Tetrahedron Vol 34, pp 641 to 644 Pergamon Press 1978 Printed in Great Britain

OXIDATIVE CLEAVAGE REACTIONS OF CATECHOL AND PHENOL TO MONOESTER OF *cis,cis*-MUCONIC ACID WITH THE OXIDIZING SYSTEMS OF O_2/CuCl, KOH/$CuCl_2$ AND KO_2/$CuCl_2$ IN A MIXTURE OF PYRIDINE AND ALCOHOL

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(*Received in Japan* 30 *May* 1977; *received in UK for publication* 3 *October* 1977)

Abstract—Oxidative cleavage reactions of catechol with CuCl to give monoester of *cis,cis*-muconic acid in pyridine containing alcohol was investigated under various conditions. The same oxidation was carried out also with the systems of KO_2/$CuCl_2$ and KOH/$CuCl_2$ in pyridine containing alcohol in the absence of oxygen. Phenol was oxidized with the same oxidizing systems to give the same monoester of muconic acid.

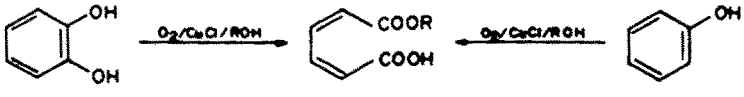
Oxidative cleavage reactions of aromatic rings is a wide spread occurrence in nature. Typically enzyme pyrocatechase catalyzes the oxidative cleavage of the aromatic ring of catechol to give *cis,cis*-muconic acid. In this oxidation reaction, an oxygen molecule is incorporated into the muconic acid.[1,2] Pyrocatechase and related enzymes are known to require either copper or iron for maximum activity, indicating an important role of these metals in biological oxidation. Several studies on *in vitro* oxidation of catechol and its derivatives as an enzyme model reaction for pyrocatechase have been attempted. Usually the *in vitro* oxidation reaction has been carried out mostly with 3,5-di-t-butylcatechol, rather than catechol itself. Oxidation of di-t-butylcatechol catalyzed by several metal salts gave the corresponding *o*-quinones.[3] Oxidation with oxygen in alkaline solution gave γ-lactone of 2,4 - di - t - butyl - 4,5 - dihydroxy - α - hydromuconic acid as a main product.[3] Photooxidative cleavage of the same catechol involving singlet oxygen produced the similar lactonic acid.[4] Recently the reaction of dibutylcatechol with superoxide ion (KO_2) was carried out and two main products, 3,5 - di - t - butyl - 5 - (carboxyhydroxymethyl) - 2 - furanone and 3,5 - di - t - butyl - 5 - (carboxyhydroxymethyl) - 2 - furanone were obtained.[5] These reactions are interesting, but the reactions do not seem to be applicable to catechol itself. Catechol and dibutylcatechol have quite different reactivity. Also, peracetic acid was used for the oxidative cleavage of phenol to *cis,cis*-muconic acid.[6,7] Recently it was found that the presence of either Fe^{3+} or Cu^{2+} ions is essential for this oxidative cleavage reaction by peracetic acid.[8]

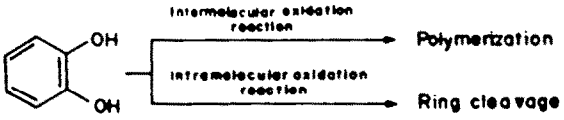
We have found that smooth oxidative cleavage of catechol to give monoester of *cis,cis*-muconic acid in a high yield proceeds with CuCl treated with molecular oxygen in pyridine containing alcohol at room temperature.[9]

Furthermore, oxidative cleavage of phenol also proceeded under similar conditions to give the same products, although the yield was lower than that of catechol.[10] The reactions have not only a theoretical significance in connection with the biological oxidation, but also considerable synthetic utility due to mild reaction conditions and high yields of muconic acid derivatives. Preliminary accounts of the work have already been given[9,10] and the details of these unique oxidation reactions are presented in this paper.

