Acylation by acetyl trifluoroacetate and trifluoroacetic anhydride.

A thesis submitted by Patricia Margaret McNamara in candidature for the degree of Doctor of Philosophy of the University of London.

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Abstract

The reaction of acetic anhydride with trifluoroacetic anhydride in carbon tetrachloride has been studied kinetically and it was found that under anhydrous conditions no reaction occurred, but when small quantities of either acetic or trifluoroacetic acid were present there was conversion of the symmetric anhydrides to acetyltrifluoroacetate. The mechanism of this acid catalysis was discussed.

The acylation of phenols in carbon tetrachloride by acetic anhydride, trifluoroacetic anhydride and acetyl trifluoroacetate was investigated in the presence and absence of pyridine. In the case of the symmetric anhydrides the presence of pyridine caused a considerable increase in the rate of the reaction and with acetyl trifluoroacetate there was a change from acetate to trifluoroacetate formation.

Pyridine had little or no effect on the rate or product of the reaction of alcohols with any of the anhydrides.

The mechanism of the effect of pyridine on the reactions between hydroxy compounds and the anhydrides mentioned above is discussed and an attempt to decide whether the catalysis is due to hydrogen bonding between the pyridine and the hydroxy compound or to reaction of the pyridine with the anhydride is made.
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SECTION 1.  INTRODUCTION.

A. Preparation of Unsymmetrical Anhydrides.

i) General.

The synthesis of unsymmetrical anhydrides was first attempted in about 1850. The early methods of preparation were:

a) Reaction of an acid chloride with the sodium salt of a different acid

\[ RCOCl + R'^{-} COONa \rightarrow NaCl + RCOO\cdot CO\cdot R' \]

b) Reaction of an acid with the anhydride of a different acid

\[ 2RCOOH + (R'^{-} CO)_{2}O \rightarrow 2RCO\cdot CO\cdot OR' \]

c) Reaction of two different symmetric anhydrides

\[ (RCO)_{2}O + (R'^{-} CO)_{2}O \rightarrow 2RCO\cdot CO\cdot OR' \]

These reactions were extensively exploited but great difficulty was experienced in the purification of the products. Rouasse\textsuperscript{1} found that distillation of both acetic butyric and acetic valeric anhydrides yielded only the two symmetric anhydrides and on this basis he decided that mixed anhydrides do not exist. Behal's\textsuperscript{2,3} attempts to purify isovaleric acetic anhydride by solvent extraction eventually yielded only isovaleric and acetic anhydride. He suggested that though unsymmetrical anhydrides are formed by these methods they exist in a disproportionation equilibrium with the symmetric anhydrides

\[ 2RCO\cdot CO\cdot OR' \rightleftharpoons (RCO)_{2}O + (R'^{-} CO)_{2}O \]
As a consequence of this equilibrium any attempt to purify the unsymmetrical anhydride by removal of the symmetric anhydrides results in the complete breakdown of the unsymmetrical anhydride.

Proof of the existence of mixed anhydrides came from the hydrolysis of acetic propionic anhydride and butyric isopropyl anhydride. These hydrolyses were first order in the unsymmetrical anhydride. This result would not be expected if the hydrolysis of a mixture of anhydrides were taking place and so the mixed anhydride must be the main species present.

Later a far better method for the preparation was discovered. This involved the reaction of a ketene with a carboxylic acid

\[ R\text{.COOH} + \text{CH}_2=\text{C}=\text{O} \rightarrow R\text{.CO.O.CO.CH}_3 \]

Since the ketene is formed by the pyrolysis of acetone, the impurities present in the unsymmetrical anhydride would probably be acetone, methane and ketene, all of which can be removed by low temperature vacuum distillation. In this way disproportionation can be kept at a minimum. This method has been very widely used because, in addition to giving reasonably pure products, it can be used for the preparation of both saturated and unsaturated unsymmetrical anhydrides.

\[ C_6\text{H}_5\text{CH}=\text{CHOH} + \text{CH}_2=\text{C}=\text{O} \rightarrow C_6\text{H}_5\text{CH}=\text{CO.O.CH}_3 \]

