Chemical reactivity and hydrogen bonding in relation to hydroxyl group acylation in carbon tetrachloride.

A thesis submitted by Kenneth Hillier in candidature for the degree of Doctor of Philosophy of the University of London.

August 1972.

Royal Holloway College, (University of London), Englefield Green, Surrey.
ACKNOWLEDGEMENTS

The author wishes to thank Prof. T. G. Bonner for his encouragement and supervision throughout this investigation, and the technical staff of the Chemistry Department of Royal Holloway College for their assistance. He is also grateful to the Science Research Council for financial assistance.
Dedication

to my wife

and

parents.
ABSTRACT

A kinetic study was made of the reaction between phenols and carboxylic acid anhydrides in the presence of pyridine bases in carbon tetrachloride. Linear free energy relationships were applied and results are consistent with a general base catalysis, i.e. reaction via a pyridine/phenol hydrogen-bonded complex. Values were found for the Hammett reaction constant, $\rho$; the Brønsted reaction constant, $b$; and the Taft (steric effects) reaction constant, $\delta$. The energy of activation was found for the reaction between $p$-chlorophenol and acetic anhydride with pyridine. The catalytic ability of bases, other than pyridine bases, was determined. The mechanism of the pyridine catalysis is discussed and a transition state proposed.

Phenols do not react with carboxylic acid anhydrides in carbon tetrachloride in the absence of a base. Although 2-picoline and 2,6-lutidine have high $pK_a$ values, they do not catalyse this reaction because of steric effects and for this reason also, 2,6-lutidine inhibits acylation in the presence of a catalytic pyridine base.

At higher base concentrations, a fast reaction was observed between phenols and anhydrides in the presence of 2,6-lutidine, but this did not go to completion. At the low base concentrations used in the work above, this fast acylation accounts for only a small percentage of the reaction and no further esterification occurs. Results are consistent with a highly reactive phenol/2,6-lutidine dimer hydrogen-bonded complex or ion pair. Acetic acid inhibits this initial rapid reaction and the solvent does not significantly affect results.
Acetylation of alcohols by acetic anhydride was studied in carbon tetrachloride. Alcohols containing intramolecular hydrogen bonds reacted slower than non-chelated alcohols. Reasons for this reduced reactivity are proposed.

Preliminary experiments are reported for an esterification at a water-carbon tetrachloride boundary.
Section 1. Introduction.
A. Hydrogen bonding in relation to hydroxyl group reactivity.
   i) General. ........................................ 1
   ii) Physical properties of hydrogen-bonded systems. ...... 3
   iii) Chemical reactivity. .................................. 6
   iv) Alkylation of hydroxy-compounds. ....................... 9
   v) Esterification reactions by acylation. ................. 11
   vi) Ester hydrolysis. ..................................... 16
   vii) Enzyme-catalysed reactions. .......................... 19
   viii) Interfacial ester hydrolysis and model enzyme
        systems ............................................. 22
B. Esterification and ester hydrolysis: General base
   and nucleophilic catalysed reactions.
   i) General base catalysis. .................................. 25
   ii) Characterization of general base catalysis. ............ 27
   iii) The reaction mechanism of general base catalysis. .. 34
   iv) The reaction mechanism of nucleophilic catalysis. .... 36
   v) General base catalysed nucleophilic catalysis. ....... 37
   vi) General base and nucleophilic catalysis in non-
       polar solvents. ...................................... 37

Section 2. Experimental.
A. Materials. ............................................ 43
B. Reaction of acetic anhydride with hydroxy-compounds
   in carbon tetrachloride.
   i) Infrared measurements. ................................ 54
   ii) Kinetic procedure. .................................... 54
iii) Quantitative analysis.

Reaction of carboxylic acid anhydrides with m-nitrophenol in carbon tetrachloride.

i) Visible measurements.

ii) Kinetic procedure.

iii) Quantitative analysis.

C. Competitive reactions.

i) Chromatographic measurements.

ii) Kinetic procedure.

iii) Quantitative analysis.

D. Association constant determinations.

Section 3. Results.

A. Reaction of phenols with carboxylic acid anhydrides in the presence of basic catalysts.

i) Acetylation of phenols with acetic anhydride in the presence of pyridine.

ii) Reaction of p-chlorophenol with acetic anhydride in the presence of pyridine bases.

iii) Reaction of p-cresol with acetic anhydride in the presence of pyridine bases.

iv) Reaction of p-chlorophenol with acetic anhydride in the presence of 4-picoline.

v) Reaction of m-nitrophenol with acetic anhydride in the presence of pyridine bases.

vi) Reaction of m-nitrophenol with isobutyric anhydride in the presence of pyridine bases.
vii) Esterification of $m$-nitrophenol with carboxylic acid anhydrides in the presence of pyridine bases

viii) Reaction of $p$-chlorophenol with acetic anhydride in the presence of pyridine.

ix) Reaction of $p$-methoxyphenol with acetic anhydride in the presence of pyridine.

x) Reaction of phenols with acetic anhydride in the presence of 4-dimethylaminopyridine.

xi) Reaction of $m$-nitrophenol with acetic anhydride in the presence of 1,3-bis(dimethylamino)-naphthalene.

xii) Reaction of $p$-chlorophenol with acetic anhydride in the presence of bases.

xiii) Reaction of $p$-chlorophenol with acetic anhydride in the presence of pyridine at different temperatures.

xiv) Reaction of $p$-chlorophenol with acetic anhydride in the presence of pyridine and 4-picoline.

xv) Reaction of $p$-chlorophenol with carboxylic acid anhydrides in the presence of tetrahexylammonium benzoate.

xvi) Reaction of $m$-nitrophenol with isobutyric anhydride in the presence of 2,6-lutidine and 3,4-lutidine.

xvii) Reaction of $m$-nitrophenol with acetic anhydride in the presence of 2,6-lutidine.
xviii) Reaction of \textit{m}-nitrophenol with acetic anhydride in the presence of 2,6-lutidine and acetic acid.  
Page 100

xix) Reaction of \textit{m}-nitrophenol with acetic anhydride in the presence of 2,6-lutidine in toluene.  
Page 103

xx) Reaction of \textit{m}-nitrophenol with acetic anhydride in the presence of 2,6-lutidine in water.  
Page 104

xxi) Reaction of \textit{m}-nitrophenol with acetic anhydride in the presence of 2,6-lutidine in water.  
Page 105

xxii) Reaction of \textit{m}-nitrophenol with acetic anhydride in the presence of 2,6-lutidine and acetic acid in water.  
Page 107

xxiii) Reaction of \textit{p}-chlorophenol with acetic anhydride in the presence of 2,6-lutidine and other pyridine bases.  
Page 109

xxiv) Reaction of \textit{p}-chlorophenol with acetic anhydride in the presence of 4-picoline and 2,6-lutidine.  
Page 111

xxv) Reaction of \textit{p}-chlorophenol with acetic anhydride in the presence of 2,6-lutidine and other bases.  
Page 112

xxvi) Reaction of \textit{p}-chlorophenol with acetic anhydride in the presence of 2,6-lutidine and 3,4-lutidine.  
Page 114

xxvii) Investigation of the initial rapid ester formation.  
Page 115

xxviii) Spectroscopic investigation of the reaction systems.  
Page 117

xxix) Competitive reactions of phenols with acetic anhydride.  
Page 123
B. Acylation reactions of compounds containing intramolecular hydrogen bonds and of compounds existing as self associated species.
   i) Acetylation of o- and p-methoxybenzyl alcohols with acetic anhydride. 125
   ii) Acetylation of pyridyl alcohols with acetic anhydride. 126
   iii) Reaction of alcohols with acetic anhydride in the presence of pyridine. 128
   iv) Reaction of phenol with trifluoroacetic anhydride. 130
   v) Reaction of ethanol with acetic anhydride. 133

C. Acylation at a water-carbon tetrachloride boundary.
   i) Reaction of m-nitrophenol with isobutyric anhydride when shaken with saturated aqueous potassium bicarbonate solution. 136
   ii) Reaction of m-nitrophenol with pivalic anhydride when shaken with saturated aqueous potassium bicarbonate solution. 138
   iii) 3-Picoline catalysed reaction between m-nitrophenol and pivalic anhydride in a two phase water-carbon tetrachloride system. 139

D. Reaction between phenols and acetic anhydride. 145

Section 4. Discussion.
A. Reaction of phenols with carboxylic acid anhydrides in the presence of bases. 148
B. Mechanism. 169
<table>
<thead>
<tr>
<th>C. Acetylation catalysed by 2,6-lutidine</th>
<th>174</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. Acetylation of compounds containing intramolecular hydrogen bonds or self associated species.</td>
<td>180</td>
</tr>
<tr>
<td>E. Reaction of phenols with acetic anhydride.</td>
<td>184</td>
</tr>
<tr>
<td>F. Interfacial esterification.</td>
<td>186</td>
</tr>
</tbody>
</table>

References. | 138 |
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>64</td>
</tr>
<tr>
<td>Figure 2</td>
<td>65</td>
</tr>
<tr>
<td>Figure 3</td>
<td>68</td>
</tr>
<tr>
<td>Figure 4</td>
<td>70</td>
</tr>
<tr>
<td>Figure 5</td>
<td>72</td>
</tr>
<tr>
<td>Figure 6</td>
<td>74</td>
</tr>
<tr>
<td>Figure 7</td>
<td>77</td>
</tr>
<tr>
<td>Figure 8</td>
<td>81</td>
</tr>
<tr>
<td>Figure 9</td>
<td>83</td>
</tr>
<tr>
<td>Figure 10</td>
<td>88</td>
</tr>
<tr>
<td>Figure 11</td>
<td>96</td>
</tr>
<tr>
<td>Figure 12</td>
<td>98</td>
</tr>
<tr>
<td>Figure 13</td>
<td>99</td>
</tr>
<tr>
<td>Figure 14</td>
<td>102</td>
</tr>
<tr>
<td>Figure 15</td>
<td>106</td>
</tr>
<tr>
<td>Figure 16</td>
<td>108</td>
</tr>
<tr>
<td>Figure 17</td>
<td>113</td>
</tr>
<tr>
<td>Figure 18</td>
<td>127</td>
</tr>
<tr>
<td>Figure 19</td>
<td>129</td>
</tr>
<tr>
<td>Figure 20</td>
<td>132</td>
</tr>
<tr>
<td>Figure 21</td>
<td>134</td>
</tr>
<tr>
<td>Figure 22</td>
<td>137</td>
</tr>
<tr>
<td>Figure 23</td>
<td>141</td>
</tr>
<tr>
<td>Figure 24</td>
<td>143</td>
</tr>
</tbody>
</table>
SECTION 1.  INTRODUCTION

A. Hydrogen Bonding in relation to hydroxyl group reactivity.

i) General.

At the first symposium on 'The Hydrogen Bond' in 1949 Hunter\textsuperscript{1} stated, 'There is now no doubt that the hydrogen atom can, in certain circumstances, link two other atoms together. Although such atoms are confined, with a few doubtful exceptions, to the electronegative elements oxygen, nitrogen, sulphur and fluorine, this nevertheless gives rise to the following variety of hydrogen-bond types: - O-H-O, O-H-N, N-H-N, O-H-S, N-H-S, F-H-F, F-H-N, F-H-O.' This was probably the first attempt to define the hydrogen bond, which is now regarded to exist if the following criteria are fulfilled\textsuperscript{2}:-

(i) A hydrogen bond occurs between a proton donor group A-H and a proton acceptor group B, where A is an electronegative atom O, N, S, F, Cl, Br, I, or C, and the acceptor group is a lone electron pair of an electronegative atom. The acceptor group may also be a \pi-electron orbital of an unsaturated system.

(ii) The total bond length $R(A...B)$ is equal to or less than the sum of the van der Waals radii of atoms A and B, that is, the total bond length contraction caused by hydrogen bond formation is equal to or greater than twice the van der Waals radius of the hydrogen atom.

(iii) Usually the hydrogen bond has an enthalpy of formation between 4 and 40 kJ/mole\textsuperscript{-1}.

The existence of a hydrogen bond was first suggested by Oddo and Puxeddu\textsuperscript{3} in the species (II) in equilibrium with (I).
This is very close to the accepted modern formula for o-hydroxyazo compounds (III) which contain intramolecular hydrogen bonds.

The incomplete ionization of the hydroxides present in aqueous solutions of ammonia and aliphatic amines was explained by Moore and Winmill\(^4\) to be due to hydrogen-bonded species of the form (IV). Hence, these compounds are weak bases compared with quaternary hydroxides, which cannot be similarly hydrated (V). Soon after this Pfeiffer\(^5\) postulated structure (VI) for 1-hydroxyanthraquinone and Morgan and Reilly\(^6\) gave the structure (VII) to certain \(\beta\)-diketones.

Huggins\(^7\) applied the hydrogen bond concept to explain tautomerism in acetooacetic acid esters and similar compounds, and also the interaction of ammonia with water.
The hydrogen bond greatly simplified existing knowledge at that time and also acted as a stimulus to seeking new knowledge. A review by Pimentel and McCallan with a bibliography through to 1956 gives a good indication of the status of the hydrogen bond to that date. The literature on this subject must now be regarded as too extensive for a comprehensive review, although Vinogradov and Limnell have attempted to collect the important works together producing a satisfactory successor to the work of Pimentel and McCallan. Tichy reviewed the intramolecular hydrogen bond and its applications in stereochemistry, giving references to 1964. Murthy and Rao recently reviewed the spectroscopic studies made on the hydrogen bond using infrared, ultraviolet or nuclear magnetic resonance spectroscopy. Numerous other reviews are available on more specialist aspects of the hydrogen bond, but the subject of hydrogen bonding related to chemical reactivity has been largely neglected. No mention will be made here of the stereochemical influence of the hydrogen bond on complex biochemical reaction mechanisms.

ii) Physical properties of hydrogen-bonded systems.

The physical properties of systems containing hydrogen bonds are discussed fully elsewhere, and only a few selected examples are given here. Gordy and Stanford related $\Delta \nu_s$ (the difference between the free and associated hydroxyl group stretching frequencies) for methanol-d in ketones and aldehydes to the logarithm of the rate constant for semi-carbazone formation. These authors also showed that a similar relationship holds between $\Delta \nu_s$ and the basicity constants, $pK_b^s$, for a series of bases. This correlation, however, was not a
study of a reactive system containing a hydrogen bond, but
simply used $\Delta \gamma_3$ as a measure of the $pK_b$ of the carbonyl
compound.

Ingraham et al.\textsuperscript{14} examined the effect of meta and para
substituents on the stretching frequencies of the free and the
hydrogen-bonded hydroxyl groups of phenols and catechols.
These frequencies each show an approximately linear dependence
on the Hammett $\sigma$ function, but the slopes of the two curves
differ. $\Delta \gamma_3$ was hence found to depend linearly on the Hammett
$\sigma$-function. This work was not extended to give a correlation
of $\Delta \gamma_3$ with reactivity.

A number of workers have tried to correlate $\Delta H^0$ with $\Delta \gamma_3$,
where $\Delta H^0$ is the enthalpy of formation of the hydrogen-bonded
adduct. Epley and Drago\textsuperscript{15} proposed the linear relationship:

$$-\Delta H^0 (\text{kJ mol}^{-1}) = 0.011 \Delta \gamma_{\text{OH}} + 2.79$$

where the $\Delta H^0$ values have been evaluated using a calorimetric
method. The $\Delta \gamma_{\text{OH}}$ values were measured using phenol adducts
with different proton acceptors of widely varying nature.
This relationship agrees extremely well with that of Singh,
Murthy and Rao\textsuperscript{16} based on infrared spectroscopic data for the
hydrogen bond enthalpy range 3–10 kJ mol$^{-1}$.

$$-\Delta H^0 (\text{kJ mol}^{-1}) = 0.010 \Delta \gamma_{\text{OH}} + 2.37$$

Strength of organic acids: The hydrogen atom of the
hydroxy-group involved in an intramolecular hydrogen bond is
held to the molecule more strongly than it would be in the
absence of such a bond. As a result, the removal of such a
proton from the molecule is more difficult than in the case of
a non-chelated hydrogen atom. The physical properties of
o-hydroxybenzaldehyde indicate the existence of a strong intramolecular hydrogen bond between the hydroxyl proton and the adjacent oxygen atom, and its $pK_a$ value (in water) is 8.14. However, m-hydroxybenzaldehyde, which contains no intramolecular hydrogen bonding, has a $pK_a$ of 7.45. Sadekov has reviewed this subject, giving numerous examples of the reduction of hydroxyl group acidity due to intramolecular hydrogen bonding. When hydrogen bonds are formed in molecules of organic carboxylic acids, the dissociation constants of these compounds may either increase or decrease. If the carboxyl group or its anion acts as a proton acceptor, the dissociation constant will usually increase. If the hydroxyl of the carboxy group acts as the proton donor, then the acidity of that compound will decrease. Branch and Yabroff pointed out that o-hydroxybenzoic acid is a much stronger acid than its meta or para isomers because the hydrogen bond saturates, in part, the proton attraction of the carboxylate ion. In water, o-hydroxybenzoic acid (VIII) ($K_a \sim 1 \times 10^{-3}$) is more than ten times as strong an acid as m-hydroxybenzoic acid ($K_a \sim 8 \times 10^{-5}$).

\[ \text{[VIII]} \]

It is expected that this hydrogen bond stabilization will be stronger in the anion than in the acid and, hence, the equilibrium will be displaced towards the dissociated form. This effect is even more pronounced in 2,6-dihydroxybenzoic acid
(\(K_a = 5 \times 10^{-2}\)), which is stronger than phosphoric acid and sulphurous acid.

iii) Chemical reactivity.

Hudson and Loveday\(^\text{20}\) have established that the rate of reaction between acid chlorides and alcohols in non-polar solvents is proportional to the concentration of associated alcohol over a wide concentration range (0.03 - 1.0 M). This is explained by assuming specific association between the alcohol and the acid chloride in the transition state (IX), and by considering the equilibria present in solution.

\[
\text{ROH}_3 + R_1-\text{O-Cl} \rightarrow \text{RO-} + R_1\text{Cl} \rightarrow \text{RO-} + R_1\text{H} \rightarrow \text{ROH} + R_1\text{Cl}
\]

The total rate of this reaction is given by:

\[
k = k_1 (\text{ROH})_{\text{Monomer}} + \sum \frac{1}{2} k_i (\text{ROH})_i
\]

Making the assumptions that (i) the reactivity of the associate (\(\text{ROH}_i\)) is proportional to the number of molecules \(i\) in it and (ii) the solvation energy provided by \(i\) molecules is independent of \(i\) above some critical value (here taken to be 2). It follows that:

\[
k = k_1 (\text{ROH})_{\text{M}} + k_1 \frac{-(\Delta H_s - E_H)}{RT} \sum \frac{i}{2} (\text{ROH})_i
\]

where \(\Delta H_s\) is the solvation energy of the transition state, and \(E_H\) the hydrogen bond energy required to form transition state (IX). This transition state also explains the lack of sensitivity of these reactions to changes in polarity of the solvent.
Similar to the above is the uncatalysed urethane reaction.\(^{21}\)

\[
(R_{OH})_n + R_1-N\equiv C\equiv O \rightleftharpoons R_1-N\equiv O\equiv O \rightarrow R_1-N-O-O-R + (ROH)_{n-1}
\]

The rate also depends essentially on the concentration of the polymeric (self associated) alcohol. The reaction is thought to proceed via the isocyanate-alcohol polymer intermediate, the rearrangement of which is the rate determining step. Pyridine and other nitrogen bases also catalyse the urethane reaction and the activated complex is given the form:

\[
R_3N\equiv C\equiv O
\]

These authors investigated how the rate was affected by changing the nature of the solvent. Eighteen solvents were used with different dielectric constants. A few selected examples are given below.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant</th>
<th>Initial Rate Constant (10^3k_2) (min^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclohexane</td>
<td>2.02</td>
<td>39</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>2.24</td>
<td>18</td>
</tr>
<tr>
<td>Benzene</td>
<td>2.28</td>
<td>5.8</td>
</tr>
<tr>
<td>Chloroform</td>
<td>4.61</td>
<td>2.9</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>36.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>6.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Dioxane</td>
<td>2.21</td>
<td>0.08</td>
</tr>
</tbody>
</table>
The observed rate constant apparently does not depend on the dielectric constant of the solvent, but increases as the case of alcohol polymer formation increases.

Koskimallio\textsuperscript{22} investigated the alcoholysis of acetic anhydride in cyclohexane and carbon tetrachloride at 60°. A first order dependence in each of the reactants was found and the rate decreased with increasing alcohol concentration. Alcoholysis proceeds by a two step mechanism with the formation of a tetrahedral intermediate $-$

$$\text{(CH}_3\text{CO)}_2\text{O} + \text{ROH} \rightleftharpoons \text{CH}_3\text{O} - \text{C(}\cdot\text{H})\text{O} \rightleftharpoons \text{CH}_3\text{O} - \text{C(}\cdot\text{H})\text{O}$$

(Schematically)

Both formation and decomposition of the tetrahedral intermediate (b) probably occur by way of the cyclic transition states (a) and (c). As the concentration of alcohol is increased, progressive self association occurs to form practically non-reactive cyclic dimers, trimers and higher associated species. To form a transition state such as (a) from an alcohol associated with another molecule involves the breaking of a hydrogen bond. The activation energy is therefore greater by about 12 $k\text{J.mole}^{-1}$, which means that the reaction
rate is reduced about 100 times at 60°.

iv) **Alkylation of hydroxy-compounds.**

In 1970 Sadelkov reviewed intramolecular hydrogen bonding in relation to chemical reactivity, which included alkylation and acylation reactions. The presence of an intramolecular hydrogen bond in the molecule is the reason for the difficulty of obtaining ethers which are derived from the hydroxyl groups involved in the hydrogen bond. This difficulty is found using all the general methods of alkylation. The hydroxyl group is not methylated when 2-pyridin (X) is treated with diazomethane in ether, or with dimethyl sulphate and alkalies.²³

![Diagram](image)

Narasimkachari in 1952 found that 2',5,7-trihydroxy-flavanone (XI), when reacted with dimethyl sulphate in acetic acid in the presence of potassium carbonate, gives only 2',5-dihydroxy-7-methoxyflavanone. Usually, chelated phenols are not methylated, and when several hydroxyl groups are together in a molecule only those not involved in hydrogen bonding are methylated. In 1964, Schönberg and Mustafa were unable to methylate o-hydroxyacetophenone or o-hydroxy-benzophenone with diazomethane in ethereal solution. This was explained by the chelated structure (XII) which had been proposed 22 years earlier by Sidgwick and Callow.²⁶
It was also found that if methanol is added to acetophenone it is readily methylated by diazomethane because the alcohol helps to break up chelation as in (XIII).

Some compounds containing strong intramolecular hydrogen bonds are apparently methylated normally with diazomethane. Mellein; 3,4-dihydro-8-hydroxy-3-methyliso-coumarone, (XIV) reacts slowly (3 days at room temperature) with diazomethane to give the methoxy-derivative. 27

Similarly, 4,7-dihydroxy-3-coumarone (XV) is readily methylated in the 4 position, but the hydroxyl group in the 6 position is non-reactive. 28 In this reaction, dioxane was present in the reaction mixture, which may help break up the chelated species.

Haines and Symes 29 reacted 1,4:3,6-dianhydro-D-glucitol with methyl iodide and silver oxide, and it was found that the intramolecularly hydrogen-bonded hydroxyl (C-5) is alkylated at a faster rate than the free, and less sterically hindered C-2-hydroxyl group. Haines 30 also found that the hydroxyl group in 2,3-o-isopropylidene-5-o-tolylsulphonyl-α-L-rhamnofuranose
(XVI, R¹ = H, R² = OH) is methylated faster than in the anomer (XVI, R¹ = OH, R² = H).

(XVI) was present in excess methyl iodide with silver oxide for 48 hours. The mechanism of methylation is a nucleophilic attack by the oxygen atom of the unionized hydroxyl group on methyl iodide, aided by an electrophilic attack of silver ions on the leaving iodide ion. It was postulated that participation of the hydroxyl group in a hydrogen bond would enhance the nucleophilicity of the oxygen.

In 1965, Bourne et al. proposed the structure (XVII) for glycerol 1,2-phenyl-boronate which did not react with methyl iodide, benzoyl chloride or toluene-p-sulphonyl chloride. Although (XVII) exists in equilibrium with an intramolecularly hydrogen-bonded form, it was proposed that the cative interaction with boron was the cause of the reduced nucleophilicity of the hydroxyl oxygen.

v) Esterification reactions by acylation.

Consider the equilibrium (1) where B is a proton accepting species and A-H is able to donate its proton.

\[ 2 \text{H}_2\text{O} + \text{A-H} \cdots \text{B} \rightleftharpoons \text{H}_2\text{O} \cdots \text{HA} + \text{HOH} \cdots \text{B} \]  (1)

The hydrogen-bonded species A-H \cdots B is unstable in aqueous
media and the system exists predominantly as two solvated species. Because of this, very few acylation or alkylation mechanisms are known in polar media which proceed through an intermolecular hydrogen-bonded species. Hydrolysis, exhibiting classical general catalysis is an exception here, as the hydrogen-bonded species itself contains a water molecule. This case will be discussed in Section 1 B.

Chelated phenolic hydroxyl groups are probably more readily acylated than alkylated. However, ester formation is also anomalously slow or does not occur at all when intramolecularly bonded hydroxyl groups are present. As with alkylation, there are exceptions to this rule.

o-Nitrophenol is benzyolated at a slower rate than is phenol itself, whereas m- and p-nitrophenols are benzyolated at a slightly faster rate. The physical properties of o-nitrophenol (XVIII) show it to have a strong intramolecular hydrogen bond, whereas this is absent in the meta and para isomers.

Bassett and O'Leary found that o-nitrophenol reacted slower than the m- and p-isomers with acetyl bromide. In 1962 Zaits and Iyashenko found that o-nitrophenol reacted with benzene sulphonyl chloride at a slightly faster rate than its isomers, and more recently, Yoneno found that again the ortho isomer reacted fastest in a urethane reaction catalysed by triethylamine.

In polyhydroxyanthraquinones the hydroxyl groups involved
in intramolecular hydrogen bonds are acetylated much more slowly than the free hydroxyl groups. Under the usual conditions (acetic anhydride with a few drops of pyridine at room temperature) many compounds are not acetylated at all. Some compounds which exhibit this non-reactivity are 4-chlorosalicylaldehyde, 5-fluoro-2-nitrophenol and 2,3,5-trinitrophenol.

1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (XIX) has been prepared and proved to exist in the more stable boat form. All attempts to acetylate this compound have failed, due to the presence of strong intramolecular hydrogen bond.

As found in methylation reactions, the selective acetylation of hydroxy-groups in polyhydroxy-compounds is due to the involvement of some of these in intramolecular hydrogen bonds. 2,4-dihydroxybenzoic acid and the corresponding aldehyde are only acetylated in the 4 position, and 2,4,6-trihydroxybenzaldehyde gives only the 4,6-diacyl derivative.

1',2',3',4-tetrahydroxy-1,2-benzocycloheptan-3-one (XX) is acetylated with acetic anhydride to give 2',3',4-triacetoxy-1-hydroxy-1,2-benzocycloheptan-3-one (XXI), which cannot be further acetylated or methylated.

2-(o-hydroxyphenyl)benzimidazole (XXII) is only acetylated at the secondary nitrogen, since the hydroxyl group is involved in a strong intramolecular hydrogen bond with the tertiary nitrogen.
The controversy as to whether a hydrogen bond enhances or reduces chemical reactivity (in acylation) now becomes apparent. The following examples indicate how the hydrogen bond concept has been used to explain increased reaction rates.

Chelated hydroxyl groups have been found to have an increased nucleophilicity in certain reactions. Buck et al.\(^{39}\) found that cis-5-hydroxy-2-phenyl-1,3-dioxan (XXIII) reacted with \(p\)-phenylasobenzoyl chloride in pyridine almost six times faster than the trans isomer (XXIV).

\[
\text{(XXIII)} \quad \text{(XXIV)}
\]

The increase in basicity of the hydroxyl oxygen in the cis isomer was explained by a bifurcated intramolecular hydrogen bond. This type of hydrogen bonding has been shown to be present in (XXIII) in carbon tetrachloride solution. To confirm these results cis and trans 4-phenylcyclohexanols were reacted under the same conditions as above in competitive reactions. No intramolecular hydrogen bonding is possible here and it was found, as expected, that the trans isomer reacted faster than the cis isomer.
1,4;3,6-dianhydro-D-glucitol (XXV) has two hydroxy groups, one of which, in the 5 position, is involved in a strong intramolecular hydrogen bond.

![Diagram](image)

Reaction of (XXV) with an equimolar amount of tosyl chloride in pyridine gave a fourfold greater yield of the endo-5-tosylate than of the exo-2-tosylate. Lemieux and McInnes also found that the exo-2-tosylate reacted 1.4 times more rapidly with tosyl chloride than did the endo-5-tosylate.

In 1971, Knoblich et al. determined the rates of esterification for 1,5-di-O-benzoyl-2,4-O-benzylidinexylitol (XXVI), -ribitol (XXVII), 1,5-di-O-benzoyl-2,4-O-methylenexylitol (XXVIII) and -ribitol (XXIX).

![Molecular structures](image)

Most work quoted here has been of a preparative nature, analysing the products of competitive reactions. These reactions were followed kinetically by an automatic titration procedure. Reactions were carried out in an anhydrous pyridine solution, using acid anhydrides, carboxylic acid chlorides and sulphonic...
acid chlorides. Acid anhydrides reacted more readily with compounds (XXVII) and (XXX), with equatorial hydroxyl groups, than with compounds with axial hydroxyl groups. The opposite order of reactivity is found with the carboxylic acid chlorides and sulphonic acid chlorides. It was suggested that the 1,3-dioxane ring has an important function in controlling reactivity. It was also proposed that dipolar interactions, both dipole-dipole and ion-dipole, serve as a more logical source of reactivity control than hydrogen bonding effects. This will be discussed in Section 4.

The influence of hydrogen bonding on the rate of benzoylation has been discussed by Williams and Richardson\textsuperscript{42} in 1967. It was considered unlikely that intramolecular hydrogen bonding would occur in pyridine, because of the strong intermolecular bonding which takes place between pyridine and alcohols.\textsuperscript{43} These authors disagree with the opinion of some workers that intramolecular bonding in alcohols can occur in pyridine solutions to produce an increase in basicity of the bonded hydroxyl oxygen. However, if hydrogen bonding to pyridine is sterically hindered in the transition state, intramolecular hydrogen bonding to a suitably disposed acceptor could assume importance.

vi) Ester hydrolysis.

Many reactions are known in which a neighbouring hydroxyl group in an ester appears to enhance the rate of alkaline hydrolysis. Capon\textsuperscript{44} gives two mechanisms by which a hydrogen bond can stabilize the transition state.
An example in which this type of catalysis could occur is the alkaline hydrolysis of $\beta$-acetoxycholestan-5$\alpha$-ol (XXX), which proceeds faster than the hydrolysis of $\beta$-acetoxycholestan-5$\alpha$-ol (XXXI).

It is generally very difficult to distinguish between mechanisms (2) and (3). The mechanism for ester hydrolysis may be written:

$$
\text{R-O-OR'} + \text{OH}^- \xrightarrow{k_1} \text{R-O-OR'} \xrightarrow{k_2} \text{R'-OH} \xrightarrow{k_3} \text{ROO}^- + \text{R'}\text{OH}
$$

The experimental rate constant is given by $k_e = k_1/(1 + k_2/k_3)^{*}$. $k_1$ will increase if the hydroxyl group participates as in scheme (2), whereas $k_1$ and $k_3$ will increase if the hydroxyl group behaves as in scheme (3). The effect of $k_1$ is expected
to be much less in (3) than in (2), and also, \( k_3 \) is not expected to affect the overall rate since, in alkaline hydrolysis, \( k_2/k_3 \) is always small. Therefore, a large increase in rate must be ascribed to mechanism (2), whereas a small increase is consistent with both (2) and (3). Unfortunately, it is found that the increase in rate is often very small.

