Hydroxylation reactions of arenes and acylation using Lewis acid catalysts

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HYDROXYLATION AND ACYLATION
REACTIONS OF ARENES USING LEWIS ACID
CATALYSTS

by

JONAS ODAME APATU, M.Sc.

A Master's Thesis
submitted in partial fulfilment of the requirements
for the award of

Master of Philosophy of the Loughborough University of Technology

September 1982

Supervisor: H. Heaney, B.A., Ph.D., D.Sc., F.R.I.C.
Department of Chemistry

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The purpose of this study was to perform hydroxylation and acylation reactions of arenes using Lewis acid catalysts in order to establish the involvement or otherwise of ipso-attack, and in addition to investigate the isomer distributions in certain reactions in order to evaluate the involvement of either radical or cationic mechanisms by comparison with results to be obtained using established free radical hydroxylating agents. No study of such reactions was available before the present study was initiated. It was hoped to design new reagents to carry out a number of electrophilic addition-with-elimination reactions of arenes.

Free-radical hydroxylation of o-, m-, and p-xylene using Fenton's reagent results in the formation of mixtures of phenols including those derived by ipso-attack followed by dealkylation. Ipso-attack by the hydroxyl radical leads solely to dealkylation.

Electrophilic (cationic) hydroxylation of o- and p-xylene using a range of peroxides; namely t-butylhydroperoxide, dibenzylperoxydicarbonate, di-t-butyldiperoxycarbonate, and bis(trimethylsilyl)peroxide in the presence of Lewis acid catalysts results in the formation of mixtures of phenols including those derived by ipso-attack followed by rearrangement. The rearranged product 2,4-xylenol was formed in all the reactions involving p-xylene. The rearranged product 2,6-xylenol was formed in all reactions involving o-xylene.

There was not much hydroxylation in the reactions involving t-butylhypochlorite or t-butylchloroperformate and silver salts, using p-xylene as the substrate.
Hydroxylation of o-, m-, and p-xylene using chemical models of hydroxylase biocatalysts gave some interesting results; the phenolic products included those derived by ipso-attack followed by rearrangement: p-xylene gave trace amounts of 2, 4-xylenol; o-xylene gave 2,6-xylenol (1%). These reactions involve oxygen atom transfer reactions that resemble the heterolytic oxidations of aromatic substrates by electrophilic metal-peroxide complexes. Thus there is the activation of molecular oxygen or hydrogen peroxide to form some type of electrophilic species.

An attempt to synthesise t-butylperoxy-tris(dimethylamino)-phosphonium hexafluorophosphate was not successful.

In the acetylation reactions involving p-xylene no ipso-attack was observed.
ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. H. Heaney, for his help, guidance and encouragement throughout the course of this work.

I am indebted to the Science Research Council for financial support, and my gratitude also goes to the technicians in the organic Chemistry Department for all their assistance.

Finally, I thank my typist for the final preparation of this manuscript.
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INTRODUCTION

Although it might have been assumed, ten years ago, that the majority of mechanistic problems connected with the reactions of arenes with electrophiles had been solved, this is now known not to be the case. Mechanistic aspects of nitration reactions have, for example, been a particularly fruitful area for further study. The present state of our knowledge has been ably summarised. (1)

Remarkably, little work has been carried out with the objective of establishing the importance of ipso attack involving electrophiles other than the nitronium ion. (2) This is in part due to the fact that the possibility of isolating adducts which result from the capture of the ipso-substituted Wheland intermediates by electrophiles is difficult. Nonetheless, arenium ion intermediates have been isolated in a number of instances. For example, (3) (A) was isolated as a solid with melting point -15°C from treatment of mesitylene with ethyl fluoride and the catalyst BF₃ at -80°C.

\[
\begin{array}{c}
\text{Me} & \text{Me} & \text{EtF/BF}_3 & \text{Me} \\
\text{Me} & \text{Me} & \text{Me} & \text{Me} \\
\end{array}
\] →

\[
\begin{array}{c}
\text{Me} & \text{Me} & \text{H} & \text{BF}_4^- & \triangle & \text{Me} & \text{Et} \\
\text{Me} & \text{Me} & \text{Me} & \text{Me} \\
\end{array}
\]

When (A) was heated, the normal substitution product (B) was obtained. Examples like this provide very strong evidence for the arenium-ion mechanism.
Certain well-known reactions must proceed by way of initial ipso attack. Examples are as follows:

(i) The reaction of hexamethylbenzene with trifluoroperoxy-acetic acid and BF$_3$ affords hexamethylcyclohexa-2,4-diene. ($^4$) (Eqn. I)

$$\text{CF}_3\text{CO}_2\text{H} \quad \text{BF}_3$$

(ii) The reaction of 1,2,3,4-tetramethylbenzene gives in addition to the expected phenol, two products where 1,2-methylshifts have occurred. ($^5$)

(iii) Durene (1,2,4,5-tetramethylbenzene) also gives a re-arranged product ($^5$) (eqn....(iii))
(iv) 1, 2, 3, 4-tetramethylnaphthalene also gives a rearranged product.

The concept of "aromaticity" in organic chemistry implies the ability of a substance to undergo substitution readily while being stable to the action of oxidants. The mechanism of the first stage in the oxidation of aromatic compounds, i.e., the hydroxylation of aromatic rings with the formation of phenolic derivatives in the liquid phase, is of particular interest. The precise nature of a number of hydroxylating agents and their interaction with the aromatic system are not entirely clear. Examination of the mechanisms of the hydroxylation of aromatic compounds will enable a deeper insight to be obtained into processes involving their oxidation and also supplement our knowledge of substitution in the aromatic series.

Methods for aromatic hydroxylations include non-enzymatic and enzymatic methods:
1. Free-Radical Aromatic Hydroxylation

(A) Mechanism of hydroxylation by Fenton’s reagent and its analogues:

Fenton’s reagent (Fe$^{2+} + H_{2}O_{2}$) is a source of reactive HO$^\cdot$ radicals, this being confirmed by its initiation of the polymerisation of vinyl compounds and oxidation of aliphatic and aromatic substances. The ferrous ion-catalysed decomposition of hydrogen peroxide may be represented by the following mechanism: (6)

\[ Fe^{2+} + H_{2}O_{2} \rightarrow Fe^{3+} + HO^\cdot + HO^- \] \hspace{1cm} (i)
\[ Fe^{3+} + H_{2}O_{2} \rightarrow Fe^{2+} + HO^\cdot + H^+ \] \hspace{1cm} (ii)
\[ Fe^{2+} + HO^\cdot \rightarrow Fe^{3+} + HO^- \] \hspace{1cm} (iii)
\[ Fe^{3+} + HO^\cdot_2 \rightarrow Fe^{2+} + O_2 + H^+ \] \hspace{1cm} (iv)
\[ HO^\cdot + H_{2}O_{2} \rightarrow H_2O + HO^\cdot_2 \] \hspace{1cm} (v)

The hydroxylation of aromatic compounds by Fenton’s reagent involves the hydroxyl radical generated by a homolytic process, i.e. HO : OH $\rightarrow$ HO$^\cdot$ + HO. The isolation of biphenyl and dibenzyl from benzene and toluene, respectively, is also indicative of a free-radical reaction. (6)

The system, titanous ion and hydrogen peroxide, hydroxylates chlorobenzene and fluorobenzene in a similar manner to Fenton’s reagent, and oxidises benzene to phenol and biphenyl. The hydroxyl radical has been identified as an intermediate in this system by electron-spin resonance spectroscopy, whereas HO$^\cdot_2$ is not present. (7) It is concluded that HO$^\cdot_2$ is not the attacking species. This may be either because it is too rapidly destroyed by further oxidation (reaction (iv)), or because it is much less reactive than HO$^\cdot$ towards benzene.

The interaction of benzene and HO$^\cdot$ -

It has been suggested that the hydroxyl radical abstracts a hydrogen atom from benzene to give a phenyl radical, and that this gives
phenol by further oxidation and biphenyl by dimerisation.\(^{(8)}\) The absence of a hydrogen isotope effect in the formation of both phenol and biphenyl when benzene and hexadeuterobenzene are separately oxidised is not consistent with this suggestion. It is, however, compatible with the addition of \(\text{H}^+\) to the aromatic nucleus to give the resonance-stabilized adduct (I)\(^{(6)}\).

There is evidence from electron-spin resonance studies that this adduct is formed when benzene is oxidised by titanous ion and hydrogen peroxide,\(^{(9)}\) and also evidence from spectroscopic studies that it is formed during the pulse-irradiation of benzene in water.\(^{(10)}\)

**Reactions of species (I)\(^{(6)}\)**

(a) **Formation of biphenyl:**

The two simplest paths by which the species (I) could give biphenyl are (i) attack on benzene followed by loss of a hydrogen atom and dehydration:

\[
\begin{align*}
\text{PhH} & \rightarrow \text{PhH} + \text{Ph} \\
\text{H} & \rightarrow \text{H} + \text{Ph}
\end{align*}
\]

or by (ii) dimerisation followed by dehydration.
(b) **Formation of Phenol:**

The first stage in the reaction between $\text{HO}^-$ and $\text{C}_6\text{H}_5\text{X}$ (where $\text{X}$ is a substituent) is the addition of hydroxyl to the benzene ring with formation of a hydroxycyclo-hexadienyl type of radical. This radical can then be oxidised to phenol both by ferric ion:

$$(I) + \text{Fe}^{3+} \rightarrow \text{PhOH} + \text{H}^+ + \text{Fe}^{2+}$$

and by oxygen, $$(I) + \text{O}_2 \rightarrow \text{PhOH} + \text{HO}_2^\cdot$$

(c) **Disproportionation:**

The adduct (I) can also undergo disproportionation as follows:

$$\begin{align*}
2 & \rightarrow \text{PhOH} + \text{PhH} + \text{H}_2\text{O}
\end{align*}$$

Important parameters of the species which attacks the benzene ring are the distribution of isomeric products which are formed. In the oxidation of toluene by Fenton's reagent the following isomer distributions of the three cresols were obtained $^{(6)}$ (o-, 71; m-, 5; p-, 24%) The ortho-isomer is the major component, followed by the para-isomer. The ortho and para positions are more reactive than the meta position. This demonstrates the electrophilic character of the hydroxyl radical.
Table I: Distribution of isomers in the hydroxylation of substituted benzenes by Fenton's reagent

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conditions</th>
<th>Phenols %</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ortho</td>
<td>meta</td>
</tr>
<tr>
<td>Toluene</td>
<td>( \text{Fe}^{2+} + \text{H}_2\text{O}_2, N_2 )</td>
<td>55.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Toluene</td>
<td>( \text{Fe}^{2+} + \text{H}_2\text{O}_2, \text{air} )</td>
<td>71.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Anisole</td>
<td>( \text{Fe}^{2+} + \text{H}_2\text{O}_2 + \text{EDTA} + ) Ascorbic Acid + Aqueous Acetone, ( N_2 )</td>
<td>84.0</td>
<td>0</td>
</tr>
<tr>
<td>Anisole</td>
<td>( \text{Fe}^{2+} \text{H}_2\text{O}_2, \text{pH 2.5, } N_2 )</td>
<td>81.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Anisole</td>
<td>( \text{Cu}^{2+} + \text{H}_2\text{O}_2 )</td>
<td>84.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>( \text{Fe}^{2+} + \text{H}_2\text{O}_2 + \text{EDTA} + ) Ascorbic acid + Aq. Acetone, ( N_2 )</td>
<td>42</td>
<td>29</td>
</tr>
<tr>
<td>Fluorobenzene</td>
<td>( \text{Fe}^{2+} + \text{H}_2\text{O}_2 + \text{EDTA} + ) Ascorbic Acid, ( N_2 )</td>
<td>37.0</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Isomer distributions for the hydroxylation of anisole were essentially unchanged when reactions were carried out (i) under heterogeneous conditions with water as solvent; (ii) without ascorbic acid or EDTA, and (iii) with cuprous instead of ferrous ion. Hydroxyl radicals were also generated by the ultraviolet irradiation of hydrogen peroxide, and under those conditions anisole and fluorobenzene gave the same isomer distributions as with Fenton's reagent.
(B) Mechanism of hydroxylation by Radiolysis

Many studies have been made of the hydroxylation of aromatic compounds under the influence of various kinds of radiation – such as the photochemical oxidation of benzene in aqueous solution on exposure to a mercury lamp,\(^{(14,15)}\) the oxidation of benzene to phenol by the action of neutrons and \(\alpha\)-particles\(^{(16)}\) and in aqueous solution by the action of \(x\)-rays.\(^{(17-20)}\)

In aqueous solution at room temperature, in the absence of oxygen and metal ions, the oxidation of aromatic compounds is effected by products of the radiolysis of water – namely \(\text{H}_2\text{O}_2\), \(\text{HO}^+\), and \(\text{HO}^\cdot\) – independently of the type of radiation employed.\(^{(17,18)}\) In the first stage of hydroxylation, as in the action of Fenton's reagent, the \(\text{HO}^\cdot\) radical "adheres" to the benzene ring.\(^{(10,21)}\) This reaction has been investigated with many benzene derivatives by pulse radiolysis and with recording of the absorption spectra of the hydroxycyclohexadienyl radicals.\(^{(22-26)}\)

Photodecomposition of \(\alpha\)-azohydroperoxide (II) in acetonitrile generates hydroxyl radicals which hydroxylate aromatic compounds.

\[
\text{Ph-C-N=N} - \text{Br} \xrightarrow{\text{hv}} \cdot\text{HO} + \text{N}_2 + \cdot\text{Br} + \text{PhCHO}
\]

Some of the results these workers obtained were as follows: (Table II)
Table II:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product(Phenols)</th>
<th>Yield,%</th>
<th>Isomer Distributions (i) o : m : p^a; o : m : p^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisole</td>
<td>Methoxyphenol</td>
<td>10^a, 32^b</td>
<td>76 : 0 : 24 64 : 0 : 36</td>
</tr>
<tr>
<td>Toluene</td>
<td>Cresol</td>
<td>7, 6</td>
<td>71 : 9 : 20 44 : 40 : 16</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>Chlorophenol</td>
<td>7, 22</td>
<td>38 :23 : 39 32 :33 : 35</td>
</tr>
</tbody>
</table>

(i) Analysed by GLC

^a under argon; ^b under oxygen

2. Catalytic Aromatic Hydroxylation
(Heterolytic)

Electrophilic mechanisms involving cations have been suggested for a number of hydroxylation reactions of aromatic compounds. A variety of catalyst systems has been employed. Acid-catalyzed electrophilic hydroxylation of aromatics has recently received considerable attention, and a number of methods has been developed to bring about such conversions. (28,29) Liquid hydrogen fluoride is an effective catalyst for the hydroxylation of aromatic compounds with aqueous hydrogen peroxide at temperatures in the range of from about -30 to +50°C. A possible mechanism of the reaction was suggested to be as follows: (30)
The designation HO⁺ may be an oversimplification for what might better be written (HO···H₂O)⁺ or H₃O⁺. Hydroxylation of toluene at about 0°C, using this system, resulted in the following products:

It is remarkable that no m-cresol was detected. The same authors also obtained a 10% yield of dihydroxylated product which was shown to include methylcatechol and methylhydroquinone. These were products of over-oxidation. These workers also obtained the following results with ethylbenzene, the xylenes; and with p-cresol:

Yield 28 mol%
(b) $\text{Me} \quad \text{Me}$

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\xrightarrow{\text{H}_2\text{O}_2 / \text{HF}} & \text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me} + \text{uncharacterized product}
\end{align*}
\]

Yield 33%

49%

(c) $\text{Me} \quad \text{Me} \quad \text{Me} \\
\xrightarrow{\text{H}_2\text{O}_2 / \text{HF}} 30^\circ\text{C} \quad \text{Me} \quad \text{Me}$

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} + \text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

Yield 20%

75% : 25%

(d) $\text{Me} \quad \text{Me} \quad \text{Me} \\
\xrightarrow{\text{H}_2\text{O}_2 / \text{HF}} 30^\circ\text{C} \quad \text{Me} \quad \text{Me}$

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \quad \text{Me} + \text{Me} \quad \text{Me} + \text{Me} \quad \text{Me}
\end{align*}
\]

46 mol% : 8 mol% : 3 mol%

(81% : 14% : 5%)

(e) $\text{Me} \quad \text{Me} \quad \text{Me} \\
\xrightarrow{\text{H}_2\text{O}_2 / \text{HF}} 0^\circ\text{C} \quad \text{Me} \quad \text{Me}$

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} + \text{OH} \quad \text{Me} + \text{OH} \quad \text{Me}
\end{align*}
\]

Dicresol

(methylhydroquinone)

41 mol% : 20 mol%
The formation of methylhydroquinone was significant. Since the recovered unreacted cresol contained no isomers, it is certain that the formation of the methylhydroquinone involved a methyl shift during the hydroxylation:\(^\text{(30)}\)

\[
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{OH} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{OH} \\
+ \\
-\text{H}^+
\end{array}
\]

Aromatic hydrocarbons (toluene and m-xylene) have also been oxidized by hydrogen peroxide-boron fluoride etherate reagent to produce phenols and other oxygenated products in low yield:\(^\text{(31)}\) For example, dropwise addition of a solution of 90% hydrogen peroxide in boron fluoride etherate to a vigorously stirred solution of m-xylene in methylene chloride at 10-25°C resulted in a 4% yield of 2, 4-dimethylphenol and a 2% yield of 2, 6-dimethyl-phenol, which were formed together with small amounts of 2, 6-dimethylhydroquinone and 2, 6-dimethyl-2-hydroxybenzoquinone. A similar reaction of toluene gave principally polymeric products with phenolic and carboxylic acidity; only a small amount (3.5%) of cresol was isolated.

