was found to be 7:9:1, respectively, by integrating the resonances for a sample of the crude, undistilled product.

C. Cyclobutane Mixture (XI + XII + XVI) from *cis*-1,2-Bis-(trifluoromethyl)-1,2-dicyanoethylene and *cis*-Propenyl *n*-Propyl Ether. A 0.21-g sample of *cis*-1,2-bis(trifluoromethyl)-1,2-dicyanoethylene was treated with 0.23 g of *cis*-propenyl *n*-propyl ether in 2 ml of methylene chloride. The solvent and excess reactant were removed *in vacuo* when the pale orange solution decolorized completely (*ca.* 6 days). The residual oily product was redissolved in fresh solvent to examine the fluorine nmr spectrum of the cyclobutane mixture.

The spectrum showed the same cyclobutane products (XI + XII + XVI) that were formed in the reaction of *trans*-fluorocyano olefin and *cis*-propenyl ether (see **B** above). The ratio of the isomers in this case was found to be XI:XII:XVI = 2.1:1.0:2.5. Similar results were obtained when the reaction was run neat and in ethyl acetate.

D. Cyclobutanes XIII or XIV from *cis*-1,2-Bis(trifluoromethyl)-1,2-dicyanoethylene and *trans*-Propenyl *n*-Propyl Ether. A solution of 0.23 g of *trans*-propenyl *n*-propyl ether in 2 ml of methylene chloride was mixed with 0.21 g of *cis*-1,2-bis(trifluoromethyl)-1,2-dicyanoethylene. After about 6 days, the product was isolated and analyzed by fluorine nmr spectroscopy as described previously (see C above). The spectrum exhibited a pair of quadruplets (equal area, J = 12 cps) at −4.36 and +1.14 ppm, establishing that only a single cyclobutane isomer, XIII or XIV, was formed.

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The Hydroxylation of Anisole by Hydrogen Peroxide in the Presence of Catalytic Amounts of Ferric Ion and Catechol. Scope, Requirements, and Kinetic Studies[1,2]

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Abstract: Anisole is hydroxylated by aqueous H_2O_2 when catalytic amounts of Fe(III) and an enediol catalyst, such as catechol, are present in solution. The scope and requirements for this reaction and its kinetics have been investigated in some detail and the results are reported here. It has been found that: Fe(III) cannot be replaced by Cr(III), Co(III), Zn(II), Mn(II), Al(III), or Mg(II), but Cu(II) may act as an inefficient catalyst; 1,2-dihydroxy or 1,4-dihydroxy aromatic compounds are catalysts, whereas monohydroxy or 1,3-dihydroxy aromatic compounds are not catalysts; the rate appears to depend on the concentration of H_2O_2 to the first power and the concentration of Fe(III) to the first power, but the reaction is inhibited by high concentrations of the enediol catalyst; the reaction rate is also decreased by high concentrations of the buffer and by the presence of organic solvents such as ether or acetone. The kinetic results do not seem consistent with any of a number of free-radical chain mechanisms. The results suggest that the hydroxylating agent is a complex of Fe(III), the enediol, and H_2O_2.

In 1954, Udenfriend and co-workers[4] reported that aromatic compounds are hydroxylated by O_2 or H_2O_2 when Fe(II), ascorbic acid, and ethylenediaminetetracetic acid (EDTA) are present in a buffered solution around neutral pH. Since this system (Udenfriend system) bears some resemblance to enzymic hydroxylations of aromatic compounds by O_2 or H_2O_2, it has been the subject of several investigations.[5-7] Although most of the early investigators concluded that the hydroxylated products obtained with this system are the same when either O_2 or H_2O_2 is used as the oxidant, it is now quite clear that different products are obtained with these two oxidants.[2,6,7] There is now strong evidence that the hydroxyl radical ($HO\cdot$) is the actual hydroxylating agent when H_2O_2 is the oxidizing agent in the Udenfriend system.[2,6] It has recently been proposed that the hydroxylating agent, when O_2 is present in the Udenfriend system, is a complex of O_2, ascorbic acid, and Fe(II), and this complex is capable of transferring an oxygen atom to the aromatic substrate.[8]

When we began our investigation of the mechanism of the Udenfriend oxidations the above conclusions were not evident. In an attempt to find a version of the Udenfriend system better suited to a study of the mechanism, we replaced ascorbic acid by other enediols and looked for hydroxylation of anisole by H_2O_2. Preliminary studies indicated that, with catechol or hydroquinone as catalyst, a hydroxylating agent different from that in either of the Udenfriend reactions (O_2 or H_2O_2) was involved.[2] Since the system bears a resemblance to some enzyme reactions we have looked at its characteristics more thoroughly. This paper presents results on the scope and kinetics of the reaction and the following paper reports product studies.[9]

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[1] This research was supported by a grant from the Institute of General Medical Sciences of the National Institutes of Health (GM-09585).