Henbest and Lovell\(^\text{45}\) have tried to distinguish between these two mechanisms by examining the esters using infrared spectroscopy. However, as in the work of Buck et al.\(^\text{39}\) (page 14), results obtained from spectroscopy in aprotic solvents were used to postulate a mechanism in a completely different medium. Since rates of reactions depend on the free energy differences between initial and transition states, it is important to know the strengths of the hydrogen bonding in these two states. Hence the nature of the hydrogen bonding in the isolated initial state in a different solvent is of little relevance.

It has been found that ethyl cis- and trans-2-hydroxycyclopentanecarboxylate have approximately equal rates of hydrolysis, both reacting faster than ethyl cyclopentanecarboxylate.\(^\text{46}\) As no intramolecular hydrogen bonding can exist in the trans-isomer, it is thought that the increased rate of hydrolysis for these esters is due to solvent sorting. Experiments were carried out with these esters in a water : dioxan medium and it was found that, as the percentage of dioxan was increased, the reduction in hydrolysis rate for the hydroxy-esters was not as great as for the non-substituted ester. This behaviour cannot be explained simply by the inductive effect of the hydroxyl group. Solvent sequestering by the alcoholic hydroxyl group could lead to a cybotactic region, different in composition
from the rest of the medium and, if sufficiently large, could
effect cis- and trans- hydroxy-esters to an equal degree. It
is suggested that solvent sorting has a greater influence on
reactivity than intramolecular hydrogen bonding.

When the ester group has a hydroxyl group situated close
to it, a faster rate of hydrolysis is not necessarily observed.
The rate of hydrolysis of phenyl acetate is some seven hundred
times faster than α-hydroxyphenyl acetate. Usually, however,
rate enhancement is observed as with α-carboxyphenyl-β-D-glucose,
which is hydrolysed ten thousand times faster than the
β-carboxyphenyl derivative. This example of intramolecular
general acid catalysis is given in scheme (4).

\[
\begin{align*}
\text{Products} \\
(4)
\end{align*}
\]

vii) Enzyme-catalysed reactions.

Only those hydrolases which possess active serine or active
cysteine residues are considered here. Chymotrypsin A (3.4.4.5)
has been studied in detail by Bender and Kezdy. As in the
case of many other enzymes, it is thought likely that
chymotrypsin A possesses an active region in the molecule which
constitutes a peculiar environment in which the reactions of
the substrates may take place. This active site is probably
hydrophobic or non-polar in nature and enables the enzyme to
form a 'hydrophobic link' with the aromatic ring of specific
substrates. In this active site the reactivity of certain groups is enhanced. For example the hydrolysis of acetyl-chymotrypsin proceeds at a faster rate than would ordinarily be expected for an O-acetyl derivative. Similar results were obtained by Bender et al. with trans-cinnamoyl-chymotrypsin.

Only the serine residue at the active site becomes acylated in chymotrypsin A during reaction with carboxy-derivatives although there are twenty nine serine residues in the whole molecule. A serine hydroxyl group would not be expected to react with these reagents under normal conditions. The interpretation of pH-rate profiles has indicated that a histidine and an aspartic acid residue are also present at the active site.

Model studies show that the imidazole group (in the histidine residue) may participate in acylation or deacylation reactions, either as a nucleophilic catalyst as shown in scheme (5), or as a general base catalyst as shown in scheme (6).

\[
\begin{align*}
(5) \quad & \text{CH}_3\text{-COO}_6\text{H}_4\text{NO}_2 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CO}_2\text{H} + \text{HOC}_6\text{H}_4\text{NO}_2 - \text{H} \\
\end{align*}
\]
Differentiation between these two mechanisms is not simple, even with nonenzymic systems (See section B). Two methods to distinguish between these mechanisms have been applied here. In nucleophilic catalysis it should be possible to observe the unstable acetylimidazole intermediate. Several attempts have been made to do this with fast reaction techniques, but so far all attempts have failed. The second method, the deuterium oxide effect, gives us more information about the role of the imidazole group in these enzyme catalysed reactions. General base catalysis, carried out by imidazole as in scheme (5), results in an isotope effect \( \frac{k_{H_2O}}{k_{D_2O}} \) of approximately 2 - 3. This arises because of the rate determining proton (deuteron) transfer in the catalysis. As would be expected in nucleophilic catalysis, where no rate determining proton transfer occurs, the deuterium oxide isotope effect is unity. However, this method is by no means foolproof and deductions from it should be viewed with caution. (Section B)

Bender found that the decylation of trans-cinnamoyl-chymotrypsin A in water is about 2.5 times greater than in deuterium oxide, and it is now generally accepted that
chymotrypsin A operates via a general base catalysis. In the active site histidine, serine and aspartate residues are arranged such that a hydrogen-bonded species such as (XXXII) is formed.

\[
\begin{align*}
\text{Asp-102} & \quad \text{His-57} & \quad \text{Ser-195} \\
\end{align*}
\]

(XXXII)

At pH values in the region of 7, the serine oxygen can be considered to be carrying far more negative charge than if it were an isolated serine residue, and therefore will be a more powerful nucleophile.

The mechanism of ester hydrolysis catalysed by chymotrypsin A is now known with some certainty and can be found in standard texts.\(^4\) Trypsin (3.4.4.4) is very similar in its mode of action to chymotrypsin, both enzymes containing an active serine residue, although trypsin shows different selectivity properties. The mechanism of catalysed hydrolysis by papain (3.4.4.10), an enzyme containing an active cysteine residue, is again very similar to that of chymotrypsin.

viii) Interfacial ester hydrolysis and model enzyme systems.

A great deal of work has been devoted to the production of a simple organic model system which can emulate the catalytic ability of the enzymes. The peptide, L-threonyl-L-alanyl-L-seryl-L-histidyl-L-aspartic acid, was synthesized in 1963 and found to be a good catalyst for the hydrolysis of p-nitrophenyl acetate.\(^4\) This peptide was of particular interest since three
of the amino acids which it contains are known to be present at the enzyme active site. Later workers succeeded in putting some of these functional groups together in large, water soluble, copolymers. Overberger et al.\(^5\) produced the copolymer of 4(5)-vinylimidazole and \(\mu\)-vinylphenol, and this was found to be a far superior catalyst at high pH values towards the hydrolysis of \(\mu\)-nitrophenyl acetate than any of its monomeric or polymeric analogs. Three possible mechanisms were suggested for this catalytic effect; these are reproduced below:

\[\text{(7)}\]

\[\text{(8)}\]

\[\text{(9)}\]

Schemes (7) and (8) involve nucleophilic attack of the imidazole group on the acetate substrate and are not considered very probable. Scheme (9) involves a hydrogen bond between the imidazole and substrate thus producing a more electrophilic centre of attack for the phenate ion. The rates of solvolysis were determined in either 28.5% ethanol : water or 30% methanol : water.

It has been recognised that hydrophobic interaction makes
a significant contribution to the structure and activity of enzymes. Kunitake and Shinkai\textsuperscript{51,52} have synthesized water soluble copolymers from \( N-(5\text{-bemimidazole})\text{acrylamide} \) and \( N-(\pi\text{-hydroxyphenyl})\text{acrylamide} \). These polymers did not show cooperative catalytic action, possibly due to the formation of a tertiary structure, where the \( \pi\text{-hydroxyphenyl} \) group simply increases the hydrophobic nature of the catalytic site. The reaction studied in this case was the hydrolysis of \( \pi\text{-acetoxybenzoic acid} \) in aqueous potassium chloride solution.

Snell\textsuperscript{53} pointed out in 1967 that, although the active site of many enzymes is now considered as a hydrophobic region, most work pertaining to model enzyme systems is still carried out in bulk aqueous media. Also, at that date, there were no reported studies of intramolecular catalytic processes in nonhydroxylic media. These workers give evidence for this type of catalysis in the amidation of methyl salicylate by \( \pi\text{-butylamine} \) in dioxan.

Menger\textsuperscript{54} has taken this point further than Snell and has investigated the imidazole-catalysed ester hydrolysis at a water-heptane boundary. Many enzymatic reactions which normally take place in the free solution, such as chymotrypsin-catalysed hydrolyses, can be considered as interfacial processes. The binding site of chymotrypsin is almost certainly hydrophobic and there is evidence that at least part of the catalytic site is aqueous.\textsuperscript{55} The dependence of interfacial hydrolysis rates on stirring speed, concentration of reactants, temperature, viscosity of the hydrocarbon, volume of heptane and water solutions, deuterium and salt content of the water, lauroyl imidazole content of the heptane (the ester hydrolysed was
p-nitrophenyl laurate), presence of an amphiphile, and the nature of the catalyst were investigated. Imidazole is shown to act as a nucleophilic catalyst rather than a general base catalyst. Perhaps the most important point of this work was to develop a methodology of interfacial bioorganic chemistry.

Part of this thesis is concerned with esterification reactions at a water-carbon tetrachloride interface.

B. Esterification and ester hydrolysis: General base and nucleophilic catalysed reactions.

This section deals with general base catalysis and nucleophilic (covalent) catalysis of esterification and ester hydrolysis. No mention will be made of specific acid or base catalysts, which have been reviewed extensively elsewhere. General acid catalysis is only mentioned briefly, when it is found to occur with general base catalysis (see also page 19 - the hydrolysis of p-carboxyphenyl-\( \beta \)-D-glucose).

i) General base catalysis.

The term general base catalysis means, in its classical sense, the attack of a general base on the substrate, removing a proton (or a deuteron) in the rate determining step. Nucleophilic catalysis occurs when a nucleophile attacks the substrate to form an unstable intermediate which breaks down to give the products and regenerates the catalyst.

It was found by Jenks and Carrinolo that the hydrolysis of esters which are activated in the acyl portion, i.e. ethyl chloroacetate and ethyl difluoroacetate, is catalysed by general bases. Jenks also found that the hydrolysis of
N,N'-diacetylserinamide, which is catalysed by imidazole, is an example of general base catalysis. Other reactions thought to proceed via general base catalysis include: the imidazole catalysed hydrolysis of dimethyl oxalate, the hydrogen phosphate catalysed hydrolysis of ethyl and methyl acetates, and the carboxylate anion catalysed hydrolysis of chloromethyl chloroacetate.

The base catalysed hydrolysis of p-nitrophenyl acetate may proceed by way of either general base or nucleophilic catalysis. Nucleophilic catalysis would have the form:

\[
\text{ArOAc} + B \rightleftharpoons \text{BAc}^+ + \text{ArO}^- \\
\text{BAc}^+ + \text{H}_2\text{O} \rightarrow \text{BH}^+ + \text{AcOH}
\]

If the base used was the acetate anion it should be possible to detect acetic anhydride as an intermediate. Gold\textsuperscript{59} added aniline to this system and then analysed the products for acetanilide by ultraviolet spectroscopy. By this method, it was deduced that p-nitrophenyl acetate was mainly hydrolysed by general base catalysis according to the mechanism below:

\[
\begin{align*}
\text{(i) } & \quad \text{Me-} \text{CO-} \text{OAr} + 2\text{H}_2\text{O} \xrightarrow{\text{fast}} \text{Me-} \text{C-OAr} + \text{H}_3\text{O}^+ \\
\text{(ii) } & \quad \text{Me-} \text{C-} \text{OAr} + \text{HX} \xrightarrow{\text{slow}} \text{Me-} \text{C-} \text{OAr} + X^- \\
\text{(iii) } & \quad \text{Me-} \text{C-} \text{OAr} \xrightarrow{\text{fast}} \text{CH}_3\text{CO}_2\text{H} + \text{ArOH}
\end{align*}
\]
However, there was some evidence for nucleophilic catalysis in this system and it was later found\textsuperscript{60} that nucleophilic catalysis predominates with acetate esters of phenols, where the phenols have a pK\texttextsubscript{a} value of less than about 5. Above pK\texttextsubscript{a} values of 8 the catalysis of these esters follows classical general base catalysis. Nucleophilic catalysis in this system would have the form:

\[
\begin{align*}
\text{ArO-CO-Me} + \text{OAc} & \overset{k_1}{\rightleftharpoons} \text{ArO-C-Me} + \text{OAc}^- \\
\text{ArO-C-Me} + \text{OAc}^- & \overset{k_2}{\rightarrow} \text{ArO}^- + \text{Ac}_2\text{O}
\end{align*}
\]

When \(k_1 \gg k_2\) these reactions do not contribute to catalysis of the hydrolysis. The stability of the ion \(\text{ArO}^-\) will increase with the acidity of the phenol \(\text{ArOH}\), and hence the nucleophilic catalysis pathway will gain importance, relative to general base catalysis.

Briody and Satchell\textsuperscript{61} have found that the neutral hydrolysis of diketen appears to occur \textit{via} acyl-oxygen fission, in contrast with other \(\beta\)-lactones, and is subject to general base catalysis by carboxylate anions. This same compound is hydrolysed by pyridine (a stronger base than the carboxylate anion) \textit{via} nucleophilic catalysis.

ii) Characterisation of general base catalysis.

The rates of general base catalysed reactions, at constant pH, are proportional to the amount of base present in the system.\textsuperscript{56} This property is also found for nucleophilic and general acid-specific hydroxide ion catalyses, which are kinetically indistinguishable from general base catalysis. Patai\textsuperscript{56} has listed the properties which are usually
characteristic of general base rather than nucleophilic catalysis.

(a) The deuterium oxide solvent isotope effect $k_{H_2O}/k_{D_2O}$ is usually between 1.9 and 4.

As stated before this effect should be treated with caution since some general base catalysed reactions are known which have only very small isotope effects. Jönck's found that the catalysed aminolysis of phenyl acetate in water is an example of general base catalysis although the rate is only slightly decreased in deuterium oxide. The nucleophilic catalysis of the hydrolysis of phenyl acetate and $p$-nitrophenyl acetate by imidazole, and of acetic anhydride by formate ions, is not decreased significantly in deuterium oxide. However, the pyridine catalysed hydrolysis of acetic anhydride is decreased in deuterium oxide, although this is an example of nucleophilic catalysis.

(b) The basicity rather than the nucleophilicity determines the effectiveness of the catalyst.

In a reaction which is known to be general base catalysed, such as the hydrolysis of ethyl dichloroacetate, imidazole and the phosphate dianion, which are of almost equal basicity, are equally effective as catalysts. However, imidazole is some 4000 times more reactive than the phosphate dianion as a nucleophilic catalyst for the hydrolysis of $p$-nitrophenyl acetate.

(c) In nucleophilic catalysis it should be possible to observe an intermediate, whereas in general base catalysis no such species should exist.

The work of Gold and Butler on the hydrolysis of phenyl
acetates has already been discussed (page 26). Similar work by Jencks\textsuperscript{57} was undertaken on the hydrolysis of ethyl chloroacetate. When aniline was added to this system no dichloroacetanilide was produced from reaction with an intermediate. With stronger bases, such as ammonia, the acyl group was transferred to form a stable product.

In 1969, Jencks\textsuperscript{65,66} observed the acetylpyridinium ion, which is formed as an intermediate in the pyridine catalysed hydrolysis of acetic anhydride in water. The reaction mechanism is given as:

\[
Py + Ac_2O \xrightarrow{k_1} AcO^- + AcPy^+ \xrightarrow{k_2} Py + AcOH
\]

This intermediate was observed by ultraviolet spectroscopy, having an absorption at 280nm. It was also found that the second order rate constants for the pyridine catalysed acetylation of \( p \)-toluidine and \( p \)-anisidine with acetic anhydride, are the same as the second order rate constant found for the production of the acetylpyridinium ion. Furthermore, the reaction rate is independent of the concentration of the acyl acceptor. These results give a very clear indication that the mechanism of pyridine catalysed acyl transfer proceeds by the mechanism:

\[
Py + Ac_2O \xrightarrow{\text{slow} k_1} AcPy^+ \xrightarrow{\text{fast} k_N} AcNHR
\]

\[
-d ArNH_2 = k_1 (Py)(Ac_2O)
\]

The rate determining formation of the acetylpyridinium ion
is followed by rapid reaction with the proton acceptor. Other aspects of this work are discussed in following sections.

(d) Entropy of activation.

It is usually found with general base catalysis, that the entropy of activation is more negative, by about 20 e.u. than in nucleophilic catalysis. This difference in activation energy was suggested from the work of Gold et al. and of Bender and Neveu. Schalager and Long in a review on activation entropies, state that 13 e.u. is a reasonable value for the loss of entropy from the incorporation of a water molecule in the transition state. However, it is stressed, that this method of distinguishing between mechanisms must be used with caution, and in conjunction with other methods.

(e) The Brønsted equation.

The Brønsted reaction constant \( \beta \) is usually of a normal magnitude (around 0.5) for general base catalysis, whereas for nucleophilic catalysis, a higher value is often found. The Brønsted catalysis linear free energy relationship is of the form:

\[
k = G e^G
\]

or \( \log k = \log G - \beta pK_B \)

for base catalysis, where \( k \) is the catalytic rate constant, \( K \) represents the strength of the base and the constants \( \beta \) and \( G \) depend on the nature of the reaction, solvent and temperature.

The efficiency of general base catalysts increases with increasing base strength of the catalyst. When \( \log k \) is plotted against \( pK_B \) for a series of catalysts, the slope of the straight line (\( \beta \)) gives a measure of the sensitivity of the reaction to
the strength of the base catalyst. The Brønsted equation is obeyed in the general base catalysed hydrolysis of ethyl dichloroacetate,\(^57\) \((\alpha = 0.47)\), and in that of chloromethyl chloroacetate \((\alpha = 0.42)\). This relationship between basicity and nucleophilicity is usually found to be linear for a given class of compounds, but may show marked deviations for different types of compounds.\(^57\) This is expected, and these correlations are best used with catalysts which are structurally similar.

It is not at first obvious why nucleophilic catalysis should obey a relationship such as that given by Brønsted.\(^70\) The Brønsted relation, originally for acid catalysed reactions, assumes a free energy relationship of electron donation (or withdrawal) of groups in any two different situations e.g., ionization and catalysis. A nucleophilic reaction involves the donation of electrons from a nucleophile to a substrate, with partial bond formation in the transition state as in scheme (14).

\[
\begin{align*}
N: + S & \rightleftharpoons \delta^+ \quad \delta^- \\
N \cdots \cdots \cdots \cdots S
\end{align*}
\tag{14}
\]

Hence, a comparison of the energy required to form the transition state for a series of different nucleophiles and substrates, with the energy of other rate or equilibrium processes, should provide us with a useful insight into the mechanism of reaction. Basicity is a measure of the tendency of a compound to donate a pair of electrons to a proton in a partly covalent, partly ionic bond.

\[
\begin{align*}
N: + H^+ & \rightleftharpoons \quad \delta^+ \\
N \cdots \cdots \cdots \cdots H
\end{align*}
\tag{15}
\]

There is a distinct similarity between schemes (14) and (15) which includes the partial formation of a positive charge on the nucleophile. Over a restricted basicity range there is usually
a good correlation of basicity with nucleophilicity, but different classes of compounds usually follow different lines, although the slopes remain equal. The slopes of Brønsted plots for nucleophilic reactions of reagents of a given chemical class usually lie in the range 0.7 - 0.8. This shows that the dependency on basicity is large and that basicity is a good model for the transition state. Also, it may be inferred that a large amount of positive charge is developed on the attacking nucleophile in the transition state. From these deductions, the transition state for nucleophilic catalysis should have the form:

\[
\text{O} \\
\text{N} \quad \text{H} \\
\text{C} \quad \text{O} \quad \text{R}
\]

(f) Steric effects.

The steric effects found in examples of general base catalysis are of a moderate size, whereas in nucleophilic catalysis, they are usually large. Proton transfer in the transition state of general base catalysis is only partial, and the steric bulk of the catalysing base would only be expected to slightly increase the activation energy of the reaction. However, in nucleophilic catalysis, the base approaches the reaction centre much more closely and the steric bulk of the catalyst produces a greater effect on the rate of reaction. In 1953, Gold found that the hydrolysis of acetic anhydride in both water and aqueous acetone solution was catalysed by pyridine, 3- and 4-picoline and isoquinoline. It was also found that 2-picoline, 2,6-lutidine and quinoline were very much less efficient in this reaction than their basicities would suggest. The low catalytic ability of the \( \alpha \)-substituted pyridine bases could result from impurities, the pure sterically hindered base
being non-reactive. There are many known examples where the rate constants for 2-picoline and 2,6-lutidine fall below the value expected from a Brønsted catalysis plot. Feather and Gold in 1965 investigated this effect in the pyridine catalysed iodination of ketones.

In the decylation of a series of acyl-α-chymotrypsines in which the acyl portion was varied with respect to the steric bulk around the carbonyl group, a linear plot of \( \log(k_3/k_0) \) vs \( E_S \), the Taft steric effects constant, was obtained with a slope of 1.1. A similar plot of \( \log(k_{\text{nuc}}/k_0) \) vs \( E_S \) for the imidazole nucleophilic catalysed hydrolysis of a series of \( p \)-nitrophenyl esters showed more sensitivity to steric hindrance, with a slope of 1.4. Fife investigated the imidazole catalysed hydrolysis of a series of esters of N-acetylserinamide, which had been proved in earlier work, to proceed via general base catalysis. A slope of 0.49 was reported which is in accordance with general base catalysis and a transition state of the form :-

![Chemical structure image]
The linear free energy relationship used was:

$$\log \frac{k}{k_0} = \sigma^* \rho^* + E_b + E_r$$

where \(k_0\) is the rate constant for the acetate ester, \(\sigma^* \rho^*\) is the measure of the polar effect of the substituents and \(E_r\) the resonance effect constant. Further discussion of this subject is found in Section 4.

iii) The reaction mechanism of general base catalysis.

All the data presented for neutral and general base catalysed hydrolysis of carboxylic esters is in agreement with the reaction mechanism (16).^77,78

This is an example of the B\(_{AC2}\) mechanism of alkaline ester hydrolysis, modified so that the attacking species is a water molecule rather than a hydroxide ion. The addition of the water molecule to the carbonyl group is catalysed by the base B.
which in neutral ester hydrolysis is a second water molecule. From this mechanism it can be seen that the expulsion of the leaving group is catalysed by the general acid HB⁺.

The structure of the transition states (a) and (b) above are by no means certain, with respect to bond formation. Jencks and Carriuolo⁵⁷ proposed the six different transition states given below:

![Transition States Diagram]

(Ia) and (IIIb) are similar to (a) and (b) in the mechanism sequence. (IIa) shows the addition of a proton to the leaving alcohol molecule, which must follow a previous proton removal from a water molecule to preserve the correct stoichiometric composition of the transition state and pH dependence of the rate. Structure (II) involves proton transfer to and from the carbonyl oxygen atom to aid hydroxide addition to the ester or alkoxide expulsion from an addition intermediate. Series (a) and (b) vary only in whether a more or less fully formed bond
exists between carbon and the attacking water molecule, i.e., whether or not there is formation of an intermediate tetrahedral addition compound.

iv) The reaction mechanism of nucleophilic catalysis.

The reaction mechanism for nucleophilic catalysis can be written as in equation (17). 79

\[
\begin{align*}
\text{R-C-OR} & \xrightarrow{k_1} \text{R-C-OH} & \xrightarrow{k_2} \text{R-C-OR} \\
+ \text{N} & \xrightarrow{k_3} \text{R-C-OH} & \xrightarrow{k_4} \text{R-C-OR} & \xrightarrow{k_5} \text{R-C-OH} + \text{HOH} + \text{N} \\
\end{align*}
\]

(a)

If the intermediate (a) is more stable than the ester, no hydrolysis will occur. Also, if step 5 is rate limiting, the nucleophile itself may act as an inhibitor to hydrolysis. For the reaction to be a true example of nucleophilic catalysis, the intermediate (a) must react faster with water than the ester.

The methods by which a nucleophilic catalysis may be distinguished from general base catalysis have already been discussed, although a few points remain which help to emphasize the importance of using the collective results of all these methods as opposed to relying on one or two isolated examples.

The deuterium oxide isotope effect \( \left( \frac{k_{\text{H}_2\text{O}}}{k_{\text{D}_2\text{O}}} \right) \) for nucleophilic catalysis, which does not contain a slow rate limiting proton transfer, should be unity. Some examples are known, however, where a secondary isotope effect plays an
important part in the mechanism and produces an isotope effect between 1 and 2. Bender et al.\textsuperscript{30} found that the hydrolysis of 2,4-dinitropheny lacetate\textsuperscript{2} catalysed by acetate ions, is an example of nucleophilic catalysis, but the deuterium isotope effect gave a value of 1.8. Similar results were obtained for the hydrolysis of aspirin (an example of intramolecular nucleophilic catalysis by the carboxylate ion). These secondary deuterium oxide effects may be calculated by assuming a transition state structure and using the method of Buntin and Shiner.\textsuperscript{31}

v) \textbf{General base catalysed nucleophilic catalysis.}

It is not always possible or necessary, to distinguish between general base catalysis and nucleophilic catalysis. Either of these two processes may be carried out by a given substance, which, by definition is at one and the same time both a nucleophile and a general base.

The imidazole catalysed hydrolysis of \textit{p}-nitrophenyl benzoates, with electron withdrawing substituents in the acyl component, has been found by Jencks and Caplow\textsuperscript{32} to contain a third order term in the rate equation. It was also found that this reaction had an isotope effect of 1.81 and it was concluded to be a general base catalysed nucleophilic reaction between imidazole and ester. The nucleophilic reaction of imidazole with phenyl acetate is catalysed by the hydroxide ion which probably acts as a general base catalyst.\textsuperscript{33}

vi) \textbf{General base and nucleophilic catalysis in non-polar solvents.}

In 1960, Bender\textsuperscript{34} compiled a review on the mechanisms of
catalysis of nucleophilic reactions of carboxylic acid derivatives. Almost all the reactions listed dealt with reaction in a polar (usually hydroxylic) medium. Relatively little work has been done to investigate the general base and nucleophilic catalysed reactions of carboxyl compounds in non-polar solvents.21,22

Litvinenko and Kirichenko35 studied the reaction of m-chloroaniline with bensoyl chloride in benzene, using substituted pyridine bases. The reaction was found to follow the rate equation:

\[
\frac{dx}{dt} = k_0(a-x)(b-x) + k_B(a-x)(b-x) + k_g(a-x)(b-x)x.
\]

where \(a = \text{BzCl}\) and \(b = m-\text{ClC}_6\text{H}_4\text{NH}_2\) and \(k_0\), \(k_B\) and \(k_g\) are the rate constants of the non-catalysed, the catalysed and the autocatalysed reactions respectively. The mechanism proposed is given below:

\[
\begin{align*}
\text{R} & \text{Cl} \quad \text{fast} \quad \text{R} & \text{Cl}^- \\
\text{(i)} + \text{ArNH}_2 & \quad \text{slow} \quad \text{R} & \text{O} \quad \text{N}^+\text{H} \quad \text{Cl}^-
\end{align*}
\]

A plot of the Hammett36 substituent effects constant, \(\sigma\), against the logarithm of the rate constant, \(k_B\), gives a straight line with a slope of -3.74. A Brønsted correlation, constructed from these results, shows considerable scatter giving a value
of $\xi = 0.46$ (ignoring $k_B$ for the reaction with dimethylamino-
pyridine which appears rather high). Usually, in polar media,
the formation of the nucleophilic intermediate is the slow step
followed by a rapid reaction with the acyl accepting molecule.
The value of $\xi$ is low for a nucleophilic reaction, falling in
the region expected for general base catalysis.

The catalytic effect of imidazole on the solvolysis of
p-nitrophenyl acetate has been investigated using various
solvents. In $N,N$-dimethylacetamide and $N,N$-dimethylformamide,
which are strong hydrogen bond accepting solvents, the reaction
velocities are large. However, when only weak hydrogen bonds
can be formed with the solvent i.e. acetone and tetrahydrofuran,
the reaction velocities are small. The mechanism was assumed
to proceed via an acylimidazole intermediate. If imidazole
were hydrogen-bonded to a hydrogen acceptor, $A$, the reaction
rate would be enhanced. If, on the other hand, imidazole acts
as a hydrogen bond acceptor to $HA$ then the rate will be
depressed.

When chloroform was used as a solvent the catalytic power
of imidazole was prohibited.

The mutarotation of glucose has been studied in benzene
solution, and although it is not a reaction of a carboxylic
acid derivative, it is interesting because of its proposed
reaction mechanism. Swain and Brown$^{39,30}$ found that the
mutarotation of 2,3,4,6-tetramethyl-$D$-glucose in benzene gave
the third order rate expression:

\[ k_{ex} = (k + k') \cdot \text{(Pyridine)} \cdot \text{(Phenol)} \]

where \( k_{ex} \) is the experimental pseudo first order rate constant, \( k \) and \( k' \) are the rate constants for the forward and reverse reactions. These workers interpreted their results to mean that this is an example of concerted general acid-base catalysis. In 1960, Pocker\(^1\) proposed the alternative mechanism of general base catalysis by a phenoxide ion within a pyridinium-phenoxide ion pair.

\[ \text{phenol} + \text{HO}^- \rightarrow \text{phenoxide}^- \]

Later work by Rony\(^2\) suggests that the latter mechanism is correct, but it is conceded that, owing to the difficulty in distinguishing between mechanisms with the same transition state stoichiometry, concerted acid-base catalysis may still occur.

Bonner et al.\(^3,4\) investigated the catalytic effect of pyridine bases on the acetylation of phenols and alcohols with acetyl trifluoroacetate in carbon tetrachloride. \( p \)-Chlorophenol reacts with this unsymmetrical acid anhydride to form, almost exclusively the acetate, the reaction being first order in both the phenol and the anhydride. Reaction occurred at the acetate carbonyl carbon for two reasons: (1) the steric hindrance afforded by the trifluoromethyl group at the other end of the molecule and (2) the ease with which the trifluoroacetate ion can act as a leaving group compared with the acetate ion. Neglecting these points one would suspect reaction to occur at
the more electrophilic carbonyl carbon next to the trifluoromethyl group.

When pyridine is added to this system, there is an increased rate of reaction, accompanied by some trifluoroacetate production. This can be explained by the increased nucleophilicity of the hydroxyl oxygen resulting from hydrogen bond formation with pyridine. Hence the bond breaking step of the acylation becomes less important. The rate constant for trifluoroacetylation of p-chlorophenol is proportional to the square of the base concentration, the second pyridine molecule probably solvating the leaving acetate group.

When a solution of phenol and acetyl trifluoroacetate in carbon tetrachloride is shaken with an alkaline aqueous phase, there is an immediate reaction producing only the trifluoroacetate. Phenol is partially converted to the phenate ion in an aqueous alkaline medium and the reaction with acetyl trifluoroacetate probably occurs via this ion in the carbon tetrachloride phase or at its interface with the aqueous medium. The two important factors which seem to determine the ester product are (i) the nucleophilicity of the phenol and (ii) the nature of the leaving group. The phenate ion is highly nucleophilic, tending to minimize the effect of the leaving group and hence reaction proceeds at the more electrophilic carbonyl carbon.