A number of workers have employed peroxytrifluoroacetic acid (prepared by the reaction of trifluoroacetic acid or anhydride with hydrogen peroxide) alone:\(^\text{(32,33)}\) or in the form of its boron fluoride complex,\(^\text{(34)}\) as the source of positive hydroxyl for the hydroxylation of aromatic hydrocarbons. With some of the substrates further oxidation of the phenolic products occurred yielding quinones. It was believed that the only aromatic hydrocarbons which gave high yields of monohydroxylated product are those leading to phenols in which
positions ortho and para to the entering hydroxyl group are blocked, as in the case of mesitylene, so that further oxidation is prevented and one can isolate the phenol in good yield. Mesitylene, for example, gave an 88% yield of mesitol. (34)

\[ \text{Mesito} \]

Good yields of phenols have also been obtained from simple aromatics by treatment with hydrogen peroxide (90% or 30%) in the presence of aluminium chloride. (29) The isomer distributions, relative reactivity, and yields with a series of aromatics were consistent with the involvement of an electrophile having hydroxyl cation character, (29) (Table III).

Table III: Aromatic hydroxylation with hydrogen peroxide - Aluminium chloride\(^a\).

<table>
<thead>
<tr>
<th>Aromatic</th>
<th>Yield %(^b)</th>
<th>Isomer Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisole</td>
<td>70</td>
<td>44 &lt; 1 55</td>
</tr>
<tr>
<td>Toluene</td>
<td>40</td>
<td>60 8 32</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>14</td>
<td>26 4 70</td>
</tr>
<tr>
<td>O-Xylene</td>
<td>35</td>
<td>2,3 : 3,4 = 60 : 40</td>
</tr>
<tr>
<td>Mesitylene</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Aromatic : AlCl\(_3\) : 90% \(\text{H}_2\text{O}_2\) = 9-20 : 1.5 : 1, 0-5\(^\circ\), 2hr

\(^b\) Based on limiting peroxide reagent
The isomer distributions, particularly with toluene and anisole, were predominantly ortho-para, indicating a fair amount of intramolecular selectivity in the attacking species. These workers proposed that the hydroxylating species in their system was the hydroxyl cation (HO\(^+\)) but they formulated the reaction as follows:

\[
\begin{align*}
\text{H-O}^+ & \quad \text{ArH} \\
\delta^- \text{AlCl}_3 & \\
& \quad \text{H}
\end{align*}
\]

A highly polarized peroxide-catalyst complex undergoing nucleophilic attack by the aromatic is more likely than the intermediacy of the energetically less favourable free hydroxyl cation.

Cresols have been prepared in about 50% yield from toluene by direct oxygenation with diisopropyl-peroxydicarbonate in the presence of aluminium chloride.\(^{(35)}\) Several reaction variables were studied including time, temperature, ratio of reactants, and nature of the catalyst. Electrophilic oxygenation was proposed on the basis of the cresol isomer distribution (ortho, 34%; meta, 11%; para, 55%), the necessity of a catalyst, and the absence of products which would be derived from free-radical reactions. From a study of various catalysts, the indicated order of reactivity obtained was: AlCl\(_3\), BF\(_3\), AlBr\(_3\), SbCl\(_3\), FeCl\(_3\), SnCl\(_4\), H\(_3\)PO\(_4\).

Some of the isomer distributions obtained\(^{(36)}\) using aluminium chloride as catalyst were as follows: (Table IV).
Table IV:  Aromatic Oxygenation with $\text{AlCl}_3$ and Diisopropylperoxodicarbonate.$^{(36)}$

<table>
<thead>
<tr>
<th>Aromatic</th>
<th>Yield, %</th>
<th>Isomer Distribution, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>52</td>
<td>$O$-(34), $m$-(11), and $p$-(55)</td>
</tr>
<tr>
<td>o-Xylene</td>
<td>34</td>
<td>3,4-(74) and 2,3-(26) Xylenol</td>
</tr>
<tr>
<td>m-Xylene</td>
<td>48</td>
<td>2,4(91) and 2,6-(9) Xylenol</td>
</tr>
<tr>
<td>p-Xylene</td>
<td>24</td>
<td>2, 5-Xylenol</td>
</tr>
<tr>
<td>Mesitylene</td>
<td>66</td>
<td>Mesitol</td>
</tr>
<tr>
<td>Anisole</td>
<td>76</td>
<td>$O$-(20) and $p$-(80) methoxyphenol</td>
</tr>
</tbody>
</table>

The mechanism they proposed was as follows:

\[
\text{ROO}_2\text{OO} + \text{ArH} \rightarrow \text{ROO}_2\text{OC}_2\text{AlCl}_2 + \text{ArR} + \text{HCl} \ldots \ldots (1)
\]

\[
\text{ROO}_2\text{OC}_2\text{AlCl}_2 + \text{ArH} \rightarrow \text{ArO}_2\text{CO}_2\text{AlCl}_2 + (\text{Cl}_2\text{Al})_2\text{CO}_3 + \text{HCl} \ldots \ldots (2)
\]

\[
\text{ArO}_2\text{CO}_2\text{AlCl}_2 \rightarrow \text{ArOH} + \text{CO}_2 + \text{AlCl}_3 \ldots \ldots (3)
\]

\[
\text{ArO}_2\text{CO}_2\text{AlCl}_2 + \text{H}_2\text{O} + \text{HCl} \rightarrow \text{ArOH} + \text{CO}_2 + \text{AlCl}_3 \ldots \ldots (4)
\]

Alternatively, oxygenation might precede alkylation thus,

\[
\text{ROO}_2\text{OC}_2\text{AlCl}_2 \rightarrow \text{ArO}_2\text{CO}_2\text{AlCl}_2 + \text{ArR} + \text{HCl} \ldots \ldots (5)
\]

It is likely that a peroxide-catalyst complex plays a crucial role since no reaction occurred in the absence of aluminium chloride.
The predominant ortho, para orientation with toluene suggested an electrophilic substitution mechanism. Subjecting a cresol mixture to simulated reaction conditions established the validity of their isomer distribution. No isomerization was found.

Methylbenzenes have also been hydroxylated using t-butylhydroperoxide in the presence of aluminium chloride. In this system, toluene gave cresols (o:56: m:8: p:26). An electrophilic mechanism was proposed on the basis of the cresol-isomer distribution and by the necessity that aluminium chloride be present. An electrophilic process was proposed for this hydroxylation, where the t-butyloxonium ion (III) is the oxidizing agent. Aluminium chloride co-ordinates with the peroxide to cause a heterolytic fission of the O-O bond. The t-butoxycation then attacks the aromatic substrate to form, presumably, a t-butylarylether (IV). The free phenol should arise from the subsequent de-alkylation of (IV) followed by treatment with hydrochloric acid:

\[
t-	ext{BuOOH} + \text{AlCl}_3 \rightarrow t - \text{BuO}^+ + \left[\text{AlCl}_3 (\text{OH})\right]^- \\
(\text{III})
\]

\[
t-	ext{BuO}^+ + \text{ArH} \rightarrow \text{ArO-Bu-t} + \text{H}^+ \\
(\text{IV})
\]

\[
\text{ArOBu-t} + \text{ArH} + \text{AlCl}_3 \rightarrow \text{ArO-AlCl}_2 + \text{ArBu-t} + \text{HCl}
\]

\[
\text{ArOAlCl}_2 \xrightarrow{\text{H}_2\text{O}} \text{ArOH} + \text{HOAlCl}_2
\]

16
3. **Enzymatic hydroxylation of aromatic compounds**

Many aromatic compounds which are foreign to animal organisms are metabolized to phenolic derivatives.\(^{(39)}\) Williams and his co-workers\(^{(39,40)}\) have studied the products excreted by rabbits and other animals after administration of substituted benzenoid compounds. For example, anisole gave p-methoxyphenol and o-methoxyphenol; aniline gave p-aminophenol and o-aminophenol; acetanilide yielded predominantly p-hydroxyacetanilide; phenylurea gave predominantly p-hydroxyphenylurea.

Mitoma et al\(^{(41)}\) have also examined the products of hydroxylation of aromatic compounds by a partially purified enzyme system from liver microsomes. Both groups of workers observed that the hydroxyl group is introduced into the aromatic nucleus at those positions which are normally the most reactive towards electrophilic reagents, and it was suggested that the species responsible for the reaction is an electrophile such as an enzyme-held iron-oxygen complex, (Enzyme – FeO\(^{2+}\)).\(^{(42)}\) The alternative suggestion, that the process involves a free-radical reaction, has also been made.\(^{(43)}\)

A constant supply of oxygen is crucial to the existence of most living things. Numerous important biochemical processes in living systems involve the participation of oxidative enzymes that can be broadly classified into three groups:\(^{(44)}\) (a) The enzymes that catalyze the dehydrogenation of primary substrates are designated dehydrogenases; (b) When oxygen serves as the intermediate electron acceptor, to form water or hydrogen peroxide, the enzymes are called oxidases; (c) The third group of enzymes participate in a diverse
group of reactions that involve a direct incorporation of molecular oxygen into organic substrates. They were discovered independently by Mason (42) and Hayaishi et al (45) and are called oxygenases (46, 47, 48, 49).

Oxygenases are found widely distributed in animals, plants, and microorganisms. They play important roles in the metabolism of aromatic alicyclic, and aliphatic hydrocarbons. Oxygenases can be conveniently divided into two types, namely, mono-oxygenases that catalyze the incorporation of a single oxygen atom into the substrate, and di-oxygenases that incorporate both oxygen atoms of an oxygen molecule into the substrate.

Most of the reactions catalyzed by mono-oxygenases result in the formation of hydroxyl groups, and, hence, the name hydroxylases.

Enzymatic oxidations are generally thought (44) to involve the following sequence of reactions: (i) binding of the substrate; (ii) reduction of the enzyme by electron transfer; (iii) binding of molecular oxygen to form a ternary reduced enzyme-substrate-O$_2$ complex; and, finally (iv), a second electron transfer resulting in the liberation of the products.

Although metal-free oxygenases are known, the majority are metallo-enzymes. Prosthetic groups containing iron or copper are particularly prevalent among these enzymes. Since the metal ions, Cu$^{2+}$, Fe$^{2+}$, Co$^{2+}$, Mn$^{2+}$, etc. contained in oxidative enzymes all readily undergo 1-electron redox reactions, one would expect 1-electron transfers and transient free radicals to be important in enzymatic oxidation. No X-ray structure of a metallo-enzyme capable of catalyzing a redox reaction has been reported. Thus, the detailed environment of the metal
ion in most redox enzymes is largely unknown.

The first, most decisive stage of oxidation i.e. - hydroxylation of the aromatic ring - is not entirely understood. This stage usually involves active catalysis by enzymes, which transfer oxygen to the reaction product. The following table (Table V) gives some examples of the hydroxylation of aromatic compounds by means of enzymes.

**Table V:**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Enzyme</th>
<th>Reaction Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>Peroxidase + dihydroxyfumaric acid</td>
<td>2,4-dihydroxybenzoic acid</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Tyrosinase</td>
<td>Tyrosine</td>
</tr>
<tr>
<td>3,4-Xylenol</td>
<td>Tyrosinase</td>
<td>4,5-dimethylcatechol</td>
</tr>
</tbody>
</table>

In the above cases oxygen is incorporated into the hydroxy-group from molecular oxygen - not from water or hydrogen peroxide. (51,52)

The oxygen molecule is a weak oxidant, since oxidation must involve rupture of the strong bond between the oxygen atoms. The addition of electrons to the oxygen molecule, as occurs on reduction to $\text{O}_2^-$ or $\text{H}_2\text{O}_2^-$, weakens the bond between the oxygen atoms. This function of reductants for the oxygen molecule is performed by metal ions, which are inevitably present in redox enzymes. (50) (Table VI)
The activation of molecular oxygen is not the only function of metal ions: they may also stabilise structures, initiate chain processes, form catalytic units having qualitatively new functions, etc.

**Proposed mechanisms of the activation of molecular oxygen:**

Ferrous ion combines with oxygen to form a perferryl ion \( \text{FeO}^{2+} \) (50) in which the bond between the oxygen atoms is less stable than in molecular oxygen, since electrons pass from iron to the oxygen. Evidence of the existence of an intermediate perferryl ion has been obtained in work (50) on the kinetics of the oxidation of \( \text{Fe}^{2+} \) by oxygen which is represented by the equations

\[
\text{Fe}^{2+} + \text{O}_2 \overset{\text{FeO}^{2+}}{\rightleftharpoons} \text{FeO}^{2+} + \text{H}_2\text{O} \rightarrow \text{Fe}^{2+}\text{O} + \text{Fe}^{2+}\text{OH}
\]

The bond in the perferryl ion may be broken with the formation of a ferryl ion \( \text{FeO}^{2+} \). Bray and Gorin (53) from kinetic data for the reaction,

\[
2\text{Fe}^{3+} + \text{H}_2\text{O}_2 \overset{\text{Fe}^{2+} + \text{FeO}^{2+} + \text{H}_2\text{O}}{\rightleftharpoons}
\]

suggested the existence of this ion in inorganic reactions.
There is evidence that FeO$^{2+}$ or a similar ion of the same degree of oxidation may be present in biological systems. The Fe$^{2+}$O$\cdot$OH, like Fe$^{2+}$OH ion, is well known in inorganic chemistry from its charge-transfer spectra in solutions containing H$_2$O$_2$ and Fe$^{3+}$. Thus enzymes may contain iron ions of different degrees of oxidation.

With iron-containing enzymes, the hydroxylating species is probably the ferryl ion (FeO$^{2+}$) as shown in the scheme below:

\[
\begin{align*}
\text{Fe}^{2+} + O_2 & \xrightarrow{\text{FeO}^{2+}} \\
\text{FeO}_2^{2+} + \text{Fe}^{2+} + H_2O & \xrightarrow{\text{FeOOH}^{2+} + \text{FeOH}^{2+}} \\
\text{FeOOH}^{2+} & \xrightarrow{H^+} \text{FeO}^{2+} \\
\text{FeO}^{2+} + \text{PhH} & \xrightarrow{\text{PhOFe}^{+} + H^+} \\
\text{PhOFe}^{+} + H^+ & \xrightarrow{\text{PhOH} + \text{Fe}^{2+}}
\end{align*}
\]

Copper is able to form complexes analogous to those of iron-containing enzymes. It is present in tyrosinase as the univalent ion; Direct reaction of molecular oxygen yields the percupryl ion CuO$_2^{+}$. The percupryl ion is then reduced to cupryl ion CuO$^{+}$, which hydroxylates the benzene ring. The mechanism of the action of tyrosinase and enzymes containing copper may be represented by the following scheme:

\[
\begin{align*}
\text{Cu}^{+} + O_2 & \xleftrightarrow{\text{CuO}_2^{+}} \\
\text{CuO}_2^{+} + 2e + 2H^+ & \xrightarrow{\text{CuO}^{+} + H_2O} \\
\text{CuO}^{+} + \text{PhH} & \xrightarrow{\text{PhOCu}^{+} + H^+} \\
\text{PhOCu}^{+} + H^+ & \xrightarrow{\text{PhOH} + \text{Cu}^{+}}
\end{align*}
\]
Evidence of the existence of the cupryl ion in tyrosinase has been obtained from the denaturation of the enzyme by acid and from kinetic investigations. (56)

Much of the current understanding of enzymatic oxidations mediated by oxygenases has resulted from extensive studies of the mono-oxygenases that catalyse the formation of phenols from a variety of aromatic substrates. Udenfriend and co-workers (57,58) showed, in studies with deuterium and tritium-labelled hydrocarbons, that aromatic hydroxylations with mono-oxygenases involve an intramolecular migration of the group displaced by hydroxyl to an adjacent position on the aromatic ring, for example,

\[
\begin{align*}
\text{Phenylalaline} & \rightarrow \text{hydroxylase} \\
\text{H}_2\text{N} & \text{COOH} \\
\text{CH} & \\
\text{CH}_2 & \\
\text{3H} & \\
\text{H}_2\text{N} & \text{COOH} \\
\text{CH} & \\
\text{CH}_2 & \\
\text{3H} & \\
\end{align*}
\]

This phenomenon has become known as the "NIH Shift."