Very little work has been done on the kinetics of formation of the mixed anhydrides. Brown and Trotter investigated the
formation of acetic butyric anhydride from acetic and butyric anhydride in carbon tetrachloride. They found that the rate of formation varied from day to day – this was probably due to absorption of atmospheric moisture by the system. However, they measured the rate of the reaction at several temperatures and obtained an energy of activation of 10,000 calories. They also found that the proportions of symmetric and unsymmetrical anhydrides present in the equilibrium mixture were unaffected by temperature in the range 0°C to 100°C.

The formation of mixed anhydrides from a symmetric anhydride and a different carboxylic acid or anhydride has been investigated by Mironov and Zharbov\textsuperscript{10} using Raman spectroscopy. Their results are shown below

<table>
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<th>Activation Energy (kcal mole(^{-1}))</th>
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<tr>
<td>(\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}-(\text{CH}_3\text{CO})_2\text{O})</td>
<td>2.4</td>
<td>15.3</td>
</tr>
<tr>
<td>(\text{CH}_3\text{CH}_2\text{COOH}-(\text{CH}_3\text{CO})_2\text{O})</td>
<td>3.8</td>
<td>12</td>
</tr>
<tr>
<td>(\text{CH}_3\text{COOH}-(\text{CH}_3\text{CH}_2\text{CH}_2\text{CO})_2\text{O})</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>(\text{CH}_3\text{COOH}-(\text{CH}_3\text{CH}_2\text{CO})_2\text{O})</td>
<td>-</td>
<td>12.5</td>
</tr>
<tr>
<td>((\text{CH}_3\text{CO})_2\text{O}-(\text{CH}_3\text{CH}_2\text{CH}_2\text{CO})_2\text{O})</td>
<td>2.0</td>
<td>-</td>
</tr>
<tr>
<td>((\text{CH}_3\text{CO})_2\text{O}-(\text{CH}_3\text{CH}_2\text{CO})_2\text{O})</td>
<td>4.6</td>
<td>-</td>
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Once again the equilibrium constant was independent of temperature.
ii) Acyl Trifluoroacetates.

Acyl trifluoroacetates were used for many years before they were actually isolated. In 1945 Newman found that the Friedel-Crafts reaction between anisole and acetic anhydride giving p-methoxyacetophenone was catalysed by trifluoroacetic acid. This was probably due to reaction of the acid with the anhydride giving the unsymmetrical anhydride which then reacted faster with the anisole than the acetic anhydride.

Morgan measured the depression of the freezing point of acetic acid caused by the addition of either trifluoroacetic acid or trifluoroacetic anhydride. He found that trifluoroacetic acid had a van't Hoff factor of 1 while that of trifluoroacetic anhydride was 2 and so he concluded that the reaction was

\[(\text{CF}_3\text{CO})_2\text{O} + \text{CH}_3\text{COOH} \rightarrow \text{CF}_3\text{CO}.\text{CO.CH}_3 + \text{CF}_3\text{COOH}\]

A van't Hoff factor of 3 would be expected for a reaction producing acetic anhydride i.e. \[(\text{CF}_3\text{CO})_2\text{O} + 2 \text{CH}_3\text{COOH} \rightarrow (\text{CH}_3\text{CO})_2\text{O} + 2\text{CF}_3\text{COOH}\]

Extensive work on acyl trifluoroacetates was performed at Birmingham. These workers prepared the acyl trifluoroacetates by mixing equimolecular amounts of trifluoroacetic anhydride with the carboxylic acid. At intervals the mixture was dissolved in carbon tetrachloride and the infrared absorption in the carbonyl region obtained. It was found that, immediately after mixing, the spectrum corresponded to that of a mixture of the two
components but on standing fresh carboxyl peaks appeared at the expense of the carbonyl peaks of the components. These new peaks were attributed to the formation of the unsymmetrical anhydride.

