Aerobic Coupling of Aqueous Phenols Catalyzed by Binuclear Copper: Ring Substituent Effect and the Kinetics of the Coupling of *o*-Methylphenol

The substituent effect on the aerobic and catalytic coupling of aqueous phenols conforms to a Hammett correlation in which the reaction constant is −2.16; the results are very similar to that of the enzymatic coupling reaction, in which the reaction constant is −2.4. Deviations from the Hammett correlation are attributed to steric factor, product inhibition, and the blocking of coupling sites on phenoxy radicals. Available evidence indicates that catalytic and enzymatic coupling reactions are strikingly similar in many respects. The striking resemblance suggests a common reaction mechanism in which binuclear metal (copper or iron) plays a key role. The common mechanistic features of the coupling reactions are suggested, and the implications of the findings are discussed with reference to (1) the design of a novel dephenolization scheme, (2) the elucidation of the widely occurring but poorly understood enzymatic coupling reactions, and (3) the synthesis of active polymer-bound coupling catalysts.

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SCOPE

This study is a part of a broader continuing effort to extend our knowledge and understanding of aerobic coupling reactions so that engineering applications of the reactions may be rationally designed and developed. The specific objective of this study is to investigate the substituent effect on the coupling of aromatic substrates as represented by the phenol family. We consider the probable underlying cause and the implications of a striking resemblance between catalytic and enzymatic coupling reactions.

CONCLUSIONS AND SIGNIFICANCE

The substituent effect on the aerobic and catalytic coupling of aqueous phenols may generally be described by the Hammett equation: $\log [k/k^o] = \rho \log [K_a/K_a^o]$, where k and k^o are the respective coupling rate constants of the substituted and unsubstituted phenols, K_a and K_a^o are the corresponding dissociation constants of the phenols, and ρ, the reaction constant characteristic of the phenol family, is found to be −2.16. According to the equation, an electron-releasing substituent group, which corresponds to a high pK_a value for the substituted phenol, will facilitate the coupling reaction, whereas an electron-withdrawing substituent group, which corresponds to a low pK_a value for the substituted phenol, will hinder the reaction.

The above results are very similar to recent findings

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on the substituent effect in the enzymatic coupling of simple phenols. The general conformity of the data with the Hammett correlation implies a common rate-determining step in the coupling of most phenols. This common rate-controlling step is postulated to be the formation of phenoxy radicals by electron transfer between phenolate anions and oxidized binuclear metal sites.

The fact that there are negative deviations from the Hammett correlation suggests that other factors may also be involved; the most likely of these factors are identified to be steric factor, product inhibition, and the blocking of a coupling site at the C_2, C_4, or C_6 position of the phenoxy radical.

The detailed kinetics of the aerobic and catalytic coupling of *o*-cresol is very similar to that of phenol. Available evidence indicates that catalytic and enzymatic coupling reactions are strikingly similar in many respects. The underlying cause of the striking resemblance is ascribed to the binuclear metal sites (copper or iron) of the coupling catalysts and enzymes. It appears that the binuclear metal sites facilitate coupling reactions on account of the following properties:

1. The ability to undergo facile redox reactions alternately with substrates and dioxygen or peroxide in a continuous cycle.
2. The ability to hold onto substrate radicals after they are formed.
3. The ability to allow the metal-bound radical to couple with a substrate or with another radical species bound to the adjacent metal site.
4. The ability to allow dioxygen and peroxide to undergo a single-step, two-electron reduction, thereby avoiding the energetically less favorable formation of radical intermediates.

Our findings and other related evidence lead us to postulate a common reaction mechanism for both catalytic and enzymatic coupling reactions. The proposed mechanism consists of the following cycle of events:

1. Diffusion of dioxygen or peroxide to the binuclear metal sites (copper or iron) of a coupling catalyst or enzyme.
2. Oxidation of the binuclear metal and the concomitant reduction of the oxidant via a single two-electron step.
3. Diffusion of the substrate species to the oxidized metal centers.
4. Formation of substrate radicals by a redox reaction between the substrate species and the oxidized metal centers.
5. Preferential coupling of the metal-bound radicals with one another or with a substrate species bound to the adjacent metal center.
6. Disengagement and diffusion of the coupling products away from the metal centers, or further oxidation and coupling of the initial products.

The recognition of a probable common reaction mechanism raises the following two intriguing possibilities: First, the possibility of using catalytic coupling systems, which are much simpler to study than the complex enzymatic systems, to model and elucidate the salient features of the latter. Second, the possibility of synthesizing polymer-bound coupling catalysts that have designed binuclear structures.

Introduction

Recent studies from our laboratory (Lim et al., 1983; Cha and Lim, 1984; Chin et al., 1985; Cha et al., 1985; Giles et al., 1985) have demonstrated that aerobic coupling reactions may provide a novel, simple, and cost-effective separation technique for the removal of certain soluble substances from solutions. By aerobic coupling reactions we mean oxidative dimerization and oligomerization reactions that are induced aerobically in the presence of a binuclear catalyst or enzyme. The usual products formed in the reactions are dimers, oligomers, and sometimes polymers, although in alkaline media hydroxylation and higher oxidation products may also be formed (Lim et al., 1983).