The ubiquitous nature of the NIH Shift among mono-oxygenases has resulted in such migrations being a criterion for this class of enzymes. To account for the NIH Shift, arene oxides were proposed as intermediates in enzymatic hydroxylations. One major aspect of the mechanism of the NIH Shift is as follows:

\[
\begin{align*}
\text{R} & \rightarrow \text{R} \\
\text{X} & \rightarrow \text{R} \\
\text{H} & \rightarrow \text{R} \\
\text{OH} & \rightarrow \text{R} \\
(x = \text{D, Cl, alkyl, etc}).
\end{align*}
\]
The intermediacy of arene oxides in these systems has been firmly established by subsequent mechanistic studies. (59-66) Jerina and co-workers, (59) in an attempt to gain further information on the metabolic significance of arene oxides, synthesized the oxides of toluene, of the three isomeric xylenes, mesitylene and other aromatic compounds and compared their phenolic rearrangement products with the phenols obtained by hepatic metabolism of the parent hydro-carbons. The range of phenolic products obtained from microsomal metabolism of the alkyl-substituted aromatic substrates was compatible with the intermediacy of certain extremely labile arene oxides.

Toluene and monoalkylbenzenes are metabolised by rat liver microsomes to mixtures of ortho and para-hydroxylated products (Table VII) (59).
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Phenolic products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image" alt="Structure" /> + <img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>2.</td>
<td><img src="image" alt="Structure" /> + <img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>3.</td>
<td><img src="image" alt="Structure" /> + <img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="Structure" /> + <img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>5.</td>
<td><img src="image" alt="Structure" /> + <img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>6.</td>
<td><img src="image" alt="Structure" /> + <img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>

Table VII: Metabolism of alkylbenzenes with rat liver microsomes
Toluene - 4 - $^2$H oxide rearranges exclusively to p-cresol.\(^{(59)}\)

The intermediacy of toluene - 4 - oxide is compatible with microsomal formation of p-cresol from toluene:\(^{(59)}\)

Non-enzymatic rearrangement of 3, 4-toluene - 4-$^2$H oxide gave 4-hydroxytoluene with the same amount of deuterium retention (in the 3-position) as that observed in the enzymatic hydroxylation of toluene-4 - $^2$H by liver microsomes:\(^{(60)}\)
Hydroxylation of toluene at either the ortho or para position is accompanied by an NIH shift of deuterium,\(^ {67,68}\) suggesting in each case the intermediacy of an arene oxide. Indeed, the extent of migration and retention of deuterium is similar when toluene - 4 - \(^2\)H is hydroxylated and when the corresponding 3, 4-toluene - 4 - \(^2\)H oxide isomerizes.\(^ {60}\)

In vitro metabolism of p-xylene leads to 2, 5-xylenol as the exclusive phenolic product.\(^ {59}\)

In addition, large amounts of p-toluic acid are produced by oxidation of a methyl group.

p-Xylene 1, 2 - oxide (VII) always rearranges to a mixture of both (VIII) and (IX):
The xylene oxide (VII) is quite stable and could be distilled as a yellow-orange oil. (59) Rearrangement of (VII) occurs in methanol at room temperature to a mixture of (VIII) and (IX). The methyl migration product (IX) predominates. (59) (Acids, even in trace amounts, brought about a rapid isomerization of p-xylene 1, 2-oxide(VII) to a mixture of 2, 5- and 2, 4-xylenol in a ratio of 26 : 74 respectively. (66) The xylene oxide (VII) and the methyl migration observed during its isomerization to phenols provide a simple chemical model for the formation of, for example, 3-methyltyrosine and 3-hydroxy-4-methylphenylalanine from 4-methyl-phenylalanine with phenylalanine hydroxylase. Under physiological conditions (pH 8), the ratio (9 : 1) of methyl migration vs direct ring opening of (VII) is similar to the ratio (11 : 1) of 4-hydroxy-3-methyl phenylalanine to 3-hydroxy-4-methylphenylalanine obtained on enzymatic oxidation of 4-methyl-phenylalanine. Substituted phenylalanines
with $^2\text{H}$, $^3\text{H}$, Cl, Br in the 4-position have also been shown to undergo the NIH shift during hydroxylation with phenylalanine hydroxylase.\textsuperscript{(69)}

1, 2-Dimethylbenzene (0-xylene) is oxidized by rat or guinea-pig liver microsomes exclusively to 2, 3-xylenol. This hydroxylation is accompanied by an NIH shift of deuterium.\textsuperscript{(68)} However, in the intact rat, 3, 4-xylenol is the predominant metabolite along with a trace of 2, 3-xylenol.\textsuperscript{(70)}

Possibly more than one arene oxide is formed in vivo and a specific enzyme activity responsible for the formation of the arene oxide that isomerizes to 3, 4-xylenol is lost on preparation of microsomes.\textsuperscript{(59)}

1, 3-Dimethylbenzene (m-xylene) is converted to 2, 4-xylenol and 2, 6-xylenol in ratio of greater than 10:1 respectively by rat liver microsomes (Table VII). In vivo in rats, the major phenolic metabolite is also 2, 4-xylenol.\textsuperscript{(70)}
The sole phenolic product obtained from mesitylene is mesitol both in vitro (59) and in vivo (70). Metabolism of mesitylene may thus proceed via formation of an arene oxide with a substituted oxirane ring.

1, 2 - Naphthalene oxide could actually be isolated as the initial product of the enzymatic hydroxylation of naphthalene (61).

Epoxides have been shown (71) to be obligatory intermediates in the metabolism of olefins to glycols.

Further examples of NIH shift of deuterium during aryl hydroxylation are as follows: Table (VIII)
Table (VIII): Percent Migration and Retention of Deuterium during Aryl Hydroxylation\(^b\) of Deuterated Aromatic Substrates.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Compd.</th>
<th>% Retention of deuterium(^a)</th>
</tr>
</thead>
</table>
| \[
\text{NH}_2 \\
\text{D} \\
\]
| \[
\text{NH}_2 \\
\text{D} \\
\text{OH} \\
\]
| 6 |
| \[
\text{NHCOCH}_3 \\
\text{D} \\
\]
| \[
\text{NHCOCH}_3 \\
\text{OH} \\
\text{D} \\
\]
| 30 |
| \[
\text{NHCONH}_2 \\
\text{D} \\
\]
| \[
\text{NHCONH}_2 \\
\text{OH} \\
\text{D} \\
\]
| 26 |
| \[
\text{OCH}_3 \\
\text{D} \\
\]
| \[
\text{OCH}_3 \\
\text{OH} \\
\text{D} \\
\]
| 60 |
| \[
\text{CH}_3 \\
\text{D} \\
\]
| \[
\text{CH}_3 \\
\text{OH} \\
\text{D} \\
\]
| 54 |

\(^{a}\) % Retention calculated from mass spectral data

\(^{b}\) Hydroxylation carried out by liver microsomes
A detailed comparison of migration and retentions of deuterium following aryl hydroxylation of a range of substrates has been made using *Aspergillus niger*, a representative fungus, and the hepatic microsomal system (Table IX). The results are consistent with the formation of arene oxide intermediates.

Table IX:

<table>
<thead>
<tr>
<th>Substrate (Ph-R)</th>
<th>Deuterium Label position</th>
<th>Product</th>
<th>% Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A.Niger</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - CH₃</td>
<td>2 - D</td>
<td>2 - OH</td>
<td></td>
</tr>
<tr>
<td>1 - CH₃</td>
<td>4 - D</td>
<td>4 - OH</td>
<td>71</td>
</tr>
<tr>
<td>1 - Me</td>
<td>2 - D</td>
<td>2 - OH</td>
<td>11</td>
</tr>
<tr>
<td>1 - Me</td>
<td>4 - D</td>
<td>4 - OH</td>
<td>49</td>
</tr>
<tr>
<td>1 - CH₂CO₂H</td>
<td>2 - D</td>
<td>2 - OH</td>
<td>7</td>
</tr>
</tbody>
</table>

Models of Hydroxylase Biocatalysts and the Mechanism of their Action

One approach to understanding the mechanism of action of hydroxylases is to devise simple chemical models for these monooxygenases and to determine the nature of the active oxidant in these model systems.

Much of the work on model systems was stimulated by the observation of Udenfriend and co-workers (73) in 1954 that a mixture of Fe²⁺, EDTA, Ascorbic Acid, and molecular oxygen could hydroxylate arenes to phenols under mild conditions.
For example, (73(b))

\[ \text{NHCOCH}_3 \]

(i) \[ \text{Fe}^{2+}, \text{EDTA, Ascorbic Acid} \]

\[ \text{O}_2, \text{Phosphate buffer pH6.7} \]

\[ \text{37}^\circ \text{C, 2 hrs.} \]

\[ \text{NHCOCH}_3 \]

These workers proposed that the hydroxyl group generated by the ascorbic acid system is electrophilic and hydroxylates aromatic rings at electron-rich sites. (73(b))

Another chemical model system that hydroxylates arenes is the Fe\(^{3+} - \text{H}_2\text{O}_2 - \text{Catechol (or hydroquinone) system devised by Hamilton and co-worker. (74)}\) The kinetic results suggested that a complex composed of one molecule of \( \text{H}_2\text{O}_2 \), ferric ion, and catechol (or other enediol) acts as the oxidizing agent. The zero-order dependence on the aromatic concentration indicated that the formation of the oxidizing agent was the rate-determining step. These workers used this system to hydroxylate anisole and compared their results with Fenton's and Udenfriend's systems (Table 3)(74).
Table X: Products from the hydroxylation of anisole by hydrogen peroxide$^a$

<table>
<thead>
<tr>
<th>Conditions</th>
<th>%yield of phenols$^b$</th>
<th>Phenol isomer distribution</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ortho</td>
<td>meta</td>
<td></td>
<td>para</td>
</tr>
<tr>
<td>Ferric-Catechol System</td>
<td>55</td>
<td>64</td>
<td>3</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Ferric-hydroquinone System</td>
<td>58</td>
<td>65</td>
<td>&lt;5</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Fenton reaction</td>
<td>20</td>
<td>86</td>
<td>0</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Udenfriend System</td>
<td>5</td>
<td>88</td>
<td>0</td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

$^a$ Analyzed by gas chromatography

$^b$ Yield based on initial amount of hydrogen peroxide

Hydroquinone gives a reaction similar to that catalyzed by catechol but both these systems give an isomer distribution of products which is different from that observed in the Fenton's reaction or in the Udenfriend system. Presumably a different hydroxylating agent is involved in the catechol and hydroquinone systems since higher yields of products are obtained and the isomer distribution is different. The following electrophilic mechanism was proposed for this system.$^{(74)}$
The function of the metal ion in the above proposed scheme is to transfer electrons from the catechol to the hydrogen peroxide and then in the hydroxylation-step back to the catechol. The kinetic dependence on catechol concentration suggests that a complex such as (X) is involved. At high catechol concentrations more than one molecule can complex with ferric ion and these complexes must be inactive since the rate decreases. The kinetic effect of hydrogen peroxide concentration is consistent with the formation of a complex such as (XI). A possible hydroxylating species can be envisaged if (XI) loses a molecule of water to give (XII). Several resonance structures of (XII) can be written. Electrophilic attack involving the intermediate
(XII) and anisole would give (XIII), which on migration of a proton and dissociation of the hydroxyanisole would give (X), thus completing the cycle. According to this mechanism the catechol is oxidized in the conversion of (XI) to (XII) and reduced in the hydroxylation step, (XII) to (XIII). With no anisole present, (XII) could react with water to give (XIV). It was also suggested that (XII) could presumably act as a free radical reagent as well, but in the present case, the isomer distribution of products suggested electrophilic rather than radical attack.

The enzymes, catalase and peroxidase, (74) are ferric-porphyrin enzymes which have characteristics similar to the ferric-catechol system described here. Porphyrins have oxidation-reduction properties related to those of catechol. Thus a similar mechanism of action presumably operates during the hydroxylation of arenes by enzymes.

Hydroxylation reactions of benzene and simple alkylbenzenes using hydrogen peroxide and various catalyst systems have been reported, as discussed earlier on. Cationic reagents were suggested. In all of the reactions using toluene as the substrate, a high o:p ratio was observed but this does not allow a distinction to be made with respect to electrophilic radical hydroxylation.

The aim of our work was to use the isomeric xylenes as substrates in a series of hydroxylation reactions and to investigate the isomer distributions of the phenolic products in order to establish the involvement of either cationic or radical mechanisms by comparison with results to be obtained using established free-radical hydroxylating agents. No study of such reactions was available before the present
The proposed dual general mechanism for acylation reactions is as follows:\(^{(75)}\)

\[
\begin{align*}
R - X & \quad + \quad AlCl_3 \quad \rightarrow \quad R - X \\
 & \quad + \quad AlCl_3 \quad \rightarrow \quad R - C\equiv O \quad \cdots AlCl_3X^- \\
\text{ArH} & \quad \downarrow \quad \quad \downarrow \\
\text{RC-AR}^+ & \quad + \quad AlCl_3X^- \\
\text{Ar}^+ \quad CO \quad \cdots AlCl_3 \\
\text{RC-AR} & \quad + \quad HCl \\
\text{Hydrolysis} & \quad \downarrow \quad \downarrow \\
\text{RC-AR} & \quad \downarrow \\
\end{align*}
\]

It has been assumed in the past that some rearrangements precede attack on the acylating agent and afford the thermodynamically more stable m-disubstituted benzene derivatives which are themselves more reactive towards acylation.\(^{(76)}\) Thus the acetylation of m- and p-xylene using acetyl chloride and aluminium chloride in 1, 2-dichloroethane...
at $25^\circ$C proceed at relative rates compared with benzene of 347 and 23.5 respectively.\(^{(77)}\) Although p-xylene reacts with acetyl chloride and aluminium chloride in carbon disulphide to afford 2,5-dimethylacetophenone,\(^{(78)}\) at higher temperatures using an excess of p-xylene the only product is 2,4-dimethylacetophenone.\(^{(79)}\)

We also intended to re-investigate the above reaction in order to establish the sequence of events leading from p-xylene to 2,4-dimethylacetophenone.
2. RESULTS AND DISCUSSION

As discussed in the introduction, we set out to use the isomeric xylenes as substrates in a series of hydroxylation reactions and to investigate the isomer distributions of the phenolic products in order to establish the involvement of either cationic or radical mechanisms by comparison with results to be obtained using established free-radical hydroxylating agents. No study of such reactions was available before the present study was initiated.

Hydroxylation reactions of benzene and simple alkyl benzenes using hydrogen peroxide and various catalyst systems have been reported.\(^{(29,30,31)}\)

Cationic reagents were suggested. t-Butylhydroperoxide reacts with toluene in the presence of aluminium chloride to afford cresols in the ratio of \(o:m:p = 56:8:36\). In this case the electrophile was suspected to be the t-butoxy-cation.\(^{(37)}\) In all of the reactions using toluene as the substrate\(^{(29,30,37)}\) a high \(o:p\) ratio was observed but this does not allow a distinction to be made with respect to electrophilic radical hydroxylation; for example, the isomer distribution in the free radical hydroxylation of toluene is \(o:m:p = 71:5:24\).\(^{(12)}\)

It was, therefore, necessary to devise means of distinguishing between hydroxylation reactions involving radicals and cations.