Randles, Tatlow and Tedder\textsuperscript{14} investigated the conductivity of mixtures of carboxylic acid anhydrides and carboxylic acids. On mixing trifluoroacetic anhydride and acetic acid heat was evolved but when the temperature became steady, after a few minutes, the conductivity remained constant. This means that the acetyl trifluoroacetate must be rapidly formed. In the case of acetic anhydride and trifluoroacetic acid the conductivity initially rose to maximum value and then slowly fell until, after about 90 minutes, it reached a constant value. This conductivity maximum is attributed to the formation of a highly conducting species which slowly decomposes giving a less highly conducting species i.e. the unsymmetrical anhydride.

A mixture of trifluoroacetic anhydride and acetic anhydride\textsuperscript{14} yielded a very slow increase in conductivity but the workers were unable to decide whether this was due to the presence of trace amounts of moisture or to a change in the constitution of the mixture.

The first attempt to isolate an acyl trifluoroacetate was due to Morgan\textsuperscript{15} who tried to obtain acetyl trifluoroacetate by the distillation of mixtures of acetic acid and trifluoroacetic
anhydride or trifluoroacetic acid and acetic anhydride but these attempts were unsuccessful. However, Ferris and Emmons\textsuperscript{16} isolated acyl trifluoroacetates by reacting the acyl chloride and silver trifluoroacetate in an ether solvent.

\[ \text{ROCl} + \text{CF}_3\text{COOAg} \rightarrow \text{R.COO.COF}_3 + \text{AgCl} \]

The acyl trifluoroacetate was then flash-distilled to minimise the disproportionation after which the unsymmetrical anhydride was distilled under reduced pressure. If the unsymmetrical anhydride was distilled before flash-distillation had been performed there was a great deal of disproportionation probably due to the presence of unreacted silver trifluoroacetate.

Another early method\textsuperscript{17} used trifluoroacetic anhydride and a carboxylic acid. The reactants were removed under vacuum and the acyl trifluoroacetate was then flash-distilled.

Bourne, Stacey, Tatlow and Worrall\textsuperscript{18} isolated many stable acyl trifluoroacetates utilising the reaction between a carboxylic acid and trifluoroacetic anhydride

\[ \text{RCOOH} + (\text{CF}_3\text{CO})_2\text{O} \rightarrow \text{RCO.COF}_3 + \text{CF}_3\text{CO.OH} \]

An ethereal solution of pyridine was then added to remove the trifluoroacetic acid as pyridinium trifluoroacetate after which the acyl trifluoroacetate was distilled. These workers also used direct distillation of the carboxylic acid and trifluoroacetic anhydride. By these methods acetyl, benzoyl and phenyl acetyl trifluoroacetates have been prepared and were found to be
stable compounds. These two methods of preparation of acetyl trifluoroacetate were later repeated by Bonner and Gabb who found that distillation of the product, instead of yielding a liquid of constant boiling point as had been reported, boiled over a range of temperature and the distillate contained both the symmetric anhydrides in addition to acetyl trifluoroacetate.

The kinetics of the formation of acetyl trifluoroacetate in carbon tetrachloride have been studied by infrared spectroscopy in the region 1000-1250 cm\(^{-1}\). By this means it was found that equimolar (0.5M) solutions of acetic and trifluoroacetic anhydride react slowly and eventually 98\% acetyl trifluoroacetate is formed. The reaction of equal concentrations of acetic acid and trifluoroacetic anhydride was considerably faster but yielded 95\% acetyl trifluoroacetate. However, though the equilibrium between equimolar solutions of trifluoroacetic acid and acetic anhydride was rapidly established only 40\% of the unsymmetrical anhydride had been formed - 60\% of the acetic anhydride being unchanged.