The coupling-phase separation technique we have advocated is based on the findings that binuclear cuprous compounds can effect aerobic coupling reactions under mild reaction conditions, and that the aqueous solubility of a substance generally decreases precipitously upon dimerization and oligomerization. Substances that have been found amenable to the proposed coupling-phase separation technique include phenol and substituted phenols, inorganic sulfides, mercapto and sulfhydryl compounds, and aromatic amines and diamines (Cha and Lim, 1984; Cha et al., 1985; Giles et al., 1985).

Aside from their engineering potential in separation processes, aerobic coupling reactions also have synthesis applications (Bach, 1968; Hay 1962a,b, 1966; Nigh, 1973; Bodek and Davies, 1978). In addition, the reactions are of interest because of their wide occurrence in nature. The enzymatic coupling of phenols, for example, has been implicated in the biosynthesis of lignins and other natural products (Freudenberg and Neish, 1968; Taylor and Battersby, 1967) and in the browning and fermentation of food products (Mathew and Parpia, 1971).

Although the substrates in many of the aerobic coupling reactions are substituted aromatic compounds, the substituent effect on the coupling reactions has not been studied until very recently. Just as our study was completed, a report did appear that addressed the substituent effect in the enzymatic coupling of phenols and anilines (Berry and Boyd, 1984). The data on the enzymatic system and our findings, reported herein, on the catalytic system are complementary to one another. The two sets of data reinforce the notion that catalytic and enzymatic coupling reactions are strikingly similar in many respects. We consider the underlying cause and the implications of the striking resemblance, and we identify salient features which are believed to be common to both catalytic and enzymatic coupling reactions. Along with the findings on the substituent effect we also present

Table 1. Substituent Effect on Aerobic Coupling of Aqueous Phenol Catalyzed by Binuclear Cuprous Chloride*

Substrate (see Fig. 1)	pK_a Value			Initial Rate, gmol/L · hr		
	Ortho	Para	Meta	Ortho	Para	Meta
Phenol (1)	9.99	9.99	9.99	0.0283	0.0283	0.0283
Aminophenol (2)	9.72	10.30	9.87	0.509	4.58	0.733
Bromophenol (3)	8.40	9.24	8.85	0.0007	0.0109	0.0071
Chlorophenol (4)	8.48	9.37	9.02	0.0003	0.0120	0.0065
Cyanophenol (5)	6.86	7.95	8.61	**	2×10^{-5}	0.0002
Ethylphenol (6)	10.20	10.01	9.90	0.0029	0.0014	0.0562
Fluorophenol (7)	8.81	9.95	9.28	0.0019	0.0121	0.0284
Dihydroxybenzene (8)	9.45	10.00	9.44	0.119	0.521	0.0925
Methoxyphenol (9)	9.98	10.21	9.65	0.076	0.451	0.104
Methylphenol (10)	10.26	10.26	10.00	0.0040	0.0020	0.0665
Nitrophenol (11)	7.23	7.15	8.40	**	**	8×10^{-5}
3,5-Dimethylphenol (12)	10.15	10.15	10.15	0.097	0.097	0.097
2,4-Dimethylphenol (13)	10.58	10.58	10.58	0.105	0.105	0.105
2,6-Dimethylphenol (14)	10.60	10.60	10.60	0.100	0.100	0.100

*T = 30°C; P_{O_2} = 880 mm Hg; $[Cu_2Cl_2]$ = 1.0 g/L; $[Substrate]_o$ = 0.020 M. Solutions contain 0.10 M NaCl and 0.30 M NH_4OH; pH ≃ 10.4.
**Rate is too low to measure with any reliability.

the results of a detailed kinetic study of the aerobic coupling of *o*-methylphenol.

Experimental

The aerobic and catalytic coupling of phenols was studied in a 1 L glass Morton reactor; the procedure was as described previously (Lim et al., 1983; Chin et al., 1985). The reactor solution typically contained 0.10 or 0.30 M of ammonium hydroxide, 0.10 M of sodium chloride, 0–2.15 g/L of cuprous chloride, and 0.005 to 0.093 M of the substrate at the start of the reaction. In studying the pH effect on the coupling of *o*-methylphenol, sodium hydroxide or hydrochloric acid was added to the solution to vary the solution pH. The reactor solution was stirred vigorously by means of a magnetic stir bar and its initial volume was kept at 250 mL to avoid the potential problem of oxygen mass transfer limitation. The reaction was initiated, following thermal equilibration of the solution, by adding to the solution the desired amount of cuprous chloride. All chemicals used were of reagent grade.

The coupling reaction was followed by monitoring the substrate concentration as a function of reaction time. Solution samples were analyzed with the help of a Perkin Elmer Series four high-performance liquid chromatograph interfaced with a Chromatographics II data station and equipped with a continuous UV detector and an HS-5 C_{18} column. The eluant was a mixture of 40% methanol, 59% water, and 1% acetic acid; its flow rate was 2.0 mL/min for 5 μL of diluted sample.

Results and Discussion

Substituent effect

Electronic Factors and the Hammett Correlation. The rates of the coupling reaction for different substituted phenols under identical set of conditions are presented in Table 1 and Figure 1. As with previous studies from our laboratory, the rates of the coupling reaction are taken to be the rates of disappearance of phenols. This is justified by the fact that autoxidation products of phenols, which are always found in small quantities in solutions, also undergo the coupling reaction. As with previous studies, we use the initial rates, which are also the maximum rates, for correlation against kinetic parameters.