2.1 Hydroxylation of \(o\)-, \(m\)-, and \(p\)-xylenes by Fenton's reagent

The average isomer distributions of the phenolic products obtained are shown in Table XI:
Table XI

Hydroxylation of xylenes by Fenton’s reagent

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Isomer distribution of xylenols(^a)(%)</th>
<th>cresol(^a) (%)</th>
<th>(K_H/K_{ipso})</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-xylene</td>
<td>(2,5) 24</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>o-xylene</td>
<td>(2,3)12 : (3,4)15</td>
<td>73</td>
<td>0.1</td>
</tr>
<tr>
<td>m-xylene</td>
<td>(2,4)56 : (2,6)14 : (3,5)3</td>
<td>27</td>
<td>1.3</td>
</tr>
</tbody>
</table>

\(^a\) The phenolic products were analysed by gas chromatography using, in the reactions involving o- and m-xylene an FFAP capillary column, and in the reactions involving p-xylene a 25m OV1 capillary column.

Fenton’s reagent is an established free-radical hydroxylating agent. Inspection of the results obtained shows the formation of a high proportion of cresols (low \(K_H/K_{ipso}\) Values) and this indicates ipso-substitution, by the hydroxyl radical, with the loss of a methyl group.

Reaction mechanism:

a) Formation of xylenols: The hydroxyl radical generated from Fenton’s reagent attacks the xylene molecule to give the hydroxycyclohexadienyl radical intermediate (xv) which then loses a hydrogen atom to give the xylenols. This is illustrated (equation 1) using p-xylene as the substrate.
b. Formation of cresol: Ipso-attack by the hydroxyl radical also
leads to the formation of a hydroxycyclohexadienyl radical intermediate (XVI)
but this then loses a methyl radical to give cresol (equation 2):

The fate of the methyl radical is unknown. Demethylation by the same
radical could give a cyclohexadiene:

but this was not detected.

Another possible reaction of the hydroxycyclohexadienyl radical inter-
mediate (XVI) is as follows: (6)
(c) **Formation of bixylenyl:**

The two simplest paths by which the species (XVI) could give bixylenyl are (i) dimerisation followed by dehydration:

\[
\begin{array}{c}
\text{2} \quad \text{2, 2' - Bixylenyl} \\
\end{array}
\]

or by (ii) attack on xylene followed by loss of a hydrogen atom and dehydration:

\[
\begin{array}{c}
\text{2, 2' - Bixylenyl} \\
\end{array}
\]
We did not examine the neutral fractions of the reactions performed with Fenton's reagent. However, the formation of biaryls such as bixylyls cannot be ruled out in these free-radical reactions. It may be noted,\(^{(6)}\) that 2,2'-bitolyl is formed during the oxidation of toluene with Fenton's reagent, and biphenyl is formed during the oxidation of benzene with the same reagent.
2.2 Hydroxylation of o-, m-, and p-xylene using t-butylhydroperoxide; dibenzylperoxydicarbonate; di-t-butyldiperoxy carbonate; bis(trimethylsilyl) peroxide and Lewis acid catalysts.

Electrophilic mechanisms involving cations have been suggested for a number of hydroxylation reactions of aromatic compounds. A variety of catalyst systems has been employed. (29,30,31,35,36,37)

Dibenzylperoxydicarbonate, di-t-butyldiperoxy carbonate and bis(trimethylsilyl) peroxide and aluminium chloride had not been used before in the hydroxylation of aromatic compounds. The results we obtained are summarised below in tables XII, XIII, and XIV.
Table XII: Hydroxylation of p-xylene

<table>
<thead>
<tr>
<th>Reagent (Mol. Ratio)</th>
<th>Reaction time (hr) at 20°C</th>
<th>Yield (%)</th>
<th>Isomer distribution of xylenols %</th>
<th>Cre- sol</th>
<th>(K_H/K_{ipso})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Bu}^+\text{OOH}/\text{AlCl}_3) (1:2)</td>
<td>2</td>
<td>40</td>
<td>70</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>(\text{Bu}^+\text{OOH}/\text{TlCl}_4) (1:3)</td>
<td>4</td>
<td>31</td>
<td>93</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>(\text{Bu}^+\text{OOH}/\text{TlCl}_4) (1:3)</td>
<td>2</td>
<td>28</td>
<td>92</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>((\text{Bu}^+\text{OO})_2\text{CO}/\text{AlCl}_3) (1:4)</td>
<td>2</td>
<td>18</td>
<td>68</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>((\text{Bu}^+\text{OO})_2\text{CO}/\text{AlCl}_3) (1:4)</td>
<td>4</td>
<td>19</td>
<td>70</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>((\text{PhCH}_2\text{OCOO})_2/\text{AlCl}_3) (1:2)</td>
<td>2</td>
<td>20</td>
<td>66</td>
<td>34</td>
<td>-</td>
</tr>
<tr>
<td>((\text{PhCH}_2\text{OCOO})_2/\text{AlCl}_3) (1:2)</td>
<td>4</td>
<td>12</td>
<td>69</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>((\text{CH}_3)_3\text{SiOOSi(CH}_3)_3/\text{AlCl}_3) (1:2)</td>
<td>2</td>
<td>18</td>
<td>70</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>((\text{CH}_3)_3\text{SiOOSi(CH}_3)_3/\text{AlCl}_3) (1:3)</td>
<td>4</td>
<td>16</td>
<td>73</td>
<td>27</td>
<td>-</td>
</tr>
<tr>
<td>((\text{CH}_3)_3\text{SiOOSi(CH}_3)_3/\text{AlCl}_3) (1:3)</td>
<td>2</td>
<td>14</td>
<td>72</td>
<td>28</td>
<td>-</td>
</tr>
</tbody>
</table>

* Yields are based on the peroxycompounds. The phenolic products were analysed using a 25m OV1 Capillary Column.
## Table XIII Hydroxylation of o-xylene

<table>
<thead>
<tr>
<th>Reagent (Mol. Ratio)</th>
<th>Reaction time (hr) at 20°C</th>
<th>Yield (%)</th>
<th>Isomer distribution of xylanols (%)</th>
<th>Cresol</th>
<th>$K_{H/K_{ipso}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,4-</td>
<td>2,3- Xylenol 2,6- Xylenol</td>
<td>o- Cresol</td>
</tr>
<tr>
<td>Bu&lt;sup+t&lt;/sup&gt;OOH/AICl&lt;sub&gt;3&lt;/sub&gt; (1:2)</td>
<td>2</td>
<td>50</td>
<td>60</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>Bu&lt;sup+t&lt;/sup&gt;OOH/TICl&lt;sub&gt;4&lt;/sub&gt; (1:2)</td>
<td>2</td>
<td>26</td>
<td>86</td>
<td>14</td>
<td>Trace</td>
</tr>
<tr>
<td>Bu&lt;sup+t&lt;/sup&gt;OOH/TICl&lt;sub&gt;4&lt;/sub&gt; (1:1)</td>
<td>2</td>
<td>28</td>
<td>88</td>
<td>12</td>
<td>Trace</td>
</tr>
<tr>
<td>Bu&lt;sup+t&lt;/sup&gt;OOH/TICl&lt;sub&gt;4&lt;/sub&gt; (1:3)</td>
<td>2</td>
<td>48</td>
<td>83</td>
<td>17</td>
<td>Trace</td>
</tr>
<tr>
<td>Bu&lt;sup+t&lt;/sup&gt;OOH/TICl&lt;sub&gt;4&lt;/sub&gt; (1:4)</td>
<td>2</td>
<td>44</td>
<td>85</td>
<td>15</td>
<td>Trace</td>
</tr>
<tr>
<td>Bu&lt;sup+t&lt;/sup&gt;OOH/TICl&lt;sub&gt;4&lt;/sub&gt; (1:3)</td>
<td>4</td>
<td>49</td>
<td>83</td>
<td>17</td>
<td>Trace</td>
</tr>
<tr>
<td>(Bu&lt;sup+t&lt;/sup&gt;OO)&lt;sub&gt;2&lt;/sub&gt;CO/AICl&lt;sub&gt;3&lt;/sub&gt; (1:2)</td>
<td>2</td>
<td>11</td>
<td>87</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>(Bu&lt;sup+t&lt;/sup&gt;OO)&lt;sub&gt;2&lt;/sub&gt;CO/AICl&lt;sub&gt;3&lt;/sub&gt; (1:4)</td>
<td>2</td>
<td>35</td>
<td>86</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>(Bu&lt;sup+t&lt;/sup&gt;OO)&lt;sub&gt;2&lt;/sub&gt;CO/AICl&lt;sub&gt;3&lt;/sub&gt; (1:5)</td>
<td>2</td>
<td>39</td>
<td>86</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>(Bu&lt;sup+t&lt;/sup&gt;OO)&lt;sub&gt;2&lt;/sub&gt;CO/AICl&lt;sub&gt;3&lt;/sub&gt; (1:4)</td>
<td>4</td>
<td>48</td>
<td>86</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>(Bu&lt;sup+t&lt;/sup&gt;OO)&lt;sub&gt;2&lt;/sub&gt;CO/AICl&lt;sub&gt;3&lt;/sub&gt; (1:4)</td>
<td>8</td>
<td>49</td>
<td>87</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>(PhCH&lt;sub&gt;2&lt;/sub&gt;OCOO)&lt;sub&gt;2&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:2)</td>
<td>2</td>
<td>42</td>
<td>82</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>(PhCH&lt;sub&gt;2&lt;/sub&gt;OCOO)&lt;sub&gt;2&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:2)</td>
<td>4</td>
<td>35</td>
<td>82</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>(PhCH&lt;sub&gt;2&lt;/sub&gt;OCOO)&lt;sub&gt;2&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:3)</td>
<td>2</td>
<td>44</td>
<td>85</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>(PhCH&lt;sub&gt;2&lt;/sub&gt;OCOO)&lt;sub&gt;2&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:4)</td>
<td>2</td>
<td>34</td>
<td>82</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;SiOOSi(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:3)</td>
<td>2</td>
<td>24</td>
<td>41</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;SiOOSi(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:2)</td>
<td>2</td>
<td>17</td>
<td>50</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;SiOOSi(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;/AICl&lt;sub&gt;3&lt;/sub&gt; (1:2)</td>
<td>4</td>
<td>22</td>
<td>45</td>
<td>38</td>
<td>17</td>
</tr>
</tbody>
</table>

*Phenolic products were analysed using a 25m Cp wax 51 Capillary column.*
Table XIV  Hydroxylation of m-xylene

<table>
<thead>
<tr>
<th>Reagent (Mol.Ratio)</th>
<th>Reaction (hr) at 20°C</th>
<th>Yield (%)</th>
<th>Isomer distribution of xylenols %</th>
<th>Creso-l</th>
<th>K H/ K ipso</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2,4-Xylenol</td>
<td>2,6-Xylenol</td>
<td>3,5-Xylenol</td>
</tr>
<tr>
<td>$\text{Bu}^t\text{OOH/AlCl}_3$ (1:2)</td>
<td>2</td>
<td>41</td>
<td>83</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>$(\text{Bu}^t\text{OO})_2\text{CO/AlCl}_3$ (1:4)</td>
<td>2</td>
<td>28</td>
<td>87</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>$(\text{Bu}^t\text{OO})_2\text{CO/AlCl}_3$ (1:4)</td>
<td>4</td>
<td>32</td>
<td>88</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>$(\text{PhCH}_2\text{OCOO})_2/\text{AlCl}_3$ (1:2)</td>
<td>2</td>
<td>27</td>
<td>88</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>$(\text{PhCH}_2\text{OCOO})_2/\text{AlCl}_3$ (1:2)</td>
<td>4</td>
<td>21</td>
<td>84</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>$(\text{CH}_3)_3\text{SiOSi(CH}_3)_3/\text{AlCl}_3$ (1:3)</td>
<td>2</td>
<td>26</td>
<td>73</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

* Phenolic products were analysed using a 25m Cp wax 51 capillary column.
Hydroxylation of p-xylene gave two isomeric products namely 2,5-xylenol and 2,4-xylenol (Table XII). In 2,5-xylenol the positions of the methyl groups are the same as those of the starting material, but in 2,4-xylenol the position of one methyl group differs from that of the starting material, thus indicating that a 1,2-methyl shift occurs during its formation. Analysis of recovered p-xylene and control experiments using standard 2,5- and 2,4-xylenol established that p-xylene and the xylenols did not isomerise in the presence of aluminium chloride under the conditions used. Therefore, the formation of the rearranged product, 2,4-xylenol, can be explained thus - that ipso-hydroxylation occurred followed by a methyl migration in an ipso-arenium ion intermediate. Alkyl migration in an ipso-arenium ion is facilitated by the relatively low energy of the transition state leading to the new arenium ion (a protonated cyclohexa-2,4-dienone) that can re-aromatise by loss of a proton (equation 3);

\[
\text{Me} \quad \text{Me}^+ \quad \text{RO} \quad \text{Me}^+ \quad \text{RO} \quad \text{Me} \quad \text{Me}^+ \quad \text{HO} \quad \text{Me}^+ 
\]

...Eqn. 3

although we should not rule out the possibility that arene oxides are involved in these reactions. (59)

Jerina and co-workers, (59) in an attempt to gain further information on the metabolic significance of arene oxides synthesised the oxides of some aromatic hydrocarbons including the isomeric xylenes. p-Xylene-1 2-oxide (VII) was obtained as a stable yellow-orange oil.
Re-arrangement of (VII) occurs in methanol at room temperature to a mixture of 2,5-xylenol (VIII) and 2,4-xylenol (IX), as shown below:

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

(VIII)

(VII)

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

methyl migration

(IX)

The methyl migration product (IX) predominates. Acids, even in trace amounts, brought about a rapid isomerization of p-xylene-1,2-oxide (VII) to a mixture of 2,5- and 2,4-xylenol in a ratio of 26:74 respectively.

We can infer from the results of the above-mentioned experiments that if arene oxides are formed during the hydroxylation of p-xylene using peroxides and Lewis acid catalysts, then these oxides could also give rise to mixtures of 2,5- and 2,4-xylenol.

We shall now discuss the possible mechanisms by which p-xylene-1,2-oxide could give rise to 2,5- and 2,4-xylenol:
(i) Formation of 2,5-xylenol:

Protonation of p-xylene-1,2-oxide could lead to direct ring opening to form the hydroxycyclohexadienyl cation intermediate (shown above) which then rearomatizes by loss of a proton to give 2,5-xylenol.

The arenium cation intermediate could form the cyclohexa-2,4 dienone (as shown below) which then leads to the formation of 2,5-xylenol. This latter possibility is not very likely in view of the step involving the high energy hydride shift and the fact that the dienone-phenol rearrangement is normally a rapid and exothermic process.

2,5-xylenol could also be formed from p-xylene-2,3-oxide as follows:
Protonation of p-xylene-2,3-oxide followed by ring opening in either direction would lead to the formation of the arenium cation intermediate which then rearomatises by loss of a proton to give 2,5-xylenol.

(ii) Formation of 2,4-xylenol:

Protonation of p-xylene-1,2-oxide could also lead to ring opening to form the ipso-substituted hydroxycyclohexadienyl cation intermediate which then rearranges to form a new arenium ion (a protonated cyclohexa-2,4-dienone) that rearomatises by loss of a proton to give 2,4-xylenol.

On the other hand, the ring opening and the alkyl migration could be concerted to form the arenium cation intermediate (the protonated cyclohexa-2,4-dienone) as shown below:
The arenium cation then rearomatizes by loss of a proton to give 2,4-xylenol.

Although we cannot rule out the possibility that some 2,5-xylenol also arises from the ipso-arenium ion such a process is very unlikely, except as indicated previously, if an arene-oxide were involved.

\[
\begin{align*}
\text{Me} & \quad \text{OR} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

The rearrangement that we suggest leads to 2,4-xylenol is energetically more favourable. It is somewhat like a pinacol-pinacolone rearrangement.

Hydroxylation of o-xylene gave 3,4-xylenol, 2,3-xylenol, 2,6-xylenol, and in some cases o-cresol (Table XIII). The formation of 2,6-xylenol (the highest amount being 17%) indicates that a 1,2-methyl shift occurred during its formation. Analysis of recovered o-xylene and control experiments using standard xylenols established that o-xylene and the xylenols did not isomerise in the presence of aluminium chloride under the experimental conditions used. Therefore, the formation of the rearranged product, 2,6-xylenol, can be explained as ipso-hydroxylation followed by a 1,2-methyl migration through an ipso-arenium ion intermediate (equation 4, cf. equation 3). The mechanism is similar to that of the formation of 2,4-xylenol from p-xylene.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]
An inspection of the isomer distribution of the phenolic products obtained from o-xylene shows a higher proportion of 3,4- to 2,3-xylenol. This may be due either to (i) the direction influence of the methyl groups or (ii) that the electrophile involved in these reactions is large and hence is a more sterically demanding species.