The trifluoroacetylation of hydroxy-compounds with trifluoroacetic anhydride in the presence of pyridine has been investigated in carbon tetrachloride. It was felt that this system may proceed through a nucleophilic catalysis, and competitive reactions between p-cresol and p-chlorophenol were
carried out to test this theory. Pyridine was found to be a better catalyst for \( \text{p-} \)chlorophenol than for \( \text{p-} \)cresol, which is indicative of general base rather than nucleophilic catalysis.

Acetic anhydride and phenols do not react alone in carbon tetrachloride, although alcohols are acetylated at a measurable rate.\(^7\) Acetylation does occur when pyridine is added to the phenolic system and the reaction is first order in the phenol. The reaction velocity, when carried out at \(0^\circ\), is observed to reach a limiting value as the pyridine concentration is increased. Similar results are obtained at \(25^\circ\). As the pyridine concentration is increased, the degree of hydrogen bonding between the pyridine and phenol increases until, when the limiting rate velocity is reached, all the phenol is complexed. A parallelism between the percentage hydrogen-bonded species and the rate constants is observed for the reaction of \(\text{p-} \)chlorophenol with acetic anhydride in the presence of pyridine at \(0^\circ\). Figures illustrating this important observation are given below.

<table>
<thead>
<tr>
<th>Pyridine ((x \times 10^2\text{M}))</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen-bonded form (%)</td>
<td>32</td>
<td>54</td>
<td>76</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>(10^5 k \text{ (sec}^{-1}))</td>
<td>1.5</td>
<td>2.0</td>
<td>2.65</td>
<td>3.03</td>
<td>3.25</td>
</tr>
</tbody>
</table>

Part of this thesis continues the investigation of the reaction of hydroxy-compounds with anhydrides in carbon tetrachloride.
SECTION 2.

EXPERIMENTAL

A. Materials.

Solvents.

Carbon tetrachloride.

"AnalaR" B.D.H. carbon tetrachloride was allowed to stand over calcium hydroxide for 12 hours and then fractionally distilled b.p. 77°.

Toluene.

"AnalaR" B.D.H. toluene was stored over calcium chloride for 24 hours and then fractionally distilled b.p. 111°.

Water.

De-ionised, distilled water was used as the reaction solvent.

Chloroform.

"AnalaR" Hopkin and Williams chloroform used without further purification.

Phenols.

m-Bromophenol.

Koch-Light. m-bromophenol was redistilled, b.p. 232-234°.

p-Bromophenol.

B.D.H. "Laboratory Reagent" p-bromophenol was redistilled, b.p. 238-239°.

m-Chlorophenol.

B.D.H. "Laboratory Reagent" m-chlorophenol was redistilled, b.p. 214°.

p-Chlorophenol.

B.D.H. "Laboratory Reagent" p-chlorophenol was redistilled, b.p. 219°.

p-Cresol.

B.D.H. "Laboratory Reagent" p-cresol was redistilled b.p. 201°.
o-Fluorophenol.

Kodak o-fluorophenol was used without further purification.

p-Fluorophenol.

Eastman p-fluorophenol was redistilled, b.p. 184-186°.

p-Methoxyphenol.

Koch-Light p-methoxyphenol was recrystallised from carbon tetrachloride, m.p. 54-55°.

o-Nitrophenol.

B.D.H. "Laboratory Reagent" o-nitrophenol was recrystallised from ethanol, m.p. 45-46°.

m-Nitrophenol.

B.D.H. "Laboratory Reagent" m-nitrophenol was recrystallised from chloroform, m.p. 94-95°.

p-Nitrophenol.

B.D.H. "Laboratory Reagent" p-nitrophenol was recrystallised from toluene, m.p. 113-114°.

Phenol.

"AnalaR" B.D.H. phenol was redistilled, b.p. 180-181°.

m-Nitrophenol-d.

m-Nitrophenol (1g) was dissolved in deuterium oxide (25g) in a stoppered flask. Warming was required to completely dissolve the phenol, and then the solution was left for 12 hours at room temperature. On cooling the solution to 0° the phenol was precipitated and the water decanted off in a "dry box". The crystals were freeze dried. The procedure was repeated and the phenol recrystallised from chloroform. An infrared spectrum of the phenol in carbon tetrachloride showed one absorption at 3611 cm⁻¹ (due to the hydroxyl stretching in m-nitrophenol) and
another at 2670 cm\(^{-1}\) (due to the OD stretching in \(m\)-nitrophenol-d). The product was found to be 71.4\% deuterated by the usual infrared method (see this Section, D), m.p. 96\°.

**Alcohols.**

**Ethanol.**

Magnesium turnings (5 g, clean and dry) and iodine (0.5 g) were placed in a round bottomed flask together with 99\% ethanol (75 cm\(^3\)). The mixture was warmed until the iodine had disappeared. Heating was then continued until all the magnesium was converted to magnesium ethylate. Absolute ethanol (900 cm\(^3\)) was then added and the mixture refluxed for 30 minutes. The alcohol was then distilled directly into a storage container, b.p. 78\°.

**\(o\)-Methoxybenzyl alcohol.**

Koch-Light \(o\)-methoxybenzyl alcohol was redistilled under reduced pressure, b.p. 86-90\°/0.5 mm Hg.

**\(p\)-Methoxybenzyl alcohol.**

Koch-Light \(p\)-methoxybenzyl alcohol was redistilled under reduced pressure, b.p. 81-85\°/0.05 mm Hg.

**2-Phenylethanol.**

Eastman 2-phenylethanol was used without further purification.

**3-Phenyl-1-propanol.**

Aldrich 3-phenyl-1-propanol was redistilled, b.p. 235\°.

**2-(2-Pyridyl)ethanol.**

Aldrich 2-(2-pyridyl)ethanol was redistilled under reduced pressure, b.p. 62-64\°/0.05 mm Hg.

**3-(2-Pyridyl)-1-propanol.**

Emmanuel 3-(2-pyridyl)-1-propanol was redistilled under reduced pressure, b.p. 92-94\°/0.2 mm Hg.
3-(4-Pyridyl)-1-propanol.

Merck 3-(4-pyridyl)-1-propanol was used without further purification.

Acid anhydrides.

Acetic anhydride.

"AnalaR" B.D.H. acetic anhydride was redistilled, b.p. 133-135°.

Benzoic anhydride.

B.D.H. "Laboratory Reagent" benzoic anhydride was recrystallised from petroleum ether, m.p. 40°.

Isobutyric anhydride.

Koch-Light isobutyric anhydride was redistilled, b.p. 179-181°.

Pivalic anhydride.

B.D.H. "Laboratory Reagent" pivalic anhydride was redistilled, b.p. 190°.

Propionic anhydride.

B.D.H. "Laboratory Reagent" propionic anhydride was redistilled, b.p. 168°.

Trifluoroacetic anhydride.

Koch-Light trifluoroacetic anhydride was placed in a round bottomed flask containing phosphorus pentoxide. This flask was then attached to a vacuum system and allowed to stand for approximately 30 minutes before being evacuated. The trifluoroacetic anhydride was then distilled very slowly at 0.1 mm Hg into a weighed flask immersed in liquid nitrogen. The second flask was provided with a tap so that it could be periodically removed from the system and weighed. When the required amount of trifluoroacetic anhydride had been
transferred, the collecting vessel was placed in a "dry box" and the anhydride used as soon as possible. Solutions of this anhydride in carbon tetrachloride were always made up to the mark in a "dry box".

Acetyl trifluoroacetate.

Acetyl trifluoroacetate was prepared by transferring a known amount of trifluoroacetic anhydride into a collecting vessel as above and then into a "dry box". A solution was then made up in carbon tetrachloride and to this was added an equimolar solution of acetic anhydride. This solution was left for at least one week. During this period the infrared absorption bands at 1760 and 1820 cm\(^{-1}\) due to acetic anhydride and those at 1800 and 1860 cm\(^{-1}\) due to trifluoroacetic anhydride, were slowly replaced by bands at 1780 and 1850 cm\(^{-1}\) due to acetyl trifluoroacetate. When these changes were complete the acetyl trifluoroacetate solution was ready for use in the quenching procedure.

**Acids.**

Acetic acid.

"AnalaR" B.D.H. acetic acid was redistilled, b.p. 118°.

Pivalic acid.

B.D.H. "Laboratory Reagent" pivalic acid was used without further purification.

**Pyridine bases.**

3-Bromopyridine.

Koch-Light 3-bromopyridine was used without further purification.

2,4,6-Collidine.

B.D.H. "Laboratory Reagent" 2,4,6-collidine was used
without further purification.

4-Dimethylaminopyridine.

Emanuel 4-dimethylaminopyridine was recrystallised from ligroin, m.p. 110-111°.

2-Dimethylaminopyridine.

Emanuel 2-dimethylaminopyridine was used without further purification.

3-Ethylpyridine.

Koch-Light 3-ethylpyridine was redistilled, b.p. 165°.

4-Ethylpyridine.

Koch-Light 4-ethylpyridine was redistilled, b.p. 167°.

2,6-Lutidine.

B.D.H. "Laboratory Reagent" 2,6-lutidine (200g) was warmed with urea (30g) and water (25 cm³) to 80°. The white crystalline complex formed was filtered off and washed rapidly with water. The crystals were added to water (130 cm³) and the azeotrope distilled at 90°. Solid sodium hydroxide was added to the azeotrope and 2,6-lutidine separated. The 2,6-lutidine was fractionally distilled over solid sodium hydroxide and the fraction collected at 141°. The procedure was repeated.

b.p. 141°.

3,4-Lutidine.

Emanuel 3,4-lutidine was redistilled, b.p. 164°.

3,5-Lutidine.

Emanuel 3,5-lutidine was redistilled, b.p. 170-171°.

2-Picoline.

B.D.H. "Laboratory Reagent" 2-picoline was redistilled, b.p. 128°.
3-Picoline.
   Aldrich 3-picoline was redistilled, b.p. 144°.
4-Picoline.
   Koch-Light 4-picoline was redistilled, b.p. 145°.
Pyridine.
   "Analar" B.D.H. pyridine was redistilled, b.p. 113-115°, and stored over potassium hydroxide.

Iso-Butylamine.
   B.D.H. "Laboratory Reagent" iso-butylamine was used without further purification.
Imidazole.
   B.D.H. "Laboratory Reagent" imidazole was recrystallised twice from carbon tetrachloride, m.p. 38.5-39.5°.
2-Methylimidazole.
   B.D.H. "Laboratory Reagent" 2-methylimidazole was used without further purification.
Triethylene diamine.
   B.D.H. "Laboratory Reagent" triethylene diamine was used without further purification.
1,3-Bis-(dimethylamino)naphthalene.
   Emanuel 1,3-bis-(dimethylamino)naphthalene was recrystallised from carbon tetrachloride, m.p. 47-49°.
Mesitylene.
   B.D.H. "Laboratory Reagent" mesitylene was redistilled, b.p. 164-165°.
M-Xylene.
   B.D.H. "Laboratory Reagent" M-xylene was redistilled, b.p. 140°.
Durone.

B.D.H. "Laboratory Reagent" Durone was used without further purification.

p-Dichlorobenzene.

B.D.H. "Laboratory Reagent" p-dichlorobenzene was recrystallised from petroleum ether, m.p. 53\(^\circ\)C.

Quinoline.

B.D.H. "Laboratory Reagent" quinoline was redistilled, b.p. 237\(^\circ\)C.

Magnesium sulphate.

B.D.H. "Laboratory Reagent" magnesium sulphate (dried) was used directly.

Potassium hydrogen carbonate.

"AnalaR" B.D.H. potassium hydrogen carbonate was used directly.

Tetrahexylammonium benzoate.\(^{100}\)

Freshly precipitated silver oxide (17.4g) was added, in several portions, with prolonged shaking, to a solution of tetrahexylammonium iodide (Kodak, 12.4g) in methanol-water (80 : 20). To ensure complete reaction, this mixture was shaken for one hour, and then filtered. The hydroxide solution was then neutralised with benzoic acid, using B.D.H. pH paper (7-3.5) as indicator. The solvent was evaporated off at about 120\(^\circ\)C using a rotary evaporator. The resulting yellow oil was dried in a vacuum desiccator, under reduced pressure, over phosphorus pentoxide for several days. After approximately six months standing this material crystallised. No impurities could be detected using thin layer or gas liquid chromatography. Element
analysis gave: C, 75.00%; H, 12.15%; N, 2.93;

$C_{31}H_57N_2O_2\cdot 0.5H_2O$ requires: C, 76.80%; H, 12.06%; N, 2.93.

The last traces of water are difficult to remove.$^{100}$

**Esters.**

p-Chlorophenyl acetate.

Ice (44g) and acetic anhydride (8 cm$^3$) were added to a solution of p-chlorophenol (6g) in 10% aqueous sodium hydroxide (40 cm$^3$). This mixture was shaken for five minutes, carbon tetrachloride was added and the organic layer separated. This was washed twice with saturated aqueous potassium hydrogen carbonate, once with water, and then dried over magnesium sulphate. The solution was then fractionally distilled and the fraction collected at 228-230°.

The following acetates were prepared in a similar manner:

- p-Bromophenyl acetate $\quad$ b.p. 233-239°
- p-Cresyl acetate $\quad$ b.p. 212-214°
- p-Methoxyphenyl acetate $\quad$ b.p. 192°
- p-Methyl phenyl acetate was recrystallised from carbon tetrachloride, m.p. 31-32°.
- p-Nitrophenyl acetate was recrystallised from petroleum ether, m.p. 54-55°.
- Phenyl acetate $\quad$ b.p. 192-193°.
- p-Chlorophenyl trifluoroacetate.

p-Chlorophenol (10g) and trifluoroacetic anhydride (30g) were refluxed in the presence of sodium trifluoroacetate (0.3g) for 30 minutes. Carbon tetrachloride (5 cm$^3$) was added and the solution washed twice with saturated aqueous potassium hydrogen carbonate and once with water. The solution was then fractionally distilled and the fraction boiling at 161-162°.
The following trifluoroacetates were prepared in a similar manner:

- Phenyl trifluoroacetate  b.p. 148°.
- m-Nitrophenyl trifluoroacetate  b.p. 233-235° (this compound was not washed with bicarbonate).

3-(4-Pyridyl)-1-propyl acetate.

3-(4-Pyridyl)-1-propanol (30g) was added to a solution of acetic anhydride (100 cm³) and pyridine (7 cm³) in carbon tetrachloride and the mixture gently refluxed for 10 hours. The solution was then cooled and washed with saturated aqueous bicarbonate (200 cm³) followed by water (200 cm³). The organic phase was then dried over magnesium sulphate, filtered, and the solvent removed by rotary evaporation. The resulting dark brown liquid was fractionally distilled under reduced pressure. The fraction boiling at 120-121°/0.4 mm Hg was collected.

3-(2-Pyridyl)-1-propyl acetate was prepared in a similar manner, b.p. 95-96°/0.4 mm Hg.

3-Phenyl-1-propyl acetate.

3-Phenyl-1-propanol (39g) was dissolved in glacial acetic acid (50 cm³) and concentrated sulphuric acid added (1 cm³). This mixture was gently refluxed for nine hours. The solution was cooled and washed with water (200 cm³), saturated aqueous bicarbonate (100 cm³) and then water again (200 cm³). The remaining liquid was then dried over magnesium sulphate, filtered and then fractionally distilled. The fraction boiling at 245-246° was collected.
Phenethyl acetate was prepared in a similar manner, b.p. 224°.

p-Chlorophenyl benzoate.

p-Chlorophenol (3g) was dissolved in 10% sodium hydroxide solution (45 cm³) in a 250 cm³ flask fitted with a cork stopper. To this flask was added benzoic chloride (6 cm³), the cork fitted, and the contents shaken vigorously for 15 minutes. Solid ester was filtered at the pump and washed with ethanol. p-Chlorophenyl benzoate was recrystallised from ethanol, m.p. 87°.

m-Nitrophenyl pivalate.

A solution of m-nitrophenol (12g) in 10% sodium hydroxide (90 cm³) was added to a mixture of pivalic anhydride (31.5g) and ice (90g). The mixture was shaken for 5 minutes and carbon tetrachloride (5 cm³) added. The pivalate was filtered at the pump and washed several times with cold water. It was then dissolved in chloroform, dried over magnesium sulphate, filtered and then the solvent removed by rotary evaporation. The cream coloured solid was recrystallised from acetone:water (30:70), m.p. 82-82.5°.

m-Nitrophenyl pivalate.

Pivaloyl chloride (10g, freshly distilled) was added to a solution of m-nitrophenol (12g) in anhydrous pyridine (30g). After the initial reaction had subsided, the mixture was warmed for 10 minutes and then poured, with vigorous stirring, into iced water. The resulting precipitate was washed extensively with 5% sodium carbonate and recrystallised twice from ethanol, m.p. 93-95°.

Ethyl acetate.

"AnalaR" B.D.H. ethyl acetate was used without further purification.
B. Kinetic experiments.

Reaction of acetic anhydride with hydroxy-compounds in carbon tetrachloride.

Only general procedures are reported in this Section. Any changes in the quenching or analysis techniques are given in Section 3.

i) Infrared measurements.

Spectra were recorded on either a Perkin-Elmer 337 Infracord or a Perkin-Elmer 257 spectrophotometer. Matched 1 mm and 5 mm potassium bromide cells were used, the reference being filled with carbon tetrachloride. The slit control was set at N.

ii) Kinetic procedure.

When acetic anhydride was reacted with a phenol, the following procedure was adopted. The reactions were usually carried out at 25±0.05°, this temperature being obtained by immersing the reaction vessel in a thermostatically controlled water bath. During variable temperature experiments (Section 3 A(xiii)), a cooling coil was used, attached to a Churchill cooling machine. The temperature of 0° was obtained by immersing the reaction vessel in a Dewar flask filled with distilled water and pure ice at equilibrium. An error undoubtedly arises because the volumetric apparatus used in this work had been calibrated at 20°. No attempt was made to recalibrate this apparatus at the temperature of the kinetic experiments. Molarity instead of molality was used throughout the work introducing another error, but for ease of calculation, and adherence to convention, molarity values were retained. These errors are usually small. Also, the conclusions drawn
from this work are mostly based on series trends and will still be valid under more stringent experimental conditions. No conclusions are drawn from small rate differences.

Reagent solutions were made up to the mark at the temperature of the kinetic experiment, 30 minutes being allowed for the solutions to attain thermal equilibrium. The reaction vessel was a 50 cm³ volumetric flask, oven baked for at least 12 hours. The vessel was cooled in a desiccator containing calcium chloride. Different reaction vessels were used in repeat kinetic experiments. To initiate the reaction, a 2 cm³ aliquot of phenol solution was added to a solution of anhydride plus any additive. A stopclock was started when half the phenol solution had been delivered, and the reaction mixture shaken thoroughly as soon as possible after initiation.

A solution of phenol and acetic anhydride, when shaken with bicarbonate solution, produces the acetate. Hence, the reaction cannot be quenched by this method (see below). When a phenol and acetyl trifluoroacetate solution is shaken with bicarbonate only the trifluoroacetate is produced and this is used in the quenching procedure. 1 cm³ samples were removed after measured time intervals, and added to a carbon tetrachloride solution of acetyl trifluoroacetate (4 cm³) and immediately shaken with saturated aqueous potassium bicarbonate (5 cm³). The anhydride is removed by hydrolysis. The organic phase was then dried over magnesium sulphate, filtered, and the infrared spectrum recorded using 5 mm cells.

iii) Quantitative analysis.

The solution to be analysed will contain a mixture of
phenyl acetate and phenyl trifluoroacetate, their added molarity equaling that of the initial phenol (0.01 M). Phenyl acetates absorb infrared light at about 1780 cm\(^{-1}\) whereas the phenyl trifluoroacetates absorb around 1810 cm\(^{-1}\). Hence, although the two absorption bands are resolved, considerable overlap between them still occurs. A calibration curve was constructed from a mixture of the two esters, the total molarity being 0.01 M. A plot of transmission (of the acetate at 1780 cm\(^{-1}\)) against molarity was a smooth curve from which the concentration of the acetate could be deduced. None of the pyridine bases, or other additives, used in this work affected this method of analysis. However, the ester mixtures used to construct the calibration curve were affected by the quenching technique, giving slightly increased transmission values. These values gave a more accurate calibration curve, from which the acetate molarity in the reaction mixture could be deduced. All the calibration curves used were constructed from esters which had been subjected to the quenching technique. Unless stated otherwise, a calibration curve was constructed separately for each phenol used.

When alcohols were reacted with acetic anhydride, the same kinetic procedure was adopted as described above. The quenching and analysis techniques were different. A solution of alcohol and acetic anhydride does not form any acetate when shaken with bicarbonate, thus making the quenching procedure more straightforward. A 2 cm\(^3\) aliquot of reaction mixture was shaken with saturated aqueous bicarbonate and then washed with water (20 cm\(^3\)). The solution was then dried over magnesium sulphate,
filtered and the infrared spectrum recorded. 1 mm cells were
used. The molarity of the acetate was determined from a
previously obtained calibration curve of the acetate alone.

Gabb investigated this analysis technique and found that
the accuracy obtained from the calibration curves varies from
15% at low ester molarity (0.002 M) to 6% at high ester molarity
(0.008 M) on the p-chlorophenyl acetate/trifluoroacetate curve.
These errors arose from a 0.02 variation in transmittance values.
Here, ± 0.01 transmittance reproducibility was obtained,
reducing the errors to 3% at low molarities and 3% at high
molarities. The alkyl acetates gave transmittance
reproducibility to ± 0.005.

Reaction of carboxylic acid anhydrides with m-nitrophenol in
carbon tetrachloride.

Saturated aqueous potassium bicarbonate does not readily
hydrolyse pivalic anhydride and, hence, cannot be used to remove
this anhydride from the reaction mixture. Stronger alkaline
solutions will remove the anhydride, but also tend to hydrolyse
the ester product. Similar observations were made in the
propionic and isobutyric anhydride systems. To avoid this
difficulty, m-nitrophenol was used in these reactions, where the
unreacted m-nitrophenol (in the form of the m-nitrophenate ion)
can be detected by visible spectroscopy.

1) Visible measurements.

Visible spectra were recorded on a Perkin-Elmer 137 UV
spectrophotometer. Matched 1 cm glass cells were used, the
reference cell being filled with distilled water.
ii) **Kinetic procedure.**

The same experimental procedure was carried out, as in the reactions with acetic anhydride. Reactions were initiated by adding the catalyst solution (2 cm³) to the reactant solution (20 cm³).

iii) **Quantitative analysis of samples.**

m-Nitrophenol can be completely removed from carbon tetrachloride by shaking with water, and the m-nitrophenate ion has a very distinct absorption in the visible region of the spectrum at 390 nm (in bicarbonate solution). A straight line calibration is obtained by plotting m-nitrophenol molarity in carbon tetrachloride against absorbance at 390 nm in bicarbonate solution, after shaking with the phenol solution (see below).

To quench a sample of reaction mixture a 1 cm³ aliquot was run into a 4 cm³ aliquot of water in a separating funnel, and shaken for one minute. One minute was then allowed for the two phases to separate and the organic phase was then removed. A 1 cm³ aliquot of saturated aqueous bicarbonate was then added and the resulting coloured solution filtered. The visible spectrum was recorded.

C. **Competitive reactions. Product analysis by gas liquid chromatography.**

i) **Chromatographic measurements.**

Gas liquid chromatograms were recorded on a Perkin-Elmer Fractometer modified with a flame ionisation detector and an all glass column (4 ft x 4 mm). The stationary phase was Apiezon K (5% w/w) on celite, with nitrogen as carrier gas. The peak areas on the chromatogram were measured with a Kent chromalog
integrator or by cutting out and weighing the individual peaks. These two methods gave identical results.

ii) **Kinetic procedure.**

All reactions were carried out at 0°, initiation being achieved by adding the pyridine solution (2 cm³) to the reactant solution (20 cm³) of p-chlorophenol (0.05 M), p-cresol (0.05 M), and acetic anhydride (0.05 M). No quenching procedure was used.

iii) **Quantitative analysis of samples.**

p-Cresol and p-cresyl acetate had equal retention times on the chromatography column, and their combined peak could be used as an internal reference. The machine was calibrated with solutions of p-cresol and p-cresyl acetate (the combined molarity of which equaled 0.05 M) and p-chlorophenyl acetate. A plot of the ratio, area of reference peak/area of p-chlorophenyl acetate peak against the p-chlorophenyl acetate molarity, was a smooth curve. Each peak area was the average of three readings from 2, 2.5 and 3x10⁻³ cm³ injections. The reproducibility was good, giving the error in the calculated acetate molarity as ±2%.

D. **Association constant determinations.**

The hydroxyl group fundamental absorption in the infrared region of the spectrum occurs at about 3600 cm⁻¹. This absorption band was used to construct a Beer's Law correlation for the phenol or alcohol in carbon tetrachloride, low molarities being used to preclude intermolecular hydrogen bonding. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. This correlation was used to calculate directly the percentage hydrogen bonding in the intramolecularly hydrogen-bonded alcohols (Section 3, B (ii)).
The association constant between a phenol and base was found by adding the base to the phenol solution and noting the reduction in hydroxyl band transmittance. This was repeated at least 5 times at different base molarities. Assuming a 1:1 association, the concentration of hydrogen-bonded complex was calculated from the calibration curve, thus enabling the association constant to be deduced. Typical results are given below.

<table>
<thead>
<tr>
<th>4-picoline ($10^{-3}$ M)</th>
<th>p-chlorophenol ($10^{-3}$ M)</th>
<th>$K_{\text{association}}$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.94</td>
<td>3.3</td>
<td>151</td>
</tr>
<tr>
<td>10.40</td>
<td>3.3</td>
<td>153</td>
</tr>
<tr>
<td>13.87</td>
<td>3.3</td>
<td>153</td>
</tr>
<tr>
<td>17.34</td>
<td>3.3</td>
<td>146</td>
</tr>
<tr>
<td>20.80</td>
<td>3.3</td>
<td>140</td>
</tr>
</tbody>
</table>

$K = 149 \pm 9$ M$^{-1}$
 SECTION 3. RESULTS

A. Reaction of phenols with carboxylic acid anhydrides in the presence of basic catalysts.

i) Acetylation of phenols with acetic anhydride in the presence of pyridine in carbon tetrachloride at 25°.

Phenols (0.01 M) do not react with acetic anhydride (0.05 M) in carbon tetrachloride, even after several weeks, but when pyridine is present a reaction does occur. To initiate the reaction, a solution of the phenol (2 cm³) was added to the mixture of anhydride and pyridine (20 cm³). A stopclock was started when half the phenol solution had been added, and when addition was complete, the flask was shaken vigorously. Fast addition of the phenol was vital, and to obtain satisfactory kinetic results, a rapid flow pipette was used. After suitable time intervals an aliquot (1 cm³) was removed and quenched. The infrared spectra was recorded. From a previously obtained calibration curve the amount of acetate present in the reaction mixture could be determined. All the acetate products, except p-bromophenyl acetate and m-nitrophenyl acetate, were estimated from the calibration of p-chlorophenyl acetate. p-Bromophenyl acetate has two absorptions in the fundamental carbonyl region (1300-1600 cm⁻¹) at 1770 and 1780 cm⁻¹. A separate calibration curve was constructed for this acetate.

m-Nitrophenol is not very soluble in carbon tetrachloride and so the concentration of this phenol was reduced to 0.005 M in the reaction mixture. The high reactivity of m-nitrophenol also made it necessary to reduce the concentration of pyridine so that the reaction proceeded at a measurable rate. Since m-nitrophenyl trifluoroacetate is hydrolysed by a saturated
aqueous solution of potassium bicarbonate, it was also necessary to change the quenching technique. A 2 cm³ sample was removed from the reaction mixture and shaken with water for one minute to remove unreacted \( m \)-nitrophenol. The organic phase was then separated and shaken for one minute with saturated aqueous potassium bicarbonate and finally washed again with water for one minute. After drying, the infrared spectrum was recorded. From a calibration curve of \( m \)-nitrophenyl acetate the product concentration could be estimated. 1 mm cells were used.

Production of the acetate followed pseudo first order kinetics in all cases. It was usual to follow a reaction between 20-80\%, all reactions eventually going to completion. The pseudo first order rate constants were determined by a graphical method (plotting \( \log \frac{a}{(a-x)} \) against time, where \( a = \) initial concentration of phenol and \( x = \) concentration of acetate; the slope of this line gives the rate constant \( k_e \)) and each value is the average from two kinetic experiments. Rate constants were reproducible to \( \pm 10^ {-3} \) although usually the results were better than this.

Shaking the reaction vessel after mixing the reactants did not appear to critically affect the rate constant. Results for one pair of experiments with \( m \)-bromophenol are given below in Table 3:1 and illustrated in Figure 1. In experiment two, the reaction mixture was not shaken until ten seconds after all the phenol solution had been added and, although there now appears to be a substantial intercept on the ordinate, the slopes of the two lines are very similar. A summary of the results obtained
for all the phenols is given in Table 3:2.

**TABLE 3:1**

Reaction of m-bromophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of pyridine (0.02 M).

**Experiment one.**

<table>
<thead>
<tr>
<th>Time (seconds)$\times 10^{-2}$</th>
<th>Molarity of acetate $\times 10^4$</th>
<th>$\log a/(a-x) \times 10^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>15</td>
<td>7.1</td>
</tr>
<tr>
<td>36</td>
<td>25</td>
<td>12.5</td>
</tr>
<tr>
<td>54</td>
<td>35</td>
<td>18.7</td>
</tr>
<tr>
<td>72</td>
<td>41</td>
<td>22.9</td>
</tr>
<tr>
<td>90</td>
<td>48.5</td>
<td>23.8</td>
</tr>
<tr>
<td>108</td>
<td>54</td>
<td>33.7</td>
</tr>
<tr>
<td>132</td>
<td>61.5</td>
<td>41.5</td>
</tr>
<tr>
<td>162</td>
<td>70</td>
<td>52.3</td>
</tr>
<tr>
<td>198</td>
<td>85</td>
<td>82.4</td>
</tr>
</tbody>
</table>

$k_e = 6.97 \times 10^{-5}$ sec$^{-1}$.

**Experiment two.**

<table>
<thead>
<tr>
<th>Time (seconds)</th>
<th>Molarity of acetate</th>
<th>$\log a/(a-x) \times 10^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>32</td>
<td>16.8</td>
</tr>
<tr>
<td>31.5</td>
<td>38.5</td>
<td>21.1</td>
</tr>
<tr>
<td>45</td>
<td>44</td>
<td>25.2</td>
</tr>
<tr>
<td>54</td>
<td>49</td>
<td>29.2</td>
</tr>
<tr>
<td>64.2</td>
<td>52.5</td>
<td>32.3</td>
</tr>
<tr>
<td>72</td>
<td>54</td>
<td>33.7</td>
</tr>
<tr>
<td>99</td>
<td>62.5</td>
<td>42.6</td>
</tr>
<tr>
<td>126</td>
<td>71.5</td>
<td>54.5</td>
</tr>
</tbody>
</table>

$k_e = 7.23 \times 10^{-5}$ sec$^{-1}$.

Average rate constant $k_e = 7.10 \times 10^{-5}$ sec$^{-1}$. 
Fig. 1 Reaction of m-bromophenol (0.01M) with acetic anhydride (0.05M) in the presence of pyridine (0.02M) in carbon tetrachloride at 25° C.
Fig. 2 Reaction between phenols (0.01M) and acetic anhydride (0.05M) in the presence of pyridine (0.02M) in carbon tetrachloride at 25°.

Slope gives 1.56
TABLE 3:2

Reaction of phenols (0.01 M) and acetic anhydride (0.05 M) in the presence of pyridine.

