the rest potential of the chlorophenol. The rest potential is defined as the potential at which no current is flowing when the electrodes are assembled into the experimental solution. All of the chlorophenols were found to have the rest potential between 0.00 volt and 0.100 volt versus SCE. At the rest potential, no electrochemical change (due to oxidation or reduction) occurs. As the potential was scanned to the positive direction, the compound was oxidized. When the potential reached 1.00 volt, the GCE reached its most positive limit. The potential was then scanned backward (to reduce the oxidized products) until it reached the most negative limit of the electrode. The cyclic potential scan was repeated four times. In the first scan, two oxidation peaks appeared, at 0.24 volt and 0.62 volt. On the reverse scan, several peaks appeared, at 0.46 volt, 0.18 volt and at –0.92 volt. After repeated scans, the oxidation peak at 0.24 volt disappeared, whereas the peak at 0.62 volt grew bigger and then became reproducible. We conclude that the peak at 0.24 volt was due to either an impurity or electrode contamination as it did not appear on another cyclic voltammogram run with fresh 2,6-dichlorophenol (Figure 2). The peak at 0.62 volt was assigned to the oxidation of the phenol. Moreover, this peak is diffusion controlled. Cyclic voltammograms at various scan rates ranging from 10 mV/sec to 1000 mV/sec showed a linear relationship when the peak current was plotted as a function of the square root of the scan rate.

It is well documented that phenols tend to foul the electrode surface rapidly, causing poorly shaped peaks (Wang and Li, 1989). Based on the results of previous observations (Hemmerich, 1983), we conclude that a one-

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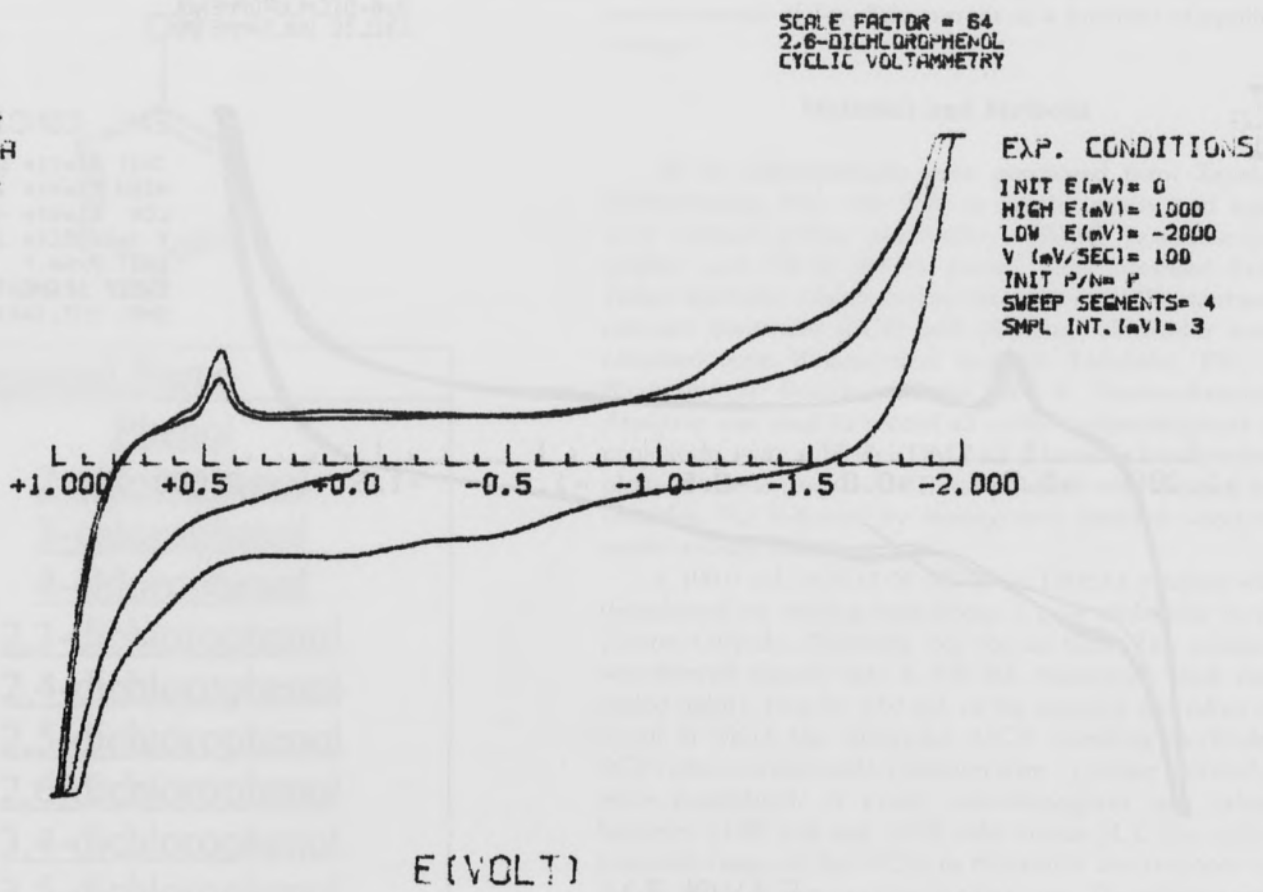