Similarly, the effect of equimolar quantities of acid on acetyl trifluoroacetate in carbon tetrachloride was investigated and it was found that, whereas trifluoroacetic acid has very little effect on the system, acetic acid causes the conversion of 50\% of the unsymmetrical anhydride to acetic anhydride. These results suggest that in the work of Morgan any acetyl trifluoroacetate formed would be converted into acetic anhydride by the
excess acetic acid i.e.

$$(\text{CF}_3\text{CO})_2\text{O} + \text{CH}_3\text{COOH} \rightarrow \text{CH}_3\text{CO} \cdot \text{O} \cdot \text{CO} \cdot \text{CF}_3 + \text{CF}_3\text{COOH}$$

$$(\text{CH}_3\text{CO})_2\text{CO} \cdot \text{CO} \cdot \text{CF}_3 + \text{CH}_3\text{COOH} \rightarrow (\text{CH}_3\text{CO})_2\text{O} + \text{CF}_3\text{COOH}$$

the overall reaction being

$$(\text{CF}_3\text{CO})_2\text{O} + 2 \text{CH}_3\text{COOH} \rightarrow (\text{CH}_3\text{CO})_2\text{O} + 2 \text{CF}_3\text{COOH}$$

Morgan's work was repeated\(^{20}\) and a van't Hoff factor of 2.5 was obtained. The low result obtained by Morgan was probably due to the absorption of atmospheric moisture.

Bonner and Gabb\(^{19}\) prepared acetyl trifluoroacetate by mixing equimolar solutions of the two symmetric anhydrides in carbon tetrachloride but they found that the time required for equilibrium to be attained varied from 1 to 7 days. Part of this thesis is concerned with the mechanism of this reaction.

B. Reactions of Monocarboxylic Anhydrides.

Acetic anhydride is widely used as an acylating agent in organic chemistry. Although the mechanism of acylation by acyl halides has been extensively studied very little mechanistic work on the monocarboxylic acid anhydrides has been performed.

1) Acylation of water.

The hydrolysis of acetic anhydride in aqueous or nearly aqueous solution has been investigated\(^{21},^{22}\) and it was found to be pseudo first order in the anhydride. Gold\(^{23}\) concluded that the mechanism was $S_{N}2$ as the addition of neutral salts reduced the speed of the reaction whereas an increase in rate would be
expected if an $S_N$ mechanism was operative. Also, since the acyl halides react by an $S_N$ mechanism, acetic anhydride (on acyl acetate) would be expected to react similarly.

Further work was performed by Butler and Gold\(^{24}\) who found that the rate of hydrolysis was reduced by a factor of 2.9 when the solvent was changed from water to deuterium oxide. This suggests that the mechanism involves a weakening of OH bonds on formation of the transition state. On this basis the following mechanism was proposed.

\[
\begin{align*}
\text{CH}_3\text{CO}\cdot\text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_2\text{O} & \overset{k_1}{\underset{k_2}{\rightleftharpoons}} \text{CH}_3\text{C} - \text{O} - \text{CO} \cdot \text{CH}_3 \quad \text{rapid}, \\
\text{CH}_3\text{C} - \text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_2\text{O} & \overset{k_3}{\underset{k_4}{\rightleftharpoons}} \text{CH}_3\text{C} - \text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_3\text{O}^+ \quad \text{rapid}, \\
\text{CH}_3\text{C} - \text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_3\text{O} & \overset{k_5}{\underset{k_6}{\rightarrow}} \text{CH}_3\text{C} - \text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_2\text{O} \quad \text{slow}, \\
\text{CH}_3\text{C} - \text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_2\text{O} & \overset{k_7}{\underset{k_8}{\rightarrow}} 2\text{CH}_3\text{COOH}
\end{align*}
\]

If the above mechanism is followed the rate of the pseudo first order hydrolysis would be \(K_1K_2k_3 [\text{Ac}_2\text{O}]\) which is equal to \(K_0 [\text{Ac}_2\text{O}]\). By analogy with the hydration equilibrium for acetaldehyde,\(^{25}\) \(K_1^H\) should be of the order of 1 and \(K_2^H\) in the range 2.5 to 4.5. Similarly by analogy with the work of Long and Watson,\(^{26}\) \(k_3^H\) is approximately 1. Therefore \(\frac{\text{rate } \text{H}_2\text{O}}{\text{rate } \text{D}_2\text{O}} = 1x(2.5 \text{ to } 4.5) \times 1\) and so the observed value of 2.9 is in agreement with the above theory.
The acid-catalysed hydrolysis of acetic anhydride in aqueous solution was first recorded by Kilpatrick who suggested that the catalysis by hydrochloric acid was due to the formation and subsequent hydrolysis of acetyl chloride. This theory was disproved by Gold and Hilton who compared the rates of aqueous hydrolysis of acetyl chloride and acetic anhydride in the presence of hydrochloric acid. However when the solvent is acetic acid reaction via an acyl chloride intermediate seems probable.