With some notable exceptions, which will be discussed later, the data on the substituent effect may be correlated by a Hammett equation, $\log [k/k^o] = \rho \log [K_a/K_a^o] = -\rho[pK_a - pK_a^o]$, where k and k^o are the respective coupling rate constants of the substituted and unsubstituted phenols, K_a and K_a^o are the corre-

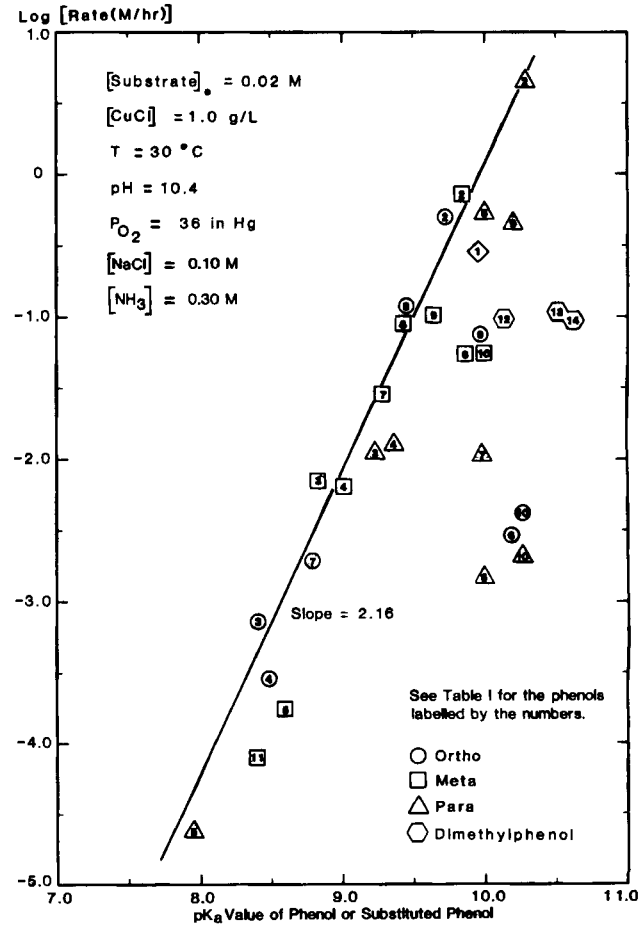


Figure 1. Substituent effect on aerobic coupling of aqueous phenol catalyzed by cuprous chloride.

sponding dissociation constants of the phenols, and ρ, the reaction constant characteristic of the phenol family, is approximately -2.16. The relatively large magnitude of ρ indicates that phenol coupling reaction is sensitive to substituent effect; the negative sign of ρ suggests that the reaction is, generally, facilitated by electron-releasing substituents and hindered by electron-withdrawing substituents.

The above findings are very similar to the results reported recently by Berry and Boyd (1984) on the enzymatic coupling of simple phenols (in which horseradish peroxidase and hydrogen peroxide are used, respectively, as the enzyme and oxidant). The enzymatic reaction is also found to be facilitated by electron-releasing substituents and hindered by electron-withdrawing substituents. The reaction constant reported by Berry and Boyd is -1.67, but this is based on an analysis of data without allowing for the possibility of deviations from the Hammett plot. If allowance is made for deviations from the Hammett plot, as seems to be called for in light of the results of this study, then a re-analysis of their data (their Figure 1) will give a reaction constant of -2.4, which is in reasonable agreement with the value of -2.16 for the catalytic reaction.

Conformity of the data with the Hammett correlation implies a common rate-determining step for both coupling reactions. This rate-controlling step may, moreover, be identified as the formation of phenoxy radicals at the metal centers of the catalyst or enzyme. The phenoxy radicals are evidently formed by a redox reaction between phenolate anions and the oxidized metal centers. As may be expected from such a rate-determining step, the greater the electron-donating tendency of the substituent group, which is indicated by a high pK_a value for the substituted phenol, the easier it is to form the phenoxy radical, and consequently the faster is the coupling reaction. Conversely, the greater the electron-withdrawing tendency of the substituent group, which is indicated by a low pK_a value for the substituted phenol, the harder it is to form the phenoxy radical, and consequently the slower is the coupling reaction.

Steric Factor, Product Inhibition, and the Blocking of Coupling Sites. The fact that there is a significant number of negative deviations from the Hammett correlation suggests that in addition to the electronic factors, other factors may also be involved in determining the substituent effect. A close examination of the negative deviations suggests that three other factors—namely, steric factor, product inhibition, and the exclusion of hydrogen shift from an ortho or para position of the phenoxy radical—may also contribute to the substituent effect. The second and third factors affect, respectively, the formation and consumption of the phenoxy radical, while the first factor affects both processes. Thus, the lower than expected coupling rates of methyl-, methoxy-, ethyl-, and dimethylphenols may be attributed in part to steric hindrance arising from the presence of the relatively bulky groups, namely, methyl, methoxy, ethyl, and dimethyl groups, in the substrates and radicals.