[2] A preliminary communication of part of this work has appeared: G. A. Hamilton and J. P. Friedman, *J. Am. Chem. Soc.*, **85**, 1008 (1963).

[3] To whom inquiries should be sent: Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802.

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Experimental Section

Materials. Unless described otherwise all compounds were commercially available and were used as received. Hydrogen peroxide (3% in water) was standardized by titration with permanganate. Sodium perchlorate, ferric perchlorate, and ferrous perchlorate were obtained from G. Frederick Smith and Co. Solutions of the iron perchlorates were stabilized by adding $HClO_4$ to pH 2. The iron solutions were standardized by permanganate titration, the Fe(III) solutions by the Jones reductor technique. β-Chloropropionate solutions were prepared fresh since the pH changed on standing, probably because of hydrolysis. Fresh enediol solutions were prepared shortly before use; deaerated water was used and the solutions were kept under N_2 until use. Catechol (mp 103–105°) was recrystallized from toluene, and the resorcinol was resublimed. For the investigation of the metal ion specificity the following salts were employed: $Al_2(SO_4)_3 \cdot 18H_2O$, $Cr(NO_3)_3 \cdot 9H_2O$, $Co(NO_3)_3 \cdot 6H_2O$, $CuSO_4 \cdot 5H_2O$, $ZnCl_2$, $Mn(NO_3)_2$, and $MgSO_4$. Commercial anisole was redistilled and was shown to be essentially pure by gas chromatography.

Kinetic Experiments. The disappearance of H_2O_2 was followed by a polarographic method. Mercury batteries connected to a Helipot were employed to generate the potential across the electrodes and the current change was measured by a recorder connected across a resistance in the circuit. Mercury dropping from a Sargent capillary served as one electrode, and the drop time was kept constant at 4 to 5 sec during each run. The other electrode was a 0.15 *M* $NaClO_4$ agar salt bridge which connected the solution being measured with a saturated calomel electrode. $NaClO_4$ (0.15 *M*) in the reaction solution served as supporting electrolyte. At −1.50 or −1.60 v *vs.* the saturated calomel electrode the current is linear with the H_2O_2 concentration. If no H_2O_2 is present there is a small background current amounting to about 20% full scale deflection. The background is the same, within experimental error, at the end of the run as at the beginning. Since the reactions are first order in H_2O_2, the rate constants were obtained by plotting the logarithm of the recorder reading at any time minus the reading at infinite time *vs.* the time. The reported rate constants are the average of a least two different runs; identical runs gave rate constants which were usually within 5% of each other. Usually the reactions were initiated by adding a small aliquot (100 μl) of 1 *M* H_2O_2 to a 50-ml solution of the rest of the reagents equilibrated at 25°. In a few cases the reaction was initiated by adding catechol last and essentially the same rate constant was obtained.

Results

When all reagents are present the H_2O_2 reacts until it is all used up. With the following concentrations the half-time for the disappearance of H_2O_2 is less than 10 min at 25°: catechol, 1.5×10^{-4} *M;* Fe(III), 3.9×10^{-5} *M;* acetate buffer (pH 4.3), 0.005 *M;* $NaClO_4$, 0.15 *M;* anisole, approximately 0.01 *M;* H_2O_2 (initial), 1.75×10^{-3} *M*. The H_2O_2 appears to react according to first-order kinetics; usually a logarithmic plot of the data gave a straight line from 10 to 75% reaction of H_2O_2.

If Fe(III) is omitted essentially none of the H_2O_2 reacts. With no enediol (such as catechol) present there is a very slow disappearance of H_2O_2, but this reaction is more than an order of magnitude slower than when catalytic amounts (10^{-4} *M*) of catechol are present. If anisole is omitted the reaction stops after approximately 20 to 30% of the H_2O_2 has reacted (presumably with the catalyst). The reaction will proceed if the buffer is omitted, but the pH varies somewhat and poor first-order kinetics are observed. Product studies indicate that $NaClO_4$ is not necessary for the hydroxylation. Oxygen has no effect on the rate of the reaction; otherwise identical runs under an air or nitrogen atmosphere proceeded at the same rate.