The majority of electrophiles react with o-xylene to give substitution at position 4. (a) When o-xylene is treated with nitric acid in acetic anhydride,\(^{(89)}\) in addition to the expected 3- and 4- nitroxylenes, 3,4-dimethylphenylacetate is formed and is the major product; the acetoxylation occurs only in the 4 position of o-xylene; (b) In the AlCl\(_3\)-CH\(_3\)NO\(_2\) catalysed benzylation of o-xylene the only product detected was 3,4-dimethyl-diphenylmethane;\(^{(90)}\) (c) Acetylation of o-xylene with aluminium chloride and acetyl chloride gives only a single isomer, 3,4-dimethylacetophenone.\(^{(91)}\)

Possible routes to the formation of 2,3-xylenol from o-xylene are discussed below:

(i) It may arise by direct attack:

$$\text{Me} \quad \text{Me}$$

An attack at position 3 of o-xylene leads to the formation of the arenium cation intermediate which loses a proton to give the xylenol.

(ii) An alternative explanation is that initial ipso-hydroxylation occurs followed by two successive methyl shifts and the loss of a proton to give 2,3-xylenol (scheme 1).
The two successive methyl shifts occur through two arenium cation intermediates.

The likely nature of the above proposed two-successive methyl shifts in the formation of 2,3-xylenol is predicted from the following data:

(a) Certain well-known reactions must proceed by way of initial ipso attack followed by a 1,2-methyl shift. Examples are:

(i) The reaction of hexamethylbenzene with trifluoroperoxyacetic acid and BF₃ affords hexamethylcyclohexa-2,4-dienone (equation 1) in which there has been a methyl shift to the adjacent substituted carbon atom.

53
(ii) The reaction of 1,2,3,4-tetramethylbenzene (prehnitene) gives in addition to the expected phenol, two products where 1,2-methyl shifts have occurred\(^5\) (equation ii)

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{OH} & \\
\text{Me} & \quad + \\
\text{Me} & \quad + \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{BF}_3 & \\
\text{CF}_3\text{CO}_2\text{H} & \\
\end{align*}
\]

In one of the products, the cyclohexa-2,4-dienone, there is a methyl shift to the adjacent already substituted carbon atom. The yields of the rearranged products represented 9% of the oxidation products of prehnitene.

(iii) The oxidation of compound C, with trifluoroperoxyacetic acid and BF\(_3\) gives the following products:\(^5\)

\[
\begin{align*}
\text{D}(36\%) & \\
\text{E}(20\%) & \\
\text{F}(24\%) & \\
\text{G}(20\%) & \\
\end{align*}
\]
Product G could arise from (D) via protonation, two methyl migrations, and deprotonation. However (D) is stable under the oxidation conditions. Though such rearrangements are known, they usually require considerably stronger acid to proceed at a rapid rate.

(iv) Durene (1,2,4,5-tetramethylbenzene) also gives a rearranged product (H):

The principal product obtained in yields as high as 75%, was the dienone (H). Attack at an already substituted position is favoured 2:1 statistically. Methyl migration occurs preferentially toward the adjacent substituted position giving (H); no iso-dureno (I) was observed among the products.
(b) In a study\(^{(94)}\) of the migratory aptitude of the nitro group in 1,2-dimethyl-1-nitrocyclohexadienyl cation (J),
it was found that the rate of migration of the nitro group to an equivalent ipso site \( K_{\text{ipso}} \) is about fifty times (50X) the rate of migration to an adjacent, open site bearing a hydrogen atom \( K_{o} \). The nitro group in the arene cation intermediate \( K \) further migrates to give the arene cation \( L \) which finally loses deuterium to give the product 1,2-dimethyl-3-nitrobenzene. Thus the nitro group undergoes two successive intramolecular 1,2-shifts to give the final product 1,2-dimethyl-3-nitrobenzene.

From all the above facts, it is not far-fetched to propose that two successive methyl shifts occur in the formation of 2,3-xylenol (scheme 1).

Experiments could be designed to confirm the likely nature of the two successive intramolecular 1,2-methyl shifts, by (i) firstly synthesising o-xylene labelled with \( ^{13}\text{C} \) at the C-1 and C-2 positions using, for example, butadiene and \( ^{13}\text{C} \)-labelled dimethylacetylene dicarboxylate in a Diels-Alder reaction followed by reduction and dehydrogenation to give the labelled o-xylene:

\[
\text{Diels-Alder reaction} \quad \text{Dimethylcyclohexa-1,4-diene-1,2-dicarboxylate}
\]
(ii) secondly, to use the $^{13}$C-labelled o-xylene in hydroxylation reactions and to isolate the 2,3-xylenol from the 3,4- and 2,6-xylenol by preparative glc or preparative HPLC. 2,3-xylenol formed by direct attack will have the $^{13}$C-label at the methyl positions (M), whereas 2,3-xylenol formed from two successive methyl shifts will have one label at one methyl position and the other label at the OH substituted position.

Carbon-13 ($^{13}$C) has a nuclear spin and, therefore, will couple with hydrogen. A careful study of the proton NMR and $^{13}$C-NMR of the isolated xylenol should confirm the location of the $^{13}$C-labels and, therefore, enable one to ascertain whether, either only (M) or (N) is formed or a mixture of the two is formed during the hydroxylation.

The above argument could also be used to establish the importance or otherwise of the mechanistic route (scheme 2), for the formation of o-cresol from toluene:

Scheme 2

\[ \text{Scheme 2} \]
1-^{13}C\text{toluene may be prepared by the following sequence of reactions:} (95) (Scheme 3)

Scheme 3

Reagents: i, sodium nitromalondialdehyde; ii, $\text{MeSO}_2\text{Cl}$; iii, KCN; iv, $\text{NH}_2\text{NH}_2$ and Pd, C; v, $\text{HNO}_2$, $\text{H}^+$; vi, $\text{H}_3\text{PO}_4$; vii, $\text{LiAlH}_4$; viii, $\text{NH}_2\text{-O-SO}_3\text{H}$, OH$^-$.

These experiments with labelled substrates will help to advance the work we've done so far.

o-Cresol was formed in some of the reactions involving o-xylene (Table XIII) and this could be accounted for as follows:
Ipso attack occurs, followed by the removal of a methyl in the arenium cation intermediate by a base/nucleophile, $\text{X}^-$, resulting in the formation of o-cresol.

With m-xylene the order of the isomer distribution of the xylenols was as follows:

$$2, 4 \rightarrow 2, 6 \rightarrow 3, 5\text{-xylenol}$$

This pattern of distribution of these isomers is accounted for by the o/p-directing influences of the methyl groups, with the consequence that less 3,5-xylenol is formed due to low electron density at the 5th carbon of 1,3-xylene (m-xylene).

Comparison of the results obtained using Fenton's reagent and the Aluminium chloride/peroxide systems.

A summary of the results is given in Table XV:
Table XV. Hydroxylation of xylenes

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent (mol ratio)</th>
<th>% Yield</th>
<th>Isomer distribution of xylenols$^a$ (%)</th>
<th>Cres-</th>
<th>$K_H$/$K_{ipso}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-xylene</td>
<td>Bu$^t$OOH/AlCl$_3$(1:2)</td>
<td>40</td>
<td>(2,5) 70:(2,4) 30</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>p-xylene</td>
<td>(PhCH$_2$OCOO)$_2$/AlCl$_3$(1:2)</td>
<td>19</td>
<td>(2,5) 70:(2,4) 30</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Bu$^t$OO)$_2$CO/AlCl$_3$(1:4)</td>
<td>20</td>
<td>(2,5) 66:(2,4) 34</td>
<td>0.0</td>
<td>0.9</td>
</tr>
<tr>
<td>p-xylene</td>
<td>(Me$_3$SiO)$_2$/AlCl$_3$(1:2)</td>
<td>18</td>
<td>(2,5) 69:(2,4) 31</td>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Fe$^{2+}$/H$_2$O$_2$</td>
<td>-</td>
<td>(2,5) 24</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Bu$^t$OOH/AlCl$_3$(1:2)</td>
<td>50</td>
<td>(2,3) 28:(3,4) 60:(2,6) 5</td>
<td>9</td>
<td>8.6</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Bu$^t$OOH/TiCl$_4$(1:3)</td>
<td>49</td>
<td>(2,3) 17:(3,4) 83:(2,6)&lt;0.5</td>
<td>0.0</td>
<td>∞</td>
</tr>
<tr>
<td>o-xylene</td>
<td>(Me$_3$SiO)$_2$/AlCl$_3$(1:2)</td>
<td>22</td>
<td>(2,3) 38:(3,4) 45:(2,6) 17</td>
<td>0.0</td>
<td>2.4</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe$^{2+}$/H$_2$O$_2$</td>
<td>-</td>
<td>(2,3) 12:(3,4) 15</td>
<td>73</td>
<td>0.1</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Bu$^t$OOH/AlCl$_3$(1:2)</td>
<td>41</td>
<td>(2,4) 83:(2,6) 15:(3,5) 2</td>
<td>0.0</td>
<td>∞</td>
</tr>
<tr>
<td>m-xylene</td>
<td>(Me$_3$SiO)$_2$/AlCl$_3$(1:3)</td>
<td>25</td>
<td>(2,4) 73:(2,6) 25:(3,5) 2</td>
<td>0.0</td>
<td>∞</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Fe$^{2+}$/H$_2$O$_2$</td>
<td>-</td>
<td>(2,4) 56:(2,6) 14:(3,5) 3</td>
<td>27</td>
<td>1.3</td>
</tr>
</tbody>
</table>

$^a$ The phenolic products were analysed by gas chromatography using, in the reactions involving o- and m-xylene a 25 m CP Wax 51 capillary column, and in the reactions involving p-xylene a 25m OV 1 capillary column.
**Similarities:** Ipso-hydroxylation occurs in both systems, as well as normal hydroxylation.

**Differences:** The significant difference between the two hydroxylating systems is the occurrence of 1,2-methyl-shift in the aluminium chloride/peroxide/xylene system, notably with p- and o-xylene, after ipso-hydroxylation. No such rearrangement occurs with Fenton's reagent, and the xylenes (Table XV). With Fenton's reagent the only consequence of ipso-hydroxy attack is dealkylation.

The 1,2-methyl shift in an ipso-arenium ion is facilitated by the relatively low energy of the transition state leading to the new arenium ion (a protonated cyclohexa-2,4-dienone) that can rearomatise by loss of a proton (equation 3) giving the rearranged product.

\[
\begin{align*}
\text{O} & \quad \text{P} \\
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array} & \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\end{align*}
\]

The new arenium cation (the protonated cyclohexa-2,4-dienone) (P), is of lower energy because of the stabilisation of its positive charge by the electrons from the oxygen atom; the positive charge of the arenium cation is dispersed to cover the oxygen atom itself. This stabilisation facilitates the 1,2-methyl migration occurring from intermediate (O) to intermediate (P); this is why the rearrangement occurs. The formation of (P) requires a lower energy of activation. An energy profile for the hydroxylation of p-xylene could be represented in the following diagram:
The methyl group migrates with two electrons, from the C-CH$_3$ bond, leading to the formation of the new arenium cation intermediate which is of low energy and which is stabilised by the electrons from the oxygen atom. This arenium cation then rearomatises by loss of a proton to give the rearranged product.

The kinetics of the reaction could be represented as follows:
Although the actual kinetics of this reaction were not studied due to the heterogenous nature of the reaction mixture and also because the reaction is exothermic, (the peroxide being added dropwise to a heterogenous mixture of xylene and aluminium chloride), it is not unreasonable to propose that the rate of reaction might be directly proportional to the concentration of the oxidising species (Rate $\propto [RO^\cdot]^n$).

The ipso-dealkylation reactions observed using Fenton's reagent presumably reflect the high energy of the transition states that would be involved if rearrangement occurred as compared with that involved in dealkylation by the same or another radical (equation 2).

If rearrangement were to occur as outlined in equation 2, there has first of all to be a homolysis of the C-Me bond of the hydroxycyclohexadienyl radical intermediate. Such homolysis would immediately lead to dealkylation and the formation of cresol.

Thus we can distinguish between hydroxylation reactions involving cations and radicals.
Proposed mechanisms for the hydroxylation of arenes by aluminium chloride/peroxide systems

(i) **Mechanism of hydroxylation using aluminium chloride/t-butylhydroperoxide system.**

The t-butoxy-cation (t-BuO\(^+\)) was suspected to be the electrophile in reactions involving t-butylhydroperoxide in the presence of aluminium chloride.\(^{(37)}\) The facility with which the t-butoxy-cation rearranges to the dimethylmethoxycarbenium ion has been demonstrated by G.A.Olah and co-workers\(^{(38)}\) in reactions of t-butylhydroperoxide with "magic acid" \(\text{FSO}_3\text{H} - \text{SbF}_5 \ (1:1) - \text{SO}_2\text{ClF}\) and of the trimethylcarbenium ion with ozone. The highly energetic oxenium ion (V) if it is formed would immediately rearrange
to the alkylated ketone (dimethylmethoxycarbenium ion) (VI).

Reaction between t-BuOOH and magic acid:\(^{(38)}\)

\[
\begin{align*}
\text{H}_3\text{C} - \text{C} - \text{O} - \text{OH} & \xrightleftharpoons[H^+]\text{ (Magic acid)} \xrightarrow{\text{H}_2\text{O}} \text{H}_3\text{C} - \text{C} - \text{O} - \text{H}_2
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{OH} + \xrightleftharpoons[H^+]{H_2O} \text{H}_3\text{C} = \text{O} - \text{CH}_3 + \text{H}_2\text{O}
\end{align*}
\]
In the above reaction, the intermediate carboxonium ions generated from the O-O cleavage reactions were examined by $^{13}$C-NMR spectroscopy. The use of super acid media enabled direct observation of the carbo-cationic intermediates formed in the acid-catalyzed transformations of hydroperoxides.

In view of the facility with which the free t-butoxy-cation rearranges, we propose the following mechanism for hydroxylation reactions involving t-butylhydroperoxide and aluminium chloride:

Aluminium chloride co-ordinates with an oxygen atom and causes polarization of the O-O bond thus facilitating a nucleophilic attack by the arene (as shown above). A highly polarized peroxide-catalyst complex undergoing nucleophilic attack is more likely than the intermediacy of the unstable free t-butoxy-cation.

The crude neutral fraction obtained from the above reaction was not examined in detail but an NMR analysis showed a singlet for the t-butyl group at about $\delta 1.25$; the signal for the two methyl groups of the xylene was split and occurred around $\delta 2.25$; the aromatic protons occurred around $\delta 7.0$. From these data it could be inferred that
t-butylated-xylenes could have been formed during the reaction, probably at the stage indicated in the above mechanism.

(ii) Mechanism of hydroxylation using dibenzylperoxydicarbonate and aluminium chloride

The following mechanism is envisaged:

Presumably, aluminium chloride co-ordinates with a carbonyl oxygen and causes polarisation of the O-O bond followed by a nucleophilic attack by the aromatic substrate to form the arenium cation intermediate which rearomatises by loss of a proton. There is evolution of carbon dioxide during the work up upon the addition of dilute acid, and the above mechanism could explain its formation.
The crude neutral fraction obtained from the reaction was not examined in detail. However, the NMR spectrum showed a split signal between about $\delta 2.15 - 2.25$ for the methyl hydrogens; a multiplet occurred between about $\delta 6.7 - 7.3$ for the aromatic protons. The integration of the two regions appeared to be the same. Could this mean that benzylated xylene was formed? In the above equation it was indicated that $\text{Ar-CH}_2\text{Ph}$ could be formed by the mechanism shown. There is no definitive information on this point at present.

(iii) Mechanism of hydroxylation using $\text{di-t-butyldiperoxycarbonate}$ and aluminium chloride.

Presumably, aluminium chloride co-ordinates with the carbonyl oxygen thus causing polarisation of an $\text{O-O}$ bond followed by a nucleophilic attack by the arene to form the arenium cation intermediate which rearomatises by loss of a proton to give the oxygenated product.
The above scheme is a rationalisation of the chemical reactions leading to the formation of the phenolic products. There is evolution of carbon dioxide during the work up upon the addition of dilute acid, and the above mechanism could explain its formation. The crude neutral fraction obtained from the reaction was not examined in detail. However, the NMR spectrum showed a singlet at about $\delta 1.25$ for the t-butyl group; the signal for the two methyl groups of the xylene was split and occurred around $\delta 2.25$; the aromatic protons occurred around $\delta 7.0$. It could be inferred from these chemical shift data that t-butylated-xlenes could have been formed during the reaction, probably at the stage indicated in the above proposed mechanism.

iv) Mechanism of hydroxylation using bis(trimethylsilyl) peroxide and aluminium chloride.