The coupling rate of simple phenol is lower than expected; on the basis of the steric consideration, it would appear that the coupling rates of dimethylphenols are higher than expected when compared with those of methylphenols. The apparent anomaly in both cases may be ascribed to differences in product inhibition. Results of control experiments, shown in Table 2, indicate that phenolic coupling products generally have an inhibiting effect on the coupling reaction. The relative magnitude of the inhibiting effect depends on the relative solubilities of the coupling products in the basic reaction solution. Thus, the coupling products of *o*-methylphenol, which are less water-soluble than the coupling products of simple phenol, exert a correspondingly smaller inhibiting effect on the coupling reaction. The product inhibition effect may be expected to diminish quickly as the coupling products become insoluble, as in the case of the coupling products of dimethylphenols.

The inhibiting effect of soluble coupling products (as well as soluble autoxidation products such as *p*-quinone, Table 2) may be ascribed to their ability to tie up and deactivate the coupling catalyst. It appears that the presence of hydroxy, carboxylic, and quinonoid groups confers upon the coupling products the ability to block the active metal sites of coupling catalysts and enzymes. It is noteworthy that the inhibiting effect of phenolic coupling products may be alleviated, but not entirely eliminated, by the use of a cationic surfactant such as hexadecyltrimethylammonium chloride, see Table 2. It is not yet clear how the beneficial effect of the surfactant is brought about; a study is presently underway to shed light on the surfactant effect.

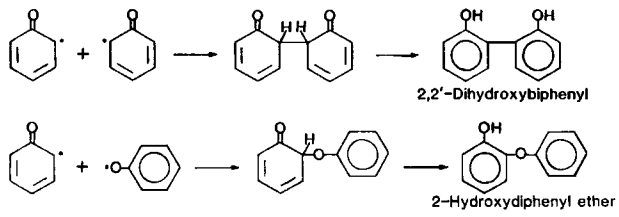
For the same substituent group, ortho and para substitution often gives rise to a lower coupling rate than meta substitution;

Table 2. Effects of Phenolic Coupling Products, *p*-Quinone, and Cationic Surfactant on Copper-Catalyzed, Aerobic Coupling of Aqueous Phenol and *o*-Methylphenol*

	Coupling Rate, M/h				
Substrate	Control Run	Coupling Products	Coupling Products & Surfactant	Surfactant	*p*-Quinone
Phenol	0.0231[a]	0.0108[b]	0.0145[b,c]	0.0342[c]	—
Phenol	0.0417[d]	—	—	—	0.0135[e]
o-Methylphenol	0.0173[f]	0.0163[g]	—	0.0234[c]	—

*Unless otherwise stated, T = 30.0°C, $[Substrate]_o$ = 0.050 M, P_{O_2} = 880 mm Hg. All solutions contain 0.30 M NH_4OH and 0.10 M NaCl (pH ≃ 10.0).
[a] $[Cu_2Cl_2]$ = 0.25 g/L.
[b] Coupling products of phenol added = 1.0 g/L, not fully dissolved.
[c] Surfactant = hexadecyltrimethylammonium chloride, concentration = 0.003 M.
[d] $[Cu_2Cl_2]$ = 0.50 g/L.
[e] $[p\text{-Quinone}]_o$ = 0.050 M.
[f] T = 45.0°C, $[Cu_2Cl_2]$ = 0.50 g/L.
[g] Coupling products of *o*-methylphenol added = 3.0 g/L, not fully dissolved.

this is exemplified by methyl- and methoxyphenols. It appears that in these cases the overall coupling rate depends, at least in part, on how fast the phenoxy radical is consumed after it is formed. An ortho or para substituent gives rise to steric hindrance to coupling at the ortho or para position; moreover, by displacing hydrogen at the ortho or para position, the substituent preempts the possibility of hydrogen shift from that site to the phenoxy oxygen. The latter reaction usually follows coupling reaction at an unsubstituted ortho or para position; this is exemplified by the carbon-carbon and carbon-oxygen coupling between two phenoxy radicals,



The presence of an ortho or para substituent, therefore, reduces the number of coupling sites and this in turn lowers the coupling rate of the phenoxy radical.

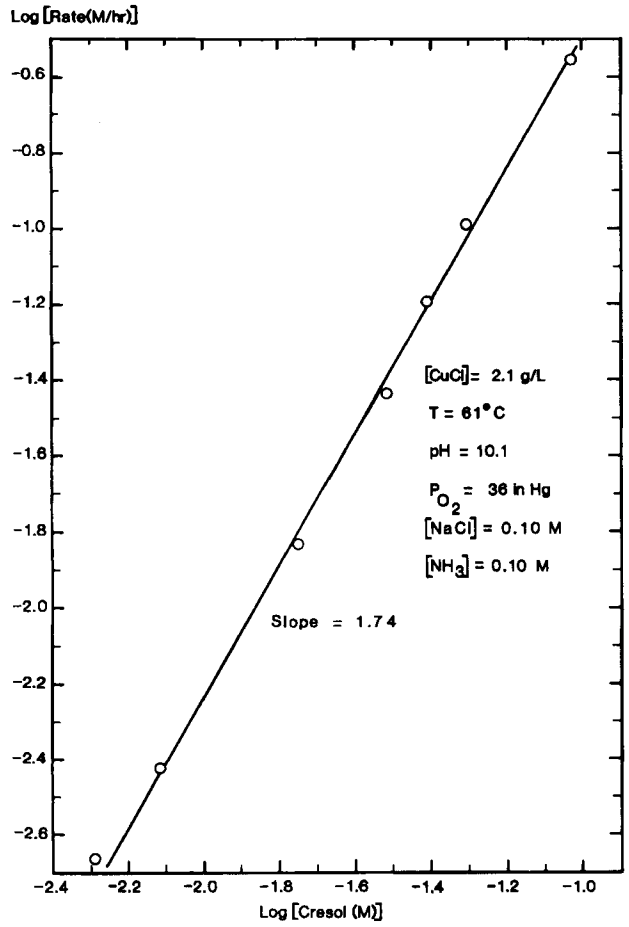


Figure 2. Rate-dependence of aerobic coupling of *o*-methylphenol on *o*-methylphenol concentration.