RESULTS AND DISCUSSION

It is more than 25 years ago that the oxidative cleavage reaction of catechol by pyrocatechase was discovered by Hayaishi *et al.*[1] Many attempts must had been carried out in order to find a model reaction of this interesting enzyme reaction, but no successful *in vitro* oxidative cleavage of catechol itself to muconic acid had been reported before we attempted the oxidation of catechol in 1974. Only oxidative cleavage of phenol to muconic acid in a low yield with peracid had been reported.[6,7] before we start our study we speculated that the difficulty in cleaving catechol to muconic acid is attributed to the fact that catechol is very susceptible to oxidation with oxygen to form an intractable polymer. Catechol is oxidized easily to *o*-quinone which is attacked by another molecule of catechol or a nucleophile at the electron-deficient 4 and 5 positions leading to polymerization. Thus in order to achieve the ring cleavage reaction selectively, the most crucial problem to be solved is how to avoid the oxidative polymerization of catechol. Apparently the use of 3,5-dibutylcatechol is one solution. Two bulky t-Bu groups protect the reactive 4 and 5 positions from intermolecular reaction. Although the polymerization can be avoided, however, the dibutylcatechol is not a suitable substrate for the model reaction of pyrocatechase.

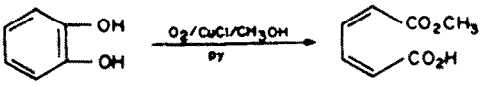




The ring cleavage reaction is an intramolecular reaction and the polymerization is an intermolecular reaction. In order to carry out the intramolecular reaction with suppression of the intermolecular reaction by selecting proper reaction conditions, one well-established method is known which is called a high dilution technique. These considerations lead us to attempt the reaction by keeping the concentration of catechol as low as possible in the presence of an excess oxidizing agent. Our success in cleaving catechol to muconate can be attributed to the high dilution technique.

As the oxidizing agent, we selected pyridine complex of CuCl, which is known to absorb oxygen at a room temperature under atmospheric pressure. This complex is used as a catalyst for the oxidative polymerization of 2,6-dimethylphenol.[11] Also the complex was used for the oxidative coupling of aniline to diazobenzene.[12] We have found that this complex is a good catalyst for the oxidative cleavage of *o*-phenylenediamine.[13] The successful ring cleavage of *o*-phenylenediamine to give *cis,cis*-muconononitrile in a high yield with this complex under the high dilution conditions gave us a strong impetus to attempt the oxidation of catechol using the same complex under similar conditions.

Oxidation of catechol. At first CuCl was dissolved in pyridine and the solution was stirred under oxygen atmosphere at room temperature. One mole of oxygen for four moles of CuCl was absorbed, and the solution turned to deep green. Then a pyridine solution of catechol was added slowly under oxygen atmosphere. Although the oxygen absorption was observed during the addition of catechol, no muconic acid was isolated even after several trials. Only polymeric product was formed. Then we found that the addition of methanol has a dramatic effect on the reaction. By the reaction carried out in the presence of methanol, monomethyl *cis,cis*-muconate was isolated as colorless needles in 82% yield.

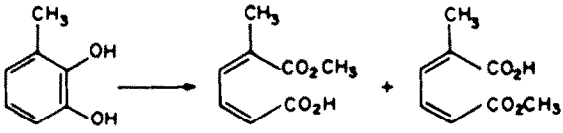


The oxidation reaction appears to be quite delicate. Persistence of the deep green color of the reaction mixture throughout the reaction is essential. When the reaction mixture turns to black or purple by adding the catechol solution too fast, the yield of muconate decreases drastically. Efficient stirring and slow addition of catechol are essential. Catechol is cleaved as soon as it is added and by this way the concentration of catechol in the reaction medium is kept low enough to avoid the polymerization.

In this reaction, monomethyl muconate was obtained irrespective of the concentration of methanol added to the reaction medium. Neither free muconic acid nor dimethyl ester was obtained under any conditions. The effect of the concentration of methanol is critical. If too much methanol is added, the yields of monomethyl muconate tend to decrease. When 20 molar equivalents of methanol were added, the yield decreased to 42%. Optimum amounts of methanol seem to be 3–8 moles for one mole of catechol. Other alcohols can be used for the oxidation to give the corresponding monoester, but the yield of the monoester decreased with increase of carbon numbers of the alcohols under the same reaction conditions as shown in Table 1. No ester was obtained with t-butyl alcohol.

Pyridine behaves as a ligand and a solvent. The coordination of pyridine to CuCl seems to be important for the smooth oxidation. When 2-methylpyridine was used instead of pyridine, the muconate was obtained only in 4% yield. With 2,6-dimethylpyridine no reaction took place. When the pyridine solution was diluted with benzene, acetonitrile and tetrahydrofuran, almost no reaction took place.