As shown above, aluminium chloride co-ordinates with an oxygen atom and causes polarisation of the $O-O$ bond followed by a nucleophilic attack by the arene to form the arenium cation intermediate which rearomatises by loss of a proton.
The crude neutral fraction obtained from the above reaction was not examined in detail. However, the NMR spectrum showed a signal at almost $\delta 0.0$ due to the trimethylsilyl hydrogens; a signal around $\delta 2.25$ due to the methyl protons of xylene and a signal around $\delta 7.0$ due to the aromatic protons.

All the chemical shifts quoted are approximations.

The signal due to the trimethylsilyl group could be due to the presence of hexamethyldisiloxane which could be formed as follows:

\[
\begin{align*}
\text{Ar}-\text{O-SiMe}_3 & \rightarrow \text{ArOH} + \text{Me}_3\text{SiOH} \\
\text{H}_2\text{O}^+ & \downarrow \\
(\text{Me}_3\text{Si})_2\text{O}
\end{align*}
\]

2.3 Hydroxylation of p-xylene with t-butylhypochlorite, t-butylchloroperformate and silver salts

In order to establish whether it is possible to generate the t-butoxy-cation and use it as a t-butoxylating agent it is clear that methods other than that originally suggested (i.e. using Lewis acids and t-butylhydroperoxide), should be found. The alternative modes of reaction of the system t-butylhydroperoxide-aluminium chloride (see page 65)
means that the mechanism of reaction of this system with arenes is ambiguous.

We considered the reaction between t-butylhypochlorite and silver salts, such as silver hexafluoroantimonate and silver trifluoromethane sulphonate, as potential routes to the t-butoxy-cation. Reactions between t-butylchloroperformate and silver salts were also considered as potential routes to the t-butoxy-cation. The principles underlying the use of these reagents are as follows:

(i) \( t\text{-BuO-Cl} \xrightarrow{\text{Ag}^+} [t\text{-BuO}^+] \xrightarrow{\text{ArH}} \text{ArOBu-t} \)

\[ \text{ArH} \]

\[ \text{AgCl} \downarrow \]

(ii) \( t\text{-BuO-O} \xrightarrow{\text{Ag}^+} [t\text{-BuO}^+] + \text{CO}_2 + \text{AgCl} \downarrow \)

\[ \text{ArH} \]

\[ \text{ArOBu-t} \]

(iii) \( t\text{-BuO - Cl} \xrightarrow{\text{AgCl}_{3}\text{SO}_3^-} t\text{-BuO} \xrightarrow{\text{ArH}} t\text{-BuO} - \text{SO}_2\text{CF}_3 + \text{AgCl} \downarrow \)

\[ \text{ArH} \]

\[ \text{ArOBu-t} + \text{CF}_3\text{SO}_3^- \]
These principles were tested but in no case was significant hydroxylation observed. The explanation could be that, if the t-butoxy-cation is formed at all it immediately rearranges to the dimethylmethoxycarbenium ion (VI) as shown below:

Two mechanisms are suggested above. In mechanism (a) it is assumed that the t-butoxy-cation is formed transiently and it rearranges rapidly to the dimethylmethoxycarbenium ion. Mechanism (b) shows a concerted mechanism for the formation of the dimethylmethoxycarbenium ion and silver chloride. This concerted mechanism (b) is more likely to occur than the formation of the energetically unstable t-butoxy-cation.
The dimethylmethoxycarbenium ion formed could then react with dilute acid, during the work up, to give acetone and methanol.

2.4 Hydroxylation of o-, m-, and p-xylenes using models of hydroxylase biocatalysts.

Interest in devising chemical models for oxygenases is two-fold: first, to provide a basis for understanding enzymatic oxidations and, second, to develop simple catalytic systems that can emulate the high selectivity under mild conditions characteristic of enzymatic oxidations.

Much of the work on model systems was stimulated by the observation of Udenfriend and co-workers (73) in 1954 that a mixture of Fe$^{2+}$, EDTA, ascorbic acid and molecular oxygen could hydroxylate arenes to phenols under mild conditions.

Another chemical model system that hydroxylates arenes consists of Fe$^{3+}$, hydrogen peroxide and catechol or hydroquinone. (74)

Our aim was to use these chemical model systems to hydroxylate the xylenes and to investigate the isomer distributions of the phenolic products in order to ascertain the involvement of either cationic or radical mechanisms by comparison with results to be obtained using established free-radical hydroxylating agents.

The isomer distributions of the phenolic products obtained are summarised in table XVI below:
Table XVI

Hydroxylation of o-, m-, and p-xlenes using chemical models of hydroxylase biocatalysts.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent and conditions</th>
<th>Isomer distribution of Xylenols a</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, air</td>
<td>(2,5) - Major: (2,4) - Trace</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, N₂</td>
<td>(2,5) - Major: (2,4) - Trace</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, N₂, 37°C</td>
<td>(2,5) - Major: (2,4) - Trace</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Fe³⁺/hydroquinone/H₂O₂, air</td>
<td>(2,5) - Major: (2,4) - Trace</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Fe³⁺/hydroquinone/H₂O₂, N₂</td>
<td>(2,5) - Major: (2,4) - Trace</td>
</tr>
<tr>
<td>p-xylene</td>
<td>Fe²⁺/EDTA/Ascorbic Acid/O₂, 37°C</td>
<td>(2,5) - Major: (2,4) - Trace</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, air</td>
<td>(3,4)73 : (2,3)27 : (2,6) &lt;0.5</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, N₂</td>
<td>(3,4)55 : (2,3)45 : (2,6) &lt;1.0</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, N₂, 37°C</td>
<td>(3,4)63 : (2,3)36.5 : (2,6)0.5</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe³⁺/hydroquinone/H₂O₂, air</td>
<td>(3,4)68 : (2,3)32 : (2,6) &lt;0.5</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe³⁺/hydroquinone/H₂O₂, N₂</td>
<td>(3,4)61 : (2,3)38.5 : (2,6)0.5</td>
</tr>
<tr>
<td>o-xylene</td>
<td>Fe²⁺/EDTA/Ascorbic Acid/O₂, 37°C</td>
<td>(3,4)66.7 : (2,3)32.5 : (2,6)0.8</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, air</td>
<td>(2,4)64 : (2,6)31 : (3,5)5</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, N₂</td>
<td>(2,4)63 : (2,6)30 : (3,5)7</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Fe³⁺/Catechol/H₂O₂, N₂, 37°C</td>
<td>(2,4)59 : (2,6)31 : (3,5)10</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Fe³⁺/hydroquinone/H₂O₂, air</td>
<td>(2,4)66 : (2,6)31 : (3,5)3</td>
</tr>
<tr>
<td>m-xylene</td>
<td>Fe²⁺/EDTA/Ascorbic Acid/O₂, 37°C</td>
<td>(2,4)67 : (2,6)30 : (3,5)3</td>
</tr>
</tbody>
</table>

a The phenolic products were analysed by gas chromatography, using in the reactions involving o- and m-xylene a 25m CP wax 51 Capillary column, and in reactions involving p-xylene a 25m OV1 Capillary column.
Inspection of the phenolic products obtained from p- and o-xylene (especially o-xylene) revealed some interesting features.

p-Xylene gave some 2,4-xylenol (trace amount) and o-xylene gave 2,6-xylenol (<1%). Although not much rearranged product was formed it can still be said that some 1,2-methyl shift occurred during the hydroxylation of o-xylene. The recovered xylene showed no isomerization. Thus the formation of 2,6-xylenol could be explained as follows: that during the hydroxylation process, ipso-hydroxylation occurred followed by alkyl migration in an ipso-arenium ion type intermediate which then rearomatises by loss of a proton (see equation 4), although the possibility that arene oxides are involved should not be ruled out.

Possible mechanisms involving arene oxides in the formation of the xylenols obtained from o-xylene are as follows:

(i) Formation of 3,4-xylenol:

The epoxide ring can also open in the other direction after protonation to give 2,3-xylenol.
(ii) Formation of 2,3-xylenol:

Ring opening after protonation of the arene oxide (shown above) could lead to two successive methyl shifts through two arenium cation intermediates with the final loss of a proton to give 2,3-xylenol.

On the other hand the protonated epoxide could open as follows: to form the arenium cation intermediate which rearomatises by loss of a proton to give 2,3-xylenol.
(iii) Formation of 2,6-xylenol:

The ring opening as shown above leads to the formation of the ipso-arenium cation intermediate which undergoes 1,2-intramolecular methyl shift to form the new arenium cation (a protonated cyclohexa-2,4-dienone) that rearomatises by loss of a proton to give 2,6-xylenol.

The active oxidant in these reactions is suggested to be an electrophilic species. These reactions involve oxygen atom transfer reactions that resemble the heterolytic oxidations of aromatic substrates by electrophilic metal-peroxide complexes. Thus there appears to be the activation of molecular oxygen or hydrogen peroxide to some form of an electrophilic species.

2.5 Attempted synthesis of t-butylperoxytris(dimethylamino)phosphonium hexafluorophosphate.

\[ \text{t-BuOO P} \left( \text{NM}_2 \right)_3 \text{PF}_6^- \]

It is known that tris-dimethylaminophosphine reacts with N-chloroamines such as N-chlorodi-isopropylamine, to afford the P-chloro salt:

\[ (\text{Me}_2\text{N})_3\text{P} + \text{R}_2\text{NCl} \xrightarrow{\text{5}} (\text{Me}_2\text{N})_3\text{PCl} \text{R}_2\text{N}^- \]
Reactions of such salts with a range of nucleophiles are well known from the work of Castro and his collaborators (96) which were developed from the original observation made by Downie and co-workers (97,98) on the reactions of alcohols with tris-dimethylaminophosphine and carbon tetrachloride:

\[
\begin{align*}
\text{R}_3\text{P} + \text{Cl}-\text{CCl}_3 & \rightarrow \text{R}_3\text{PCl} + \text{CCl}_3 \\
\text{RCH}_2\text{OH} + \text{CCl}_3 & \rightarrow \text{RCH}_2\text{O} + \text{CHCl}_3 \\
\text{RCH}_2\text{O}^- + \text{PR}_3^- & \rightarrow \text{R} - \text{CH}_2 - \text{O}^- \text{PR}_3 \\
& \rightarrow \text{R} - \text{CH}_2\text{Cl} + \text{R}_3\text{P} = \text{O}
\end{align*}
\]

We hoped that a similar sequence would allow the isolation of \textit{t}-butylperoxytris (dimethylamino)-phosphonium hexafluorophosphate (XVII), especially since salts of type (A) can be isolated.

In one such attempt to synthesise compound XVII, the following reaction sequence was envisaged, using \textit{N}-chloro-benzotriazole, tris-dimethylamino-phosphine, sodium \textit{t}-butylperoxide and ammonium hexafluorophosphate:

\[
\begin{align*}
\text{Cl} + (\text{Me}_2\text{N})_3\text{P} & \rightarrow (\text{Me}_2\text{N})_3\text{Cl} + \text{Cl} \\
\text{tBuOO}^-\text{Na} & \rightarrow \text{tBuOO-P(NMe}_2)_3\text{PF}_6 \\
& \leftrightarrow \text{tBuOO-P(NMe}_2)_3\text{PF}_6
\end{align*}
\]
However, it appears the following reaction occurred:

\[
\text{leading to the formation of } N\text{-benzotriazo-tris(dimethylamino)phosphonium hexafluorophosphate (XVIII) (12.5%).}
\]

\[
13C - NMR (CDCl}_3/DMSO}_d6) : \begin{align*}
3_j_{pc} &= 0.3H_Z \\
\delta &= 145.9 \end{align*}
\]

\[
2_j_{pc} = 9.9H_Z \quad \delta &= 134.4 \end{align*}
\]

\[
2_j_{pc} = 4.4H_Z \quad \delta &= 37.5 \end{align*}
\]
The following reaction sequence is proposed for the preparation of salts of the type of compound (XVII) \((t-\text{BuO}^+\text{Pr}^-\text{NMe}_2)_3\text{PF}_6^-\):

\[
\begin{align*}
R & \quad P: + \quad iPr \quad N - Cl \\
t-BuO & \quad O
\end{align*}
\]

\[
\begin{align*}
R & \quad P \quad \Phi \\
t-BuO & \quad O
\end{align*}
\]

The above compound (XVIV) could then be tested as a potential hydroxylating agent:

\[
\begin{align*}
R & \quad P \quad \Phi \\
t-BuO & \quad O
\end{align*}
\]

\[
\begin{align*}
R & \quad P \quad N(Pr_1)_2\text{PF}_6^- \\
t-BuO & \quad O
\end{align*}
\]

\[
\begin{align*}
ArH & \quad \Delta \\
& \quad \rightarrow \\
ArOBu^+ + R_3P & = O + H^+
\end{align*}
\]

If a compound such as (XVIV) can be prepared and if it can prove to be an effective mild hydroxylating agent for arenes, then it could serve as a basis for developing and designing hydroxylating or alkoxylation reagents of that type.
2.6 Acetylation of p-Xylene

It has been assumed in the past that some rearrangements precede attack on the acylating agent and afford the thermodynamically more stable m-disubstituted benzene derivatives which are themselves more reactive towards acetylation. Thus the acetylation of m- and p-xylene using acetyl chloride and aluminium chloride in 1, 2-dichloroethane at 25°C proceed at relative rates compared with benzene of 347 and 23.5 respectively. Although p-xylene reacts with acetyl chloride and aluminium chloride in carbon disulphide to afford 2,5-dimethylacetophenone, at higher temperatures using an excess of p-xylene the only product is 2,4-dimethylacetophenone.

We also intended to re-investigate the above reaction in order to establish the sequence of events leading from p-xylene to 2,4-dimethylacetophenone.

Experiments were performed in which the sequence of addition of the reactants namely p-xylene, aluminium chloride and acetyl chloride was varied. The sequence of addition and the results obtained were as follows:

Expt.1 CS₂ + AlCl₃ + CH₃COCI → CH₃COCI·AlCl₃ + p-xylene

A ratio of AlCl₃ : CH₃COCI of 1:1 was used in all reactions.

In the above reaction, aluminium chloride and acetyl chloride were mixed in carbon disulphide followed by the gradual addition of p-xylene. The only product obtained (as shown by glc) was 2,5-dimethylacetophenone, (55.5% yield) bp 74-76°C (Lit : 80-85°C);

IR (Nujol) cm⁻¹ : 1680 (C = O)

N,MRI(CDCl₃) δ 6.95 - 7.5 (3 Aromatic protons) δ 2.15 - 2.7 (3-methyls)

Analysis of the recovered p-xylene showed no isomerization.
Exp. (2):

In this experiment aluminium chloride was added portionwise to a mixture of p-xylene, acetyl chloride and carbon disulphide.

\[
\text{Ph} + \text{CH}_3\text{COCl} + \text{CS}_2 \xrightarrow{\text{AlCl}_3} \text{PhCOCH}_3
\]

The only product obtained was 2,5-dimethylacetophenone (53% yield).

Analysis of the recovered p-xylene showed no isomerization.

Exp. (3):

In the third experiment acetyl chloride was added gradually to a mixture of p-xylene, aluminium chloride and carbon disulphide.

\[
\text{Ph} + \text{AlCl}_3 + \text{CS}_2 \xrightarrow{\text{CH}_3\text{COCl}} \text{PhCOCH}_3 + \text{PhCOCH}_3
\]

% Ratio : 93 : 7

In this reaction two products were obtained namely 2,5-dimethylacetophenone and 2,4-dimethylacetophenone in a ratio of 93:7 respectively. Analysis of the recovered p-xylene showed some isomerization of p-xylene to m-xylene.

This isomerization occurred because of the presence of HCl gas (generated during the acetylation reaction), and of excess catalyst during the gradual addition of acetyl chloride. Thus the 2,4-dimethylacetophenone was formed directly from m-xylene which had been formed by the isomerization of p-xylene.
Inspection of the products of the above reactions shows that carrying out acetylation reactions by the procedures outlined in experiments (1) and (2) would ensure that the starting aromatic substrates do not isomerise.