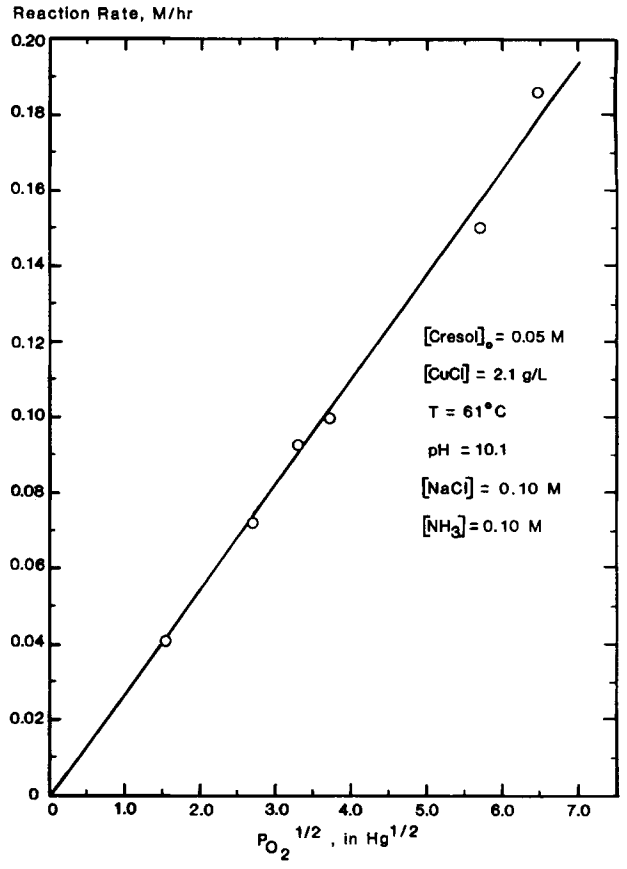


Figure 3. Rate-dependence of aerobic coupling of *o*-methylphenol on oxygen partial pressure.

The results of the study of the substituent effect on the whole reinforce the promising nature of the coupling-dephenolization scheme we have proposed for the treatment of phenolic wastewaters in general and coal-conversion wastewaters in particular (Chin et al., 1985). The major pollutant in phenolic wastewaters is phenol; substituted phenols that are present in minor amounts

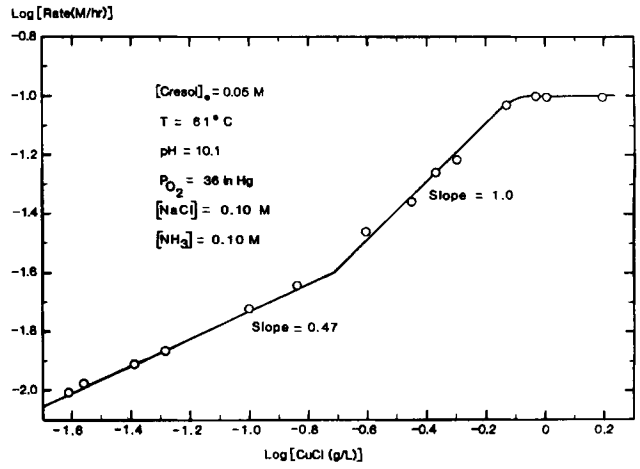


Figure 4. Rate-dependence of aerobic coupling of *o*-methylphenol on *cuprous chloride* concentration.

are dihydroxybenzenes, methylphenols, and dimethylphenols (Chin et al., 1985). Since the substituted phenols all contain electron-releasing groups favorable to the coupling reactions, they too can be readily removed from the wastewaters as insoluble precipitates.

Kinetic Study of o-Methylphenol Coupling

The results of a detailed kinetic study of the coupling of *o*-methylphenol are presented in Figures 2–7. The results indicate that the reaction is empirically 1.7th-order with respect to *o*-methylphenol, half-order with respect to oxygen, and first-order with respect to cuprous chloride and a chloride salt within certain catalyst and chloride concentration ranges.