<table>
<thead>
<tr>
<th>Phenol</th>
<th>$10^5 k_e$ (sec$^{-1}$)</th>
<th>$\sigma^0$</th>
<th>Kassociation (M$^{-1}$)</th>
<th>$R^o$</th>
<th>$10^5 k_b$ (sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-cresol</td>
<td>1.16</td>
<td>-0.15</td>
<td>33.8</td>
<td>0.323</td>
<td>3.54</td>
</tr>
<tr>
<td>phenol</td>
<td>1.98</td>
<td>0</td>
<td>46.3</td>
<td>0.398</td>
<td>4.98</td>
</tr>
<tr>
<td>p-fluoro-</td>
<td>3.45</td>
<td>+0.17</td>
<td>69.1</td>
<td>0.483</td>
<td>7.07</td>
</tr>
<tr>
<td>p-chloro-</td>
<td>5.92</td>
<td>+0.27</td>
<td>112.8</td>
<td>0.602</td>
<td>9.83</td>
</tr>
<tr>
<td>p-bromo-</td>
<td>4.86</td>
<td>+0.26</td>
<td>110.0</td>
<td>0.594</td>
<td>8.19</td>
</tr>
<tr>
<td>m-chloro-</td>
<td>6.86</td>
<td>+0.37</td>
<td>98.9</td>
<td>0.570</td>
<td>12.03</td>
</tr>
<tr>
<td>m-bromo-</td>
<td>7.10</td>
<td>+0.38</td>
<td>124.0</td>
<td>0.621</td>
<td>11.43</td>
</tr>
<tr>
<td>m-nitro-a</td>
<td>17.50</td>
<td>+0.70</td>
<td>217.7</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ phenol concentration = 0.005 M, pyridine concentration = 0.01 M.

The association constant values are those found by Dierckx et al.\textsuperscript{102} using the infrared technique in carbon tetrachloride at 27$^\circ$. $\sigma^0$ values are those given by Taft.\textsuperscript{103}

The Hammett reaction constant, $\rho$, was found by plotting log $k_e$ against $\sigma^0$, to be +1.56 from the "best fit" straight line, Figure 2. Least squares analysis on this data gives $\rho = +1.52 \pm 0.03$. The use of $R^o$ and $k_b$ is discussed in Section 4.

The infrared spectrum of a solution of phenol and pyridine exhibits two absorption bands in the fundamental OH stretching region. The band at higher frequency is due to the free OH group, whereas the broader and more intense band at lower frequency can be attributed to the hydrogen-bonded OH group. It was of interest to determine whether any relationship exists between the rate constant and $\Delta \gamma_s$ (the difference in the two
absorption band frequencies). The same pyridine and phenol solutions, as used in the kinetic experiments, were subjected to infrared analysis using a Perkin-Elmer 325 spectrophotometer. The instrument slit program was set at 5, gain 3.50 and suppression 10. Matched 5 mm potassium bromide cells were used, the reference cell containing an equal concentration of pyridine as in the sample cell. Results, together with literature values, are given in Table 3:3.

**TABLE 3:3**
The difference in frequencies, $\Delta \nu_B$, between the free and the hydrogen-bonded hydroxyl groups in carbon tetrachloride solutions of phenols (0.011 M) and pyridine (0.022 M).

<table>
<thead>
<tr>
<th>Phenol</th>
<th>$\Delta \nu_B$ (this work)</th>
<th>$\Delta \nu_B$ (lit. value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-cresol</td>
<td>468</td>
<td>468-473</td>
</tr>
<tr>
<td>phenol</td>
<td>471</td>
<td>471</td>
</tr>
<tr>
<td>p-fluoro-</td>
<td>487</td>
<td>489</td>
</tr>
<tr>
<td>p-chloro-</td>
<td>510</td>
<td>510</td>
</tr>
<tr>
<td>p-bromo-</td>
<td>510</td>
<td>511</td>
</tr>
<tr>
<td>m-bromo-</td>
<td>-</td>
<td>517</td>
</tr>
<tr>
<td>m-chloro-</td>
<td>-</td>
<td>525</td>
</tr>
</tbody>
</table>

It was very difficult to determine the value for $\Delta \nu_B$ for the complexes involving m-bromo- and m-chlorophenol. Agreement with literature values for these two phenols was not obtained, due to the difficulty in estimating the centre of the hydrogen-bonded hydroxyl absorption. Towards lower frequencies the hydrogen-bonded absorption of the m-chlorophenol/pyridine complex shows considerable structure which masks the band centre, Figure 3. Only an approximate value can be found for $\Delta \nu_B$. The m-nitro-
Fig. 3 Infrared Spectra.

p-cresol (0.011M) with pyridine (0.022M).

m-chlorophenol (0.011M) with pyridine (0.022M).

m-nitrophenol (0.01M) with 4-picoline (0.011M).
phenol/4-picoline complex gives a more extreme example, showing well the difficulty in measuring $\Delta q$ as the strength of the hydrogen bond increases. No correlation was observed between $\Delta q$ and $\log k_c$ (or $\log k_b$), probably because of errors inherent in $\Delta q$.

ii) Reaction of p-chlorophenol (0.011 M) with acetic anhydride (0.05 M) in the presence of substituted pyridine bases (0.02 M) in carbon tetrachloride at 25°.

Fresh solutions of p-chlorophenol, acetic anhydride and pyridine were prepared and two reactions were followed kinetically to give an average value of the pseudo first order rate constant $k_c = 5.93 \times 10^{-5} \text{ sec}^{-1}$. This value is in good agreement with that found in the previous experiment. With the other pyridine bases the same first order dependence in the phenol was always observed. Results are given in Table 3:4.

<table>
<thead>
<tr>
<th>Base</th>
<th>$pK_a$</th>
<th>rate constant x $10^5$ (sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>5.20</td>
<td>5.93</td>
</tr>
<tr>
<td>3-picoline</td>
<td>5.65</td>
<td>17.1</td>
</tr>
<tr>
<td>3-ethylpyridine</td>
<td>5.65</td>
<td>21.8</td>
</tr>
<tr>
<td>4-picoline</td>
<td>6.00</td>
<td>34.7</td>
</tr>
<tr>
<td>4-ethylpyridine</td>
<td>6.00</td>
<td>39.7</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>6.46</td>
<td>99.6</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>6.73</td>
<td>0</td>
</tr>
<tr>
<td>2-picoline</td>
<td>5.96</td>
<td>0</td>
</tr>
</tbody>
</table>

As expected, the reaction rate increased as the basicity of the pyridine catalysts became greater. 2-Picoline and
Fig. 4 Reaction of p-chlorophenol (0.011M) with acetic anhydride (0.05M) in the presence of pyridine bases (0.02M) in carbon tetrachloride at 25°.

1. pyridine
2. 3-picoline
3. 3-ethylpyridine
4. 4-picoline
5. 4-ethylpyridine
6. 3,4-lutidine
2,6-lutidine are not catalysts for this reaction. A Brönsted plot (logarithm of the rate constant against the base strength of pyridine) gives a satisfactory straight line whose slope, determined by least squares analysis, is 0.93. These results are illustrated in Figure 4. The pK_a values are those of Feather and Gold.73

iii) Reaction of p-cresol (0.01 M) with acetic anhydride (0.05 M) in the presence of pyridine bases (0.02 M) in carbon tetrachloride at 25°C.

The catalytic effect of various pyridine bases on the reaction between p-cresol and acetic anhydride was investigated and the results are summarised in Table 3:5.

<table>
<thead>
<tr>
<th>Base</th>
<th>rate constant x 10^5 (sec^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>1.16</td>
</tr>
<tr>
<td>3-picoline</td>
<td>3.54</td>
</tr>
<tr>
<td>4-picoline</td>
<td>6.83</td>
</tr>
<tr>
<td>4-ethylpyridine</td>
<td>7.16</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>15.20</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>0</td>
</tr>
</tbody>
</table>

All these reactions showed a first order dependence in the phenol and a Brönsted plot gave β = 0.85.

iv) Reaction of p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of 4-picoline in carbon tetrachloride at 25°C.

Bonner and McNamara97 found that, in the reaction of p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of pyridine at 0°C, a limiting rate was reached as the
Fig. 5 Reaction of p-chlorophenol (0.01M) with acetic anhydride (0.05M) in the presence of 4-picoline.

![Graph showing the reaction rate constant]
pyridine concentration was increased. A similar result was found at 25° although the limiting rate value was not reached. The effect was explained by the complete formation of the hydrogen-bonded species between the phenol and pyridine at the higher base concentrations. Results obtained here with 4-picoline verify these earlier results and data are given in Table 3:6. These results are plotted in Figure 5. A plot of the concentration of the hydrogen-bonded complex at 50% reaction versus 4-picoline concentration is linear.

<table>
<thead>
<tr>
<th>4-picoline (M)</th>
<th>rate constant x 10^4 (sec^-1)</th>
<th>R</th>
<th>10^4k_b (sec^-1)</th>
<th>H-bonded complex (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.005</td>
<td>1.62</td>
<td>0.331</td>
<td>4.89</td>
<td>0.00156</td>
</tr>
<tr>
<td>0.010</td>
<td>2.54</td>
<td>0.520</td>
<td>4.88</td>
<td>0.00260</td>
</tr>
<tr>
<td>0.015</td>
<td>2.91</td>
<td>0.630</td>
<td>4.58</td>
<td>0.00315</td>
</tr>
<tr>
<td>0.020</td>
<td>3.47</td>
<td>0.709</td>
<td>4.89</td>
<td>0.00355</td>
</tr>
</tbody>
</table>

A close parallelism can be observed between the concentration of the hydrogen-bonded species (calculated at 50% reaction) and the experimental rate constant. As there was still approximately 30% p-chlorophenol present, which had not been complexed at the highest 4-picoline concentration, it is not surprising that a limiting reaction rate was not reached.

v) Reaction of m-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of pyridine bases in carbon tetrachloride at 25°.

The same type of rate dependence on the concentration of the base is seen here, as in previous reactions. The data in Table 3:7 are plotted in Figure 6. K_{ass} values for m-nitrophenol with 3-picoline and 4-picoline are 269 and 309 M^{-1} respectively.
Fig. 6 Reaction of $m$-nitrophenol (0.005M) with acetic anhydride (0.05M) in the presence of pyridine bases in carbon tetrachloride at 25°.
\[3'-\text{nicoline rate constant } \times 10^6 \quad R \quad 10^4 k_p \]

<table>
<thead>
<tr>
<th>(II) ( (\text{sec}^{-1}) )</th>
<th>( 10^4 k_p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0005</td>
<td>0.56</td>
</tr>
<tr>
<td>0.0025</td>
<td>2.09</td>
</tr>
<tr>
<td>0.0050</td>
<td>3.40</td>
</tr>
<tr>
<td>0.0100</td>
<td>5.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(II) ( (\text{sec}^{-1}) )</th>
<th>( 10^4 k_p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00125</td>
<td>2.72</td>
</tr>
<tr>
<td>0.00250</td>
<td>4.66</td>
</tr>
<tr>
<td>0.00315</td>
<td>5.48</td>
</tr>
<tr>
<td>0.00500</td>
<td>6.97</td>
</tr>
<tr>
<td>0.01000</td>
<td>8.8</td>
</tr>
</tbody>
</table>

From the curves in Figure 6 it is possible to estimate a value for the Brønsted reaction constant, \( c \), of about 1.0.

With 3-bromopyridine and quinoline acting as the base catalysts, rate constants of \( 5.13 \times 10^{-6} \text{sec}^{-1} \) and \( 1.70 \times 10^{-6} \text{sec}^{-1} \) respectively were obtained. These slow reactions did not give good straight lines when \( \log a/(a-x) \) was plotted against time, and were not studied further.

vi) Reaction of \( m \)-nitrophenol (0.005 M) with isobutyric anhydride (0.05 M) in the presence of pyridine bases (0.005 M) in carbon tetrachloride at 25°.

The reaction of \( m \)-nitrophenol with isobutyric anhydride was investigated in the presence of pyridine and substituted pyridine bases. The quenching technique was changed as reported
in Section 2. m-Nitrophenol was the only phenol which, when used in this reaction, allowed the products to be accurately estimated. As expected, isobutyric anhydride was less reactive than acetic anhydride due to steric, ponderal, and electronic field effects. First order dependence in the phenol was found in all the reactions. A Brönsted plot of log $k_e$ against $pK_a$ is linear, although the point for 3,5-lutidine lies below the line. A summary of results is given in Table 3:8. The $\sigma$ values are taken from a compilation made by McDaniel and Brown and the additivity of these constants is assumed. Brönsted and Hammett correlations are illustrated in Figure 7.

**TABLE 3:8**

<table>
<thead>
<tr>
<th>Base</th>
<th>$pK_a$</th>
<th>$10^6k_e$ (sec$^{-1}$)</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>5.20</td>
<td>0.60</td>
<td>0</td>
</tr>
<tr>
<td>2-picoline</td>
<td>5.96</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3-picoline</td>
<td>5.65</td>
<td>1.37</td>
<td>-0.069</td>
</tr>
<tr>
<td>4-picoline</td>
<td>6.00</td>
<td>2.79</td>
<td>-0.170</td>
</tr>
<tr>
<td>3-ethylpyridine</td>
<td>5.65</td>
<td>1.48</td>
<td>-0.07</td>
</tr>
<tr>
<td>4-ethylpyridine</td>
<td>6.00</td>
<td>3.29</td>
<td>-0.151</td>
</tr>
<tr>
<td>3,5-lutidine</td>
<td>6.15</td>
<td>2.89</td>
<td>-0.138</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>6.46</td>
<td>7.47</td>
<td>-0.239</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>6.73</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

The Brönsted reaction constant, $\beta$, obtained from Figure 7 is 0.87 and it is expected that the corresponding $\sigma$ value will be about -5. A good straight line is observed for the Hammett plot, the slope of which gives a value $\beta = -4.83$. The point for 3,5-lutidine lies on this line, suggesting that either the
Fig. 7 Reaction of m-nitrophenol (0.005M) with isobutyric anhydride (0.05M) with pyridine bases (0.005M) at 25°.

1. pyridine
2. 3-picoline
3. 4-ethylpyridine
4. 4-picoline
5. 4-ethylpyridine
6. 3,5-lutidine
7. 3,4-lutidine
experimentally determined value for the $pK_a$ is too high, or its value in water (the solvent in which the $pK_a$ was determined) is not a good measure of its electron donating power in carbon tetrachloride.

A typical kinetic experimental result is given in Table 3:9 for the reaction of $m$-nitrophenol ($0.005$ M) with isobutyric anhydride ($0.05$ M) in the presence of 3,5-lutidine ($0.005$ M) at $25^\circ$. In this work two principal analysis techniques have been used (see Section 2), and a comparison of the experimental data and accuracy of the two methods can be made from Tables 3:1 and 3:9.

<table>
<thead>
<tr>
<th>Time (seconds)</th>
<th>Phosphate ion $\times 10^4$ (M)</th>
<th>$\log a/(a-x)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>47.0</td>
<td>0.027</td>
</tr>
<tr>
<td>600</td>
<td>41.5</td>
<td>0.081</td>
</tr>
<tr>
<td>1020</td>
<td>37.0</td>
<td>0.131</td>
</tr>
<tr>
<td>1500</td>
<td>32.5</td>
<td>0.187</td>
</tr>
<tr>
<td>2100</td>
<td>27.5</td>
<td>0.260</td>
</tr>
<tr>
<td>2700</td>
<td>23.0</td>
<td>0.337</td>
</tr>
<tr>
<td>3300</td>
<td>19.0</td>
<td>0.420</td>
</tr>
<tr>
<td>3900</td>
<td>16.0</td>
<td>0.495</td>
</tr>
<tr>
<td>4500</td>
<td>13.5</td>
<td>0.569</td>
</tr>
<tr>
<td>5100</td>
<td>11.0</td>
<td>0.658</td>
</tr>
<tr>
<td>5700</td>
<td>9.0</td>
<td>0.745</td>
</tr>
</tbody>
</table>

$k_c = 2.92 \times 10^4$ sec$^{-1}$.

$m$-Nitrophenol-d was reacted under the same conditions as above, with isobutyric anhydride in the presence of 3-picoline and with 4-ethylpyridine. $m$-Nitrophenol was 71.4% converted to
m-nitrophenol-d after two exchange reactions with deuterium oxide. The pseudo first order rate constant for the reaction of m-nitrophenol-d, $k_D$, was determined from the corrected slope of a log $a/(a-x)$ against time plot. Correction was made at each time interval by calculating the m-nitrophenyl acetate produced by m-nitrophenol from the known $k_H$, and subtracting this value from the acetate product.

Analysis by visible spectroscopy depends, in this case, on m-nitrophenol and m-nitrophenol-d ionizing to the same degree in aqueous potassium bicarbonate solution. It was found that solutions of m-nitrophenol and 71.4% deuterated m-nitrophenol have the same absorbance value at 290 nm. Results are given in Table 3:10.

**TABLE 3:10**

Reaction of m-nitrophenol-d (0.0034 M) with isobutyric anhydride (0.05 M) in the presence of pyridine bases (0.005 M) at 25°C.

<table>
<thead>
<tr>
<th>Base</th>
<th>rate constant $k_D \times 10^4$</th>
<th>$k_H/k_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(sec$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>3-picoline</td>
<td>1.03</td>
<td>1.33</td>
</tr>
<tr>
<td>4-ethylpyridine</td>
<td>3.13</td>
<td>1.05</td>
</tr>
</tbody>
</table>

vii) Esterification of m-nitrophenol (0.005 M) with carboxylic acid anhydrides (0.05 M) in the presence of pyridine bases (0.005 M) in carbon tetrachloride at 25°C.

The effect of increasing the steric bulk around the anhydride carbonyl group on the rate of esterification has been investigated. From the dependence of reaction rate on steric
factors it is possible to obtain a useful insight into the structure of the transition state. The reaction series chosen was acetic, propionic, isobutyric and pivalic anhydrides with \( m \)-nitrophenol in the presence of bases. These reactions were followed as in the previous reaction (vi) and as described more fully in Section 2. The results obtained are summarized in Table 3:11, and illustrated in Figure 8 for the 4-picoline catalysed reaction.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>( E_g )</th>
<th>( E^c_g )</th>
<th>( 10^4 k_e )</th>
<th>( 10^4 k_b )</th>
<th>( 10^4 k_e )</th>
<th>( 10^4 k_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(sec(^{-1}))</td>
<td>(sec(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetic</td>
<td>0.00</td>
<td>0.00</td>
<td>6.97</td>
<td>13.15</td>
<td>3.40</td>
<td>6.79</td>
</tr>
<tr>
<td>Propionic</td>
<td>-0.07</td>
<td>-0.33</td>
<td>4.40</td>
<td>8.30</td>
<td>1.71</td>
<td>3.41</td>
</tr>
<tr>
<td>Isobutyric</td>
<td>-0.47</td>
<td>-1.08</td>
<td>2.79</td>
<td>5.26</td>
<td>1.37</td>
<td>2.74</td>
</tr>
<tr>
<td>Pivalic</td>
<td>-1.54</td>
<td>-2.46</td>
<td>0.54</td>
<td>1.02</td>
<td>0.11</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The rate constants for the acetic anhydride reactions are as given previously in Table 3:7. \( E_g \) and \( E^c_g \) values are those given by Taf\( t \)\(^{76} \) and Hancock\(^{105} \) respectively. A plot of \( \log k_e/k_o \) against \( E_g \), where \( k_o \) is the rate constant for the acetic anhydride, gives \( \delta \) values (the reaction constant) of \( 0.77 \pm 0.08 \) and \( 0.85 \pm 0.10 \) for the 4-picoline and 3-picoline reactions respectively. The Taft steric effects linear free energy relationship is given by:

\[
\log k_e/k_o = \sigma^{*} \epsilon^{*} + E_T + \delta E_g
\]

This equation can only be used to determine the steric effect of a group, if the polar term \( \sigma^{*} \epsilon^{*} \) is small, and the
Fig. 8 Reaction of m-nitrophenol (0.005M) with carboxylic acid anhydrides (0.05M) in the presence of 4-picoline (0.005M) at 25°.
resonance term, $E_r$, is negligible. The applicability of this equation to base catalysed reactions is discussed in Section 4.

viii) Reaction of $p$-chlorophenol (0.01 M) with acetic anhydride in the presence of pyridine (0.02 M) in carbon tetrachloride at $25^\circ$.

To determine the order of this reaction with respect to the anhydride, the pseudo first order rate constant was determined using different concentrations of the anhydride. The usual quenching and analysis techniques were unaffected by the larger anhydride concentrations. The results are summarized in Table 3:12. A plot of log acetic anhydride concentration against log rate constant is linear with a slope of 1.08. Hence, acetic anhydride has the order of one in the reaction. This is expected for both general base and nucleophilic catalysis. A graph of the rate constant plotted against the acetic anhydride concentration is also linear, Figure 9, the slope of which can be used to check values of $k_p$ calculated from preceding experiments (see Section 4).

<table>
<thead>
<tr>
<th>Rate constant $k_e \times 10^5$ (sec$^{-1}$)</th>
<th>acetic anhydride (M)</th>
<th>$\log(\text{Ac}_2\text{O})+2$</th>
<th>$\log k_e+5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.30</td>
<td>0.0523</td>
<td>0.719</td>
<td>0.799</td>
</tr>
<tr>
<td>12.7</td>
<td>0.1046</td>
<td>1.020</td>
<td>1.104</td>
</tr>
<tr>
<td>19.2</td>
<td>0.1569</td>
<td>1.196</td>
<td>1.274</td>
</tr>
<tr>
<td>27.4</td>
<td>0.2092</td>
<td>1.321</td>
<td>1.438</td>
</tr>
<tr>
<td>33.5</td>
<td>0.2615</td>
<td>1.418</td>
<td>1.519</td>
</tr>
</tbody>
</table>

Previous workers have shown that acetic acid has no effect on the rate of the reaction between $p$-chlorophenol and acetic
Fig. 9 Reaction of p-chlorophenol (0.01M) with acetic anhydride in the presence of pyridine (0.02M) at 25°C
anhydride in the presence of pyridine. Here, when acetic acid (0.01 M) was added to the reaction mixture; acetic anhydride (0.1569 M), p-chlorophenol (0.01 M) and pyridine (0.02 M); the pseudo first order rate constant observed was $1.95 \times 10^{-4} \text{ sec}^{-1}$, which is close to the value $1.92 \times 10^{-4} \text{ sec}^{-1}$ obtained in the absence of acetic acid.

ix) Reaction of $p$-methoxyphenol (0.10 M) and acetic anhydride (0.002 M) in the presence of pyridine in carbon tetrachloride at 35°.

An alternative method for finding the order of the reaction in the anhydride is to place the phenol in excess over the anhydride and determine the form of the integrated rate expression. $p$-Methoxyphenol does not react with acetic anhydride after several days, but in the presence of pyridine a measurable rate was observed. The production of $p$-methoxyphenyl acetate, and hence the disappearance of acetic anhydride, was found to follow the equation:

$$k_a t = 2.303 \log \frac{a}{(a-x)}$$

where $a =$ initial concentration of acetic anhydride, $x =$ the concentration of acetate at time $t$. A good straight line was obtained by plotting $\log \frac{a}{(a-x)}$ against time and, hence, the reaction is first order in the anhydride. A previously determined calibration curve of $p$-methoxyphenyl acetate was used to find $x$. The quenching and analysis procedure is described below.

None of the phenols used previously could be employed here, for two reasons. (I) It was impossible to completely remove any of these phenols, at the required higher concentrations, by the
usual quenching technique. In all cases, the residual phenol absorbed enough energy in the fundamental carbonyl stretching region to make quantitative infrared measurements impossible.

(2) When a solution of any phenol (0.10 M, including \( p \)-methoxyphenol) and acetic anhydride (0.002 M) in carbon tetrachloride was shaken with saturated aqueous potassium bicarbonate, acetate was produced, making it impossible to use the normal quenching technique. This was overcome by adding pyrogallol (0.25 M) to the potassium bicarbonate solution. It is believed that the pyrogallol successfully competes with the residual phenol for the anhydride and pyrogallol monoacetate, being soluble in the aqueous phase, does not interfere with the analysis technique. \( p \)-Methoxyphenol can be completely removed from the carbon tetrachloride phase by shaking a 4 cm\(^3\) aliquot of the reaction mixture with saturated aqueous potassium bicarbonate (20 cm\(^3\), 1 minute), and then with water (10 cm\(^3\), 1 minute). The reaction was initiated by adding the acetic anhydride solution to the \( p \)-methoxyphenol and pyridine solution. Results are given in Table 3:13.

TABLE 3:13

<table>
<thead>
<tr>
<th>pyridine (M)</th>
<th>rate constant ( \times 10^4 ) (sec(^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.03</td>
<td>3.06</td>
</tr>
<tr>
<td>0.04</td>
<td>3.64</td>
</tr>
<tr>
<td>0.05</td>
<td>4.19</td>
</tr>
</tbody>
</table>

The low sensitivity of the rate constant to changes in the pyridine concentration must reflect the small association constant between \( p \)-methoxyphenol and pyridine at 35\(^0\).
Reaction of phenols with acetic anhydride (0.05 M) in the presence of 4-dimethylaminopyridine (4-DMAP) in carbon tetrachloride at 25°C.

4-Dimethylaminopyridine (pK_a = 9.71) is a good catalyst for the acetylation of a phenol with an anhydride in carbon tetrachloride. Only very low base concentrations can be used because of the fast reaction rate. Hence, the saturation effect found with other bases is avoided (see Figure 5), and the order of the reaction in pyridine can be calculated. Data are given in Table 3:14.

### Table 3:14

<table>
<thead>
<tr>
<th>Phenol (0.01 M)</th>
<th>4-DMAP x 10^5</th>
<th>10^5 k_e</th>
<th>10^4 k_R</th>
<th>10^2 k_b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M)</td>
<td>(sec^-1)</td>
<td>(sec^-1)</td>
<td>(sec^-1)</td>
</tr>
<tr>
<td>0.412</td>
<td>4.00</td>
<td>4.38</td>
<td>9.15</td>
<td></td>
</tr>
<tr>
<td>0.824</td>
<td>9.80</td>
<td>8.12</td>
<td>12.07</td>
<td></td>
</tr>
<tr>
<td>1.236</td>
<td>13.9</td>
<td>10.6</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>1.648</td>
<td>19.0</td>
<td>14.4</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td>2.060</td>
<td>23.6</td>
<td>18.3</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>2.47</td>
<td>28.2</td>
<td>21.0</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>v. fast</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td>v. fast</td>
</tr>
</tbody>
</table>

A plot of log 4-DMAP concentration against log k_e is linear for both the phenol and p-chlorophenol reactions with slopes of 0.97 and 1.36 respectively, indicating that the reaction is first order in the base.

The reaction between p-chlorophenol (0.01 M) and acetic anhydride (0.05 M) in the presence of 2-dimethylaminopyridine
was investigated. After one day, only about 4% reaction could be detected, which illustrates two points; (I) the steric effect which operates when the pyridine base is -substituted, inhibits the reaction, and (2) the basic centre is the ring nitrogen. If the side-chain nitrogen were the basic centre the catalytic ability of 2- and 4-DMAF should be very similar.

xi) Reaction of μ-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 1,8-bis(dimethylamino)-naphthalene in carbon tetrachloride at 25°.

1,8-Bis(dimethylamino)naphthalene exists in a strained conformation whose strains can be relieved by protonation at one of the nitrogen ring atoms. It is hence expected that this compound will be highly basic (pK_a = 12.34) and, if the catalytic ability needed in this acetylation depends solely on basicity, this compound should be a very good catalyst.

Results are given in Table 3:15 and illustrated in Figure 10. It was found that simple first order kinetics were not obeyed, and reproducibility was only good up to about 40% reaction. Considering the pK_a of this compound, it was not a good catalyst for this reaction. Stock solutions of 1,8-bis-(dimethylamino)naphthalene readily deposit a pink precipitate on standing, probably arising from an interaction with carbon tetrachloride. To avoid this, only dilute solutions of the base were prepared, which were used immediately. The reaction mixture remained clear after three hours reaction time. However, a slow reaction with the solvent destroying the base could explain the curvature in Figure 10.
Fig. 10 Reaction of m-nitrophenol (0.005M) with acetic anhydride (0.05M) in the presence of 1,8-bis(dimethylamino)naphthalene (0.005M) in carbon tetrachloride at 25°.
TABLE 3.15

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Acetate ( \times 10^4 )</th>
<th>( \log a/(e-x) \times 10^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment one.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>4.1</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>9.7</td>
</tr>
<tr>
<td>16</td>
<td>14.5</td>
<td>14.9</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td>22.2</td>
</tr>
<tr>
<td>45</td>
<td>24</td>
<td>23.4</td>
</tr>
<tr>
<td>60</td>
<td>27</td>
<td>33.7</td>
</tr>
<tr>
<td>90</td>
<td>29.5</td>
<td>33.7</td>
</tr>
<tr>
<td>120</td>
<td>30.5</td>
<td>40.9</td>
</tr>
<tr>
<td>Experiment two.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
<td>4.1</td>
</tr>
<tr>
<td>37</td>
<td>24</td>
<td>23.4</td>
</tr>
<tr>
<td>51</td>
<td>27.5</td>
<td>34.7</td>
</tr>
<tr>
<td>65</td>
<td>29.5</td>
<td>33.7</td>
</tr>
<tr>
<td>90</td>
<td>33</td>
<td>46.9</td>
</tr>
<tr>
<td>120</td>
<td>35.5</td>
<td>53.8</td>
</tr>
<tr>
<td>150</td>
<td>37</td>
<td>53.5</td>
</tr>
<tr>
<td>1 day</td>
<td>44</td>
<td>67.8</td>
</tr>
</tbody>
</table>

1,8-Bis(dimethylamino)naphthalene molarity = 0.005 M.

xii) Reaction of \( p \)-chlorophenol (0.01 \( \text{M} \)) with acetic anhydride (0.05 \( \text{M} \)) in the presence of bases in carbon tetrachloride at 25°.

(a) Aniline.

Aniline (0.02 \( \text{M} \)) was added to the reaction mixture, but no \( p \)-chlorophenyl acetate could be detected, even after one day
(using the normal quenching and analysis technique for p-chlorophenol). An infrared spectrum and a gas liquid chromatogram of the reaction mixture after one day gave no indication that acetanilide was present.

(b) **Imidazole.**

The solubility of imidazole in carbon tetrachloride is low and the concentration used in the reaction mixture was only \(2.16 \times 10^{-3} \text{M}\). A good straight line was obtained when \(\log a/(a-x)\) was plotted against time, the slope of which gave \(k_c = 1.18 \times 10^{-5} \text{sec}^{-1}\).

(c) **2-Methylimidazole.**

The reaction with 2-methylimidazole acting as the catalyst, at the same concentration as imidazole, was very slow. Only 18% reaction could be detected after one day and 60% after four days.

(d) **Triethylenediamine.**

Triethylenediamine \((2.5 \times 10^{-3} \text{M})\) catalysed a pseudo first order reaction with a rate constant of \(5.25 \times 10^{-4} \text{sec}^{-1}\).

(e) **Dimethyl Sulphoxide.**

The reaction with dimethyl sulphoxide \((0.02 \text{M})\) was very slow and did not appear to follow simple first order kinetics. A plot of \(\log a/(a-x)\) against time was a curve, but a plot of \(1/(a-x)\) against time was linear. 60% reaction was reached after two days. This is a surprising result because dimethyl sulphoxide is known to have a large association constant with phenols to form a hydrogen-bonded complex. If this reaction is an example of general base catalysis, one would expect that the stronger the base, the better will be its catalytic power.
Usually the hydrogen bonding ability of compounds and their basicity form a linear correlation. The association constants of the bases 4-picoline, 2,6-lutidine and dimethyl sulphoxide with p-chlorophenol have been determined by the usual infrared technique as described in Section 2. The results are listed below.