Then the effect of substituents on catechol was studied. Catechols substituted by an electron donating group can be oxidized smoothly to give substituted muconates. 4-Methylcatechol was cleaved to give a mixture of monomethyl methylmuconates in 79% yield. Simarly 3-methylcatechol was converted into a mixture of monoesters in 81% yield which is a useful starting material for the synthesis of chrysantemumdicarboxylic acid.[14]



From 4-chlorocatechol, a mixture of corresponding monoester of chloromuconate was obtained in 37% yield. On the other hand, catechols substituted by electron withdrawing groups can not be oxidized to muconate even though oxygen absorption was observed. For example, nitrocatechol and protocatechuic acid (3,4-dihydroxy-benzoic acid) were not oxidized to muconate.

For this reaction, two moles of CuCl for one mole of catechol are necessary in order to obtain the muconate above 80% yield. When one mole of CuCl was used, the yield decreased to 60%. At least one reason for the stoichiometric consumption of CuCl is inhibition by water formed by the oxidation. As shown in Table 2, the addition of water to the reaction system decreased the yield. Anhydrous magnesium sulfate was added as an absorber of water to the reaction medium, but no effect was observed. These results indicate that the water formed combines strongly with copper salt and inhibits the reaction. Monomethyl muconate, the main product of the reaction showed some inhibiting effect. These inhibitions by the products of the reaction at least partly contribute the equimolar consumption of CuCl.

Oxidation of phenol. It is known that in the metabolic

Table 1. Syntheses of various monoesters of *cis,cis*-muconate

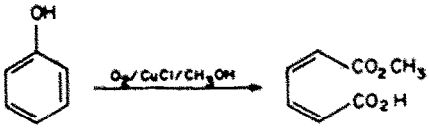
Alcohol	Yield(%)	m.p.(°C)
CH_3OH	82	80
C_2H_5OH	59	102
$n\text{-}C_3H_7OH$	45	74
$i\text{-}C_3H_7OH$	7	-
$t\text{-}C_4H_9OH$	0	-

Table 2. Effect of added water on the oxidation of catechol

H_2O[a]	Yield(%)
0	82
2	67
4	47
10	6
20	trace

a: mol/mol Catechol

pathway aromatic compounds are converted at first into phenols which are then oxygenated further by a hydroxylase to catechols before being cleaved to the muconate. Thus the direct oxidative cleavage reaction of phenol to muconate is a challenging problem. We tried the oxidation of phenol under similar conditions as adopted in the catechol oxidation, and again monomethyl *cis,cis*-muconate was obtained, although the reaction was slow. For example in the oxidation of four mmoles of phenol with eight mmoles of CuCl at room temperature, slow absorption of oxygen stopped after 60 hr and monomethyl muconate was obtained in 44% yield.



The formation of monomethyl muconate as a sole isolable product of the oxidation of phenol suggests that the oxidation proceeds through the formation of catechol. This step seems to be very slow. In order to accelerate the oxidation, other metal salts such as $CuCl_2$, $FeCl_3$, $FeCl_2$ were added, but no effect was observed. The effect of methyl substitution on phenol is delicate. 2,6-Dimethylphenol is polymerized efficiently with CuCl in pyridine under oxygen. This is the established industrial process.[11] We have tried the oxidation of m- and p-cresols, but only resinous product was formed.

Oxidizing species of copper. In this oxidation, CuCl is the most efficient oxidizing agent. CuBr in pyridine absorbs oxygen, but gave 34% yield of muconate. No other cupric and cuprous salts by themselves were found to be active for the oxidative cleavage reaction.

In connection with the active species in the oxidative polymeriation of 2,6-dimethylphenol catalyzed by CuCl in pyridine containing methanol under oxygen, Finkbeiner *et al.*[15] suggested the formation of Cu(II) species as the active catalytic species by the reaction of CuCl with oxygen in pyridine containing methanol.