The leveling of the reaction rate beyond the same concentration value of 0.010 M for cuprous chloride and the chloride salt is noteworthy, since the concentration value is in approximate agreement with the aqueous solubility of the cuprous chloride-chloride complex, which is known to be 0.017 M at 60°C (Fritz, 1982). A similar leveling effect has also been observed in the coupling of phenol (Chin et al., 1985) at about the same catalyst concentration, namely, 0.010 M. The results suggest that the active catalyst species in the reaction is the dissolved form of cuprous chloride. Evidently, the chloride salt increases the coupling rate by increasing the solubility of cuprous chloride through complex formation (Fritz, 1982). The fact that the leveling of coupling rate occurs at about the same catalyst and chloride concentrations suggests the formation of a stoichiometric catalyst-chloride complex that may have the following structure:

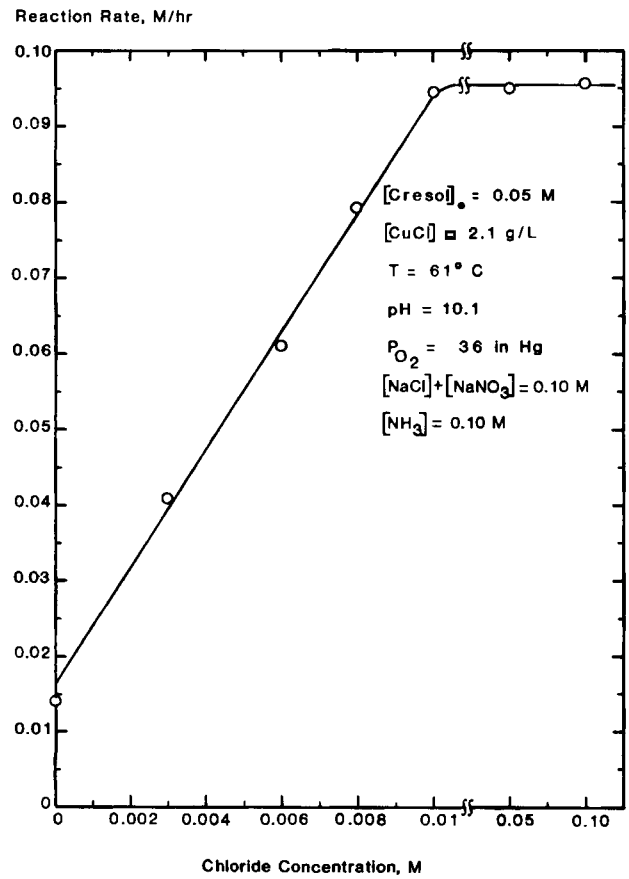


Figure 5. Rate-dependence of aerobic coupling of *o*-methylphenol on concentration of chloride as a catalyst ligand.

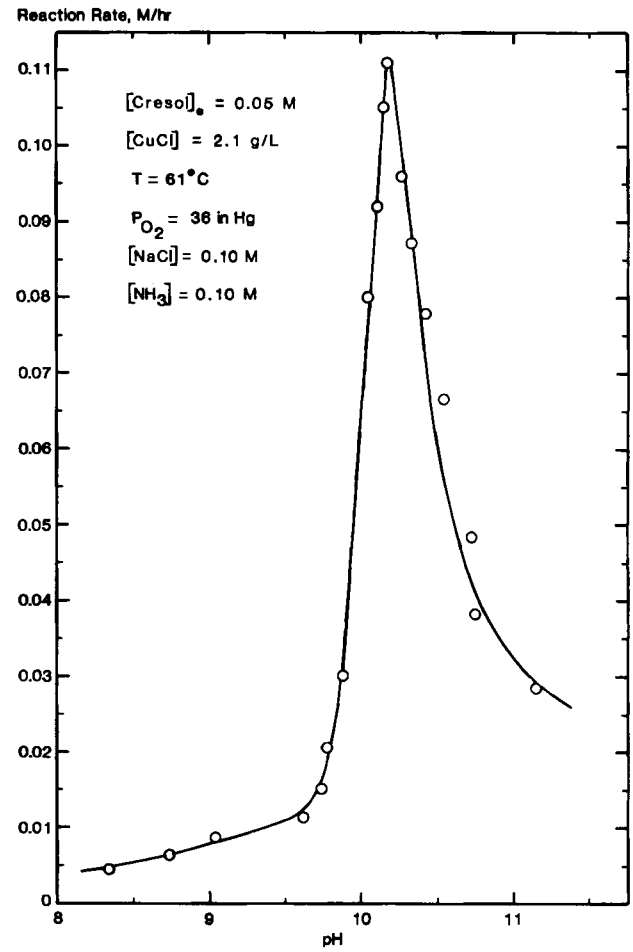
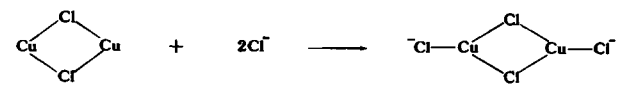


Figure 6. Rate-dependence of aerobic coupling of *o*-methylphenol on solution pH.



The results of the pH study, shown in Figure 6, indicate that the coupling rate changes sharply in the vicinity of the pK_a value of *o*-methylphenol, which is 10.26; the reaction order is 1.5 with respect to basicity in the pH range of 9.75–10.25. The results indicate that the active substrate species in the coupling reaction is the phenolate anion. The sharp drop in the reaction rate above pH 10.35 may be ascribed to an increased competition brought against the substrate and oxygen molecules for the coordination sites of the copper catalyst (Lim et al., 1983; Chin et al., 1985); evidently, the increased competition comes from increased amounts of hydroxy ion and base-soluble coupling products at a higher pH.