<table>
<thead>
<tr>
<th>Base</th>
<th>Association constant $(M^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-picoline</td>
<td>$148 \pm 8$</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>$179 \pm 9$</td>
</tr>
<tr>
<td>dimethyl sulphoxide</td>
<td>$403 \pm 28$</td>
</tr>
</tbody>
</table>

xii) Reaction of p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of pyridine (0.02 M) in carbon tetrachloride at different temperatures.

To determine the activation parameters of this reaction the temperature was varied over the range $0 - 45^\circ$. A summary of the results is given in Table 3:16 together with association constant values calculated, using the van't Hoff isochore, from the values $K = 113 \text{ M}^{-1}$ at $27^\circ$ and $\Delta H = -29.29 \text{ kJ mole}^{-1}$ ($-7 \text{ kcal. mole}^{-1}$). The enthalpy of formation of the hydrogen-bonded complex is approximate and no attempt has been made to convert literature molarity values to molality values.

A plot of log rate constant against reciprocal temperature gives a good straight line, the slope of which gives an activation energy of $33.9 \text{ kJ mole}^{-1}$. 
TABLE 3:16

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>rate constant x 10(^5) (sec(^{-1}))</th>
<th>(10^5k_b) (sec(^{-1}))</th>
<th>K (M(^{-1}))</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.72</td>
<td>2.02</td>
<td>361</td>
<td>0.850</td>
</tr>
<tr>
<td>15</td>
<td>3.95</td>
<td>5.27</td>
<td>185</td>
<td>0.749</td>
</tr>
<tr>
<td>25</td>
<td>6.29</td>
<td>9.32</td>
<td>126</td>
<td>0.675</td>
</tr>
<tr>
<td>30</td>
<td>7.51</td>
<td>11.96</td>
<td>102</td>
<td>0.628</td>
</tr>
<tr>
<td>35</td>
<td>9.29</td>
<td>15.80</td>
<td>85</td>
<td>0.588</td>
</tr>
<tr>
<td>45</td>
<td>14.60</td>
<td>23.30</td>
<td>60</td>
<td>0.516</td>
</tr>
</tbody>
</table>

xiv) Reaction of \(p\)-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of pyridine (0.01 M) and 4-picoline (0.01 M) in carbon tetrachloride at 0°C.

To initiate the reaction, the two pyridine bases were added to the acetic anhydride and \(p\)-chlorophenol solution. A graph of \(\log a/(a-x)\) against time is linear. Results are given in Table 3:17 together with a typical kinetic experiment.

TABLE 3:17

<table>
<thead>
<tr>
<th>Pyridine (M)</th>
<th>4-Picoline (M)</th>
<th>Rate constant x 10(^5) (sec(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>-</td>
<td>1.72</td>
</tr>
<tr>
<td>-</td>
<td>0.02</td>
<td>10.9</td>
</tr>
<tr>
<td>0.01</td>
<td>0.01</td>
<td>7.31</td>
</tr>
<tr>
<td>Time (min)</td>
<td>Molarity of acetate x 10^4</td>
<td>log a/(a-x) x 10^2</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>5</td>
<td>17.5</td>
<td>3.4</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>10.8</td>
</tr>
<tr>
<td>40</td>
<td>27</td>
<td>13.7</td>
</tr>
<tr>
<td>60</td>
<td>32.5</td>
<td>17.1</td>
</tr>
<tr>
<td>80</td>
<td>38</td>
<td>20.3</td>
</tr>
<tr>
<td>120</td>
<td>43.5</td>
<td>23.8</td>
</tr>
<tr>
<td>180</td>
<td>60.5</td>
<td>40.3</td>
</tr>
<tr>
<td>300</td>
<td>73.5</td>
<td>66.3</td>
</tr>
</tbody>
</table>

The reaction between acetic anhydride (0.05 M) and p-chlorophenol in the presence of tetrahexyammonium benzoate in carbon tetrachloride at 25° was completed after one hour. Two extra absorptions at 1820 and 1750 cm⁻¹ in the carbonyl stretching region of the infrared spectrum made kinetic measurements difficult. These extra absorptions were not assigned. No p-chlorophenyl acetate was produced when tetrahexyammonium benzoate was added to carbon tetrachloride solutions of (i) acetyl trifluoracetate, (ii) acetic anhydride or (iii) p-chlorophenol and acetyl trifluoroacetate immediately prior to quenching.

Benzoic anhydride (0.01 M) reacted with p-chlorophenol (0.01 M) in the presence of tetrahexyammonium benzoate (12.5 x 10⁻³ M) to give only one absorption in the carbonyl region of the infrared spectrum of the reaction mixture after
five minutes. This absorption corresponded to that of the carbonyl group in \( p \)-chlorophenyl benzoate and no residual benzoic anhydride could be detected.

To check that this catalytic reactivity of the salt was not due to trace impurities of tetrahexylammonium iodide (the starting material in the preparation of the salt), benzoic anhydride was reacted with \( p \)-chlorophenol in the presence of the iodide \((12.5 \times 10^{-3} \text{ M})\). After five minutes about 50\% reaction was monitored, but the reaction was not completed after two hours. Kinetic measurements were not carried out because of the difficulty in removing benzoic anhydride from the carbon tetrachloride phase.

xvi) Reaction of \( p \)-nitrophenol \((0.005 \text{ M})\) with isobutyric anhydride \((0.05 \text{ M})\) in the presence of 2,6-lutidine together with 3,4-lutidine in carbon tetrachloride at 25\°C.

\( p \)-Nitrophenol and isobutyric anhydride do not react in the presence of 2,6-lutidine (Table 3:18). 3,4-Lutidine is a very good acetylation catalyst giving a pseudo first order rate constant of \(7.47 \times 10^{-4} \text{ sec}^{-1}\). The effect of adding 2,6-lutidine together with 3,4-lutidine to the reaction mixture was investigated, and the results are given in Table 3:18 and illustrated in Figure 11.

<table>
<thead>
<tr>
<th>3,4-lutidine (M)</th>
<th>2,6-lutidine (M)</th>
<th>rate constant x 10^4 (sec^{-1})</th>
<th>ordinate intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>0</td>
<td>7.47</td>
<td>0</td>
</tr>
<tr>
<td>0.005</td>
<td>0.0025</td>
<td>5.71</td>
<td>0.10</td>
</tr>
<tr>
<td>0.005</td>
<td>0.0050</td>
<td>5.07</td>
<td>0.20</td>
</tr>
<tr>
<td>0.005</td>
<td>0.0075</td>
<td>3.99</td>
<td>0.30</td>
</tr>
</tbody>
</table>
As the 2,6-lutidine concentration is increased, the intercept on the ordinate of a log \( a/(a-x) \) against time plot increases uniformly and the rate of reaction decreases. At the two higher 2,6-lutidine concentrations the points on the log \( a/(a-x) \) against time diagrams showed considerable scatter making the intercept values only approximate. For this reason higher 2,6-lutidine concentrations were not investigated.

There are three reasons why an intercept could occur on the log \( a/(a-x) \) axis; (i) the \( m \)-nitrophenol and 2,6-lutidine may form a non-reactive species, the concentration of which could be deduced from the intercept, (ii) there could be a fast localised reaction before homogeneous reaction conditions are obtained or (iii) a highly reactive species could be present which produces \( m \)-nitrophenyl acetate very quickly, but the reaction ceases short of completion. Subsequent work has shown that the last explanation is the most reasonable. 2,6-lutidine does not effect the quenching or analysis techniques at these concentrations.

If the concentration of \( m \)-nitrophenol used in this initial fast reaction (calculated from the ordinate intercept) is subtracted from the total initial \( m \)-nitrophenol concentration and log \( a/(a-x) \) plotted against time, where \( a \) is the remainder, a straight line through the origin is obtained. The slope of this line equals that of the original log \( a/(a-x) \) correlation. This is illustrated in Figure 11 for the reaction with 2,6-lutidine (0.005 M) and close similarity is evident with the lines obtained in Figure 1.
Fig. 11 Reaction of \( m \)-nitrophenol (0.005M) with isobutyric anhydride (0.05M) in the presence of 2,6-lutidine and 3,4-lutidine (0.005M) in carbon tetrachloride at 25\(^\circ\).

1. 2,6-lutidine 0.0025M
2. 2,6-lutidine 0.005M
3. 2,6-lutidine 0.0075M
4. 2,6-lutidine 0.005M, \( m \)-nitrophenol calculated at 0.0031M
xvii) Reaction of $m$-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine in carbon tetrachloride at 25°.

When $m$-nitrophenol (0.005 M) is reacted with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.10 M), complete reaction occurs immediately (100% $m$-nitrophenyl acetate production was monitored after one minute, the fastest possible sampling time). Reduction of the 2,6-lutidine concentration to 0.02 M produces 65% reaction after one minute but there appears to be no further reaction, even after several hours. In order to investigate how this initial acetate was produced, the 2,6-lutidine concentration was varied between 0.004 and 0.024 M. The reaction mixture was sampled after two minutes and each result is the average of two experiments. Results are summarized in Table 3:19. Figures 12 and 13 show how the initial fast acetate production varies with 2,6-lutidine concentration, and the square of the 2,6-lutidine concentration.

<table>
<thead>
<tr>
<th>2,6-lutidine (M)</th>
<th>$m$-nitrophenyl acetate (M)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.004</td>
<td>0.00035</td>
<td>7</td>
</tr>
<tr>
<td>0.008</td>
<td>0.00115</td>
<td>23</td>
</tr>
<tr>
<td>0.012</td>
<td>0.00200</td>
<td>40</td>
</tr>
<tr>
<td>0.016</td>
<td>0.00295</td>
<td>59</td>
</tr>
<tr>
<td>0.020</td>
<td>0.00375</td>
<td>75</td>
</tr>
<tr>
<td>0.024</td>
<td>0.00410</td>
<td>82</td>
</tr>
</tbody>
</table>

The concentration of the anhydride was reduced to 0.02 M.
Fig. 13 Reaction of \( m \)-nitrophenol (0.005M) with acetic anhydride (0.05M) in the presence of 2,6-lutidine in carbon tetrachloride at 25°.

\[
(2,6\text{-lutidine molarity})^2 \times 10^4
\]
to establish how this effected the initial rapid production of acetate. It was usual to initiate \( p \)-nitrophenol reactions by adding acetic anhydride (5 cm\(^3\)) to the reaction mixture. Reduction of the anhydride concentration was achieved in two ways, (i) by adding 2.5 cm\(^3\) of the stock anhydride solution and (ii) by diluting this stock solution to half its molarity and adding 5 cm\(^3\) to the reaction mixture in the usual way. Both methods show a decrease in the initial rapid formation of acetate; Table 3:20

<table>
<thead>
<tr>
<th>time</th>
<th>acetic anhydride</th>
<th>2,6-lutidine</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min)</td>
<td>(M)</td>
<td>(M)</td>
<td></td>
</tr>
<tr>
<td>Method (i)</td>
<td>2</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Method (ii)</td>
<td>2</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

xviii) Reaction of \( p \)-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.02 M) with acetic acid in carbon tetrachloride at 25\(^\circ\).

The reason that the initial fast reaction between acetic anhydride and \( p \)-nitrophenol in the presence of 2,6-lutidine does not go to completion may be due to an inhibition effect by acetic acid produced in the reaction. To test this theory, acetic acid was added to the reaction mixture and the results are given in Table 3:21.
TABLE 3:21

<table>
<thead>
<tr>
<th>Total acetic acid (M)</th>
<th>m-nitrophenyl acetate (M)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00335</td>
<td>0.00335</td>
<td>65</td>
</tr>
<tr>
<td>0.00415</td>
<td>0.00315</td>
<td>62</td>
</tr>
<tr>
<td>0.00490</td>
<td>0.00290</td>
<td>58</td>
</tr>
<tr>
<td>0.00570</td>
<td>0.00270</td>
<td>54</td>
</tr>
<tr>
<td>0.00725</td>
<td>0.00225</td>
<td>45</td>
</tr>
<tr>
<td>0.00705</td>
<td>0.00205</td>
<td>41</td>
</tr>
<tr>
<td>0.00800</td>
<td>0.00200</td>
<td>40</td>
</tr>
<tr>
<td>0.01125</td>
<td>0.00125</td>
<td>25</td>
</tr>
<tr>
<td>0.01120</td>
<td>0.00120</td>
<td>24</td>
</tr>
<tr>
<td>0.01555</td>
<td>0.00055</td>
<td>11</td>
</tr>
<tr>
<td>0.02030</td>
<td>0.00030</td>
<td>6</td>
</tr>
</tbody>
</table>

The reproducibility of these results is approximately 2%. A graph of the total acetic acid concentration (at the end of the reaction) against percentage reaction gives a smooth curve as shown in Figure 14. The straight line through the origin shows how the acetic acid concentration increases throughout the reaction in the absence of added acetic acid. Four experimental points fall on this line.
Fig. 14 Reaction of m-nitrophenol (0.005M) with acetic anhydride (0.05M) in the presence of 2,6-lutidine (0.02M) with acetic acid.
xix) Reaction of m-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.02 M) in toluene at 25°.

To determine whether the solvent plays any part in the initial fast production of m-nitrophenyl acetate, the solvent was changed from carbon tetrachloride to toluene. m-Nitrophenol and acetic anhydride do not react alone in toluene solution.

Toluene is not a good solvent for this infrared spectroscopic method of analysis, since the region transparent to infrared radiation in the carbonyl region is very narrow. However, by using matched 1 mm potassium bromide cells, the carbonyl absorption frequency of m-nitrophenyl acetate can be observed at 1775 cm⁻¹ and the concentration can be estimated quantitatively. A calibration curve of m-nitrophenyl acetate in toluene was constructed immediately prior to the kinetic experiments, using a Perkin-Elmer 257 infrared spectrometer with slit width set at 7.

To quench the reaction, a 2 cm³ aliquot was removed from the reaction mixture and shaken for one minute with water (10 cm³). The organic phase was then separated and shaken with saturated aqueous potassium bicarbonate (10 cm³) for thirty seconds. The toluene solution was then dried over magnesium sulphate. Results are given in Table 3:22.

<table>
<thead>
<tr>
<th>Experiment 1</th>
<th>Time (min)</th>
<th>m-nitrophenyl acetate (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>0.00350</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.00340</td>
</tr>
<tr>
<td>Experiment 2</td>
<td>1.5</td>
<td>0.00345</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.00345</td>
</tr>
</tbody>
</table>

TABLE 3:22
These experiments indicate that the solvent does not play a part in the initial fast reaction. In toluene about 69% reaction occurs initially with no further reaction after thirty minutes. This agrees well with the results found in carbon tetrachloride (Table 3:21).

Reaction of \( m \)-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.02 M) in water at 25\(^\circ\)C.

As the organic solvent does not appear to play any part in the mechanism of the initial fast production of acetate, the role of water as solvent was investigated. \( m \)-Nitrophenol and 2,6-lutidine stock solutions were made up in water in the usual manner. Acetic anhydride solution was made up in small quantities immediately prior to reaction, to eliminate any side effects due to the hydrolysis of this anhydride. No reaction could be detected between \( m \)-nitrophenol (0.005 M) and acetic anhydride (0.05 M) in water after one minute or after one day.

A 1 cm\(^3\) aliquot was removed from the reaction mixture after one minute and shaken with a 5 cm\(^3\) aliquot of carbon tetrachloride. This procedure transfers any \( m \)-nitrophenyl acetate produced into the organic phase and analysis then proceeded as usual. The organic phase was washed with saturated aqueous potassium bicarbonate (10 cm\(^3\)), separated and dried over magnesium sulphate. Results are given in Table 3:23.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>( m )-nitrophenyl acetate (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0030</td>
</tr>
<tr>
<td>60</td>
<td>0.0030</td>
</tr>
<tr>
<td>1440</td>
<td>0.0030</td>
</tr>
</tbody>
</table>
Considering the differences in the solvents studied, this initial 60% reaction is very similar to the results obtained in toluene and carbon tetrachloride. Jencks et al. have suggested that pyridine bases may exist as dimers in aqueous solution which are non-reactive as nucleophilic catalysts. These dimers could be very strong general base catalysts and an explanation for the initial fast reaction involving these dimers is discussed in Section 4.

xxi) Reaction of m-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine in water at 25°.

To determine if the reaction in water is similar to that in carbon tetrachloride with respect to changes in the 2,6-lutidine concentration, a reaction series similar to that of experiment (xvii) was carried out. Once again the acetic anhydride solutions were made up immediately prior to the reaction. Results are given in Table 3:24 and Figure 15 illustrates how the initial m-nitrophenyl acetate concentration (measured after one minute) varies with 2,6-lutidine concentration. A linear correlation is obtained.

<table>
<thead>
<tr>
<th>2,6-lutidine (M)</th>
<th>m-nitrophenyl acetate (M)</th>
<th>acetic anhydride (g/25 cm³)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0.612</td>
<td>0</td>
</tr>
<tr>
<td>0.0077</td>
<td>0.00110</td>
<td>0.569</td>
<td>22</td>
</tr>
<tr>
<td>0.0116</td>
<td>0.00170</td>
<td>0.566</td>
<td>34</td>
</tr>
<tr>
<td>0.0154</td>
<td>0.00220</td>
<td>0.552</td>
<td>44</td>
</tr>
<tr>
<td>0.0193</td>
<td>0.00285</td>
<td>0.558</td>
<td>57</td>
</tr>
<tr>
<td>0.0232</td>
<td>0.00345</td>
<td>0.562</td>
<td>69</td>
</tr>
<tr>
<td>0.0270</td>
<td>0.00440</td>
<td>0.560</td>
<td>88</td>
</tr>
</tbody>
</table>
Fig. 15 Reaction of m-nitrophenol (0.05M) with acetic anhydride (0.05M) in the presence of 2,6-lutidine in water at 25°C.
xxii) Reaction of m-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.02 M) and acetic acid in water at 25°C.

This experiment was carried out to test further the similarity between the initial fast reactions in water and carbon tetrachloride (see experiment xviii). The results obtained here did not give the same degree of reproducibility as found in experiment (xviii). The initial m-nitrophenyl acetate concentration values were reproducible to ± 2%. Similar dependence of initial percentage reaction on added acetic acid concentration was observed. These results are given in Table 3:25 and illustrated in Figure 16.

<table>
<thead>
<tr>
<th>Total acetic acid (M)</th>
<th>m-nitrophenyl acetate (M)</th>
<th>Acetic anhydride (g/25 cm³)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0065</td>
<td>0.0025</td>
<td>0.560</td>
<td>49</td>
</tr>
<tr>
<td>0.0063</td>
<td>0.0023</td>
<td>0.569</td>
<td>46</td>
</tr>
<tr>
<td>0.0100</td>
<td>0.0020</td>
<td>0.575</td>
<td>39</td>
</tr>
<tr>
<td>0.0137</td>
<td>0.0017</td>
<td>0.571</td>
<td>34</td>
</tr>
<tr>
<td>0.0175</td>
<td>0.0015</td>
<td>0.571</td>
<td>29</td>
</tr>
<tr>
<td>0.0212</td>
<td>0.0012</td>
<td>0.565</td>
<td>24</td>
</tr>
<tr>
<td>0.0210</td>
<td>0.0010</td>
<td>0.571</td>
<td>20</td>
</tr>
</tbody>
</table>

When the acetic anhydride molarity was reduced, a quite different result was obtained from that found in carbon tetrachloride. Results are given in Table 3:26.
The percentage initial reaction increased as the acetic anhydride concentration was reduced from 0.05 M to 0.025 M. Further reduction of the anhydride concentration did lead to a reduction in acetate produced.

xxiii) Reaction of p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.02 M) in addition to other pyridine bases in carbon tetrachloride at 25°C.

2,6-Lutidine (0.02 M) does not catalyse a reaction between p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in carbon tetrachloride. If 2,6-lutidine is added to the pyridine catalysed reaction, a reduction in rate may be expected due to the competitive formation of a non-reactive hydrogen-bonded species (assuming general base catalysis) of the form:

Steric hindrance due to the α-methyl groups will prevent this species approaching close to the anhydride molecule, thus
preventing reaction. The reactions of \( p \)-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of (i) pyridine (0.02 M), (ii) 4-picoline (0.02 M) and (iii) 3,4-lutidine (0.02 M) were repeated in the presence of 2,6-lutidine. The results are given below in Table 3:27.

<table>
<thead>
<tr>
<th>Base</th>
<th>2,6-lutidine (M)</th>
<th>Rate constant ( \times 10^5 ) (sec(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>0</td>
<td>5.93</td>
</tr>
<tr>
<td>pyridine</td>
<td>0.02</td>
<td>3.81</td>
</tr>
<tr>
<td>4-picoline</td>
<td>0</td>
<td>34.7</td>
</tr>
<tr>
<td>4-picoline</td>
<td>0.02</td>
<td>22.7</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>0</td>
<td>99.6</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>0.02</td>
<td>64.0</td>
</tr>
</tbody>
</table>

For each of these reactions, the rate is reduced by the addition of 2,6-lutidine. Also noted here was that the intercept on the ordinate of a log \( a/(a-x) \) against time plot was always larger when 2,6-lutidine was present than in its absence.

It is known that dimethyl sulfoxide forms strong hydrogen bonds with phenols and, from experiment (xii), this compound is not a good acetylation catalyst. It may be expected then, from their similarity in hydrogen bonding ability, that dimethyl sulfoxide and 2,6-lutidine will have similar catalytic properties towards this reaction. The reaction of \( p \)-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of 4-picoline (0.02 M) and dimethyl sulfoxide (0.10 M) has a pseudo first order rate constant of \( 8.10 \times 10^{-5} \) sec\(^{-1}\), compared with
1.71 \times 10^{-4} \text{ sec}^{-1} for the reaction without dimethyl sulphoxide. Hence, once again the reaction rate was reduced, but the intercept value was unchanged.

xxiv) Reaction of p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of 4-picoline (0.02 M) and 2,6-lutidine (0.10 M) in carbon tetrachloride at 25°C.

The effect of 2,6-lutidine on the ordinate intercept value in a log a/(a-x) against time graph (i.e., the concentration of p-chlorophenyl acetate produced in the initial fast reaction) was studied by increasing the 2,6-lutidine molarity to 0.10 M. A large intercept is observed but the following slow reaction gives only a poor linear correlation. Approximate values for the intercept and rate constant are 0.6 (equivalent to 75% reaction) and 20.0 \times 10^{-5} \text{ sec}^{-1} respectively.

2,6-Lutidine was purified by a different method from the other pyridine bases and this could account for its anomalous behaviour (Section 2). To check that no impurity in 2,6-lutidine, resulting from the different purification technique, was the cause of the initial fast reaction, a sample of 2,6-lutidine was fractionally distilled and the reaction repeated. No difference in the intercept or rate constant could be detected.

The fast initial production of acetate could be due to a reaction taking place only during the quenching procedure. This explanation is unlikely, however, as the reactions with p-nitrophenol, where a different quenching technique was used, also showed this fast initial reaction. This possibility was eliminated by using a gas liquid chromatography technique. The reaction mixture, p-chlorophenol (0.01 M) with acetic anhydride
(0.05 M) in the presence of 2,6-lutidine (0.10 M) and 4-picoline (0.02 M), was injected after one minute, onto an Apiezon K column at 120°, with nitrogen as the carrier gas. The chromatogram illustrated in Figure 17(a) was obtained, which shows a large peak corresponding to \( \text{p-chlorophenyl acetate} \). The retention times of all the reactants and products were determined immediately prior to reaction mixture analysis, and it was also shown that a mixture of \( \text{p-chlorophenol (0.01 M)} \) and acetic anhydride (0.05 M) gave no acetate peak after several hours. The acetate peak in the chromatogram corresponds to 69% reaction.

xxv) Reaction of \( \text{p-chlorophenol (0.01 M)} \) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (0.10 M) and various bases in carbon tetrachloride at 25°.

A series of bases were used in order to study their effect on the initial fast reaction observed in the presence of 2,6-lutidine. Samples were taken from the reaction mixture after one minute and, as the subsequent reaction was slow, the acetate concentration found after one minute was taken to be solely produced by the initial rapid reaction. Reproducibility was very good and the results are given in Table 3:28.

By plotting the base \( pK_a \) against \% reaction, a linear correlation is obtained which shows that as the base \( pK_a \) increases the molarity of acetate produced in the initial fast reaction also increases (Figure 17 (b)). The results in Table 3:28 also show that as the base molarity is reduced, the percentage initial reaction decreases.
Fig. 17(a) Gas chromatogram of reaction mixture. Experiment xxiv.

Apiezon K at 120°, 15 p.s.i. N₂

A. p-chlorophenol
B. p-chlorophenyl acetate
C. 4-picoline
D. 2,6-lutidine

Fig. 17(b) Reaction of p-chlorophenol (0.01M) with acetic anhydride (0.05M) in the presence of 2,6-lutidine (0.10M) and various bases.
xxvi) Reaction of p-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine together with 3,4-lutidine in carbon tetrachloride at 25°.

2,6-Lutidine does not catalyse a reaction between p-chlorophenol and acetic anhydride. Even at higher concentrations than 0.05 M the initial fast reaction produces only a small amount of p-chlorophenyl acetate and no further reaction occurs, Table 3:29.

<table>
<thead>
<tr>
<th>Base</th>
<th>base molarity (M)</th>
<th>p-chlorophenyl acetate (M)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>0.02</td>
<td>0.00350</td>
<td>35</td>
</tr>
<tr>
<td>3-picoline</td>
<td>0.02</td>
<td>0.00525</td>
<td>52.5</td>
</tr>
<tr>
<td>4-picoline</td>
<td>0.02</td>
<td>0.00655</td>
<td>65.5</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>0.02</td>
<td>0.00850</td>
<td>85</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>0.01</td>
<td>0.00690</td>
<td>69</td>
</tr>
<tr>
<td>3,4-lutidine</td>
<td>0.005</td>
<td>0.00445</td>
<td>44.5</td>
</tr>
</tbody>
</table>

p-Chlorophenol (2 cm³) was added to a solution of acetic anhydride (0.05 M) and 2,6-lutidine (0.10 M) and three samples taken in the first hour. After eighty minutes a solution of 3,4-lutidine (2 cm³) to give 0.02 M in the reaction mixture was
added which initiated a fast reaction giving over 70% reaction in one minute. The resulting reaction was then slow compared with the expected rate for 3,4-lutidine catalysis. The reproducibility of these reactions was excellent and the same results were obtained using polythene reaction vessels. This reaction was repeated using 2,6-lutidine (0.02 M) solutions which gave more than 90% fast production of acetate.

Experiments were carried out in which (i) the 2,6-lutidine was added after the 3,4-lutidine and (ii) both 2,6-lutidine and 3,4-lutidine were added together to initiate reaction. In both cases an initial fast production of p-chlorophenyl acetate was observed.

xxvii) Investigation of the initial rapid formation of ester in the reaction between phenols and acetic anhydride in the presence of bases.

The effect of pyridine bases substituted with methyl groups in the α-position were studied to determine the effect of increased base strength (of the normally non-catalytic base) on the initial acetate formation. The reaction investigated was that between p-chlorophenol (0.01 M) and acetic anhydride (0.05 M) in the presence of 4-picoline. Results are given in Table 3:30.

<table>
<thead>
<tr>
<th>4-picoline</th>
<th>base</th>
<th>base molarity</th>
<th>time (min)</th>
<th>% initial reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td></td>
<td>0.30</td>
<td>1</td>
<td>63.5</td>
</tr>
<tr>
<td>0.02</td>
<td>2-picoline</td>
<td>0.30</td>
<td>1</td>
<td>65.5</td>
</tr>
<tr>
<td>0.02</td>
<td>2,6-lutidine</td>
<td>0.10</td>
<td>1</td>
<td>81.5</td>
</tr>
<tr>
<td>0.02</td>
<td>2,4,6-collidine</td>
<td>0.10</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>0.20</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>17 a</td>
</tr>
</tbody>
</table>
Concentration of acetate after 1 min. normal reaction time.

From these results it can be seen that the effectiveness of the sterically hindered bases, in catalysing the initial rapid reaction, is in the order:

$$2,4,6\text{-collidine} > 2,6\text{-lutidine} > 2\text{-picoline}.$$  

It is also apparent that the non-sterically hindered bases also produce this fast reaction, although in these cases the initial production of acetate is much more difficult to determine quantitatively, due to the ensuing fast reaction. The initial rapid reaction was not followed kinetically for two reasons; (i) the conventional quenching technique used here could only sample the reaction mixture after a minimum time of one minute, and (ii) continuous product analysis techniques for this reaction are not possible, eliminating the possible use of flow or stopped-flow techniques.

Several reactions were carried out in which the mixture was stirred continuously, using a magnetic stirrer and follower (teflon coated), in polybutylene reaction vessels. When $p$-chlorophenol (0.01 M) is reacted with acetic anhydride (0.05 M) in the presence of pyridine (0.02 M) at 0° in carbon tetrachloride, a first order reaction is observed with a rate constant $k_0 = 1.72 \times 10^{-5}$ sec$^{-1}$. The intercept on the log $a/(a-x)$ ordinate represents 7% reaction. These reactions thus gave very similar results to the non-stirred reactions.

Various phenols were used in this reaction to study how the acidity of the phenol affected the initial acetate production. Results are given in Table 3:31.
TABLE 3:31

Reaction of phenols with acetic anhydride (0.05 M) in the presence of 2,6-lutidine at 25°.

<table>
<thead>
<tr>
<th>Phenol</th>
<th>Phenol molarity (M)</th>
<th>2,6-Lutidine (M)</th>
<th>% Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-fluoro</td>
<td>0.01</td>
<td>0.10</td>
<td>13</td>
</tr>
<tr>
<td>p-chloro</td>
<td>0.01</td>
<td>0.10</td>
<td>6</td>
</tr>
<tr>
<td>m-nitro</td>
<td>0.005</td>
<td>0.10</td>
<td>100</td>
</tr>
<tr>
<td>o-fluoro</td>
<td>0.01</td>
<td>0.10</td>
<td>0</td>
</tr>
<tr>
<td>o-nitro</td>
<td>0.005</td>
<td>0.10</td>
<td>0</td>
</tr>
</tbody>
</table>

The reaction of o-nitrophenol was followed by infrared spectroscopy in the fundamental carbonyl stretching region without quenching and, after four hours, no absorptions due to o-nitrophenyl acetate could be detected. This method of analysis was checked by gas liquid chromatography, which again showed no peaks other than those attributable to the reactants.

The reaction of o-fluorophenol was quenched and analysed as for p-chlorophenol.

xxviii) Spectroscopic investigation of the reaction systems.

Gold and Jefferson studied a pyridine and acetic anhydride equimolar mixture in carbon tetrachloride by infrared spectroscopy. They could find no evidence for any complex formation between these two compounds. It was also found that the ultraviolet absorption spectra of pyridine and acetic anhydride in cyclohexane was strictly additive. In this work an infrared spectrum of the system 2,6-lutidine (0.088 M), 3,4-lutidine (0.044 M) and acetic anhydride (0.044 M) was examined. This spectrum was additive, there being no evidence
for any change in intensity or position of the bands due to carbonyl vibrations.

Gold and Jefferson also measured the conductivity of a solution of pyridine and acetic anhydride in dry acetone and determined the freezing point of solutions in benzene. Neither of these experiments indicated any interaction between these two compounds.