Under conditions which gave a reaction with a half-time of less than 10 min with 4×10^{-5} *M* Fe(III) as catalyst, the following ions at 6×10^{-4} *M* did not catalyze appreciable reaction of H_2O_2 after 25 min: Co(III), Zn(II), Mn(II), and Mg(II). Al(III) at 6×10^{-5} *M* concentration also did not catalyze the reaction. Fe(III) was added to each solution after 25 min and in all cases it catalyzed the reaction of H_2O_2 as it does in the absence of other ions. With 6×10^{-4} *M* Cr(III) a small amount of H_2O_2, reacted but then the reaction stopped, and the addition of Fe(III) did not cause any further reaction. If more catechol was then added a small amount of H_2O_2 would again react, but the reaction would soon stop. It appears that Cr(III) catalyzed the oxidation of catechol by H_2O_2, but it does not cause a catalytic reaction of H_2O_2 with anisole. There were indications that Cu(II) catalyzed a slow disappearance of H_2O_2, but the reaction was much slower than with a comparable amount of Fe(III). Fe(III) can be replaced by Fe(II), but in the presence of H_2O_2 Fe(II) would be rapidly converted to Fe(III).[10]

In the absence of catechol the following compounds catalyze the disappearance of H_2O_2 in qualitatively the same way as catechol but at somewhat different rates: hydroquinone, 3,4-dihydroxybenzoic acid, 2,3-dihydroxyanisole, chloranilic acid (2,5-dihydroxy-3,6-dichloroquinone), and chromotropic acid (4,5-dihydroxy-2,7-naphthalenedisulfonic acid) (practical grade). The following compounds showed no catalytic activity or very little activity under the same conditions: phenol, resorcinol, benzoquinone, ascorbic acid, tetrahydroxy-1,4-quinone, sodium rhodizonate, α,α'-dipyridyl, tetrabromocatechol (insoluble in water). For the easily oxidized substances such as ascorbic acid, tetrahydroxy-1,4-quinone, etc. there was an initial rapid reaction of H_2O_2 but then the reaction would stop. Apparently these compounds are merely oxidized by a stoichiometric amount of H_2O_2.

The rate of disappearance of H_2O_2 is directly proportional to the ferric ion concentration when the concentrations of the other reactants are kept constant and the catechol concentration is in excess of that of the ferric ion. When the catechol or hydroquinone concentration is varied the first-order rate constant for the disappearance of H_2O_2 varies as shown in Figure 1. For solubility and other technical reasons it is difficult to obtain the kinetic dependence on the anisole concentration, but semiquantitative experiments indicate that the rate of disappearance of H_2O_2 is independent of the

Table I. The Effect of pH and Buffer Concentration on the Catalytic Reaction[a]

Concn of buffer, *M*	$k \times 10^4$ sec^{-1}[b] pH 4.17[c]	pH 3.85[c]	pH 3.54[c]
0.005	8.5	7.2	6.0
0.010	6.4	6.3	4.0
0.025	4.5	4.6	2.4_4
0.050	3.6	1.7_4	1.0_1

[a] In all runs the buffer was β-chloropropionate; the Fe(III) concentration was 3.32×10^{-5} *M;* the catechol concentration was 1.05×10^{-4} *M;* the solution was saturated in anisole; and the temperature was 25.0°. [b] Observed first-order rate constants for the disappearance of H_2O_2. [c] The pH measured at the end of the run. An average value is given but for each buffer concentration the final pH was always within 0.04 unit of the average and usually within 0.01 unit.

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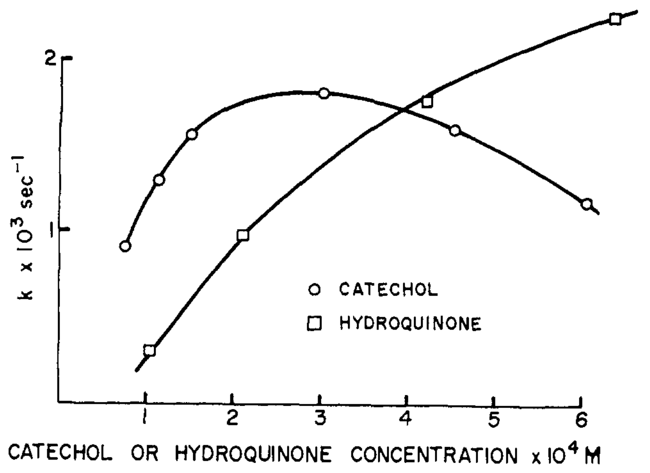