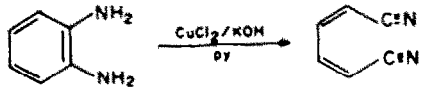
$$4\,CuCl + O_2 + 4\,CH_3OH + 4\,Py \longrightarrow$$
$$2[PyCuCl(OCH_3)]_2 + 2\,H_2O$$

Recently Rogic *et al.* carried out the oxidation of catechol to monomethyl muconate with $CuCl(OCH_3)$ in pyridine.[16] In order to clarify the active species of the oxidation further, we carried out the oxidation of catechol with $CuCl_2$ pretreated with KOH. $CuCl_2$ dissolved in pyridine containing methanol was treated by one equivalent of powdered KOH. The mixture was stirred under nitrogen atmosphere for 20 hr. During this period, a blue solution turned to dark green. This is the same color observed by the treatment of CuCl in pyridine with molecular oxygen. To this solution catechol was added slowly and monomethyl muconate was obtained in high yield. In this reaction the addition of more than 1 mole of KOH for 1 mole of $CuCl_2$ decreased the yield. Also four or five molar excess of $CuCl_2$ was necessary. The addition of methanol is essential and only polymeric product was formed in the absence of methanol. No reaction took place with $Cu(OH)_2$.

$$CuCl_2 + KOH \xrightarrow{-KCl} CuCl(OH) \underset{H_2O}{\overset{CH_3OH}{\rightleftharpoons}} CuCl(OCH_3).$$

Our results, taken together the Finkbeiner's and Rogic's results, suggest that the necessary species for the oxidative cleavage of catechol is Cu(II)Cl ion combined with either hydroxide or methoxide and coordinated by pyridine. In the reaction mixture, the hydroxide and methoxide of Cu(II)Cl seem to exist as an equilibrium mixture. It is certain that the same species is formed by the treatment of CuCl with oxygen in the presence of methanol and water as suggested by Finkbeiner *et al.*[15] Thus we can conclude that the necessary conditions for the catechol oxidation is the presence of appropriate amounts of Cu(II)Cl, water, methanol and pyridine.

As the related reaction[13] we carried out the oxidation of phenylenediamine with $CuCl_2$ similarly pretreated with KOH, but in the absence of methanol. *cis,cis*-Muconononitrile was isolated in 80% yield.



It is apparent that both catechol and phenylenediamine can be oxidized with the Cu(II) species in the absence of oxygen. However, it should be pointed out that a considerably large amount of Cu(II) salt is necessary to obtain the products in high yields. Therefore, it is more convenient to carry out these oxidations using one equivalent of CuCl under oxygen atmosphere for practical synthetic purpose.

In connection with the enzyme reactions catalyzed by dioxygenase, special attention has been directed to superoxide ion as a possible active species for biological oxidation. Now KO_2 as a convenient source of superoxide ion is commercially available. Morooka and Foote have carried out the oxidative cleavage of 3,5-di-t-butylcatechol with KO_2.[5] Recently Kametani *et al.* carried out a novel oxidative coupling of certain phenolic isoquinoline alkaloids with KO_2 treated with $CuCl_2$ in pyridine.[17] We tried the oxidation of catechol under Morooka's condition without success. We then tried the oxidation of catechol by Kametani's method with KO_2 pretreated with $CuCl_2$ in pyridine containing methanol, and found that the smooth oxidative cleavage took place to give monomethyl muconate. The result does not necessarily support that the oxidation takes place by the direct attack of superoxide ion to catechol. Superoxide ion is known to behave as an efficient reducing agent of Cu(II) ion.[18] Thus it is reasonable to assume that KO_2 converts $CuCl_2$ to CuCl, KCl and oxygen. Then the reaction of CuCl with oxygen in pyridine generates the same active

species for oxidative cleavage of catechol. Actually we observed the evolution of oxygen by the reaction of KO_2 and $CuCl_2$.

$$CuCl_2 + KO_2 \xrightarrow[CH_3OH]{} CuCl + KCl + O_2 \longrightarrow CuCl(OCH_3).$$

Similarly, phenol was oxidized to monomethyl muconate in 42% yield with KO_2 and $CuCl_2$.

EXPERIMENTAL

Materials. Commercially available catechol, phenol, CuCl, $CuCl_2$ were used without further purification. Pyridine was dried with KOH pellets and distilled before use. KO_2 (90%) was purchased from Alfa.

Oxidation method. The oxidation was carried out in a glass vessel used for catalytic hydrogenation. The vessel is connected to a gas buret to measure the oxygen absorption, and either stirred magnetically, or shaken.