Jencks\textsuperscript{65,66} was able to observe an acetylpyridinium ion by mixing aqueous solutions of pyridine and acetic anhydride in a stopped-flow apparatus. The formation and disappearance (hydrolysis) of this species was measured at 280 nm by ultraviolet spectroscopy over a time scale of approximately one minute. The existence of such a species is now certain in aqueous media but in non-polar solvents there is still no evidence for its formation. The stability and reactivity of such a species in non-polar solvents is discussed in Section 4.

Solutions of \( p \)-nitrophenol and triethylenimine in aprotic solvents have been investigated by Bell and Barrow\textsuperscript{113} using ultraviolet spectroscopy. The ultraviolet spectrum usually appears as two broad, partly overlapping bands, one in the vicinity of 320 nm and the other at 400 nm. The \( p \)-nitrophenate ion is known to have an absorption at 400 nm and so the existence of a tautomeration, of the form shown below, was suggested. The solvent used was chloroform.

\[
\begin{align*}
\text{O}_2\text{N} & \rightleftharpoons \text{O}_2\text{H} \\
\text{OH} & \rightleftharpoons \text{HNRR}_3
\end{align*}
\]
The existence of a \( m \)-nitrophenate ion could readily explain the initial rapid formation of \( m \)-nitrophenyl acetate in the acylation reaction investigated here.

Libus and Moska\textsuperscript{114} have studied solutions of \( p \)-nitrophenol and pyridine (and its substituted derivatives) in chlorobenzene by ultraviolet spectroscopy and have been unable to observe a phenate ion in this solvent. However, Hudson et al.\textsuperscript{115} have observed the absorption due to the \( p \)-nitrophenate ion in cyclohexane, but here \( n \)-butylamine was acting as the base and was present at very high concentrations (5% by volume), thus changing appreciably the solvent properties.

Here, a solution of \( m \)-nitrophenol \((5.5 \times 10^{-4} \text{M})\) and 2,6-lutidine \((0.02 \text{ M})\) in carbon tetrachloride was studied using a Pye Unicam SP 1800 UV spectrometer. 1 cm matched silica cells were used. The \( m \)-nitrophenol solution alone gave an absorption band centred at 316 nm, which moved to 330 nm in the presence of 2,6-lutidine. This latter band was assigned to the hydrogen-bonded complex. No other absorption bands were present in the region 390 - 400 nm, characteristic of a \( m \)-nitrophenate ion, even when the \( m \)-nitrophenol concentration was increased to \( 1.1 \times 10^{-3} \text{ M} \). It can be concluded from this work that, if any \( m \)-nitrophenate ion exists in the reaction mixture, it must be present in very small quantities.

No evidence has been reported for a \( m \)-nitrophenate ion in aprotic solvents. Even the positive identifications of the \( p \)-nitrophenate ion have usually been in solvents containing a considerable amount of base. Two further experiments were carried out to observe the \( m \)-nitrophenate ion in the ultraviolet
region of the spectrum. Chloroform was used as solvent for the phenol and the base, and the experimental conditions were as described above.

(a) A solution of m-nitrophenol \((5 \times 10^{-4} \text{ M})\) and 2,6-lutidine \((5 \times 10^{-3} \text{ M})\) showed no absorption band due to the \(\text{m}-\text{nitrophenate ion}\).

(b) A solution of \(\text{m}-\text{nitrophenol} (5 \times 10^{-4} \text{ M}), \text{iso-butylamine} (5 \times 10^{-3} \text{ M})\) and dimethyl sulphoxide \((0.25 \text{ M})\) also showed no absorption band due to the \(\text{m}-\text{nitrophenate ion}\).

Scott has shown that primary aliphatic amines have larger association constants with \(\text{m}-\text{nitrophenol}\) than tertiary aliphatic amines in dimethyl sulphoxide. This is due to dimethyl sulphoxide acting as a proton acceptor to form hydrogen-bonded complexes with the \(-\text{NH}_2\) group of the form: -

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{O}_2\text{N} \\
\text{H} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3
\end{array}
\]

No similar species was observed here with \(\text{m}-\text{nitrophenol}\) acting as the proton donor.
The fast production of \( m \)-nitrophenyl acetate could be due to a rapid equilibrium of the form:

\[
\begin{align*}
\text{CH}_3\text{O} & \text{O} \text{O} \text{CH}_3 \\
\text{H} & \text{O} \text{H} \text{CH}_3 \\
\text{NO}_2 & \text{H} \text{O} \text{H} \text{CH}_3
\end{align*}
\]

This type of equilibrium would explain why, at some 2,6-lutidine concentrations, the reaction does not go to completion. The components on the right hand side of this equilibrium were put together at various concentrations and the system analysed by ultraviolet spectroscopy for the hydrogen-bonded \( m \)-nitrophenol complex. Systems studied were:

(a) 2,6-lutidine (0.01 M), acetic acid (0.005 M) and \( m \)-nitrophenyl acetate.
(b) 2,6-lutidine (0.02 M), acetic acid (0.02 M) and \( m \)-nitrophenyl acetate (0.01 M).
(c) as (a) with acetic anhydride (0.04 M).
(d) as (b) with acetic anhydride (0.04 M).

No evidence could be found in any of these solutions for \( m \)-nitrophenol existing in the free or hydrogen-bonded state.

Recently, Wood and his co-workers recorded the infrared spectra of species such as (1) and (2) and others formed from different substituted pyridine bases.
These cations are thought to be linear (N...H...N) and coplanar. Species (3) has not been observed. These species usually exhibit at least two $\nu_3$ bands between 2000 and 2700 cm$^{-1}$, where excess base acts as the solvent for these pyridine salts. Spectra have also been recorded in acetonitrile and nitromethane. No spectra of these salts could be obtained in carbon tetrachloride due to low solubility when counterions such as $\text{BF}_4^-$ or $\text{ClO}_4^-$ are present.$^{119}$ Here, infrared spectra were run of the following systems in carbon tetrachloride:

(a) $p$-chlorophenol (0.011 M)
(b) $p$-chlorophenol (0.011 M) with 2,6-lutidine (0.12 M)
(c) $p$-chlorophenol (0.011 M) with 3,4-lutidine (0.02 M)
(d) $p$-chlorophenol (0.011 M) with 2,6-lutidine (0.12 M) and 3,4-lutidine (0.02 M).

No new absorption bands appeared in these spectra although the region between 2000 and 2700 cm$^{-1}$ was considerably masked by the absorption of the hydrogen-bonded hydroxyl group.

Leszina et al.$^{120}$ have studied solutions of 2,6-lutidine and $m$-nitrophenol in carbon tetrachloride and have found evidence for the protonated 2,6-lutidine ion by NMR spectroscopy ($\text{HM}^{+}-\text{H}$ at $\delta_{\text{TMS}} = 12.5$ ppm).$^{121}$ These experiments were repeated here using a 100 MHz Varian NMR spectrometer, but no signal could be assigned to the protonated lutidine species. The concentration of $m$-nitrophenol was varied from 0.5mg/cm$^3$ to 30mg/cm$^3$ and that of 2,6-lutidine from 0.5mg/cm$^3$ to 50mg/cm$^3$.

Solutions of $p$-chlorophenol (0.01 - 0.10 M) and 2,6-lutidine (0.02 - 0.10 M) in carbon tetrachloride were studied using a 60 MHz Varian NMR spectrometer coupled to a computer of averaged transients. Again, no signal corresponding to a protonated
pyridine ion could be detected. All spectra were recorded at the ambient temperature of the machine.

Competitive reactions of phenols with acetic anhydride in carbon tetrachloride.

(1) Reaction of p-cresol (0.05 M) and p-chlorophenol (0.05 M) with acetic anhydride (0.05 M) in the presence of pyridine in carbon tetrachloride at 0°.

After one week, no reaction could be detected in a solution of p-cresol (0.05 M), p-chlorophenol (0.05 M) and acetic anhydride (0.05 M) in carbon tetrachloride at 0°. To initiate the reaction pyridine solution was added and the reaction mixture left for several days. The results obtained here were very similar to those obtained if the reaction mixture was left for several weeks. The results are summarized in Table 3:32.

Experimental details are given in Section 2.

<table>
<thead>
<tr>
<th>pyridine (M)</th>
<th>p-chlorophenyl acetate (M)</th>
<th>ratio of rates (p-chlorophenol/p-cresol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>0.0295</td>
<td>1.44</td>
</tr>
<tr>
<td>0.010</td>
<td>0.0330</td>
<td>1.94</td>
</tr>
<tr>
<td>0.020</td>
<td>0.0330</td>
<td>1.94</td>
</tr>
<tr>
<td>0.030</td>
<td>0.0330</td>
<td>1.94</td>
</tr>
<tr>
<td>0.050</td>
<td>0.0330</td>
<td>1.94</td>
</tr>
<tr>
<td>0.100</td>
<td>0.0330</td>
<td>1.94</td>
</tr>
<tr>
<td>0.200</td>
<td>0.0330</td>
<td>1.94</td>
</tr>
<tr>
<td>0.250</td>
<td>0.0335</td>
<td>2.03</td>
</tr>
</tbody>
</table>

At all concentrations of pyridine studied, more p-chlorophenyl acetate is produced than p-cresyl acetate.
(2) Reaction of p-nitrophenol (0.005 M) and other phenols (0.005 M) with acetic anhydride (0.005 M) in the presence of 4-dimethylaminopyridine (0.02 M) at 25°C.

Less than one minute is required for complete reaction between p-nitrophenol (0.005 M) and acetic anhydride (0.005 M) in the presence of 4-DMAP (0.02 M). When another phenol is present in a competitive reaction for the anhydride, the residual p-nitrophenol may be estimated at the end of the reaction by shaking the organic phase with water and analysing for the p-nitrophenolate ion by visible spectrophotometry in the usual way. Results are given in Table 3:33. The product analysis was carried out one hour after reaction initiation.

<table>
<thead>
<tr>
<th>phenol</th>
<th>p-nitrophenyl acetate (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenol</td>
<td>0.0029</td>
</tr>
<tr>
<td>p-chlorophenol</td>
<td>0.0026</td>
</tr>
<tr>
<td>p-bromophenol</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

These results are inaccurate since p-nitrophenyl acetate is slightly hydrolysed by an aqueous solution of 4-DMAP (the 4-DMAP is transferred to the aqueous phase during analysis). p-Nitrophenyl acetate solution (2.5 x 10⁻³ M) in carbon tetrachloride, when shaken with an aqueous solution of 4-DMAP (0.02 M), transfers 8 x 10⁻⁴ M p-nitrophenolate ion into the aqueous phase after one minute. Since this inaccuracy depends upon the shaking time in the analysis procedure, which is very difficult to keep constant (time of shaking, vigour of hand shaking, etc.), exact quantitative results were not possible.
However, this inaccuracy will, in all cases, tend to give low results for the quantity of \( m \)-nitrophenyl acetate produced and it is reasonable to say that, in the reactions studied, \( m \)-nitrophenol reacts to give over 50% \( m \)-nitrophenyl acetate in the final product analysis.

B. Acylation reactions of compounds containing intramolecular hydrogen bonds and of compounds existing as self-associated species.

1) Acetylation of \( o \)- and \( p \)-methoxybenzyl alcohols with acetic anhydride in carbon tetrachloride at 25°.

The hydroxyl group in \( o \)-methoxybenzyl alcohol is substantially intramolecularly hydrogen-bonded in carbon tetrachloride,\(^{122,123}\) whereas that of \( p \)-methoxybenzyl alcohol shows no such interaction. The infrared spectra of these compounds in the fundamental hydroxyl stretching region have not been reported elsewhere and are illustrated in Figure 18.

\( p \)-Methoxybenzyl alcohol has just one sharp absorption in this region at 3620 cm\(^{-1}\) whereas the \( o \)-methoxy compound has a broader absorption at 3610 cm\(^{-1}\) with a shoulder at 3630 cm\(^{-1}\). The oxygen atoms of the hydroxy and \( o \)-methoxy groups can approach as near as 0.25 nm allowing a hydrogen bond to be formed, and indeed, such a configuration is probably the most stable one allowed in a non-polar solvent. Kinetic studies were carried out on these two isomers and results are given below. Good linear correlations were obtained up to 80% reaction when \( \log a/(a-x) \) was plotted against time, where \( a \) = initial concentration of alcohol and \( x \) = concentration of acetate after time \( t \). No
initial rapid production of acetate could be detected.

**TABLE 34**

The reaction of methoxybenzyl alcohols (0.01 M) with acetic anhydride (0.10 M) at 25°.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Rate constant x 10^6 (sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-methoxybenzyl alcohol</td>
<td>4.42</td>
</tr>
<tr>
<td>p-methoxybenzyl alcohol</td>
<td>6.48</td>
</tr>
</tbody>
</table>

ii) Acetylation of pyridyl alcohols (0.02 M) with acetic anhydride (0.10 M) in carbon tetrachloride at 35°.

Strong intramolecular hydrogen bonds are known to exist in 3-(2-pyridyl)-1-propanol (I) and 2-(2-pyridyl)ethanol (II) in carbon tetrachloride solutions.¹²⁴

![Chemical structures](image)

(I) ![Chemical structure of 3-(2-pyridyl)-1-propanol](image)

(II) ![Chemical structure of 2-(2-pyridyl)ethanol](image)

Infrared spectra in the fundamental hydroxyl stretching region of (I) and (II) are given in Figure 18, together with that of 3-phenyl-1-propanol. The concentrations of all these compounds are equal. The extinction coefficients of 3-phenyl-1-propanol and the pyridyl alcohols were assumed to be equal and, using a calibration curve of the free hydroxyl group absorption of 3-phenyl-1-propanol, the degree of hydrogen bonding in the pyridyl alcohols was deduced. Kinetic experiments were carried
Fig. 18  Infrared Spectra

- 3-phenyl-1-propanol
- o-methoxybenzyl alcohol
- p-methoxybenzyl alcohol

Wavenumber (cm⁻¹)

Transmittance (%)
out at higher temperatures than in previous work so that the
rates of reaction could be measured over a convenient time
interval. Results are given in Table 3:35. First order
dependence was observed in all the alcohols and no initial rapid
formation of acetate could be detected.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>degree of hydrogen bonding</th>
<th>rate constant $\times 10^6$ (sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-(2-pyridyl)-1-propanol</td>
<td>66%</td>
<td>6.91</td>
</tr>
<tr>
<td>3-(4-pyridyl)-1-propanol</td>
<td>-</td>
<td>95.0</td>
</tr>
<tr>
<td>2-(2-pyridyl)ethanol</td>
<td>84%</td>
<td>1.18</td>
</tr>
<tr>
<td>2-phenylethanol</td>
<td>-</td>
<td>7.39</td>
</tr>
<tr>
<td>3-phenyl-1-propanol</td>
<td>-</td>
<td>13.5</td>
</tr>
</tbody>
</table>

The infrared spectrum of 2-phenylethanol has been reported
by Krueger and Mettee$^{125}$ and, in the fundamental hydroxyl
stretching region, consists of two fairly well resolved
absorption bands (see Figure 19(a)). The high frequency component
at 3635 cm$^{-1}$ is assigned to the free hydroxyl group and the low
frequency component at 3605 cm$^{-1}$ is assigned to the hydroxyl
group intramolecularly hydrogen-bonded to the aromatic ring
electrons.

iii) Reaction of alcohols (0.02 M) with acetic anhydride (0.10 M)
in the presence of pyridine at 35°.

Alcohols generally tend to have low association constants
with pyridine, compared to those of phenols.$^{126}$ If the reaction
between alcohols and acetic anhydride in the presence of pyridine
is an example of general base catalysis, it would be expected
that the reaction would be insensitive to changes in pyridine
Fig. 19(a) Infrared spectrum of phenylethyl alcohol.

Fig. 19(b) Reaction of alcohols (0.02M) with acetic anhydride (0.10M)
in the presence of pyridine at 35°.
concentration compared with the phenolic reaction (see this section A. iv). Experiments were carried out on two systems, results are given in Table 3:36.

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>pyridine</th>
<th>rate constant x 10^6</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-(2-pyridyl)-1-propanol</td>
<td>(M)</td>
<td>(sec^-1)</td>
</tr>
<tr>
<td>0</td>
<td>7.03</td>
<td></td>
</tr>
<tr>
<td>0.04</td>
<td>8.33</td>
<td></td>
</tr>
<tr>
<td>0.09</td>
<td>8.68</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>9.31</td>
<td></td>
</tr>
<tr>
<td>3-phenyl-1-propanol</td>
<td>(M)</td>
<td>(sec^-1)</td>
</tr>
<tr>
<td>0</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>0.03</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>0.06</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>0.09</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>0.12</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

First order dependence was found in the alcohol in all these reactions and no initial rapid formation of acetate could be detected.

3-Phenyl-1-propanol (0.02 M) was reacted with acetic anhydride (0.10 M) in the presence of 2-picoline (0.12 M). A pseudo first order rate constant of 6.62 x 10^-6 sec^-1 was obtained, showing the reaction to be slower if no pyridine base was present in the system. These results are illustrated in Figure 19(b).

iv) Reaction of phenol with trifluoroacetic anhydride in carbon tetrachloride at 0°.

Phenol is known to self-associate, through hydrogen bonding, in carbon tetrachloride. It was of interest to determine
whether this associated species is reactive or non-reactive towards acylating reagents in non-polar media. (See the work of Koskikallio in Section 1 and the following experiment B (v)).

Unfortunately phenol and acetic anhydride do not react alone in carbon tetrachloride. Phenol does react with trifluoroacetic anhydride\(^9\) and, with phenol in excess, pseudo first order rate constants could be obtained. Results are given in Table 3:37.

<table>
<thead>
<tr>
<th>Phenol (M)</th>
<th>(k_0 \times 10^4) (sec(^{-1}))</th>
<th>Trifluoroacetic anhydride (M)</th>
<th>(k_0/(\text{Phenol}) \times 10^4) (M(^{-1}) sec(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025</td>
<td>0.74</td>
<td>0.0048</td>
<td>29.6</td>
</tr>
<tr>
<td>0.050</td>
<td>2.34</td>
<td>0.0048</td>
<td>46.8</td>
</tr>
<tr>
<td>0.100</td>
<td>5.24</td>
<td>0.0048</td>
<td>52.4</td>
</tr>
<tr>
<td>0.150</td>
<td>9.89</td>
<td>0.0048</td>
<td>65.9</td>
</tr>
<tr>
<td>0.200</td>
<td>13.1</td>
<td>0.0048</td>
<td>65.5</td>
</tr>
</tbody>
</table>

The second order rate constant (found as the ratio \(k_0/(\text{Phenol})\) for this reaction) can be seen to increase up to 0.15 M. A plot of \(\log k_0\) against \(\log\) phenol concentration is linear with a slope of 0.72, which implies that this reaction remains first order in the phenol throughout this concentration range. The rate constants were reproducible to about 10%. The ordinate intercept of the logarithmic plot in Figure 20 is 0.74, which should equal \(\log k_0 + 3\), where \(k_0\) is the second order rate constant, if the rate equation can be expressed as:

\[
\text{Rate} = k_0(\text{Phenol})(\text{Trifluoroacetic anhydride}) = k_0(\text{Trifluoroacetic anhydride})
\]

The pseudo first order rate constant increases linearly at the higher phenol concentrations and the experimental second
Fig. 20 Reaction of phenol with trifluoroacetic anhydride (0.0048M) in carbon tetrachloride at 0°C.

\[ \log (\text{phenol molarity}) + 5 \]

Rate constant $\times 10^6$ (sec$^{-1}$)

Phenol molarity $\times 10$
order rate constant becomes constant at about $65.5 \times 10^{-4} \text{M}^{-1}\text{sec}^{-1}$.

This value would give an ordinate intercept, on the logarithmic plot, of 0.32 which agrees, within experimental error, with the value of 0.74 obtained above.

v) Reaction of ethanol with acetic anhydride (0.25 M) in carbon tetrachloride at 40°.

Koskikallio\textsuperscript{22} found that in the reaction between ethanol and acetic anhydride, as the ethanol molarity was increased, the second order rate constant decreased. Work was carried out here to verify these results.

The reaction was quenched by shaking an aliquot (2 cm\textsuperscript{3}) of reaction mixture with saturated aqueous potassium bicarbonate (5 cm\textsuperscript{3} for 1 minute), the organic phase was then separated and shaken with water (10 cm\textsuperscript{3} for 1 minute) and dried over magnesium sulphate. An infrared spectrum was recorded.

At the low ethanol concentrations the rate constant may be calculated by assuming pseudo first order kinetics or by plotting $\log \left(\frac{a-x}{b-x}\right)$ against time, where $a=$ concentration of anhydride, $b=$ concentration of ethanol and $x=$ concentration of ethyl acetate at time $t$, the slope of this straight line giving the second order rate constant directly. These two methods give consistent results. At higher ethanol concentrations, simple second order kinetics were not observed, a plot of $\log \left(\frac{a-x}{b-x}\right)$ against time having an upward curvature. A good linear correlation is observed up to 40% reaction and this was used to calculate the rate constant. The results of a typical kinetic experiment are given in Table 3:38 and illustrated in Figure 21.
Fig. 21 Reaction of ethanol (0.125M) with acetic anhydride (0.25M) in carbon tetrachloride at 40°.
TABLE 3:38
Reactivity of ethanol (0.125 M) with acetic anhydride (0.25 M) in carbon tetrachloride at 40°.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Molarity of acetate x 10^3</th>
<th>log (a-x)/(b-x) x 10^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>4.8</td>
<td>31.9</td>
</tr>
<tr>
<td>98</td>
<td>29</td>
<td>36.2</td>
</tr>
<tr>
<td>140</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>180</td>
<td>48.5</td>
<td>42.1</td>
</tr>
<tr>
<td>235</td>
<td>59.5</td>
<td>46.4</td>
</tr>
<tr>
<td>290</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>345</td>
<td>77.5</td>
<td>56</td>
</tr>
<tr>
<td>423</td>
<td>88</td>
<td>64.1</td>
</tr>
</tbody>
</table>

This apparent autocatalysis (Figure 21) is caused by the acetic acid produced during the reaction. Acetic acid (0.10 M) was added to the reaction mixture of ethanol (0.125 M) and acetic anhydride (0.25 M) and second order kinetics were observed. Results are given in Table 3:39.

TABLE 3:39

<table>
<thead>
<tr>
<th>Ethanol (M)</th>
<th>Acetic acid (M)</th>
<th>Rate constant x 10^4 (M^-1 sec^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0125</td>
<td>-</td>
<td>2.27</td>
</tr>
<tr>
<td>0.125</td>
<td>-</td>
<td>2.09</td>
</tr>
<tr>
<td>0.25</td>
<td>-</td>
<td>1.79</td>
</tr>
<tr>
<td>0.125</td>
<td>0.10</td>
<td>6.84</td>
</tr>
</tbody>
</table>
Acylation reactions occurring at a water-carbon tetrachloride boundary.

1) The reaction of m-nitrophenol (0.005 M) and isobutyric anhydride (0.05 M) in carbon tetrachloride when shaken with a saturated aqueous solution of potassium bicarbonate.

m-Nitrophenol (0.005 M) does not react with isobutyric anhydride (0.05 M) in carbon tetrachloride. However, when this solution was shaken with saturated aqueous potassium bicarbonate, some m-nitrophenyl isobutyrate could be detected. (i) analysis of the organic phase by gas liquid chromatography shows the presence of isobutyrate, (ii) analysis of the aqueous phase by visible spectroscopy indicates a decrease in m-nitrophenate ion concentration i.e., reaction has occurred. It was found that shaking these reactions by hand gave good reproducible results and it was felt that this method was preferable to mechanical agitation for time intervals between one and ten minutes.

A solution of m-nitrophenol (0.005 M) and isobutyric anhydride (0.05 M) was prepared in carbon tetrachloride and maintained at 25º in a thermostatted water bath for 30 minutes. A 1 cm³ aliquot of this solution was added to a 5 cm³ aliquot of saturated aqueous potassium bicarbonate at 25º in a 25 cm³ separating funnel, and shaking started immediately. After a measured time interval, shaking was stopped and the two phases allowed to separate for one minute. The organic phase was then run off and the aqueous phase filtered (this latter procedure removing also any carbon tetrachloride in suspension). A visible spectrum was then run of the aqueous phase on a Perkin-Elmer 137 UV spectrometer. The m-nitrophenate ion was then estimated.
Fig. 22 Reaction of $m$-nitrophenol (0.005M) with anhydrides (0.05M) when shaken with saturated aqueous potassium hydrogen carbonate solution.

- isobutyric anhydride
- pivalic anhydride

Time (minutes)
from a calibration curve, previously obtained in the usual manner. Results are given in Table 3:40.

**TABLE 3:40**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>m-nitrophenolate ion x 10^4 (M)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44.7</td>
<td>10.5</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>2.5</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>25.3</td>
<td>49.5</td>
</tr>
<tr>
<td>4</td>
<td>21.3</td>
<td>57.5</td>
</tr>
<tr>
<td>5</td>
<td>16.5</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>36</td>
</tr>
</tbody>
</table>

A graph of percentage reaction against time is a smooth curve which does not pass through the origin. This is illustrated in Figure 22. A solution of isobutyric anhydride, when shaken with saturated aqueous potassium bicarbonate, does not show any decrease in the anhydride concentration.

i) Reaction of p-nitrophenol (0.005 M) and pivalic anhydride (0.05 M) in carbon tetrachloride when shaken with saturated aqueous potassium bicarbonate solution.

The same procedure was used here as in the preceding experiment. Results are given in Table 3:41. The smooth curve obtained by plotting percentage reaction against shaking time is also shown in Figure 22. The reaction appeared to give a maximum pivalate production after about ten minutes. The reproducibility in this and the preceding experiment is about 1.5%.
### TABLE 3:41

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>m-nitrophenate ion ( \times 10^4 )</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36.7</td>
<td>26.5</td>
</tr>
<tr>
<td>2</td>
<td>27.5</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>19.3</td>
<td>61.5</td>
</tr>
<tr>
<td>7</td>
<td>17.8</td>
<td>64.5</td>
</tr>
<tr>
<td>10</td>
<td>16.5</td>
<td>67</td>
</tr>
<tr>
<td>14</td>
<td>17.5</td>
<td>65</td>
</tr>
</tbody>
</table>

iii) 3-Ficoline catalysed reaction between \( p \)-nitrophenol and pivalic anhydride in a two phase water-carbon tetrachloride system at 25°.

Menger\(^5\) has shown that \( p \)-nitrophenyl laurate is hydrolysed at a heptane-water boundary if imidazole is present in the aqueous phase. It was the aim of this work to determine if an esterification could be observed at a water-carbon tetrachloride boundary between a phenol and a carboxylic acid anhydride. A phenol had to be selected which was soluble in water but insoluble in carbon tetrachloride. \( p \)-Nitrophenol had not been used previously in this work because of its very low solubility in carbon tetrachloride, and it was shown that if an aqueous solution of \( p \)-nitrophenol was stirred with carbon tetrachloride for several hours, no \( p \)-nitrophenol could be detected, by infrared analysis, in the organic phase. \( p \)-Nitrophenol also has the advantage of being easily detected, in the form of its anion, by visible spectrophotometry at 400 nm. \( m \)-Nitrophenol is too soluble
in carbon tetrachloride to be of use in this experiment.

No reduction in the absorbance of the carbonyl stretching band in the infrared spectrum could be detected when a solution of pivalic anhydride (in carbon tetrachloride) was stirred for eight hours with water. Under the conditions used here pivalic anhydride is not soluble in water, nor is it hydrolysed. A solution of p-nitrophenyl pivalate in carbon tetrachloride was also stirred with water for eight hours, but no p-nitrophenyl pivalate could be detected in the aqueous phase. Thus we have here a system which should be suitable for two phase kinetic study, i.e. (i) both the reactants are soluble in one phase but insoluble in the other, (ii) the p-nitrophenyl pivalate produced is only soluble in the carbon tetrachloride phase.

The reaction vessel and stirrer used in this work are illustrated in Figure 23. The cylindrical "Pyrex" glass vessel was constructed with an off centre side arm to allow samples to be withdrawn without dismantling the apparatus. The glass stirrer was fitted to a Citenco electric motor (maximum rpm = 1200) modified with an integrated circuit amplifier to maintain constant stirring speeds. The apparatus was marked so that after each experiment the vessel could be washed, dried and reassembled in exactly the same way. Stops were provided on the stirring rod to ensure that the stirrer blade was always in the same place, approximately at the interface of the two phases.

Kinetic experiments were carried out as follows. A solution of p-nitrophenol in water (5 cm³, 25°C) and a solution of pivalic anhydride in carbon tetrachloride (5 cm³, 25°C) were added to the reaction vessel via the side arm, the apparatus being immersed
Fig. 23 3-Picoline catalysed reaction between p-nitrophenol and pivalic anhydride in two phase system. Ultraviolet spectra of the aqueous phase

Aqueous phase after 30 minutes stirring. Aqueous phase before reaction (a solution of p-nitrophenol and 3-picoline).
in a thermostatted water bath at 25°. Stirring was started immediately addition was complete. After a measured time interval the stirring was stopped and one minute was allowed for the two phases to separate. A 3 cm³ aliquot of the organic phase was then removed, shaken with water (10 cm³), separated and dried over magnesium sulphate. A 0.5 cm³ aliquot of this solution was then shaken with 0.1 M sodium hydroxide solution until the colour in the aqueous phase was fully developed. This procedure hydrolysed any p-nitrophenyl pivalate present in the organic phase, and the p-nitrophenolate ion concentration could be estimated from a previously obtained calibration curve. This calibration was unaffected by any pivalic acid present in the system.

Pivalic anhydride (0.05 M, CCl₄) was stirred with p-nitrophenol (0.001 M, H₂O) for 3 hours at 25°. No reaction could be detected after this time interval. This experiment was repeated using a higher concentration of p-nitrophenol (0.01 M), but again no reaction could be detected.

3-Picoline was added to the above system in the carbon tetrachloride phase and 100% reaction was observed after 30 minutes stirring time. This result remained constant after 6 hours stirring, indicating that the p-nitrophenyl pivalate product is not hydrolysed. To determine that there was no anomalous effect producing the pivalate during the analysis procedure, the organic phase was analysed by gas liquid chromatography (Apiezon K, 175°, 15 psi, nitrogen carrier gas). A peak was observed in the chromatogram which corresponded to p-nitrophenyl pivalate.
Fig. 24 J-Picoline catalysed reaction between p-nitrophenol and pivalic anhydride at a water-carbon tetrachloride interface at 25°.

% Reaction

Stirring time (minutes)
The 3-picoline concentration was reduced to $4.4 \times 10^{-3}$ M in the carbon tetrachloride and the results obtained are listed in Table 3:42.

<table>
<thead>
<tr>
<th>Stirring time (min)</th>
<th>% reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32.3</td>
</tr>
<tr>
<td>2.5</td>
<td>35.9</td>
</tr>
<tr>
<td>5</td>
<td>37.5</td>
</tr>
<tr>
<td>10</td>
<td>40.6</td>
</tr>
<tr>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>60</td>
<td>49</td>
</tr>
</tbody>
</table>

Each of the above values is the average of two experimental results. The reproducibility was about 1%. An ultraviolet spectrum was recorded, of the aqueous phase, after 30 minutes and is represented in Figure 23. Also shown in Figure 23 is the ultraviolet spectrum of an aqueous solution of p-nitrophenol ($0.001$ M, $5 \text{ cm}^3$) which has been shaken with a carbon tetrachloride solution of 3-picoline ($0.044$ M, $1 \text{ cm}^3$). This is equivalent to an ultraviolet spectrum of the aqueous phase before reaction. Figure 24 shows how the percentage reaction varies with stirring time.

It was of interest to determine the acidity of the aqueous phase before and after reaction. Acidity measurements were recorded on a Pye Unicam 290 pH meter. Results are given below.