The results of the temperature study, shown in Figure 7, give an apparent activation energy of 15.6 kcal/gmol; the high activation energy, which has been corrected for variations in the

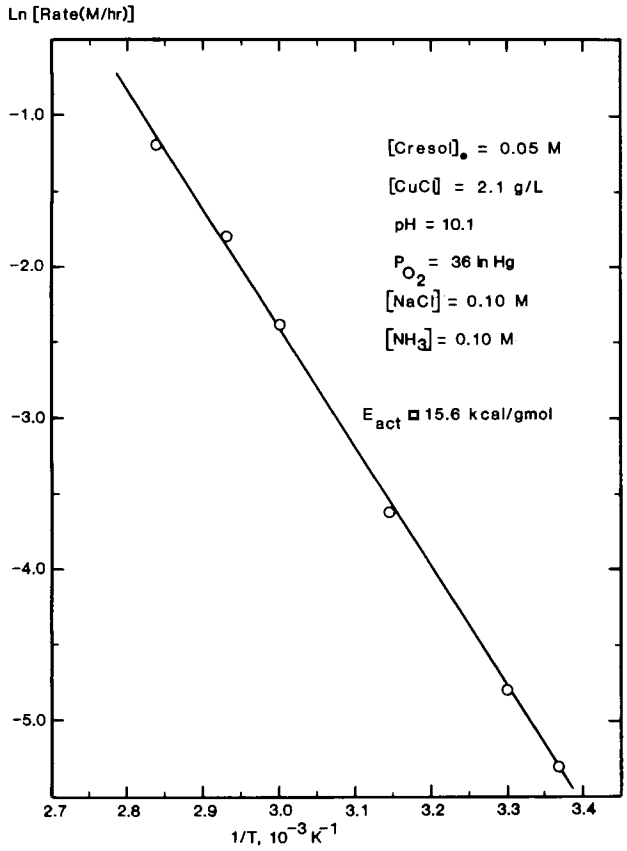


Figure 7. Rate-dependence of aerobic coupling of *o*-methylphenol on reaction temperature.

temperature-dependent oxygen solubility, indicates that the coupling of *o*-methylphenol is not diffusion-controlled under the set of reaction conditions employed in this study.

The kinetic results of the coupling of *o*-methylphenol are strikingly similar to those of the coupling of the simple phenol (Lim et al., 1983). Both reactions have the same reaction orders with respect to the substrate, oxygen, and catalyst, and similar rate dependence on the reaction temperature and solution pH. The similarity extends to include a sharp break, which is evident in Figure 4, in the rate vs. catalyst concentration plot. The similarity lends support to the postulate of a common reaction mechanism for the coupling of phenols.

Additional support for the notion of a common coupling mechanism is provided by the formation of the same coupling products, namely, humic acids, in both catalytic and enzymatic coupling reactions (Lim et al., 1983; Berry and Boyd, 1984; Klibanov et al., 1983; Taylor and Battersby, 1967; Benfield et al., 1964; Fahraeus, 1961). Both reactions are affected similarly by product inhibition (Lim et al., 1983; Klibanov et al., 1983), and both reactions exhibit similar substituent effects.

Moreover, both reactions depend critically on the presence of metal sites in close proximity for reactivity. Naturally occurring coupling reactions are promoted by copper and iron enzymes, such as laccase, tyrosinase, and peroxidase. The first two contain binuclear or type 3 copper in addition to types 1 and 2 mononuclear copper (Levine, 1966; Reinhammer and Malmstrom, 1981; Solomon, 1981); the last contains dimeric iron (Dunford and Stillman, 1976). The coupling activity of laccase has been ascribed specifically to type 3 copper (Reinhammer and Malmstrom, 1981; Solomon, 1981). It is noteworthy that in the catalytic coupling of phenol, only those copper compounds, such as cuprous chloride and cuprous bromide, which can exist as binuclear entities (Cotton and Wilkinson, 1972; Uechi et al., 1980; Remy, 1956) have the ability to catalyze the coupling reaction (Lim et al., 1983). Copper compounds such as cupric sulfate and cupric nitrate, which dissociate fully in solutions to give mononuclear copper ions, do not promote the coupling reaction; instead, they promote autoxidation reaction which yields different products.

Common Mechanistic Features of Catalytic and Enzymatic Coupling Reactions

In light of the foregoing discussion and evidence, it seems clear that the fundamental cause for the striking resemblance between catalytic and enzymatic coupling reactions is the presence of binuclear metal centers in the coupling catalysts and enzymes. The binuclear metal centers may facilitate coupling reactions on account of the following properties:

1. The ability to undergo facile redox reactions alternately with substrates and dioxygen or peroxide in a continuous cycle (Bodek and Davies, 1978; Levine, 1966; Reinhammar and Malmstrom, 1981).
2. The ability to hold onto substrate radicals (Danner et al., 1973; Jenkins and Kochi, 1972; Kharasch and Fono, 1959) after they are formed.
3. The ability to allow the metal-bound radical to couple with a substrate or with another radical species bound to the adjacent metal site.
4. The ability to allow dioxygen and peroxide to undergo a single-step, two-electron reduction, thereby avoiding the energetically less favorable formation of radical intermediates (Urbach, 1981; Reinhammar and Malmstrom, 1981; Balch, 1983).