**Mechanism of acylation**

Friedel-crafts acylation exhibit a duality of mechanism as shown on p. 36.
At one extreme a free acylium ion is involved while at the other end of the spectrum the arene attacks the (1:1) RCOCl. AlCl₃ complex directly. The product in either case, is co-ordinated to aluminium chloride which upon hydrolysis liberates the aryl ketone.
3. EXPERIMENTAL

3.1 Hydroxylation of o-, m-, and p-xylene by Fenton's reagent

Materials: o-xylene, m-xylene, p-xylene, ferrous sulphate were Anal. reagents. The xylenes were each analysed by glc and found to be pure. 30% H₂O₂ was analysed by iodometry before use.

Aromatic Hydroxylations: General Procedure: Reactions were carried out in air at room temperature.

A suspension of the xylene (25ml) in 0.4N sulphuric acid (500ml) containing ferrous sulphate (6.7g, 0.024 mol). was vigorously stirred while diluted (1 : 15) 100 - volume hydrogen peroxide (62.5 ml, 1.25g, 0.037 mol) was added during a period of 15 secs. After 15 mins the reaction mixture was extracted repeatedly with ether, washed with water, dried over anhydrous MgSO₄ and then the ether and much of the solvent were distilled off under reduced pressure. The remaining liquid was extracted by refluxing with 40 ml of 10% sodium hydroxide solution for 1 hr. After cooling, the reaction mixture was extracted thoroughly with ether to remove neutral substances. The alkaline aqueous layer was then acidified with concentrated hydrochloric acid solution and extracted repeatedly with ether. The combined ether extract was washed with water, dried over anhydrous MgSO₄ and the solvent is distilled under reduced pressure.

The residue obtained was then mixed with 5 ml of 10% sodium bicarbonate solution to remove any carboxylic acids. The whole mixture was then extracted repeatedly with ether to re-extract the phenolic compounds. The combined ether extract was washed with water, dried over
anhydrous MgSO\textsubscript{4} and the ether distilled off under reduced pressure to a small volume which was then analysed by gas-liquid-chromatography.

The aqueous sodium bicarbonate extract was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with water, dried over anhydrous MgSO\textsubscript{4} and the ether distilled off. To the residue was added 15ml methanol, containing concentrated sulphuric acid (4 drops), and refluxed on a water bath for 40 mins. The excess alcohol was distilled off and 15ml of water added and the mixture shaken in a separating funnel with 25ml ether. The two layers were separated and the ether extract was shaken with dilute sodium bicarbonate solution to neutralize the sulphuric acid. The ethereal extract was then washed with water, dried over anhydrous MgSO\textsubscript{4} and distilled to a small volume which was then analysed by glc.

**Analytical Procedures:**

(i) **Xylenes:** The xylenes were analysed by gas-liquid chromatography using the following column and conditions:

- **Stationary phase:** 5% Bentone, 5% didecyl phthalate
- **Support:** Chromosorb W 100/120 mesh.
- **Temperature:** 75°C
- **Carrier gas:** Nitrogen (40 ml/min)
- **Detector:** FID
- **Instrument (Chromatograph):** PYE series 104 chromatograph coupled with a w + w recorder 600 (TARKAN).

(ii) **Phenolic products:** (a) The phenolic products obtained from o-, and m-xylenes were analysed using the following column and conditions:

- **Column:** FFAP (SCOT) Glass Capillary Column,
  Number of plates (N) about 35,000;
- **Carrier gas:** Helium (3ml/min) make-up gas, Nitrogen (40ml/min).
(b) The phenolic products obtained from p-xylene were analysed using the following:

**Column**: OVI (Dimethylsilicone) Capillary column (25m x 0.3mm ID), film thickness 0.17μm

**Carrier gas**: Helium

**Temperature**: Program 35°C → 45°C at 0.5°C/min; Hold at 45°C for 5 mins; Program 45°C → 70°C at 2°C/min.

**Detector**: FID

**Chromatograph**: Carlo Erba Strumentazione, Fractovap Series 2150, coupled with an RE 511.20 Potentiometric Recorder (venture).

**Chart speed**: 1cm/min.

(iii) **Esters**: The esterification products were analysed using the FFAP capillary column. Temperature used was 125°C (isothermal).

**Product Identification**: Products were identified first by comparison of retention times with those of authentic standards and, secondly (most importantly), by peak enhancement technique with the authentic standards.
3.2 Catalytic Aromatic Hydroxylation

3.2.1 Hydroxylation of o-, m-, and p-xylenes using a range of peroxides and Lewis Acid catalysts.

Materials: o-xylene, m-xylene, p-xylene, t-butylhydroperoxide, dibenzylperoxydicarbonate, di-t-butyldiperoxycarbonate, bis (trimethyl silyl) peroxide, aluminium chloride (powdered), and titanium tetrachloride (distilled before use). All reagents used were of high purity.

(i) Preparation of t-butylhydroperoxide (80) (t-BuOOH)

t-Butylhydrogen sulphate was prepared by adding, at 5°C, 74g (1 mole) of t-butylalcohol (freshly distilled) to 140g (1 mole) of 70% sulphuric acid. To this mixture was then added at 0-5°C with stirring 126g (1 mole) 27% hydrogen peroxide in the course of thirty minutes. The ice-bath was then removed and the mixture allowed to stand overnight at room temperature. The mixture had separated into two layers, and the organic layer (the upper layer) was removed, neutralized with a suspension of magnesium carbonate in 10ml of water, then washed with 20ml of water and dried over anhydrous magnesium sulphate. Yield of the crude product was 74g which was fractionally distilled to give 43.5g (48% yield) of t-butylhydroperoxide (b.p. 26-28°C;

Lit: 80 bp 26-28°C; 

IR (neat) 3400cm⁻¹ (OH, broad and strong), 850cm⁻¹ (O=O stretch).

NMR (CDCl₃/TMS) : δ 8.23 (singlet, OH) δ 1.28 (singlet, (CH₃)₃⁻)
(ii) (a) Preparation of benzyl chloroformate $^{(81)}(\text{PhCH}_2\text{OCCl})$

Dry diethyl ether (100ml) was placed in a 250ml 3-necked round-bottomed flask, and the flask and its contents were weighed and then cooled in an ice/salt bath. Phosgene was bubbled through the ether till about 35g (0.35mol) had been absorbed. Then benzyl alcohol (freshly distilled) (27g, 0.25mol) was added slowly from a dropping funnel with stirring. After the addition, the flask was allowed to stand in the ice-salt bath for 30 minutes with stirring, and then at room temperature for one and half hours. The reaction mixture was washed with 3 x 100ml water, dried over anhydrous CaCl$_2$ and the ether and any excess phosgene distilled off under reduced pressure, while heating at 30°C on a waterbath. The yield of product was 38g (89%).

Benzyl chloroformate cannot be purified by distillation. $^{82}$

IR Spectrum (Neat): 1780cm$^{-1}$ (C=O stretch);

NMR ($\text{CDCl}_3$): $\delta$ 7.35 (singlet, 5 aromatic protons) $\delta$ 5.25 (singlet, 2 methylene protons)

(b) Preparation of dibenzyl peroxydicarbonate $^{81}(\text{PhCH}_2\text{OOC}-\text{O-COCH}_2\text{Ph})$

A sodium peroxide solution was prepared by adding 27.4 (0.2mol) of 30% $\text{H}_2\text{O}_2$ hydrogen peroxide (analyzed iodometrically before use) to a cooled solution of 17.6g (0.44mol) of sodium hydroxide in 120ml water, keeping the temperature in the range 10-15°C. Some solid sodium peroxide octahydrate separated out (addition of about 50ml water dissolved the precipitate). The sodium peroxide solution was then added slowly through a dropping funnel to 68g (0.4mol) of vigorously stirred benzyl chloroformate, cooling with an ice/salt mixture and adjusting the rate of addition so
that the reaction temperature was maintained at 6 to 10°C. Stirring was continued for 30 minutes after all of the sodium peroxide solution had been added.

The white precipitate which had formed was filtered off and was then dissolved in chloroform. The chloroform solution was washed with 2 x 100ml cold distilled water, then dried over anhydrous sodium sulphate and distilled under reduced pressure. A white "oily" precipitate was obtained, and 50ml dry ether was then added and filtered. A fine powder was obtained which was further mixed with ether and filtered again. The product was air-dried for a while and then placed in a vacuum desiccator. The dibenzyl peroxydicarbonate was obtained as white powdery crystals, (27g, 45% yield)

m.p.t. = 97 - 100°C (dec.with gas evolution)

Lit. 81 : Mpt.101 - 102°C dec.; Lit 83 : 99 - 100 dec.with gas evolution

IR (Nujol) : 1750 - 1800 cm\(^{-1}\) (C=O)

NMR(CDCl\(_3\)) : \(\delta\) 7.35 (s, 10 aromatic protons)

\(\delta\) 5.28 (s, 4H, 2CH\(_2\))

\(^{13}\)C-NMR:

1. 153.2
2. 75.6
3. 133.7
4. 128.9
5. 128.7
6. 129.3

Active Oxygen content >97%, by iodometric titration
(iii) **Preparation of di-**-**t-**-**butyl** diperoxycarbonate \( ^{81,84} (t-\text{BuOO})_2 \) **(t-BuOO)OOCB**

A solution of phosgene (24g, 0.24mol) in 200ml dry ether was added at 0-5\(^\circ\)C during 2hrs. to a stirred solution of tert-butyl-hydroperoxide (38g, 0.42mol) in pyridine (49.8g, 0.63mol). After a further 60 mins, water was added and the ether layer was separated and thoroughly washed with 5% aqueous hydrochloric acid, and then with water until free from chloride ion. The ether solution was then dried over anhydrous magnesium sulphate, filtered and the ether distilled off under reduced pressure. The crude product obtained was distilled and the fraction boiling at bp\(_{0.5\text{mm}}\) 50 - 51\(^\circ\)C was collected.

(Lit \( ^{84} \): bp\(_{0.5\text{mm}}\) 54-55\(^\circ\)C). Yield was 20g (46%)

IR (Neat) : 3000 cm\(^{-1}\) (CH\(_3\) stretch), 1810cm\(^{-1}\) (C=O), 850cm\(^{-1}\) (O-O, stretch)

NMR (CDCl\(_3\)/TMS) : \( \delta H 1.32 \) (singlet,)

\( (\text{CH}_3)_2 \text{C}= \)

(iv) **Preparation of bis(trimethylsilyl) peroxide**. \( ^{85} \) \( (\text{CH}_3)_3 \text{SiO} \text{Si}(\text{CH}_3)_3 \)

A 250ml 3-necked round-bottomed flask was fitted with a mechanical stirrer, and 10ml ether was placed followed by 1.98g of 86% w/w H\(_2\)O\(_2\) (1.7g, 0.05mol). The flask was cooled in an ice-salt bath and 7.91g (0.1mol) pyridine in 80ml dry ether was added. The mixture was stirred while 10.86g (0.1mol) trimethylchlorosilane in 15ml ether was added over a period of 10mins., with the precipitation of pyridine hydrochloride. After stirring for a further 30 mins., the reaction mixture was allowed to warm up to room temperature over a period of 1hr and then
filtered. The filtrate was washed with water, dried over anhydrous magnesium sulphate and distilled under reduced pressure using a Claisen-Vigreux column distillation flask. The fraction boiling at bp_{5mm} 20-22^\circ was collected. (1.7g, 19\%). (based on chlorotrimethylsilane)

\textit{Lit}^{85} : bp_{30mm} 38^\circ

IR (Neat) : 3000 - 2900 cm\(^{-1}\) (CH\(_3\)-stretch),

850 cm\(^{-1}\) (O - O stretch)

N.M.R.(CDCl\(_3\)) : \delta 0.2 (singlet, (CH\(_3\))\(_3\) Si-)

3.2.1.1 Hydroxylation of xylenes with t-butylhydro-peroxide and Lewis acid Catalysts.

General Procedure:

A 100ml 3-necked round-bottomed flask was fitted with a thermometer, a pressure-equalising dropping funnel, and an inlet/outlet for nitrogen gas. Xylene (20ml) was placed in the flask and a slow stream of dry nitrogen gas was maintained through the flask. Then aluminium chloride (1.86g, 0.014 mol) was added into the flask and the mixture was stirred.

t-Butylhydroperoxide (0.65g, 0.007mol) dissolved in 10ml xylene was added dropwise over a period of 30 minutes at 20^\circ C. Stirring was continued for a further 2hrs. at 20^\circ C. Then a mixture of concentrated hydrochloric acid and water was added slowly, with stirring and cooling, to the reaction mixture. The mixture was shaken in a separating funnel and the two layers separated. The aqueous layer was extracted with some ether and the combined organic layer was washed with water, and extracted with 40ml of 10\% \(\text{NaOH}\) solution.
After cooling, the two layers were shaken and separated and the organic layer (containing the neutral fraction) was washed with some water. The combined alkaline aqueous extract was extracted thoroughly with ether to remove any neutral materials and was then acidified with concentrated hydrochloric acid, with cooling. A milky precipitate was obtained which was extracted repeatedly with ether. The combined ether extract was washed with water, dried over anhydrous MgSO₄ and the ether distilled off under reduced pressure. The phenolic residue obtained was analysed by glc (see analytical procedures).

Titanium tetrachloride was also used and the proportions were worked out accordingly.

Experiments were also conducted varying the ratio of catalyst to peroxide.

3.2.1.2 Hydroxylation of xylenes with bis(trimethylsilyl) peroxide and aluminium chloride.

General Procedure: A 100ml 3-necked round-bottomed flask was fitted with a thermometer, a pressure-equalising dropping funnel, and an inlet/outlet for nitrogen gas. Xylene (20ml) was placed in the flask and a slow stream of dry nitrogen gas was maintained in the flask. Then aluminium chloride* (3.6g, 0.027mol) was added and the mixture was stirred. Then bis(trimethylsilyl)peroxide (1.6g, 0.009mol) dissolved in 10ml xylene was added dropwise over a period of 30 mins. at 20°C and stirring continued for a further 2hrs. at the same temperature. A mixture of concentrated hydrochloric acid and water was added slowly, with stirring and cooling, to the reaction mixture. The mixture was then shaken

* (Experiments were also conducted varying the ratio of the catalyst to the peroxide)
in a separating funnel and the two layers separated. The aqueous layer was extracted with some ether, and the combined organic layer was washed with water, 2 x 100ml 4% sodium bicarbonate solution, and water. The organic layer was then extracted with 40ml of 10% sodium hydroxide solution by refluxing for 1hr. After cooling, the mixture was shaken in a separating funnel and the two layers separated. The organic layer (containing the neutral fraction) was washed with a little water. The combined aqueous alkaline solution was then extracted thoroughly with ether, to remove any neutral materials, and was then acidified with conc. hydrochloric acid, with cooling. A milky precipitate was obtained which was extracted repeatedly with ether. The combined ethereal extract was washed with water, dried over anhydrous MgSO₄ and the ether distilled off under reduced pressure. The phenolic residue obtained was analysed by glc. (see analytical procedures).

3.2.1.3 Hydroxylation of xylenes with di-t-butyl-diperoxycarbonate and aluminium chloride.

General Procedure: A 100ml 3-necked round-bottomed flask was fitted with a thermometer, a pressure-equalising dropping funnel, and an inlet/outlet for nitrogen gas. Xylene (50ml) was placed in the flask and a slow stream of dry nitrogen gas was maintained through the flask. Then Aluminium Chloride (3.73g, 0.028mol) was added and the mixture stirred.

Di-t-butyl diperoxycarbonate (1.44g, 0.007mol) dissolved in 20ml aromatic (xylene) was added dropwise over a period of 15 minutes at 20°C. After stirring for a further 2hrs. a mixture of water and conc. hydrochloric acid was poured slowly into the reaction mixture with stirring and cooling. Evolution of gas (carbon dioxide) occurred. The mixture was shaken in a separating funnel and the two layers separated.
The aqueous layer was extracted with some ether, and the combined organic layer was washed with water, 1 x 100ml of 4% sodium bicarbonate solution, and with water again. The organic layer was then extracted with 40ml of 20% sodium hydroxide solution boiling under reflux for 1hr. After cooling, the mixture was shaken in a separating funnel and the two layers separated. The organic layer (containing the neutral fractions) was washed with a little water, and the combined aqueous alkaline extract was extracted thoroughly with ether to remove any neutral substances, and was then acidified with concentrated hydrochloric acid, with cooling. A milky precipitate was obtained which was extracted repeatedly with ether. The combined ether extract was washed with water, dried over anhydrous MgSO₄, and the ether distilled off under reduced pressure. The phenolic residue was analysed by glc.