1. Aqueous p-nitrophenol ($0.001$ M) $\quad$ pH = 5.25
2. Aqueous p-nitrophenol ($0.001$ M) stirred with 3-picoline ($4.4 \times 10^{-3}$ M, $\text{CCl}_4$) $\quad$ pH = 6.80
3. Aqueous phase of reaction mixture after 30 minutes $\quad$ pH = 4.50
The reaction was repeated using a 2,6-lutidine/glycine buffer (2,6-lutidine (9.55 cm³) with glycine (3.43g) made up to 250 cm³ with water), pH = 8.40. p-Nitrophenol (0.001 M) in the buffer solution was stirred for 16 minutes with a solution of pivalic anhydride (0.04 M). 100% reaction was recorded. The buffer concentration was reduced ten times and the reaction repeated. This time only 30% reaction was observed after 10 minutes, which was unchanged after 80 minutes (separate experiments). The pH of the aqueous phase after 10 minutes was 5.35.

A solution of p-nitrophenol (0.001 M) and 2,6-lutidine (at the same concentration as in the buffer) was stirred for 6 hours with a solution of pivalic anhydride (0.04M). 15% reaction was recorded. The 2,6-lutidine solution stirred alone with the pivalic anhydride solution for 6 hours had a pH = 6.30 (reduced from 8.40 at the beginning of the experiment).

A solution of pivalic anhydride (0.01 M) and 3-picoline (0.02 M) in carbon tetrachloride was stirred with water for 7 hours. At the end of this time the organic phase was separated, dried and an infrared spectrum recorded. Comparison of this spectrum with the one recorded before the experiment revealed a slight reduction in the intensity of the anhydride carbonyl absorption band.

D. The reaction between phenols and acetic anhydride in carbon tetrachloride.

It has been stated that phenols do not react with acetic anhydride in carbon tetrachloride (see refs. 97, 107, and in this Section A (i)). This is not always the case and this
Section deals with the slow, non-reproducible reactions, which were sometimes observed throughout the course of this work.

A number of experiments have been studied which appeared to proceed at a rate faster than expected. A repeat of this anomalous reaction invariably resulted in the expected rate. Whenever a series of kinetic experiments were carried out, it is normally expected that one or two experiments will give rate constants which are undoubtedly wrong. These results are usually ignored. In some of the work carried out here, however, these anomalous results appeared too often to be ignored and the reason for this reactivity was investigated. Some examples of where these reactions occurred are given below.

The reaction was studied between $p$-chlorophenol and acetic anhydride in the presence of methyl substituted benzene derivatives. Yoshida and his co-workers\textsuperscript{123,129} have shown that toluene, the xylenes and mesitylene form weak hydrogen-bonded complexes with phenol in carbon tetrachloride. The association constants here are very low ($0.57 \pm 0.03 \text{ M}^{-1}$ at $29^\circ$ for the association of phenol with mesitylene). It was not expected that these compounds would catalyse a reaction between $p$-chlorophenol and acetic anhydride for two reasons (i) the hydrogen bond is too weak and (ii) the configuration of such a hydrogen-bonded species would be sterically unfavourable to reaction, i.e.

\[
\begin{align*}
Ph-O-H & \quad \text{CH}_3 \\
& \quad \text{CH}_3 \\
& \quad \text{CH}_3 \\
\end{align*}
\]
p-Chlorophenol (0.01 M) was added to a solution of acetic anhydride (0.05 M) in the presence of mesitylene (0.04 M) at 25°. After 3.5 days, 30% reaction had occurred and a plot of log (a-x) against time was linear, where a = initial concentration of phenol and x = concentration of acetate at time t. Hence, it appeared that a slow first order reaction was occurring. This reaction was repeated using different solutions and reaction vessels but this rate could not be reproduced. Similar anomalous, non-reproducible results were obtained when using m-xylene and duroene as additives. No reaction was observed when polybutylene containers were used as reaction vessels. It was concluded that the methylbenzenes do not catalyse a reaction between p-chlorophenol and acetic anhydride and any reaction is probably the result of a glass surface effect.

Owing to the inconsistencies found in the above experiments the analysis technique was checked by following the reaction by gas liquid chromatography. p-Dichlorobenzene was used as an internal standard because of (i) its favourable retention time, compared to the reactants and products, on an Apiezon K column, and (ii) its assumed inertness towards the reactants. The reactions were repeated using m-xylene, mesitylene and duroene as catalysts but once again a few anomalous results were obtained. Again, no reactions were observed when polybutylene containers were used. The possibility of a glass surface effect is discussed in Section 4.
SECTION 4. DISCUSSION

A. Reaction of phenols with carboxylic acid anhydrides in the presence of bases in carbon tetrachloride.

Pseudo first order kinetics were observed when p-chlorophenol was reacted with excess acetic anhydride in the presence of pyridine. Rate constants were calculated from the slopes of log $a/(a-x)$ against time graphs, where $a$ is the initial concentration of phenol and $x$ is the acetate produced after time $t$. This procedure assumes a rate equation of the form:

$$\text{Rate} = k \text{(Phenol)}(\text{Ac}_2\text{O})(\text{Pyridine})$$

$$= k_e \text{(Phenol)}(\text{Pyridine})$$

where $k_e$ is the experimentally determined pseudo first order rate constant. The use of 'a' in the integrated rate equation implies that the reactive species is the free phenol or a species that is directly proportional to the free phenol throughout the reaction.

Nucleophilic catalysis (see Section 1, B (ii), equation 12), where the pyridine attacks the anhydride molecule to form an intermediate, has the form:

$$\begin{array}{c}
\text{CH}_3\text{C}O\text{O} \text{C}O\text{C}H_3 + \text{N} \xrightarrow{K_n} \text{CH}_3\text{C}O\text{N} \text{Phenol} + \text{CH}_3\text{CO}_2\text{H} \\
\xrightarrow{k_n} \text{CH}_3\text{C}O\text{N} \text{Phenol} + \text{CH}_3\text{CO}_2\text{H} \\
\text{CH}_3\text{CO}_2\text{H} + \text{CH}_3\text{CO}_2\text{H}
\end{array}$$

$$\text{Rate} = k_n k_e \text{(Phenol)}(\text{Acetic anhydride})(\text{Pyridine}).$$

Here, the free phenol is the reactive species and, when log $a/(a-x)$ is plotted against time, a straight line is expected.
General base catalysis (see Section 1, B (i)) would have the form:

\[
\text{Phenol} + N \xrightarrow{K_b} (\text{Phenol...Pyridine}) \xrightarrow{K_b} \text{Products (2)}
\]

H-bonded complex

Rate = \( k_k' \frac{K_b}{(\text{Phenol})(\text{Ac}_2\text{O})(\text{Pyridine})} \)

= \( k_k' (\text{Phenol...Pyridine})(\text{Ac}_2\text{O}) \)

A straight line is not expected here, when \( \log a/(a-x) \) is plotted against time, unless it can be shown that the hydrogen-bonded (H-bonded) complex molarity, throughout the reaction, is directly proportional to the stoichiometric phenol. The ratio

\[
\frac{(\text{H-bonded complex})}{(a-x)} = R
\]

was calculated throughout the reaction of \( p \)-chlorophenol (0.01 M) with acetic anhydride in the presence of pyridine (0.02 M). Values are given in Table 4:1.

<table>
<thead>
<tr>
<th>( x ) reaction</th>
<th>( R )</th>
<th>( R' )</th>
<th>( R'' )</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.628</td>
<td>0.600</td>
<td>0.606</td>
</tr>
<tr>
<td>30</td>
<td>0.638</td>
<td>0.591</td>
<td>0.606</td>
</tr>
<tr>
<td>40</td>
<td>0.646</td>
<td>0.583</td>
<td>0.606</td>
</tr>
<tr>
<td>50</td>
<td>0.654</td>
<td>0.577</td>
<td>0.601</td>
</tr>
<tr>
<td>60</td>
<td>0.662</td>
<td>0.570</td>
<td>0.599</td>
</tr>
<tr>
<td>70</td>
<td>0.671</td>
<td>0.560</td>
<td>0.597</td>
</tr>
<tr>
<td>80</td>
<td>0.678</td>
<td>0.552</td>
<td>0.593</td>
</tr>
</tbody>
</table>

The association constant between \( p \)-chlorophenol and pyridine is 112.8 M\(^{-1}\) at 27° in carbon tetrachloride.\(^{102}\) The value of \( R \) remains fairly constant throughout the reaction.
The overall steady increase in \( R \) would manifest itself as a very slight upward curvature on a log \( a/(a-x) \) versus time graph. This would affect the value of the calculated rate constant by about 5\%, which is within the experimental error of these experiments. However, this very slight upward curvature was not observed, and hence other factors must be considered for a general base catalysed mechanism to be consistent with the experimental facts.

Acetic acid is known to form strong hydrogen bonds with pyridine in carbon tetrachloride. The \( R' \) values given in Table 4:1 were calculated assuming that the acetic acid liberated in the reaction completely hydrogen bonds to pyridine molecules, forming a non-reactive species. Here then:-

\[
K_1 = \frac{(PH)}{(0.01 - PH)(Py - A - PH)}
\]

where \( PH = p\)-chlorophenol/pyridine H-bonded complex molarity, \( Py = \) pyridine molarity, \( A = \) acetic acid molarity and \( K_1 = 112.8 \text{ M}^{-1} \).

\( R' = 0.58 \pm 0.03 \), which has about the same percentage error as the \( R \) value. The steady decrease in \( R' \) between 20 - 80\% would be observed as a slight downward curvature on the log \( a/(a-x) \) against time graph. The assumption that the acetic acid and base form a non-reactive species, which does not subsequently dissociate, is unreasonable. If this were so, reactions where the phenol molarity was greater than the base molarity would not go to completion (see experiments 3 A, (iv); (v); (x)). All reactions investigated went to completion unless otherwise stated.

\( R'' \) was calculated by solving the following five equations:-
(i) \[ K_1 = \frac{(PH)}{(P)(PY)} \]
(ii) \[ K_2 = \frac{(AH)}{(A)(PY)} \]
(iii) \[ (AH) + (A) = (x) \]
(iv) \[ (PH) + (P) = (a-x) \]
(v) \[ (PY) + (AH) + (PH) = 0.02 \]

where \( AH = \) acetic acid/pyridine H-bonded complex molarity, \( A = \) acetic acid molarity, \( P = \) p-chlorophenol molarity and \( K_2 = 220 \text{ M}^{-1} \).

Equation (iii) assumes that all the acetic acid produced \((i.e.\) equivalent to \(x\), the acetate produced) is either free or hydrogen-bonded with pyridine. Likewise, equation (iv) assumes that all the phenol present in the system is either free or hydrogen-bonded with pyridine. The last equation adds the molarities of the phenol and acetic acid hydrogen-bonded complexes to the free pyridine molarity and sets this sum equal to 0.02 M, the initial molarity of pyridine.

\( R^\circ \) varies by only 1.5\% between 20 - 80\% reaction. This small variation would be impossible to detect under the experimental conditions used. The constant \( R^\circ \) value throughout the acetylation of p-chlorophenol by acetic anhydride is probably fortuitous because no account has been taken of associations of other kinds, \(i.e.\) acetic acid with acetic anhydride, \(131\) the acetate and phenol. Also acetic acid is known to dimerize in non-polar solvents. \(132\) Other phenols do not show such good, constant values of \( R^\circ \) between 20 - 80\% reaction but the deviations are not large enough to invalidate results found using \( R^\circ \). Results for phenol are given below, calculated from an
association constant\textsuperscript{102} with pyridine, $K_{\text{ass}} = 46.3 \text{ M}^{-1}$.

<table>
<thead>
<tr>
<th>$%$ reaction</th>
<th>$R^n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.412</td>
</tr>
<tr>
<td>50</td>
<td>0.398</td>
</tr>
<tr>
<td>80</td>
<td>0.370</td>
</tr>
</tbody>
</table>

Through lack of knowledge of the other interactions of acetic acid, more refined values of $R^n$ cannot be calculated. However, it is now possible to say that both nucleophilic and general base catalysis in this acetylation could exhibit first order kinetics in the phenol.

Table 3:2 lists $R^n$ values for all the phenols, calculated at 50\% reaction. The rate equation for general base catalysis can be rearranged in a form to include $R^n$:

$$\text{Rate} = k^b (\text{Pyridine} \ldots \text{Phenol})(\text{Ac}_2\text{O})$$

$$= k^b R^n (a-x)(\text{Ac}_2\text{O})$$

$$= k_b R^n (a-x)$$

where $k_b$ is the pseudo first order rate constant. The experimental rate constant, $k_0$, found in experiment (i) equals $k_b R^n$ and hence $k_b$ can be calculated. These rate constant values take into consideration the different hydrogen bonding abilities of each of the phenols. $k_b$ gives a more accurate value for the nucleophilicity of the hydrogen-bonded complex than does $k_0$.

From these $k_b$ values it can be seen that the complex reactivity increases as the phenol acidity increases. The $p$-cresol complex is less reactive than the $p$-chlorophenol complex even though $p$-cresol is more nucleophilic than $p$-chlorophenol (see experiment xxix). However, it is known that as the phenol acidity increases, the strength of the hydrogen bond increases.\textsuperscript{133} The energy of
the hydrogen bond is essentially electrostatic and the following
three main valence bond structures can be drawn\textsuperscript{134}:-

(a) \( \text{H}^- \text{O}^+ \)

(b) \( \text{H}^+ \text{O}^- \)

(c) \( \text{H}^- \text{O}^- \)

where \( X \) is an electronegative element. In (b) and (c) the
oxygen of the hydroxyl group has more electron density than in
the free state, increasing its basicity and hence its
nucleophilicity. The stronger the hydrogen bond, the greater is
the negative charge residing on the oxygen atom. A phenol has
acidic properties, partly through its ability to form the
resonance structures:-

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

Why similar charge delocalization does not occur within
the hydrogen-bonded species, decreasing the electron density on
the oxygen atom and hence decreasing the bond strength, is not
fully understood.

The effect of substituents in the phenol. The Hammett equation.

A Hammett plot of \( \log k_b \) against \( \sigma^0 \) is linear, giving

\( \rho = 1.91 \pm 0.02 \) (c.f. \( \rho = 1.52 \) when \( \log k_o \) is plotted against
\( \sigma^0 \))(Table 3:2). In the Hammett equation, \( \log k/k_o = \sigma \rho \), the
reaction constant, \( \rho \), gives an indication of the demand placed
on the substituent in the transition state to donate or withdraw electrons. Consider a nucleophilic catalysis for this reaction, as depicted in equation (1). The hydrolysis of acetic anhydride in the presence of pyridine occurs via a limiting rate formation of the acetylpyridinium ion. If a similar mechanism occurred here, the sensitivity of the reaction towards substituents on the phenol should be low, i.e., \( \rho \approx 0 \). If the rate determining step is the breakdown of the intermediate, a negative \( \rho \) would be expected. Neither of these possibilities is in agreement with experimental facts.

General base catalysis (equation (2)), where the rate limiting step is the interaction of the hydrogen-bonded complex with the anhydride, would give a positive \( \rho \), as observed. The possibility of the equilibrium step being slow cannot be overlooked, but if this were the case, the rate would be independent of the anhydride molarity. This again is not in agreement with experimental facts.

Regardless of the favourable slope (\( \rho \)) obtained from the Hammett plot, the linearity itself is consistent with a reaction in which the pyridine/phenol hydrogen-bonded complex is involved in the rate determining step.

The effect of substituents in the pyridine. The Brönsted equation.

All the reaction series investigated involving pyridine bases gave good linear Brönsted correlations when \( \log k_a \) was plotted against the base \( pK_a \). 2-Picoline and 2,6-lutidine do not catalyse these acylations due to steric effects (see experiment xxiii). The ability of pyridine bases to hydrogen bond with
phenols is not hindered by groups substituted in the $\alpha$-positions of the bases. However, the hydrogen-bonded complex will be sterically crowded about the hydroxyl oxygen, preventing reaction with the anhydride molecule (see Section 1.8(ii)).

The degree to which the hydroxyl bond is broken or formed in a transition state is generally believed to be reflected in the Brønsted reaction constant, $\beta$. $\beta$ is usually found to be larger in nucleophilic catalysis ($0.7 - 0.8$) than in general base catalyses ($0.5$, see Section 1). However, these figures are derived from hydrolyses where the attacking nucleophile is water. In this work a phenol molecule is the nucleophile. The values of $\beta$ appear high for a general base catalysis but it would be expected that, as the acidity of the attacking species was increased i.e. increasing the polarisation of the OH bond, the $\beta$ value would become larger. $\beta$ increases as the acidity of the phenol increases (Table 4:2).

**TABLE 4:2**

Reactions of carboxylic acid anhydrides with phenols and pyridine bases.

<table>
<thead>
<tr>
<th>anhydride</th>
<th>phenol</th>
<th>$\beta$</th>
<th>$pK_a$(phenol$^{137}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetic</td>
<td>$p$-cresol</td>
<td>0.85</td>
<td>10.26</td>
</tr>
<tr>
<td>&quot;</td>
<td>$p$-chlorophenol</td>
<td>0.93</td>
<td>9.42</td>
</tr>
<tr>
<td>&quot;</td>
<td>$m$-nitrophenol</td>
<td>0.96</td>
<td>8.39</td>
</tr>
<tr>
<td>isobutyric</td>
<td>$m$-nitrophenol</td>
<td>0.87</td>
<td>8.39</td>
</tr>
</tbody>
</table>

**Variation in rate with base molarity.**

When the base molarity is increased, both nucleophilic and general base catalysis would be expected to give curves similar
to Figure 5, at constant anhydride concentrations. For nucleophilic catalysis one would expect the slope to level, due to complete complex formation between the anhydride and the base. Similarly, in general base catalysis the phenol will become completely hydrogen-bonded and a further increase in base molarity will not effect the rate.

Listed in Table 3:6 are \( R \) values calculated at each 4-picoline concentration for the reaction of \( m \)-chlorophenol with acetic anhydride. From these values \( k_b \) may be calculated and these are listed below.

<table>
<thead>
<tr>
<th>4-picoline molarity ( \times 10^3 )</th>
<th>5.0</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_b \times 10^4 ) (sec(^{-1}))</td>
<td>4.89</td>
<td>4.88</td>
<td>4.58</td>
<td>4.89</td>
</tr>
</tbody>
</table>

\( k_b \) is constant throughout the 4-picoline concentration range (within experimental error), implying that this reaction is general base catalysed. Similar results were obtained in other systems.

**TABLE 4:3**

Reaction of \( m \)-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of bases. Experiment (v).

<table>
<thead>
<tr>
<th>3-picoline molarity ( \times 10^3 )</th>
<th>0.5</th>
<th>2.5</th>
<th>5.0</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_b \times 10^4 ) (sec(^{-1}))</td>
<td>7.27</td>
<td>6.63</td>
<td>6.79</td>
<td>7.39</td>
</tr>
<tr>
<td>4-picoline molarity ( \times 10^3 )</td>
<td>1.25</td>
<td>2.5</td>
<td>3.15</td>
<td>5.0</td>
</tr>
<tr>
<td>( k_b \times 10^4 ) (sec(^{-1}))</td>
<td>14.17</td>
<td>13.80</td>
<td>13.77</td>
<td>13.15</td>
</tr>
</tbody>
</table>

Unfortunately only \( R \) and not \( R'' \) values can be calculated for bases other than pyridine, because association constants between these bases and acetic acid are not known. \( R' \) values could be used, but these contain the same degree of error as \( R \) itself.
To avoid the saturation effects of complex formation, 4-dimethylaminopyridine (4-DMAP) was employed as the catalyst (experiment x). The association constant for 4-DMAP is not known but can be estimated graphically. Rubin and Panson\textsuperscript{136} plotted log $K_{\text{association}}$ against $\sigma^0$ for various substituted pyridines with phenol in carbon tetrachloride and obtained a straight line. This graph can be extrapolated to include 4-DMAP using a $\sigma^0$ value for the $n$-dimethylamino group\textsuperscript{103} of $0.44$. From this approximate method, $K_{\text{ass}}$ of 4-DMAP with phenol is estimated at 160 M$^{-1}$. $R$ can now be calculated from this $K_{\text{ass}}$ value and, hence, $k_b$ found. Results are given below and in Table 3:14.

<table>
<thead>
<tr>
<th>4-DMAP molarity $\times 10^5$ (M)</th>
<th>$k_b \times 10^2$ (sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.412</td>
<td>9.15</td>
</tr>
<tr>
<td>0.824</td>
<td>12.7</td>
</tr>
<tr>
<td>1.236</td>
<td>13.1</td>
</tr>
<tr>
<td>1.643</td>
<td>13.2</td>
</tr>
<tr>
<td>2.060</td>
<td>12.6</td>
</tr>
<tr>
<td>2.47</td>
<td>13.4</td>
</tr>
</tbody>
</table>

There are two reasons why this reaction may be regarded as first order in 4-DMAP.

(i) When log $k_o$ is plotted against log (4-DMAP) a straight line is obtained, with a slope of 0.97. The rate equation for a general base catalysis will have the form:

$$ k_o \text{ (Phenol)}_g = k_b K_{\text{ass}} \text{ (Phenol)}_f (4-\text{DMAP})_f $$

where $(\text{Phenol})_g = \text{stoichiometric concentration of phenol},$
(Phenol) = free (uncomplexed) phenol and (4-DMAP) = free 4-DMAP.

At the very small 4-DMAP concentrations:

\[(\text{Phenol})_s = (\text{Phenol})_f\]

\[k_c = k_b K_{\text{ass}} (4-\text{DMAP})_f\]

It can be shown in this reaction that \((\text{Phenol} \cdots 4-\text{DMAP})/\)

\((4-\text{DMAP})_s\) is constant throughout the concentration range studied and, as \((\text{Phenol} \cdots 4-\text{DMAP}) = (4-\text{DMAP})_s-(4-\text{DMAP})_f\), a plot of \(\log k_c\) against \(\log (4-\text{DMAP})_s\) should be linear with a slope equal to the order of the reaction with respect to 4-DMAP.

(ii) \(k_b\) may be regarded as constant within the experimental error for the reactions with 4-DMAP concentrations between \(0.824 - 2.47 \times 10^{-5} \text{ M}\). The \(K_{\text{ass}}\) value used to calculate \(k_b\) was determined assuming a 1:1 complex between the pyridine and the phenol. If other complex stoichiometries were present, the \(k_b\) values would change as the base molarity is increased. Whenever \(k_b\) is found to be constant throughout a reaction series, an order of one is suggested for both the phenol and the pyridine base.

Other evidence against nucleophilic catalysis is also obtained from the 4-DMAP reactions. Jencks\(^{66}\) found that the acetylpyridinium ion derived from p-methoxypyridine is hydrolysed more slowly than the \(pK_a\) of the base would suggest. This behaviour was attributed to resonance stabilised structures of the form:

\[
\begin{align*}
\text{CH}_3\text{C}-\text{N} & \leftrightarrow \text{CH}_3\text{C}-\text{N}^+ \\
\text{OCH}_3 & \leftrightarrow \text{OCH}_3^+ \\
\text{O}^- & \leftrightarrow \text{O}^+ \\
\end{align*}
\]
In the reaction investigated here, a similar resonance stabilised species may be drawn:

\[
\begin{align*}
\text{CH}_3-O-\text{N} & \quad \text{CH}_3-O-\text{N} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

It would, therefore, be expected that the point for 4-DMAP represented on a Brønsted catalysis graph (Figure 4) would fall below the line. Because of the large differences in molarity and \( pK_a \) between 4-DMAP and the other pyridine bases, only estimations can be made here, but these indicate no apparent reduction in rate for the 4-DMAP catalysed reaction.

4-DMAP \((pK_a = 9.71)\) could ionise the phenol to the phenate ion, which would be highly reactive in this acetylation reaction. Because of the difficulty in distinguishing between transition states of the same stoichiometry by kinetic measurements, this possibility can only be noted here.

**Nucleophilic versus general base catalysis.**

At this stage in the discussion it is necessary to indicate why nucleophilic catalysis would be an unfavourable acetylation mechanism in carbon tetrachloride, although in the pyridine catalysed hydrolysis of acetic anhydride (the acetylation of water) this mechanism is predominant.

For nucleophilic catalysis to occur, the intermediate must be more reactive than the reactants. It is difficult to see, in the nucleophilic catalysed hydrolysis of acetic anhydride, why the acetylpyridinium ion is more readily hydrolysed than acetic
anhydride because these two species are combinations of acetylum cations with bases of almost identical strength (the acetate ion and pyridine). This difference in reactivity is usually explained by an entropy effect. The hydrolysis of the acetylpyridinium ion does not involve a change in the total electrical charge of the reagents and would not require a significant re-orientation of the solvation shell. The hydrolysis of acetic anhydride does involve charge separation which requires a creation of order in the solvent. The entropy change is thus unfavourable for the uncatalysed hydrolysis of acetic anhydride.

There are virtually no solvation effects in carbon tetrachloride, which should make the acetylpyridinium ion and acetic anhydride equally reactive towards hydrolysis (or any nucleophilic reaction at the carbonyl carbon). However, the generation of ionic species in non-polar solvents is energetically unfavourable, making the formation of acetylpyridinium ions unlikely. No physical evidence has been found for nucleophilic type intermediates in carbon tetrachloride.

The effect of substituents in the anhydride. The Taft equation.

The Taft equation for the acidic hydrolysis of esters may be written in the form:

$$\log \frac{k}{k_0} = \sigma^* \rho^* + \epsilon E_s + E_r$$

where $k_0$ is the rate constant for the acetate ester and $\sigma^* \rho^*$ is a measure of the polar effect of the substituents. $E_r$ and $E_s$ are the resonance and steric effects constants respectively. In acid catalysed hydrolyses the polar effect is negligible. The lack of effect of substituents arises because
it is a multistep reaction, with the effect of substituents for some steps cancelling those of others.

\[
\begin{align*}
R-C-OR' + H^+ & \rightleftharpoons R-C-OR' + OH^- \\
R-C-OR' & \rightleftharpoons R-C-OR + OH^- \\
\end{align*}
\]

Electron releasing substituents will aid step 1 and hinder step 2, thus producing a fortuitous balancing effect leading to a reaction which is apparently independent of the nature of substituent R. If the terms \( \sigma^* \) and \( E_r \) are negligible in a base catalysed system, a plot of log \( k/k_o \) against \( E_s \) will be linear, with slope \( \delta \). In the reactions investigated, \( \sigma^- \)-nitrophenol with acetic, propionic, isobutyric and pivalic anhydrides, the range of \( \sigma^* \) is very low (\( \sigma^- \) = -0.30) but \( \sigma^* \) may be appreciable (+2.5 for alkaline aliphatic ester hydrolysis). However, for a comparison of the steric effects felt by general base and nucleophilic catalyses, it is usual to neglect this term, \( \sigma^* \). \( E_r \), a measure of the resonance between the substituent and the carbonyl group, is negligible. It was assumed that the Taft equation can be applied to esterifications in the same way as it has been successfully applied to hydrolyses.

In nucleophilic catalysis the base closely approaches the reaction centre and will thus experience a large steric effect as the anhydride (or ester) is substituted about the carbonyl carbon (\( \delta = 1.4 \) in the imidazole catalysed hydrolysis of \( \sigma^- \)-nitrophenyl esters). General base catalysis usually gives
lower $\delta$ values (0.49 in the imidazole catalysed hydrolysis of
N-acetylserinamide esters. Section 1, B(ii)). Figure 3 gives
$\delta = 0.77 \pm 0.08$ and $0.88 \pm 0.10$ for the 4-picoline and 3-picoline
catalysed reactions respectively. These values are regarded as
rather high for general base catalysis, compared with ester
hydrolysises, but the added steric requirement for a phenol to act
as the nucleophile, as opposed to a water molecule, undoubtedly
explains this increase.

Whether hyperconjugation is important in these reactions is
a subject of dispute. Taft indicates that hyperconjugation
effects (in ester hydrolysises) are generally much smaller than
steric effects. For $\text{RCO}_2\text{R'}$, with $\alpha$-hydrogens in $\text{R}$,
hyperconjugation will stabilise the unsaturated reactant state
relative to the saturated transition state and, therefore, will
increase the activation energy and decrease the rate constant.
When the acetate ester or anhydride has $\alpha$-hydrogens replaced by
alkyl groups, the steric effect is increased, reducing the rate
of reaction, but the hyperconjugation effect is decreased,
increasing the rate. Hancock proposed a revised Taft steric
constant:

$$E^\circ = E_s - h(n-3)$$

where $h$ is a reaction constant for hyperconjugation and $n$
is the number of $\alpha$-hydrogen atoms. Quantum mechanical
calculations by Kreevoy and Eyring were used as the basis for
taking $h = -0.306$. A slightly better linear correlation is
obtained here for the 4-picoline catalysed reaction using $E^\circ$
values; $\delta = 0.44 \pm 0.05$. 
The deuterium isotope effect.

The reaction rates of \( \text{m-nitrophenol} \) with isobutyric anhydride in the presence of 3-picoline and 4-ethylpyridine are reduced when the phenolic hydrogen is replaced by deuterium (Table 3:10). Nucleophilic catalysis is not expected to show any deuterium isotope effect, because the rate determining step will not involve the cleavage or partial cleavage of an OH bond. General base catalysis should show a sizeable isotope effect (see Section 1, B(ii)).

Information on the deuterium isotope effects in hydrogen bonding is both limited and confusing. Singh and Rao\(^{140}\) report that the association constant between phenol and pyridine in carbon tetrachloride is greater than that between phenol-d and pyridine. Also, the enthalpy of formation is less (more negative) for the deuterated species. More recently, however, Kolbe\(^{141}\) has reported the figures below for the pyridine base/phenol interaction in toluene.

**TABLE 4:4**

<table>
<thead>
<tr>
<th>Base</th>
<th>( K_H/K_D )</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>0.44</td>
</tr>
<tr>
<td>4-picoline</td>
<td>1.40</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>1.18</td>
</tr>
</tbody>
</table>

The experimental rate differences found in these acylations were small and no mechanistic information was deduced from them.

Order of the reaction with respect to the anhydride.

Experiments (viii) and (ix) have established that these acylations are first order in the anhydride throughout the
concentration range studied. Figure 9 shows the straight line obtained when the acetic anhydride molarity is plotted against the pseudo first order rate constant for the reaction of p-chlorophenol with acetic anhydride in the presence of pyridine. The rate equation from (3) is:

\[ \text{Rate} = k^\prime_b R(a-x)(Ae^2_2) \]

The slope of the line will equal \( k^\prime_b R \) where \( k^\prime_b \) is the second order rate constant. Now \( k^\prime_b \) (Table 3:2) is \( 9.83 \times 10^{-5} \text{ sec}^{-1} \) and, hence, \( k^\prime_b \) is \( 1.97 \times 10^{-3} \text{ M}^{-1}\text{sec}^{-1} \) (calculated by dividing \( k^\prime_b \) by the anhydride molarity, 0.05 M). \( k^\prime_b \) calculated from the slope of Figure 9 is \( 2.12 \times 10^{-3} \text{ M}^{-1}\text{sec}^{-1} \), showing good agreement between the two experimental determinations. 

Reaction of p-chlorophenol with acetic anhydride in the presence of bases other than pyridine bases. (Experiment xii).

It is usually found that a good Brönsted correlation is only obtained when the bases studied are constitutionally similar. It was no surprise to find that constitutionally different bases had higher or lower catalytic abilities than their \( pK_a \) values would suggest when compared with the pyridine bases.

(a) Aniline.