Further work on the catalytic effect of strong acids on the hydrolysis of acetic anhydride was performed by Gold and Hilton. They found that the rate of hydrolysis was approximately proportional to the Hammett acidity function \((H_0)\) and not to the hydrogen ion concentration and therefore the following mechanism (I) was proposed

\[
(\text{RCO})_2\text{O} + \text{H}^+ \quad \overset{\text{fast}}{\longrightarrow} \quad [\text{RCOOHCOR}]^+ \\
[\text{RCOOHCOR}]^+ \quad \overset{\text{slow}}{\longrightarrow} \quad \text{RCO}^+ + \text{RCOOH} \quad \text{I.}
\]

This system has also been studied using an aqueous dioxan solvent. In this case the kinetic deuterium isotope effect and the entropy of activation indicate that the reaction probably follows mechanism II. A similar mechanism has been proposed for the hydrolysis in aqueous acetone.

\[
(\text{RCO})_2\text{O} + \text{H}^+ \quad \overset{\text{fast}}{\longrightarrow} \quad [\text{RCO}_2\text{HCOR}]^+ \\
[\text{RCO}_2\text{HCOR}]^+ + \text{H}_2\text{O} \quad \overset{\text{slow}}{\longrightarrow} \quad 2 \text{RCOOH} + \text{H}^+ \quad \text{II.}
\]
This means that the mechanism in water differs from that in non aqueous media. The aqueous acid-catalysis was therefore reinvestigated by Bunton and Fender who studied the hydrolysis of acetic and trimethyl acetic anhydride. If the hydrolysis follows mechanism I both anhydrides would react at about the same rate. If, however, mechanism II is followed the trimethyl acetic anhydride would hydrolyse more slowly due to the steric hindrance. The uncatalysed hydrolysis was shown to be bimolecular and the trimethyl acetic anhydride is hydrolysed more slowly than acetic anhydride. Similarly in aqueous acid catalysis the acetic anhydride hydrolysis is faster and so mechanism II must be the operative mechanism. Further evidence comes from the entropy of activation which was in the range expected for mechanism II and not mechanism I.

It has been found that the hydrolysis of acetic anhydride is catalysed by the addition of formate ions and that the hydrolysis of propionic and acetic propionic anhydrides is catalysed by acetate and formate ions though the latter are more efficient in both cases. This catalysis is due to the nucleophilic reaction of the ions with the anhydride to form a different anhydride

\[(\text{RCO})_2\text{O} + \text{H}_2\text{COO}^- \leftrightarrow \text{RCO.O.COR}' + \text{RCOO}^-\]

If this anhydride is more susceptible to hydrolysis than the original anhydride the rate of hydrolysis will be increased.
Since the ease of hydrolysis is formic anhydride > acetic anhydride > propionic anhydride this theory explains the catalysis by formate and acetate ions. Further it would be predicted that if the intermediate anhydride is less susceptible to hydrolysis than the original anhydride the hydrolysis would be retarded. Kilpatrick and Kilpatrick\textsuperscript{34} found that propionate and butyrate ions inhibit the hydrolysis of acetic anhydride so confirming the above explanation.