On the basis of the evidence presented above, we may postulate a common reaction mechanism for both catalytic and enzymatic coupling reactions. The proposed mechanism is composed of the following six steps:

1. Diffusion of dioxygen or peroxide to the binuclear metal centers of a coupling catalyst or enzyme.
2. Oxidation of the binuclear metal centers and the concomitant reduction of the oxidant in a single two-electron step (Urbach, 1981; Balch, 1983).
3. Diffusion of substrate species to the oxidized metal centers.
4. Formation of substrate radicals via a redox reaction between the substrate species and the oxidized metal centers.
5. Preferential coupling of the metal-bound radicals with one another or with a substrate species bound to the adjacent metal center.
6. Disengagement and diffusion of the coupling products away from the binuclear centers or further oxidation and coupling of the initial products.

The proposed six-step mechanism does not explicitly account for configurational complexities that may be important under certain conditions; as such, the proposed mechanism will not be a valid model for those enzymatic reactions in which the spatial characteristics of the enzymes are of critical importance. However, in other cases we believe the proposed mechanism may serve as a useful and convenient model for understanding the salient features of coupling reactions. Thus in the context of the

proposed mechanism, the results of Berry and Boyd (1984) may be taken to mean that step 4, the formation of substrate radicals, is generally a slow step in the enzymatic coupling reaction, just as it is a slow step in the catalytic coupling reaction. The phenomenon of product inhibition, which becomes significant at high conversion in both catalytic and enzymatic coupling reactions (Lim et al., 1983; Klibanov et al., 1983), may be explained in terms of a slow step 6, i.e., a slow removal of coupling products from the reaction sites with the result that substrate accessibility to the sites is blocked. Likewise, other phenomena, such as two-electron redox process and denaturation, may also be rationalized in terms of the binuclear structure of the enzyme or catalyst.

Implications of a common reaction mechanism for coupling reactions

The recognition that coupling reactions share common mechanistic features raises two intriguing possibilities: the possibility of using catalytic coupling systems, which are much simpler to study than the complex enzymatic systems, to model and elucidate the salient features of the latter; and the possibility of synthesizing polymer-bound coupling catalysts with binuclear structures that are designed rather than incidental.

Our present understanding of enzymatic coupling reactions is, in general, not commensurate with their widespread and important occurrence. The main stumbling block is the complex nature of enzymatic systems, which makes it difficult if not impossible to delineate the various factors which affect the reactions. It appears to us that a judicious choice of simple catalytic systems would eliminate complexities of secondary importance and would provide more tractable model systems for illuminating the truly important features of enzymatic coupling reactions. The results of Berry and Boyd (1984) suggest that the possibility is realistic, at least for simple phenolic substrates.

The possibility of anchoring coupling catalysts to polymer supports has obvious advantages, and several attempts have been made recently to synthesize polymer-supported coupling catalysts (Meinders and Challa, 1980; Challa et al., 1980). However, only limited success has so far been achieved in these attempts. It appears that the main reason for the limitation on the success is the rather large separations between adjacent copper centers in the polymer-bound monoamine-copper complexes. The present approach makes use of polymer-bound monodentate amines as binding sites for copper ions. With a single copper ion attached to each monoamine ligand, the distance between adjacent copper neighbors must, on the average, be much larger than 2.8–5.6 Å (0.28–0.56 nm), which is the range of copper-copper separations that have been found in known binuclear copper compounds (Churchill and Kalra, 1974; Remy, 1956; Kahn, 1982). A large separation between nearest copper neighbors is not conducive to coupling reaction, and in accordance with this expectation, the catalytic activities of the polymer-bound copper complexes prepared by Meinders and coworkers are about two orders of magnitude lower than that of the N,N,N′,N′-tetramethylethylenediamine-copper complex (the latter can exist as a binuclear complex).

It appears that the key to the synthesis of an active polymer-bound coupling catalyst is the placement of coordinatively unsaturated metal centers (copper or iron) in close proximity to one another. The desired proximity may be attained by using a multidentate amine ligand, which prefers to form a multinuclear complex with two or more metal ions, instead of a chelate complex with a single metal ion. In this connection it shoul be noted that while N,N,N′,N′-tetrasubstitutedethylenediamines form effective coupling catalysts with copper (Hay, 1962b, 1966; DeJongh et al., 1971); ethylenediamine, on the other hand, is not only an ineffective ligand but actually inhibits coupling reactions (Hayashi et al., 1976; Hay, 1966). The observation may be explained in terms of the formation of binuclear copper complexes in the former case and mononuclear copper chelate in the latter. It appears that steric crowding may prevent the four bulky substituent groups of an N,N,N′,N′-tetrasubstitutedethylenediamine from coming together to form a chelate with a single copper ion; the tetrasubstituteddiamine may instead form a binuclear copper complex with two copper ions. Ethylenediamine, on the other hand, chelates preferentially with a single copper ion, and the result is that substrate accessibility to the copper is blocked.

Binuclear amine ligands may be grafted onto polymer supports using, for example, a modification of a technique developed recently by Drago et al. (1980). By using iminodipyridine or an iminobis(N,N-disubstitutedalkylamine) in place of iminodipropionitrile, it would appear to be possible to attach a binuclear amine ligand onto chloromethylated polystyrene. The resulting polymer-bound iminodiamine ligand may take up two copper ions to form a binuclear complex that has high coupling activity. We are now studying this possibility.

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