3.2.1.4. Hydroxylation of xylenes with dibenzylperoxydicarbonate and aluminium chloride.

General Procedure: The general procedure described above was used, with the following exceptions: Dibenzylperoxydicarbonate is not very soluble in the aromatics used and, therefore, it was added as a suspension in 50ml xylene into a mixture of 20ml xylene and aluminium chloride. The ratio of aluminium chloride to dibenzylperoxydicarbonate was 2:1 respectively, or varied as to the particular investigation.

Analytical Procedures:

(i) Xylenes: The xylenes were analysed using the column mentioned under Fenton's reaction.
(ii) **Phenolic products:** The phenolic products from reactions involving o-, and m-xylenes were analysed using:

**Column:** CP wax 51 capillary column (WSCOT) (CHROMPACK) 25m x 0.5mm (id):

Number of theoretical plates (N) : 37,500

Carrier gas: He (3ml/min); N₂ make up gas, 40ml/min.

Temperature: Hold at 120°C for 35 mins; then programmed, 120°C - 175°C at 1.5°C/min.

Detector: FID

Chart Speed: 0.5cm/min.

Chromatograph: PYE Series 104 chromatograph coupled with a w+w Recorder 600 (TARKAN) gave a linear response.

Phenolic products from reactions involving p-xylene were analysed using the 25m OV1 capillary column (see details under analytical procedures under Fenton's reaction).

(iii) **Product Identification:** Products were identified first by comparison of retention times with those of authentic standards and, secondly (and most importantly), by peak enhancement technique with the authentic standards.

3.2.2. **Hydroxylation of p-xylene with t-butylhypochlorite, t-butylchloroperformate and silver salts.**

**Materials:** p-xylene, t-butylhypochlorite, t-butylchloroperformate, silver trifluoromethane sulphonate and silver hexafluoroantimonate (the silver salts were used directly as supplied by the Aldrich chemical Co.Ltd.).

All reagents used were of high purity.

* **NB:** The FFAP Capillary column mentioned earlier was also used to analyse these phenols with similar results.
Preparation of t-butylhypochlorite

A 3-litre 3-necked round-bottomed flask was fitted with a thermometer, a mechanical stirrer and an inlet-outlet for gas. A solution of 80g (2 mol) of sodium hydroxide in 500ml of water was placed in the flask, and 74g (1mol) of t-butyl alcohol was added, followed by sufficient water (about 500ml) to give a homogeneous solution. The flask was cooled in an ice water bath, and chlorine gas was passed steadily into the solution, with stirring. The chlorine gas was passed through the solution till no more gas was absorbed and the greenish-yellow colour of chlorine became visible in the flask, and the solution had become yellow; then the gas was passed slowly for a further 15 minutes. The temperature of the reaction mixture was kept below 20°C throughout the addition.

The reaction mixture was transferred to a separating funnel and the lower aqueous phase was discarded. The upper yellow layer was washed with 50ml portions of 10% sodium carbonate solution until the washings were no longer acidic to congo red indicator. Finally the product was washed three times with 50ml cold water and dried over anhydrous calcium chloride. Yield was 93g (85.8%). (According to the literature, the yield of t-butylhypochlorite, which is usually about 98% pure, is 74-92%)

The product was stored in a stoppered dark bottle in the cold.

N.M.R. (CDCl₃) : δ1.3 (singlet, \((\text{CH}_3\))₃\text{C}⁻)

Preparation of t-butylchloroperformate

A 50ml 3-necked round-bottomed flask was fitted with an inlet/outlet for gas. t-Butylhydroperoxide (1.35g, 0.015mol) was placed in the flask and cooled in an ice/salt bath. Phosgene gas (COCl₂) was
passed slowly through the t-butylhydroperoxide till about 1.7g of phosgene had been absorbed. The reaction mixture was then allowed to warm up to room temperature during 90 mins. Excess phosgene and HCl were driven off under reduced pressure.

Wt. of produce was 1g (43.8%)

IR(Neat) : 3000 - 2900 (CH₃ stretch)

1820 cm⁻¹ (C=O stretch, strong)

N.M.R.(CDCl₃) : 1.32 ( (CH₃)₃ C-, singlet)

3.2.2.1 Hydroxylation of p-xylene using t-butylhypochlorite and silver salts.

General procedure:

A 100 ml 3-necked round-bottomed flask was fitted with a thermometer and an inlet/outlet for dry nitrogen gas. The flask was covered with aluminium foil, 20ml of p-xylene was added and a slow stream of dry nitrogen gas was maintained in the flask. Then silver trifluoromethane sulphonate (1.285g, 0.005mol) was added and the mixture was stirred. t-Butylhypochlorite (0.55g, 0.005mol) dissolved in 5ml p-xylene was added drop wise over a period of 10 minutes at 20°C, and stirring continued for a further 4 hrs. A mixture of conc.HCl and water was added, stirred and filtered, to remove the white precipitate. The organic and aqueous layers were shaken together in a separating funnel and separated. The aqueous layer was extracted with ether and the combined organic layer washed with water, dried over anhydrous MgSO₄, filtered and much of the excess solvents distilled off under reduced pressure. A pale yellow liquid residue was obtained which was extracted with 20ml of 20% sodium hydroxide solution by refluxing for 1hr.
After cooling, the aqueous alkaline layer was separated. The organic layer was washed with 2 x 10 ml 10% sodium hydroxide solution and the combined alkaline aqueous extract was thoroughly extracted with ether and then acidified with concentrated hydrochloric acid. The mixture was then extracted repeatedly with ether, washed with water, dried over anhydrous MgSO₄ and the ether distilled off under reduced pressure. The residue obtained was analysed by glc. (using FFAP Capillary Column).

(A similar procedure was used for t-butylchloroperformate and the silver salts mentioned earlier)

ISOMERIZATION STUDIES

(a) Xylenes (o-, m, and p-) (control experiments)

Procedure: A 100ml 3-necked round-bottomed flask was fitted with an inlet/outlet for nitrogen gas. Xylene (30ml) was placed in the flask and a slow stream of dry nitrogen gas was maintained through the flask. Aluminium chloride (1.86g, 0.014 mol) was added and the mixture was stirred for 2½ hrs. at 20°C. Then a mixture of water and conc. HCl was poured slowly into the reaction mixture, with stirring and cooling. The two layers were separated in a separating funnel and the aqueous layer extracted with ether. The combined organic phase was washed with water, dried over anhydrous MgSO₄ and the ether distilled off under reduced pressure. The remaining xylene was analysed by glc. (The recovered xylenes showed no isomerization).
(b) Xylenols (control experiments)

General procedure: A 100ml 3-necked round-bottomed flask was fitted with an inlet/outlet for nitrogen gas and a thermometer. 20ml xylene (o-, m-, or p-, depending upon the xylenol) was placed in the flask and aluminium chloride (1.86g, 0.014 mol) was added and stirred.

Xylenol (0.4g, 0.0033 mol) dissolved in 10ml xylene was added dropwise over a period of 30 minutes at 20°C, and stirring continued for a further 2 hrs. Then a mixture of conc.HCl and water was added slowly with stirring and cooling. The two layers were shaken in a separating funnel and separated. The aqueous layer was extracted with ether and the combined organic layer was washed with water, and extracted with 40ml of 10% sodium hydroxide solution by refluxing for 1 hr. After cooling, the two layers were shaken in a separating funnel and separated. The organic layer was washed with water and the combined aqueous alkaline extract was extracted thoroughly with ether to remove neutral material and was then acidified with conc.HCl, with cooling and stirring. The mixture was extracted repeatedly with ether, washed with water, dried (anhydrous MgSO₄) and the ether distilled off under reduced pressure.

The residue was then analysed by glc. (The recovered xylenols showing no isomerization).

3.3 Hydroxylation of o-, m, or p-xylenes, using Models of Hydroxylase Biocatalysts.

3.3.1 Hydroxylation of xylenes using hydrogen, peroxide, ferric ion, and catechol (or hydroquinone)

Materials All materials used were "Analar" grade. Melting points were checked where applicable.
o-, m, α-p-xylenes, ferric chloride hexahydrate, catechol, hydroquinone, 10% mol hydrogen peroxide (30%) (analysed before use).

Hydroxylations:

General procedure:

A 500 ml 3-necked round-bottomed flask was fitted with a mechanical stirrer. 250 ml of an acetate buffer solution (pH 4.6, 0.005 M) containing ferric chloride hexahydrate (0.0265 g, 9.8 x 10^{-5} mol), and catechol (0.0412 g, 3.7 x 10^{-4} mol) was added in the flask, followed by 20 ml of xylene.

The mixture was stirred vigorously while diluted (1 in 120) 100-volume hydrogen peroxide (62.5 ml, 0.156 g, 4.6 x 10^{-3} mol) was added. Vigorous stirring was continued for 2½ hrs after the addition at room temperature. The reaction mixture was then made more acidic by adding concentrated HCl and extracted repeatedly with ether. The combined ethereal extract was washed with water, then with 4% sodium bicarbonate solution, and water and then extracted with 40 ml of 20% sodium hydroxide solution by boiling under reflux for 1 hr. After cooling, the mixture was shaken in a separating funnel and the two layers were separated. The organic layer was washed with a little water and the combined alkaline aqueous layer was extracted thoroughly with ether, to remove any neutral materials, and was then acidified with concentrated hydrochloric acid. The mixture was then extracted repeatedly with ether, washed with water, dried over anhydrous MgSO_{4}, and the ether distilled off to a small volume which was then analysed by glc (using in the reactions involving o- and m-xylene 25 m CP Wax 51 Capillary Column).

* with reactions performed at 37°C, this mixture was allowed to equilibrate at 37°C, on a waterbath, before the hydrogen peroxide solution was added.
and in reactions involving p-xylene a 25m OVI Capillary Column; the conditions were the same as described elsewhere.

3.3.2 Hydroxylation of xylenes using oxygen, ferrous ion, EDTA, and L-Ascorbic acid.

Materials: o-, m-, p-xylene, ferrous sulphate (AnalaR), Ethylenediaminetetra-acetic acid disodium salt (EDTA), and L-ascorbic acid. All reagents used were of high purity.

Aromatic Hydroxylations:

General procedure: The system used for the production of the hydroxylated products consisted of 1.3mM of FeSO₄·7H₂O, 6.5mM of EDTA, 14mM of ascorbic acid and 20ml of xylene, in a volume of 250ml of 0.1m phosphate buffer pH 6.7. The mixture was allowed to equilibrate at 37°C and then oxygen was bubbled through it for 2 hours with vigorous stirring, using a mechanical stirrer. After the reaction period the mixture was made more acidic by adding conc. hydrochloric acid and extracted repeatedly with ether. The combined ethereal extract was washed with water, 4% sodium bicarbonate solution, water and then extracted with 40ml of 20% sodium hydroxide solution by refluxing for 1hr. After cooling, the mixture was shaken in a separating funnel and the two layers were separated. The organic layer was washed with a little water and the combined alkaline aqueous layer was extracted thoroughly with ether and was then acidified with conc. HCl. The mixture was extracted repeatedly with ether, washed with water, dried over anhydrous MgSO₄ and the ether distilled off to a small volume and analysed by glc.
3.4 Attempted synthesis of t-butylperoxytris (dimethylamino) - 
phosphonium hexafluorophosphate.

\[
t - \text{Bu} \quad \text{OO} \quad \text{P} + (\text{NMe}_2)_3 \quad \text{PF}_6
\]

Materials: Tris-(dimethylamino) phosphine (freshly distilled), 
N-chlorobenzotriazole, sodium t-butylperoxide, ammonium hexa-
fluorophosphate.

(i) Preparation of N-Chlorobenzotriazole

A mixture of 17.85g (0.15mol) of benzotriazole in 800ml dry ether 
was cooled to 0°C in an ice/salt bath. t-Butylhypochlorite (17.9lg, 
0.165mol) was added rapidly and stirred for 2 hrs. The ether was dis-
tilled off under reduced pressure. A white crystalline precipitate 
was obtained and was re-crystalised from ethylacetate to give 19g 
(82%) of N-Chlorobenzotriazole. (m.pt. = 105 - 108°).

(Iodometric titration showed 99% active chlorine content)

(ii) Preparation of sodium t-butylperoxide

Toluene (60ml) was placed in a round-bottomed flask and sodamide 
(1.3g, 0.033mol) was added and stirred. Then t-butylhydroperoxide (3.5g, 
0.038mol) was added and stirring continued for 14 hrs. The mixture 
was filtered and the residue was washed thoroughly with dry ether, and 
dried in a vacuum desiccator (wt = 3.8g, 95%).

Available oxygen content = 14.2% \( w / w \).

(Iodometric titration)

Theoretical oxygen content = 14.3% \( w / w \).

3.4.1 The attempted preparation of t-butylperoxy-tris(dimethylamino) 
phosphonium hexafluorophosphate.

A solution of N-Chlorobenzotriazole (5.2g, 0.034mol) in 300ml 
dry ether was added slowly to tris-(dimethylamino) phosphine (6.19g,
0.038 mol) in 60 ml dry ether cooled in an ice/salt bath, and under nitrogen. After the addition (about 50 mins) the mixture was stirred for a further 20 mins. Then sodium t-butylperoxide (3.8 g, 0.034 mol) was added and stirring continued for a further 2 hrs. at ice/salt bath temperature. The mixture was then allowed to warm up to room temperature over a further 1 hr, and an ice-cold solution of ammonium hexafluorophosphate (8 g, 0.049 mol) in 50 ml water was added with stirring. A precipitate was formed which was filtered, rinsed with ether, and crystallised from absolute ethanol. The product was re-crystallised from absolute ethanol to give N-benzotriazo-tris(dimethylamino) phosphonium hexafluorophosphate as colourless crystals (1.8 g, 12.5%)

m.p.t. : 150-152°C

\[ \text{N.M.R (CDCl}_3/\text{DMSO}_d) \] : \[ \delta \ 2.9 - 3.1 \text{(doublet, J10 Hz, 18 protons)} \]
\[ \delta \ 7.5 - 8.3 \text{ (multiplet, 4 aromatic protons)} \]

\[ \text{C}_{12}\text{H}_{22}\text{N}_6\text{F}_6\text{P}_2 \] requires C, 33.8%; H, 5.2%; N, 19.7%; P, 14.5%; F, 26.8%

found C, 34.0%; H, 5.25%; N, 19.7% P, 14.5%; F, 27.2%.

m/e 265.

3.5 Acetylation of p-xylene

Materials: p-xylene (pure, analysed by gc), carbon disulphide (freshly distilled), acetyl chloride (freshly distilled), powdered aluminium chloride (used as supplied)

Acetylation:

General procedure *

A 250 ml 3-necked round-bottomed flask was fitted with a thermometer, a pressure-equalising funnel and an inlet/outlet for nitrogen gas.

* Some variations were carried out in which the order of addition of the reagents namely p-xylene, aluminium chloride and acetyl chloride were changed. (see results and discussions section).
Carbon disulphide (50ml) was placed in the flask and aluminium chloride (25.5g, 0.191mol) was added and stirred under dry nitrogen. The flask was cooled in an ice/salt bath and acetyl chloride (15.28g, 0.195mol) dissolved in 10ml carbon disulphide was added dropwise over a period of 5 minutes. After a further 10 minutes, p-xylene (50g, 0.47mol) was added slowly with stirring and cooling, keeping the temperature below 20°C. After the addition, stirring continued for 1 hr. in the ice/salt bath and a further 1 hr. at room temperature. The nitrogen supply was disconnected and the mixture allowed to stand overnight at room temperature, and then poured onto cracked ice to which conc. HCl has been added. The mixture was thoroughly stirred and extracted with ether, washed with water and dried over anhydrous calcium chloride, filtered and distilled. The recovered p-xylene was analysed by glc.

Wt. of product was 16g (55.5%), bp_{1.5\text{mm}} 74-76°C

Lit\text{78}: \text{bp}_{4-5\text{mm}} 80 - 85°C

IR (neat): 1680\text{cm}^{-1} (\text{C=O})

NMR(CDCl₃): \delta 6.95 - 7.5 (3 aromatic protons)
\delta 2.15 - 2.7 (triplet, 9 protons, 3-methyls)

GLC (using Cp wax 51 Capillary column : Temperature - isothermal 120°C)

GLC showed the product to consist only of 2, 5-dimethylacetophenone.
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