Further evidence comes from the work of Bender and Neveu\textsuperscript{35} who used O\textsuperscript{18} labelled acetate in the hydrolysis of 2,4-dinitrophenyl benzoate in a 1:1 water dioxan solvent. The benzoic acid so obtained contained 38\% of the O\textsuperscript{18} derived from the labelled acetate. Therefore the mechanism must have been

\[ \text{C}_6\text{H}_5\text{CO} \cdot \text{OC}_6\text{H}_3(\text{NO}_2)_2 \xrightarrow{\text{CH}_3\text{CO}^{18}O^{18}} \text{C}_6\text{H}_5\text{C}^{0} - O^{18} \xrightarrow{\text{3-C-H}_3} \]

\[ \rightarrow \text{C}_6\text{H}_5\text{COO}^{18}\text{H} + \text{CH}_3\text{C}^{0}\text{OH} \]

From previous work\textsuperscript{36} on acid-catalysed oxygen exchange the authors estimated that the maximum amount of O\textsuperscript{18} incorporated into the benzoic acid by exchange with the solvent would be 1\%.

The mixed anhydride theory does not explain the catalysis of acetic anhydride by acetate ions because, in this case, reaction between the anhydride and the acetate does not produce any new products.
Butler and Gold investigated the effect of changing the solvent from $H_2O$ to $D_2O$ and found that the isotopic ratio was about 1.7. They proposed the following mechanism.

$$\text{(CH}_3\text{CO)}_2\text{O} + \text{CH}_3\text{COO}^- \leftrightarrow \text{(CH}_3\text{CO)}_2\text{O} + \text{CH}_3\text{COO}^-'$$

$$\text{CH}_3\text{COO}^- \cdot \text{CH}_3 + \text{OH}^- \overset{K}{\rightarrow} \text{CH}_3\text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{H}_3\text{O}^+ \quad \text{rapid.}$$

$$\text{CH}_3\text{C} \cdot \text{O} \cdot \text{CO} \cdot \text{CH}_3 + \text{HOOCCH}_3 \overset{k_2}{\rightarrow} \text{CH}_3\text{C} \cdot \text{C} \cdot \text{CO} \cdot \text{CH}_3 + \text{AcO}^- \quad \text{slow.}$$

$$\text{CH}_3\text{C} \cdot \text{O} \cdot \text{CO} \cdot \text{CH}_3 \rightarrow 2 \text{CH}_3\text{COOH}$$

The first step is the same as that proposed by these workers for the spontaneous hydrolysis of acetic anhydride. The rate of the reaction would be $k_3 [\text{AcO}^-][\text{AcOH}]$, where $K_{\text{AcOH}}$ is the acid dissociation constant for acetic acid. As before $k_3^H$ lies in the range 2.5 to 4.5 and $K_{\text{AcOH}} = 3.3$. They decided that $k_3^H$ would be greater than 2 and therefore the deuterium isotope effect predicted on this basis was compatible with the experimental value. This mechanism assumes that the $C\cdot O$ bond breaking is faster than a proton transfer between two oxygen atoms. However comparison of rates for some typical examples shows that the proton transfer must be faster than the $C\cdot O$ bond breaking.
Johnson investigated the reaction of benzoic anhydride with water in the presence of acetate and N-methylimidazole catalysts and proposed a different mechanism.

\[
\begin{align*}
R - C - O - CO_2H + B + H_2O & \xrightarrow{k_1} \text{slow} \quad O^8- \\
& \xrightarrow{R.C.O.C.O.R \quad \text{or} \quad R - C \cdots \cdots CO_2R^8} \\
& \xrightarrow{O^8-} \quad \text{products} \\
& \xrightarrow{0-H} \\
\text{H-C-C-0-R}
\end{align*}
\]

Further work on this topic is required before any firm conclusions can be drawn.