Figure 1. The effect of catechol and hydroquinone concentration on the rate constant for reaction of H_2O_2. Initial reactant concentrations for the catechol experiments were: acetate buffer, 0.005 *M*, pH 4.3; $NaClO_4$, 0.15 *M*; Fe(III), 3.94 × 10^{-5} *M*; anisole, approximately 0.01 *M*; H_2O_2, 1.75 × 10^{-3} *M*. For the hydroquinone experiments the conditions were: β-chloropropionate buffer, 0.01 *M*, pH 3.8; $NaClO_4$, 0.15 *M*; Fe(III), 3.32 × 10^{-5} *M*; anisole, approximately 0.01 *M*; H_2O_2, 1.95 × 10^{-3} *M*. Temperature 25.0°.

anisole concentration when anisole is in excess of the H_2O_2 concentration. The effect of pH and buffer concentration is shown by the results summarized in Table I.

The reaction proceeds effectively only in aqueous medium; most common water-soluble organic solvents at low concentrations inhibit the reaction markedly. A 1% acetone solution caused a 50% decrease in the rate of disappearance of H_2O_2 and a 5% acetone solution decreased the rate fivefold. A solution saturated with ether caused a fivefold decrease in rate. If anisole is omitted the H_2O_2 does not react completely; thus, the organic solvents must intercept some intermediate in the catalytic reaction.

Discussion

As indicated in the accompanying paper[9] the main products of the reaction here studied are phenols. One of the more interesting aspects of the reaction is the requirement for catalytic amounts of certain aromatic enediols.[11] The observation that aromatic enediols which are capable of oxidation by two electrons are the most effective catalysts suggests that the reaction involves oxidized forms of the catalysts as intermediates. However, since very easily oxidized enediols[14] (such as ascorbic acid, tetrahydroxyquinone, etc.) are not catalysts, presumably the catalyst must be reversibly oxidized and reduced during the catalytic reaction. Nevertheless, the fully oxidized form of the catalyst never becomes free in solution because benzoquinone is not a catalyst whereas hydroquinone is.

Two general types of mechanisms should be considered for the catalytic oxidation: (1) a free-radical chain reaction, and (2) direct oxidation of the substrate by some intermediate with concomitant regeneration of the catalyst. Several attempts have been made to rationalize the kinetics of the reaction in terms of some free-radical chain mechanism involving ferrous and ferric ions; catechol, catechol quinone, and catechol semiquinone; the hydroxyl and perhydroxyl radicals; and various radical intermediates involving the aromatic compound. Of the schemes which were tried none were consistent with the observed kinetics; most would require a zero to one-half power dependence on the concentration of one of: metal ion, catechol, or H_2O_2. The possibility of some chain mechanism is made even less probable by the product studies[9] which indicate that neither the hydroxyl nor the perhydroxyl radical is the hydroxylating agent.

Therefore, it seems more likely that the oxidation occurs by the direct oxidation of anisole by some intermediate. The kinetic results suggest that a complex composed of one molecule of H_2O_2, ferric ion, and catechol (or other enediol) acts as the oxidizing agent.[15] The zero-order dependence on the anisole concentration indicates that the formation of the oxidizing agent is the rate-determining step in the reaction. This conclusion is substantiated by the observation[17] that alcohols are oxidized to aldehydes or ketones at the same rate as anisole is hydroxylated by the catalytic system.

The rate of the oxidation is inhibited by increasing concentrations of buffer (Table I) as expected, since ferric ion forms a number of complexes with carboxylic acids,[18] and would thus not be available for complexing with the enediol. Extrapolation of the results at the different pH's to zero buffer concentration indicates that the rate is not dependent on the pH from 3.5 to 4.2. Thus, over this pH range the charge on the transition state is the same as the sum of charges on the reactants. Further mechanistic considerations will be discussed in the following paper.[9]

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(11) Norman and Smith[12] state that some monohydroxybenzene compounds act as catalysts. However, very low yields (usually less than 1%) of products were obtained with monohydroxybenzene compounds as catalysts and possibly these were formed by some mechanism (such as the Fenton reaction[13]) not related to the catalytic reaction.

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(13) For a review see G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960, p 110 ff.

(14) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams & Wilkins Co., Baltimore, Md., 1960.

(15) The rate decreases at high catechol concentrations (Figure 1) presumably because several molecules of the enediol can complex with ferric ion[16] and these complexes are inactive (or less active).

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