Fig. 2. Cyclic voltammogram of 2,6-dichlorophenol in 0.10 M tetrabutylammonium perchlorate in dimethylsulfoxide performed at a scan rate of 0.10 volt/sec. Five repeated scans were performed without renewing the GCE surface. Two scans were performed without renewing the surface between 0.60 volt and –2.00 volt.

electron oxidation took place at 0.62 volt. On the reverse scan, the peak at 0.46 volt is typical of reduction of a thin film deposit, producing a soluble species which further reduces at 0.18 volt. Figure 2 shows the cyclic voltammogram where the potential was switched backward at 0.60 volt (before oxidation of the phenol occurred) when no peak appeared at 0.46 volt. This observation unequivocally confirms that the peak at 0.62 volt is indeed due to the oxidation of the phenol. It also proves that this peak is reproducible, and electrode fouling is not as severe in DMSO as observed in aqueous solution. All chlorophenols studied behave in a similar manner, showing only one peak due to oxidation in the positive potential range, although the magnitude of this potential changed according to the number and the position of chlorine substitutions. Based on our results, we conclude that 2,6-dichlorophenol undergoes oxidation-reduction processes as shown in Fig. 3. At 0.62 volt, phenol undergoes oxidation to form a stable phenoxyl radical intermediate (I), which dimerizes to form a quinone ether (II). The ether forms a deposit on the electrode surface and then is reduced, successively at 0.46 volt to form a phenol ether (III) and then at 0.18 volt to form phenol again. At –0.92 volt, phenol probably undergoes an aromatic ring reduction which is oxidized again at 0.0 volt (on reverse scan) to phenol. The entire oxidation-reduction process is electrochemically irreversible (the separation between oxidation and reduction peaks for phenol is 0.44 volt, much larger than 0.059 volt predicted by theory of cyclic voltammetry), although the process is chemically reversible. No attempts