The hydrolysis of acetic anhydride in both water and aqueous acetone solution is catalysed by the presence of pyridine and the related pyridine bases. Gold found that, whereas pyridine, 3- and 4-piclines and isoquinoline are very effective catalysts the ortho substituted bases i.e. 2-picoline, 2,6-lutidine and quinoline are less efficient by an order of ten. Also the bases, except for those with ortho substituents, followed the Brönsted catalysis law. It has been proposed that the catalysis of the Perkin reaction by triethylamine is due to the formation of the complex \(\text{CH}_3\text{CO}_2\text{MgBr} \cdots \cdots \text{H}^+\text{Na}_2\text{C}_2\) by the acetic anhydride and triethylamine. A similar complex could be formed by pyridine.
and acetic anhydride i.e. \( \text{CH}_3\text{CO.O.CO.CH}_2\text{—} \ldots \cdot \text{H}^+\text{PY.} \). However it was found that the hydrolysis of benzoic anhydride\(^{38} \) is also catalysed by pyridine and since this anhydride has no hydrogen atom that can be transferred to the catalyst this mechanism can be rejected.

The hydrolysis of acetic anhydride may be catalysed by reaction of the pyridine with the water. However the hydrolysis of acetic formic anhydride in aqueous acetone and the decomposition of this anhydride in toluene\(^{40} \) have been investigated. Both these reactions were catalysed by the presence of pyridine and once again the ortho substituted bases were less efficient than would be expected from their basic strengths. The rate of the reactions increased linearly with the base concentrations and was first order in the unsymmetrical anhydride. The pyridine catalysis of the decomposition of acetic formic anhydride could only be due to interaction of the anhydride and the pyridine since the reaction was carried out in an inert solvent and it is probable that the same intermediate would be formed in the hydrolysis of this anhydride. From this it seems probable that the pyridine catalysis of the hydrolysis of acetic anhydride, which exhibits the same features as the above reactions, occurs via a pyridine-acetic anhydride complex. Gold proposed that the reaction occurs via an acetyl pyridinium ion which then reacts
with the water
\[ \text{CH}_3\text{CO}_2\text{CO}_2\text{CH}_3 + \text{py} \rightarrow \frac{k_1}{k_{-1}} [\text{CH}_3\text{CO py}]^+ + \text{CH}_3\text{COO}^- \]
\[ [\text{CH}_3\text{CO py}]^+ + \text{H}_2\text{O} \rightarrow \text{py} + \text{CH}_3\text{CO}_2\text{H}^+ \quad \text{rapid} \]
\[ \text{CH}_3\text{COOH} + \text{H}^+ + \text{py} \]

On a further investigation they found that the rate of hydrolysis is directly proportional to the acetate ion concentration. This is in agreement with the proposed mechanism since the acetate would reduce the concentration of acetyl pyridinium ion by a common ion effect. These workers also found that the deuterium isotope effect \( k_{\text{H}_2\text{O}} \) is 5 which is in agreement with the above conclusions if the reaction with water is considered to be the slow step.

When \( \alpha \)-picoline or 2,6-lutidine were used there was little, or no, catalytic effect. It was thought that the presence of a methyl group in the ortho position results in compressional strain between it and the N-acetyl group. This strain can be relieved by rotation of the N-acetyl group but this means that this group is no longer co-planar with the pyridine ring and so resonance between the ring and the acetyl group is inhibited. Thus the stability of the acetylpyridinium ion is reduced. From these results it was predicted that the hydrolysis of trimethylacetic anhydride would hardly be catalysed by any pyridine base and this has been verified by experiment.

Pyridine had no catalytic effect on this reaction when it
was carried out in a 60:40 dioxan-water solvent. This means that when a lower dielectric constant solvent is used the value of $k_1$ is reduced and $k_{-1}$ is increased.

Govitz and Westheimer studied the catalytic effect of pyridines on general base-catalysed reactions. The reactions studied were the mutarotation of glucose, the hydrolysis of methyl-ethylene phosphate and the inversion of menthone. In each case they found that the catalytic effect of 2-substituted pyridines was less than would be expected from their basicity. They concluded that, although the steric effects are large for nucleophilic attack at carbon, the steric effects for general acid and general base catalysis are of moderate size and not negligible as had previously been thought. A possible mechanism for the hydrolysis of acetic anhydride is therefore

$$
\text{CH}_3\text{CO}_2\text{H} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CO}_2\text{H}^+ + \text{OH}^-
$$

$$
\text{CH}_3\text{CO}_2\text{H} + \text{C}_2\text{H}_4\hat{\text{O}}\text{C}_2\text{H}_5 \rightarrow \text{CH}_3\text{CO}_2\text{H} + \text{C}_2\text{H}_4\text{O}^- + \text{H}_2\text{O}
$$