The \( pK_a \) of aniline\(^1\) is 4.63 and, if basicity alone determined the effectiveness of the catalyst, this compound should catalyse the reaction at a slow, but measurable rate. No reaction could be detected after one day. The association constant of p-chlorophenol with aniline in carbon tetrachloride\(^2\) at 27° is 6.16 M\(^{-1} \), which is very low compared to 112.8 M\(^{-1} \) for p-chlorophenol and pyridine (\( pK_a \) pyridine = 5.20).
Nucleophilic catalysis with aniline would proceed through an intermediate which could easily lose a proton, to form acetanilide as an alternative reaction product.

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{\textsuperscript{H} \quad \text{H}} \\
\quad & \quad \text{\textsuperscript{H}} \\
\text{H} & \quad \quad \text{\textsuperscript{H}} \\
\quad & \quad \text{\textsuperscript{H}} \\
\text{H} & \quad \text{\textsuperscript{H}} \\
\text{\textsuperscript{H} \quad \text{\textsuperscript{H}}} & \quad \text{\textsuperscript{H}} \\
\end{align*}
\]

\[
\text{CH}_3\text{O} \quad \text{N} \quad \text{\textsuperscript{H} \quad \text{\textsuperscript{H}}} \\
\quad & \quad \text{\textsuperscript{H}} \\
\text{\textsuperscript{H} \quad \text{\textsuperscript{H}}} & \quad \text{\textsuperscript{H}} \\
\end{align*}
\]

No acetanilide could be detected, and the low catalytic ability of this base is assigned to its low ability to form hydrogen bonds with the phenol.

(b) Imidazole.

First order kinetics were observed when this base catalysed the reaction, although direct comparison of the rate with those found in the pyridine system is impossible due to concentration differences. Imidazole is known to polymerise in carbon tetrachloride to form oligomers, containing up to 5 monomer units.\(^{143}\) This association makes the system more complex than those already studied and 3-methylimidazole may be more suitable for further investigation.\(^{144}\)

2-Methylimidazole was only a very poor reaction catalyst due to the steric effect of the methyl group. This group prevents close approach between the hydroxyl oxygen (in the phenol/2-methylimidazole hydrogen-bonded complex) and the anhydride reaction centre.

(c) Triethylenediamine.

A study has been made by Schenk et al.\(^{145}\) on a triethylene- diamine/acetic anhydride mixture in carbon tetrachloride and
The investigation was carried out at high concentrations (0.7 M \text{CH}_3\text{NO}_2, 0.2 M \text{AgNO}_3). Triethylamine is also known to hydrogen bond strongly with $p$-chlorophenol. 146

No deductions were made about the mechanism of this reaction. 

Dimethyl sulfoxide (DMSO) was only a very poor catalyst for this reaction, even though it has a very high ability to form hydrogen bonds. Gurka and Tar67 have shown that the association constant of DMSO with $p$-Chlorophenol in carbon tetrachloride is high compared with the value expected from its basicity ($pK_a = 2.6$, unpublished results of Dr. J. R. Rakes). 147
The sulphur-oxygen interaction would reduce the nucleophilicity of the hydroxyl oxygen and the steric configuration would be unfavourable to reaction.

(e) Tetrahexylaipmonium benzoate. (Experiment xiv).

The catalytic power of the benzoate anion was assessed by adding tetrahexylaipmonium benzoate to a carbon tetrachloride solution of \( p \)-chlorophenol and benzoic anhydride. A fast rate was observed, which suggests that the benzoate anion is a good general base catalyst. Nucleophilic catalysis cannot occur in this system since the intermediate formed would be identical to the benzoic anhydride starting material.

The energy of activation. (Experiment xiii).

To evaluate \( E_a \), the activation energy, \( \log k_a \) is plotted against \( 1/T \) and the slope of the straight line obtained equals \(-E_a/2.303 \). For the reaction studied, between \( p \)-chlorophenol and acetic anhydride in the presence of pyridine, \( E_a = 33.9 \text{ kJ. mole}^{-1} \). However, this result does not take into consideration the changing degree of hydrogen bonding experienced between the phenol and the base as the temperature is increased, and so it is better to use \( k_b \) values. The association constant for \( p \)-chlorophenol and pyridine is only known at \( 27^0 \) and, hence, \( K_{ass} \) was calculated, using the van't Hoff isochore, at each of the experimental temperatures. Values are listed in Table 3:16. The plot of \( \log k_b \) against \( 1/T \) gives \( E_a = 42.6 \text{ kJ. mole}^{-1} \) and
\[ \Delta H^* = 40.1 \pm 0.4 \text{ kJ mole}^{-1} \] (between 0 - 40\(^\circ\)C), where \( \Delta H^* \) is the enthalpy of activation.

If the hydrogen bond between \( p \)-chlorophenol and pyridine is broken in the rate limiting step of the reaction, the enthalpy of this bond must be incorporated in the activation energy as proposed by Koskicalie.\(^{22} \) If this is so, in this reaction it appears that the enthalpy of activation consists mostly of this hydrogen bond enthalpy of formation\(^{148} \) (\( \Delta H = 28 \text{ kJ mole}^{-1} \)). When one considers the very fast reaction between phenate ions and acetic anhydride this seems reasonable.\(^{149} \) Further discussion of this subject is deferred until the transition state proposed for the reaction is described in the next section.

Simultaneous reactions. (Experiment xiv).

Simultaneous first order reactions, giving a common product, usually give a curve when log (a-x) is plotted against time, where \( a = \) total concentration of reactants. The reaction of \( p \)-chlorophenol with acetic anhydride in the presence of both pyridine and 4-picoline gave a straight line when log \( a/(a-x) \) was plotted against time. This reaction cannot be regarded as truly simultaneous.\(^{150} \) However, the implication which can be made from the kinetic data is interesting. Simultaneous reactions (4) do not show simple kinetic behaviour because, from the rate equations \(-dA/dt = k_1A \) and \(-dB/dt = k_2B \), if \( k_1 \) is different from \( k_2 \) the reactions are going to have different half lives.

\[
\begin{align*}
A & \rightarrow C + \ldots \ldots \\
B & \rightarrow C + \ldots \ldots
\end{align*}
\]

In the acetylation the pyridine bases are not used up (found
by physical techniques and verified kinetically here) and the integrated rate expression will have the form:

\[ \log (a-x) = \log (A_o e^{-k_1 t} + B_o e^{-k_2 t}) \]

where \(A_o\) and \(B_o\) are the initial concentrations of the two hydrogen-bonded species. Unfortunately, accurate figures are not available for \(A_o\) and \(B_o\).

B. Mechanism.

Alcohols are less sensitive to pyridine concentration than phenols in these acylation reactions (see Figure 19 b). If a nucleophilic catalysis were taking place the opposite order would be expected or at least the alcohol and phenol reactions would have similar rates. This again makes nucleophilic catalysis look doubtful in this reaction.

General base catalysis is the only mechanism which is consistent with experimental facts, and the mechanism for this catalysis is now discussed. (Hardly any other mechanism is possible in this system except nucleophilic catalysis. Attack by the base at the \(\alpha\)-hydrogen atoms of the anhydride, as in the halogenation of ketones,\(^\text{73}\) is not considered likely since benzoic and pivalic anhydrides react readily, although no \(\alpha\)-hydrogens are present.)

A transition state for general base catalysis is proposed of the form (I). There are several points in favour of such a transition state:

(a) By constructing models of this transition state, assuming that the hydroxyl oxygen attacks the carbonyl carbon from a direction perpendicular to the carbonyl group,\(^\text{151}\) it can be seen
that the pyridine molecule closely approaches the other carbonyl group of the anhydride molecule.

\[ \text{(I)} \]

An interaction of the form (II) is the accepted precursor to the acylpyridinium ion formation, but as there is no definitive cationic character, it is difficult to observe.

\[ \text{(II)} \]

An interaction such as this probably occurs in (I) and can be likened to a solvation effect. No experimental evidence has been found for a second pyridine molecule acting as the solvating species.

(b) A bifurcated hydrogen bond exists between the hydroxyl group and the pyridine and the carbonyl oxygen. Bifurcated hydrogen bonds were proposed as long ago as 1940 by Errea et al.\textsuperscript{152}
in dilute water systems in dioxane and pyridine. Buck et al. used a bifurcated hydrogen bond to explain the reactivity of cis-5-hydroxy-2-phenyl-1,3-dione (see Section 1, XXIII).

This bond removes the necessity of adding the complete hydrogen bond enthalpy to the activation energy since, in (I), the hydrogen bond to pyridine is being broken whilst that to acetic acid is being formed. This interaction should also make the reaction more thermodynamically favoured by the production of a more stable hydrogen bond with acetic acid ($K_{\text{ass phenol...pyridine}} = 46.3 \text{ M}^{-1}$, $K_{\text{ass acetic acid...pyridine}} = 220 \text{ M}^{-1}$).

(c) In this transition state there is virtually no separation of charge which would be energetically unfavourable in a nonpolar medium. Also there is no necessity for a tetrahedral complex to be postulated.

(d) There are two other interactions which may be of importance in this transition state. (i) Feather and Gold postulated an interaction of the form (III) when investigating the iodination of ketones.

![Diagram](image)

(iii)

The interaction between the pyridine nitrogen and the carbonyl carbon is similar to that proposed in (I). The additional interaction between the $-\text{hydrogen atom of the ketone}$ (or anhydride) and the pyridine nitrogen is more doubtful.
(ii) Davis showed that in acetic acid a cis- carbonyl group is favoured thermodynamically over a trans- group. This cis-conformation may also be favoured in the hydrogen-bonded complex by a stabilising interaction between the carbonyl oxygen atom and the $\alpha$-hydrogen atom of the base molecule.

\begin{center}
\includegraphics[width=0.5\textwidth]{diagram.png}
\end{center}

(IV)

The cis- form of acetic acid in (IV) can be obtained from (I) without significant molecular orientation.

(e) This section is really an extension of (a) but its importance warrants separate discussion. The charge distribution in the hydrogen bond represented in (I) is not usual, i.e.

\[ \sigma- \sigma+ \sigma- \]

\[ \longrightarrow \overset{O}{\longrightarrow} \longrightarrow \overset{H}{\longrightarrow} \]

It is much more usual to depict the hydrogen bond as the intermediate step, before complete charge separation.

\[ \sigma- \longrightarrow \overset{O}{\longrightarrow} \overset{H}{\longrightarrow} \sigma+ \]

Experimental evidence for the charge distribution in the hydrogen bond is very difficult to find. What is certain is that the hydrogen atom is always demided of electrons such that the proton signal in NMR spectroscopy moves downfield.

Recently, the theory of the hydrogen bond was reviewed by Kollman and Allen and the following generalisations were made from population analyses on both the isolated species and the hydrogen-bonded complex:
(i) The hydrogen in the hydrogen bond loses electrons upon hydrogen bonding.

(ii) The electronegative atoms gain electrons; more electrons are gained by the electronegative atom on the proton donor molecule.

(iii) The largest loss of electrons occurs at the hydrogens (or carbon) immediately attached to the proton acceptor molecule.

Although the energy and atomic population of the hydrogen bond between phenol and pyridine have not yet been calculated, the results for simpler systems are very interesting. The ammonia/water and ammonia/hydrogen fluoride systems have been investigated. In both cases it was found that the atom donating the lone pair, the ammonia nitrogen, first gains electron density (as the molecules approach each other) and then loses electron density upon closer approach. In neither case, however, was the electron density less at the hydrogen bond distance than in the free ammonia molecule. Similar calculations have been made by other workers, with the same overall results.

The rate determining step.

A general base catalyzed substitution on the carbonyl carbon can conceivably take place by a synchronous one-step process, or by an addition-elimination mechanism. These two processes are kinetically equivalent and can only be distinguished by indirect evidence, such as the physical detection of an intermediate. Bimolecular acylation reactions are usually considered to be dominated by bond-forming processes (although an exception has been postulated by Broidy and Satchell) and this probably occurs here.
Acetylation catalysed by 2,6-lutidine.

2,6-lutidine catalyses a very fast reaction between p-chlorophenol and acetic anhydride to form the acetate (experiment XXVI). Only small amounts of acetate are produced and no further reaction can be monitored. Similar results were found in the m-nitrophenol systems (experiments XVII and XVIII) and the solvent does not appear to affect the results significantly (experiments XIX, XX, XXI and XXII). Figures 12 and 13 show how the initial fast acetate production varies as the 2,6-lutidine concentration is changed. Figure 13, a plot of percentage reaction against the square of the 2,6-lutidine molarity, is similar to Figures 5 and 6. This similarity suggests that the mechanism of this reaction may involve two base molecules.

Whilst investigating the pyridine catalysed hydrolysis of acetic anhydride, Jencks found that a plot of rate constant against pyridine molarity gave a downward sloping curve and not the expected straight line. The self association of pyridine (in water) causes this deviation from linearity. This hydrolysis is an example of nucleophilic catalysis (see Section 1B(ii)) and the associated pyridine was assumed to be non-catalytic because of the large steric hindrance felt when the dimer approaches the electrophilic centre. Similar results were obtained with 3,4-lutidine and an association constant of $10^{-1}$ was suggested for this base as the value best fitting the experimental results.

There is ample physical evidence that pyridine bases dimerise in solution. The NMR experiments of Hatton and
Richards\textsuperscript{162} gave evidence for a 4-picoline dimer in carbon tetrachloride of the form (V) :-

![Diagram of compound V]

(V)

In this type of association, enhanced shielding would be felt by the methyl and K protons by a ring current effect, thus shifting the resonances of these protons to higher field. Similar evidence was found by Murrell and Gil\textsuperscript{163} whose work included solutions of 2,6-lutidine (0.25 M) and 2,4,6-collidine in carbon tetrachloride. These workers favour a more symmetrical association of the form (VI) :-

![Diagram of compound VI]

(VI)

The polarization of charge in the pyridine ring would favour this more symmetrical association, i.e. one in which the centre of one molecule is more nearly above the centre of the other. The crystal structure of the aza-aromatics shows that
the nitrogens tend to lie directly above positive carbons in adjacent molecules. Assuming values of $K_{\text{association}}$ of 10, 20 and 30 M$^{-1}$ successively for the self association of 2,6-lutidine in carbon tetrachloride, the following values for dimer molarity were calculated at increasing base molarities.

**TABLE 4:6**

<table>
<thead>
<tr>
<th>2,6-lutidine (10$^{-2}$ M)</th>
<th>dimer molarity x 10$^3$</th>
<th>acetate molarity x 10$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 M$^{-1}$</td>
<td>20 M$^{-1}$</td>
</tr>
<tr>
<td>2.0</td>
<td>2.90</td>
<td>4.68</td>
</tr>
<tr>
<td>1.6</td>
<td>1.95</td>
<td>3.25</td>
</tr>
<tr>
<td>1.2</td>
<td>1.15</td>
<td>2.00</td>
</tr>
<tr>
<td>0.8</td>
<td>0.55</td>
<td>1.00</td>
</tr>
<tr>
<td>0.4</td>
<td>0.15</td>
<td>0.28</td>
</tr>
</tbody>
</table>

The acetate molarity values are taken from the reaction of $m$-nitrophenol (0.005 M) with acetic anhydride (0.05 M) in the presence of 2,6-lutidine (experiment xvii). It can be seen that up to 60% initial reaction, the values for the dimer molarity, calculated from the association constant value of 20 M$^{-1}$, closely follow the experimental results. If the dimer is completely complexed with the $m$-nitrophenol, and if this complex is very reactive (nucleophilic), then the above results would be expected. What is not immediately apparent is why the reaction stops short of completion. However, it is evident that the fast reaction is very sensitive to added acetic acid (see experiment xviii and Figure 14) and the reaction can be almost stopped if enough acetic acid is present. If the initial fast reaction proceeds through the transition state (I), the 2,6-lutidine dimer can complex with
the liberated acetic acid, which would effectively stop the reaction. Acetic acid also forms strong hydrogen-bonded complexes with 2,6-lutidine monomers and this could inhibit further dimerization of the base.

When the anhydride concentration is reduced (experiment xvii), only a small decrease in the initial acetate production is observed, as would be expected if this mechanism is correct.

From the curve in Figure 14, a value for the association constant between m-nitrophenol and the 2,6-lutidine dimer may be found. Only an approximate value can be estimated because of the various assumptions made.

\[
\frac{K_m}{(m-\text{NO}_2\text{phenol} \cdots 2,6\text{-lutidine}) + 2,6\text{-lutidine}} = \frac{K_1}{(m-\text{NO}_2\text{phenol} \cdots (2,6\text{-lutidine})_2)}
\]

Four assumptions must be made:

(1) The equation above is assumed to represent the association equilibria. This is by no means certain since the phenol may associate directly with the 2,6-lutidine dimer. This point is discussed further below.

(2) All the m-nitrophenol is associated with at least one 2,6-lutidine molecule.

(3) All the acetic acid produced in the reaction is associated with at least one 2,6-lutidine molecule.

(4) All other interactions are negligible compared with those concerned in the equilibrium.

The association constant will have the form:

\[
K_1 = \frac{(y)}{(0.005-y)(2,6\text{-lutidine})}
\]
where y is the initial molarity of acetate produced in the reaction (equivalent to the molarity of the highly reactive $m$-nitrophenol/dimer complex). 0.005 M is the initial molarity of $m$-nitrophenol. The 2,6-lutidine molarity is given by:

$$(2,6\text{-lutidine}) = (2,6\text{-lutidine})_{\text{initial}} - 0.005 - (\text{AcOH})$$

where (AcOH) is the total acetic acid present at the end of the reaction. At any percentage reaction the acetic acid molarity may be read from Figure 14 and $K_1$ can be calculated. Results are given below in Table 4:7.

**TABLE 4:7**

<table>
<thead>
<tr>
<th>% reaction</th>
<th>$K_1$ (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>25</td>
<td>86</td>
</tr>
<tr>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>35</td>
<td>88</td>
</tr>
<tr>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>45</td>
<td>104</td>
</tr>
<tr>
<td>50</td>
<td>114</td>
</tr>
</tbody>
</table>

$K_1 = 96 \pm 8$ M⁻¹

Below 20% reaction the error in the 2,6-lutidine molarity term becomes large and negative. Considering the errors introduced by making the assumptions, the value of $K_1 = 96 \pm 8$ M⁻¹ is surprisingly good (a maximum error of about 10% is usually allowed on association constant values). There are two forms which the phenol/dimer hydrogen-bonded complex could take:-
The NMR evidence presented by Murrell and Gill\(^{163}\) for 2,6-lutidine dimer formation showed only a very small difference between the proton resonances of the methyl groups in pure liquid base and carbon tetrachloride solution. This suggests that the methyl groups are not in the close proximity of the nitrogen atom as in (V) and (VI). The phenate ion is known to be highly reactive towards acetic anhydride and if this species is formed in (VII) the very fast initial reaction is explained. Whether the phenol would be deprotonated directly by the dimer, or by a monomer with the ion pair then formed solvated by a second base molecule, would be difficult to establish.

(2) It was found with the less acidic phenols, that the presence of another base, e.g. 3,4-lutidine, greatly enhanced the initial acetate production (experiment xxv). If 3,4-lutidine (0.02 M) is added to a solution of \(p\)-chlorophenol (0.01 M), acetic anhydride (0.05 M) and 2,6-lutidine (0.10 M), nearly 80% reaction was observed after one minute. There are two reasons why this may happen.

(i) The 2,6-lutidine and 3,4-lutidine could associate together to form a system as in (VII).
(ii) The second base molecule could solvate a 2,6-lutidine/phenol hydrogen-bonded complex to give a species of the form (VIII):

\[
\text{Me}^+\text{N}^+\text{H}---\text{O}\text{phenol} \quad \text{Me}^+\text{N}^+\text{H}---\text{O}\text{phenol}
\]

This species could easily be derived from the phenol/dimer complex as in (VII). As the pK_a of the second base increases, then so does the percentage initial reaction. This is expected if solvation, as depicted in (VIII), takes place (see experiment xxv and Figure 17(b)).

D. Acetylation of compounds containing intramolecular hydrogen bonds or self associated species.

Tables 3:34 and 3:35 show that alcohols containing intramolecular hydrogen bonds are acetylated at a slower rate than compounds which do not contain such bonds. Also, as expected in a general base catalysis, the reaction of an alcohol is rather insensitive to added pyridine compared to the reaction with a phenol. (Table 3:36 and Figure 19(b)).

There are several reasons why a reduction in rate would be expected for those alcohols containing intramolecular hydrogen bonds.
(i) The steric effect.

In the reactions with phenols, a substituent in the α-position of either the pyridine base or the phenol will prohibit reaction. Similarly, it was found that when 2-picoline was added to a 3-phenyl-1-propanol and acetic anhydride solution, the acetylation rate was reduced. Both the pyridyl alcohols studied here, containing intramolecular hydrogen bonds, consist essentially of a pyridine molecule substituted in the α-position.

(ii) Solvation.

If a transition state such as (I) is formed in these acetylations, the solvation effect of the pyridine on the anhydride could be very important in reducing the activation energy. No such solvation effect would be possible in the 2-methoxybenzyl alcohol reaction, which would explain the reduced reactivity of this compound. Molecular models indicate that such an effect is still possible with the pyridyl alcohols.

(iii) The strength of the hydrogen bond.

If the intramolecular hydrogen bond has to be broken before reaction can proceed, then the activation energy is increased by at least a substantial part of the energy required to break this bond. If this energy were 12.5 kJ mole⁻¹, then the rate will be retarded about 30 times at 25°C, provided that the entropy of activation remained unchanged. The reaction would then be slow compared to the reaction of alcohol molecules not containing intramolecular hydrogen bonds.

With these intramolecularly hydrogen-bonded alcohols the bond energy effect cannot be offset by the production of a more stable acetic acid hydrogen-bonded species because (a) inter-
molecular hydrogen-bonded species with the acid will be sterically hindered, \(^{166}\) (b) it is debatable whether the acetic acid/\(\alpha\)-methoxybenzyl acetate hydrogen-bonded species would contain a stronger hydrogen bond than that in the alcohol (no figures available) and (c) formation of an acetate/acid hydrogen-bonded species directly from the proposed transition state would not give an overall favourable entropy of reaction.

These three effects can clearly account for the observed higher acetylation rate of 3-(4-pyridyl)-1-propanol (9.50 \(\times\) 10\(^{-5}\) sec\(^{-1}\)) over 3-(2-pyridyl)-1-propanol (6.91 \(\times\) 10\(^{-6}\) sec\(^{-1}\)). No comparison was made between the ortho and para substituted pyridyl ethanol due because 2-(4-pyridyl)ethanol was unavailable. However, phenylethanol was studied, giving a rate constant of 7.39 \(\times\) 10\(^{-5}\) sec\(^{-1}\) compared to 1.18 \(\times\) 10\(^{-6}\) sec\(^{-1}\) for 2-(2-pyridyl)ethanol. Direct comparison between these two compounds cannot be made for two reasons, (i) the inductive effects of the phenyl- and pyridyl- groups are different (c.f. \(pK_a\) = 4.19 benzoic acid; \(pK_a\) = 4.85 3-pyridinecarboxylic acid) and this effect will be appreciable through only two carbon atoms. (ii) Phenylethanol is intramolecularly hydrogen-bonded in carbon tetrachloride (see Section 3.B (ii)) which introduces further complications. Phenylethanol reacted about 7 times faster than 2-(2-pyridyl)ethanol suggesting that the intramolecular hydrogen bonding present in the latter alcohol does not significantly enhance the reactivity.

**Acetylation of ethanol with acetic anhydride.**

Ethanol is known to self associate in carbon tetrachloride to form linear dimers and trimers, cyclic tetramers and small
amounts of higher polymers.\textsuperscript{169} In the reaction between acetic anhydride and ethanol (experiment B (v)), as the concentration of the alcohol was increased the second order rate constant decreased. The self association of the alcohol is responsible for this decrease, since a hydrogen bond in the associated species has to be broken before reaction can proceed.\textsuperscript{22} Also observed here was an apparent autocatalysis by the liberated acetic acid. Hydrogen bonding of this acid to the anhydride would be expected to increase the rate of reaction whereas hydrogen bonding to the alcohol should decrease its nucleophilicity and reduce the rate. Here, the rate enhancing effect with the anhydride is more important than the retarding effect felt by the alcohol.

**Trifluoroacetylation of phenol.**

At a concentration of 0.1 M in carbon tetrachloride, phenol is present as 77% monomer and the dimer concentration is 4 - 5 times the trimer concentration. These estimates were made by Huggins and his co-workers\textsuperscript{167} from the data of Coggeshall and Saier.\textsuperscript{168}

Phenol (0.025 - 0.2 M) was reacted with trifluoroacetic anhydride to observe if phenol dimers or trimers are non-reactive (or exhibit reduced reactivity) towards acylation (experiment B (iv)). No reduction in the second order rate constant could be observed in the concentration range studied. There are several reasons which could account for this result. (1) The concentration of the polymeric phenol species may be too small to have any effect on the rate. (2) The phenol to phenol hydrogen bond may be weaker than in the self association of
alcohols. (3) A cyclic associated species is not formed in the phenol system. The reduction in rate found when the ethanol concentration is increased in acetylation is due to the energy required to break a hydrogen bond (or two) in a cyclic species.

E. The reaction of phenols with acetic anhydride.

In all the work reported previously, phenols apparently do not react with acetic anhydride.$^{107}$ In this work a slow reaction has been found, but this is non-reproducible (Section 3 D). The reactions reported here are probably caused by a glass surface effect since no reaction could be detected in polybutylene containers.

Hydroxyl groups on the surface of silica exist in several different forms.$^{170}$ The terminal isolated SiOH groups are the most stable, whereas the hydrogen-bonded hydroxyls on adjacent terminal SiOH groups start to desorb water above about $200^\circ$. Those SiOH groups on the surface of the silica can absorb water, which can be rapidly pumped off at room temperature.

Sewell and Morgan$^{171}$ investigated the adsorption of methanol vapour on vitreous silica and soda-lime-silica glasses. The heats of adsorption indicate that after low temperature degassing treatments each methanol molecule is adsorbed by the formation of more than one hydrogen bond. A model for this methanol adsorption is given below:

![Diagram of methanol adsorption on silica surface](attachment:diagram.png)
Porter\textsuperscript{172} found that methanol, after being stored in "Pyrex" glass, contains an appreciable amount of trimethyl borate which could be detected by mass spectroscopy. Similar results were obtained with methanol vapour in "Pyrex" vessels. Sancier\textsuperscript{173} was unable to study the self association of methanol in low molarity carbon tetrachloride solutions because of the adsorption of methanol on the glass surfaces.

Very little work has been done on the adsorption of phenol on silica surfaces but results indicate that an interaction does exist.\textsuperscript{174} Pyridine is known to bind strongly with the hydroxyl group on silica.\textsuperscript{175}

Swain and Okamoto\textsuperscript{176} investigated the role of added pyridine in the methanolysis of triphenylmethyl chloride in benzene solution. The rate of methanolysis is independent of the pyridine concentration but the pyridine has a triple purpose in the reaction scheme, (1) it removes liberated hydrochloric acid as the pyridinium chloride, (2) it is present in the transition state and (3) it prevents the serious adsorption of methanol on, and reaction with, the glass walls of the vessel. Pyridine greatly decreases the adsorption of methanol on the walls, evidently by itself becoming hydrogen-bonded, instead of the methanol, to the hydroxyl groups on the glass surface. In the absence of amines, when a methanol solution in benzene (4 x 10\textsuperscript{-3}M) was allowed to stand in 100 cm\textsuperscript{3} "Pyrex" volumetric flasks for 24 hours at 25\degree\textsuperscript{C}, 10 - 50% methanol disappeared from the solution. When pyridine was present (0.02 M) in the solution, no methanol loss could be detected. It was concluded that pyridine had the very useful effect of eliminating the adsorption of methanol on
the glass surface throughout the methanolysis.

The above reasoning could apply to the acetylation investigated here. Although no evidence has been found for an interaction of the form (IX) the possibility cannot be ignored. The fact that pyridine will destroy such an interaction is indeed very useful and holds with the fact that none of these anomalously fast reactions were ever observed when a base catalyst was present in the reaction mixture.

F. Interfacial esterification.

The aim of this work (experiments 0 (i), (ii) and (iii)) was to develop a methodology of interfacial esterification. The techniques described by Menger\textsuperscript{54} were followed whenever possible.

Menger studied the hydrolysis of p-nitrophenyl laurate at a heptane-water interface (see Section 1) and was able to follow the reaction kinetically. Substantial evidence was found to prove that this reaction proceeded at the heptane-water interface. In this system, one of the reactants (i.e., water) is also one of the liquid phases. This considerably reduces experimental difficulty. A similar system was not possible for esterification. p-Nitrophenol was the only hydroxyl compound found suitable which was soluble in water but virtually insoluble in the carbon tetrachloride phase. Alcohols generally dissolve to a considerable extent in both phases. Pivalic anhydride does not dissolve in the aqueous phase (nor in aqueous p-nitrophenol solution) but cannot be used as a separate liquid phase because p-nitrophenol is soluble in this anhydride.

The preliminary reactions of p-nitrophenol with isobutyric and pivalic anhydrides when shaken with saturated aqueous
potassium bicarbonate cannot be regarded as two phase because 
\( p \)-nitrophenol is slightly soluble in carbon tetrachloride. It 
is thought improbable that these reactions occur via the 
\( p \)-nitrophenate anion because reactions with this ion would be 
expected to be rapid. The difference between the plots of 
percentage reaction against time (Figure 22) for the two 
anhydrides cannot be explained.

\( p \)-Nitrophenol and pivalic anhydride solutions do not react 
when stirred together and a catalyst, e.g. 3-picoline, must be 
added. No pyridine base could be found which dissolved only in 
the aqueous phase. This introduced a solubility problem which 
could not be overcome (see below). When the 3-picoline molarity 
was reduced to \( 4.4 \times 10^{-3} \) M a reaction could be followed, which 
is illustrated in Figure 24. In all the systems studied, the 
aqueous phase after reaction was acidic and gave no ultraviolet 
absorption due to the \( p \)-nitrophenate anion. The form of Figure 
24 suggests that a fast reaction is taking place between the 
\( p \)-nitrophenate anion and the anhydride which is stopped as the 
aqueous phase becomes more acidic. The unreacted \( p \)-nitrophenol 
could be detected in the aqueous phase by ultraviolet 
spectroscopy to be present in the hydrogen-bonded form (Figure 
23).

When pivalic anhydride (0.01 M) was stirred with an aqueous 
3-picoline solution for 7 hours, the anhydride concentration 
was slightly reduced in the carbon tetrachloride phase. There 
is, hence, doubt as to whether this reaction is truly 
interfacial and experiments were not continued.
REFERENCES
3. Oddo and Puxeddu, Gazzetta, 36, ii, 1, (1906).
5. Pfeiffer, Annalen, 398, 137, (1913).
74. Fife and Milstein, Biochemistry, 6, 2901, (1967).
104. (i) Ingold, Quart. Rev., 1, (1957).
119. Wood, personal communication.
120. Lezina, Bystrov, Smirnov and Dyumaev, Teoreticheskaya i Eksperimental'naya Khimiya, 4, 379, (1968).


142. "Handbook of Chemistry and Physics", The Chemical Rubber Co.,
144. Oakenfull, Salvesen and Jencks, J. Amer. Chem. Soc., 92,
188, (1971).
146. Zharkov, Zhitinkina and Zhokhova, Zhur. fiz. Khim., 44,
(1971).
150. Frost and Pearson, "Kinetics and Mechanism", J. Wiley and
158. Senatore, Ciuffarin and Fava, J. Amer. Chem. Soc., 92,
    Chem. Abs. 70:99909h.