Oxidation with CuCl. To pyridine (20 ml) were added MeOH (0.4 ml) and CuCl (0.79 g, 8 mmol) to form a yellow soln. The mixture was stirred in the glass vessel connected to the gas buret. Absorption of O_2 (50 ml) was observed and the soln turned to dark green. Catechol (0.44 g, 4 mmol) was dissolved in pyridine (20 ml) and the soln was added slowly in 2 hr with efficient stirring. During the addition, the absorption of O_2 (100 ml) was observed. After the addition, the mixture was stirred for 1 hr. The mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of 3NHCl and CH_2Cl_2. The organic layer was separated and washed with water. Evaporation of the solvent gave monomethyl muconate as a solid, which was recrystallized from hexane to give colorless long needle crystals of monomethyl *cis,cis*-muconate (0.51 g, 82%). m.p. 80–81° (reported 80°).[19] (Found: C, 53.78; H, 5.22; mol. wt. 156. Calc. for $C_7H_8O_4$: C, 53.85; H, 5.16% mol. wt. 156.14). NMR (CCl_4) δ 4.17 (s, 3H), 6.30–6.35 (m, 2H), 8.3–8.65 (m, 2H), 12.55 (s, 1H). The monoester was converted into dimethyl *cis,cis*-muconate by treating with diazomethane and identified by m.p. (73°) and characteristic NMR pattern.[20]

Oxidation of 3-methylcatechol and 4-methylcatechol. A pyridine soln of 3-methylcatechol (0.50 g, 4 mmol) was added dropwise in 4 hr to an oxygen treated soln of CuCl in pyridine (1.0 g in 20 ml) and MeOH (0.4 ml) at 0°. After the usual workup, a mixture of monomethyl ester of methylmuconate was obtained in 81% (0.55 g) yield. The ester was treated with 20% NaOH to give the *trans,trans* isomer and then methylated with diazomethane to form dimethyl *trans,trans*-2-methylmuconate as crystals, m.p. 57° (reported 55.5°).[14] Similarly, 4-methylcatechol (0.288 g, 2 mmol) was oxidized with CuCl (0.5 g, 5 mmol) in pyridine (15 ml) and MeOH (0.2 ml) at 5°. A mixture of monomethyl methylmuconates was obtained in 79.4% (0.27 g) yield.

Oxidation with $CuCl_2$. A mixture of $CuCl_2$ (1.3 g, 10 mmol), powdered KOH (0.62 g, 10 mmol) and MeOH (1 ml) in pyridine (50 ml) was stirred under N_2 at a room temp. for 20 hr. During this period, the blue soln turned to dark green. A pyridine soln of catechol (0.11 g, 1 mmol in 20 ml) was added slowly during 2 hr. After the usual work-up, crystalline monomethyl muconate was isolated in 82% (0.12 g) yield.

Oxidation of phenol. A mixture of CuCl (1.6 g, 16 mmol), MeOH (0.64 ml) and pyridine (30 ml) was shaken under O_2. Absorption of 100 ml of O_2 (4 mmol) was observed. Then phenol (0.376 g, 4 mmol) dissolved in pyridine (20 ml) was added. The mixture was shaken at room temp. Slow absorption of O_2 was observed; 160 ml in 30 hr and 200 ml after 40 hr and the absorption stopped after 60 hr absorbing 222 ml (9 mmol). After the usual work-up, monomethyl muconate was obtained; 0.274 g, 44% yield.

Oxidation of catechol with KO_2 *and* $CuCl_2$. $CuCl_2$ (0.78 g, 5.5 mmol) was dissolved in pyridine (30 ml) under N_2. After 30 min, powdered KO_2[21] (0.45 g, 5.8 mmol) was added to the soln at once and the light blue soln was stirred overnight (15 hr). The soln was turned to deep green. MeOH (0.44 ml, 11 mol) was added to the soln, and then a pyridine soln (25 ml) of catechol (0.11 g, 1.0 mmol) was added dropwise over 3 hr with stirring under N_2. Pyridine was evaporated and the residue was treated with CH_2Cl_2 and 3NHCl. From the organic layer, monomethyl *cis,cis*-muconate was obtained in 85% yield (0.133 g, m.p. 80°).

Acknowledgement—The authors want to express their appreciation for stimulating and helpful suggestion given by Prof. Hiroshi Kobayashi of Tokyo Institute of Technology.

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