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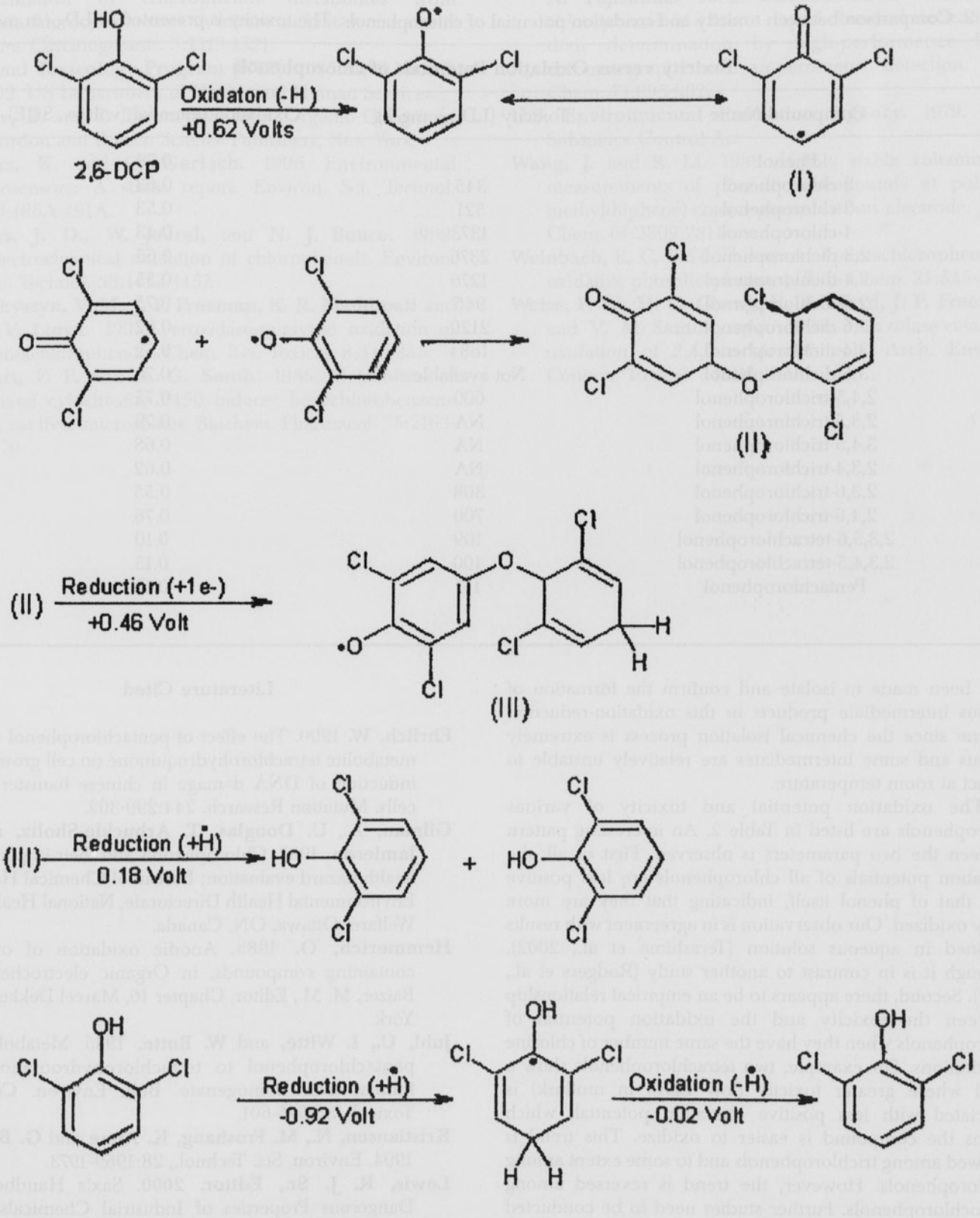

Fig. 3. Proposed reaction mechanism of oxidation and reduction of 2,6-dichlorophenol in dimethylsulfoxide.

Table 2. Comparison between toxicity and oxidation potential of chlorophenols. The toxicity is presented as LD_{50} in mollusk.

Toxicity versus Oxidation Potentials of chlorophenols

Compound Name	Toxicity (LD_{50}), mg/kg	Oxidation potential (volt vs. SCE)
Phenol		0.78
2-chlorophenol	345	0.63
3-chlorophenol	521	0.53
4-chlorophenol	1373	0.43
2,3-dichlorophenol	2376	0.65
2,4-dichlorophenol	1276	0.55
2,5-dichlorophenol	946	0.75
2,6-dichlorophenol	2120	0.62
3,4-dichlorophenol	1684	0.52
3,5-dichlorophenol	Not available	0.70
2,4,5-trichlorophenol	600	0.75
2,3,5-trichlorophenol	NA	0.79
3,4,5-trichlorophenol	NA	0.68
2,3,4-trichlorophenol	NA	0.62
2,3,6-trichlorophenol	308	0.55
2,4,6-trichlorophenol	700	0.76
2,3,5,6-tetrachlorophenol	109	0.10
2,3,4,5-tetrachlorophenol	400	0.15
Pentachlorophenol	117	0.18

have been made to isolate and confirm the formation of various intermediate products in this oxidation-reduction scheme since the chemical isolation process is extremely tedious and some intermediates are relatively unstable to extract at room temperature.

The oxidation potential and toxicity of various chlorophenols are listed in Table 2. An interesting pattern between the two parameters is observed. First of all, the oxidation potentials of all chlorophenols are less positive than that of phenol itself, indicating that they are more easily oxidized. Our observation is in agreement with results obtained in aqueous solution (Terashima et al., 2002), although it is in contrast to another study (Rodgers et al., 1999). Second, there appears to be an empirical relationship between the toxicity and the oxidation potential of chlorophenols when they have the same number of chlorine substitutions. For example, two tetrachlorophenols show a trend where greater toxicity (low LD_{50} in mollusk) is associated with less positive oxidation potential, which means the compound is easier to oxidize. This trend is followed among trichlorophenols and to some extent among dichlorophenols. However, the trend is reversed among monochlorophenols. Further studies need to be conducted to establish such a relationship.

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