**ii) Acylation of Alcohols and Phenols.**

Conant and Bramann investigated the acylation of &alpha; - naphthol by acetic anhydride in an acetic acid solvent. They used several mineral acids as catalysts and measured the hydrogen ion activity
of the medium by a chloranil electrode. By this method they found that the rate of acetylation was determined by the hydrogen ion activity of the medium and proposed that the catalytic species was $\text{AcOH}_2^+$. Later work showed that the chloranil electrode could not be used in the presence of acetic anhydride because of acetylation of the indicator substances. Russell and Cameron estimated the hydrogen ion activity using a hydrogen electrode and their results differed greatly from those of Conant and Bramann. They also found evidence of complex formation between the acetic anhydride and sulphuric and perchloric acid and suggested that the complex was the unsymmetrical anhydride.

The catalytic effect of various mineral acids on the acylation of $\beta$-naphthol in an acetic acid solvent has been studied by Satchell. He found that when a ten fold excess of acetic anhydride over the $\beta$-naphthol was used the reaction was first order in the $\beta$-naphthol. When the anhydride was present in a lower concentration than the hydrochloric acid the order with respect to the anhydride was unity and similarly for HCl concentrations below that of the anhydride the order was 1 for the HCl. At higher relative concentrations the order decreased in both cases. Also the rate of the reaction was found to be the same whether acetic anhydride and HCl or acetyl chloride were used. On this basis Satchell decided that the anhydride reacted with the HCl forming acetyl chloride.
\[
\text{Ac}_2\text{O} + \text{HCl} \quad \rightleftharpoons \quad \text{AcCl} + \text{AcOH} \quad \text{fast.}
\]
\[
\text{AcCl} + \text{ROH} \quad \rightarrow \quad \text{ROAc} + \text{HCl} \quad \text{slow.}
\]

Satchell also reported infrared evidence for the formation of small quantities of acetyl chloride from the hydrochloric acid and acetic anhydride in acetic acid. This mechanism is similar to that proposed for the hydrolysis of acetic anhydride in the presence of mineral acid and acetic acid. This mechanism was also proposed for the systems propionic anhydride - propionic acid - hydrochloric acid and acetic anhydride - acetic acid - hydrobromic acid.

The reaction of \(\beta\)-naphthol with benzoic anhydride in the presence of hydrochloric acid in acetic acid yielded \(\beta\)-naphthyl acetate. This is due to the reaction of the benzoyl chloride (formed as in the case of acetic anhydride) with the acetic acid giving acetyl chloride which then acylates the \(\beta\)-naphthol. This also occurs with butyric anhydride.

A study of the effect of sulphuric acid on the acylation of \(m\)-nitrophenol by acetic anhydride in acetic acid has been carried out. The order with respect to the phenol was 1 but for the acetic anhydride was about 1.5. When butyric anhydride and butyric acid were used the order was 1.3 in the anhydride. If the mechanism was the same as that for catalysis by mineral acids i.e.

\[
\begin{align*}
(\text{CH}_3\text{CO})_2\text{O} + \text{H}_2\text{SO}_4 & \quad \xrightarrow{\text{fast}} \quad \text{CH}_3\text{COOH} + \text{CH}_3\text{COHSO}_4 \\
\text{CH}_3\text{COHSO}_4 + \text{ArOH} & \quad \xrightarrow{\text{slow}} \quad \text{ArOCCH}_3 + \text{H}_2\text{SO}_4
\end{align*}
\]
the order would either be less than or equal to 1. The authors considered the possibility of the formation of addition complexes between the anhydride and sulphuric acid

\[(RCO)_2O + H_2SO_4 \rightleftharpoons (RCO)_2OH^+ \cdot HSO_4^-\]

This theory was, however, rejected in favour of a mechanism which took into account the dibasic nature of sulphuric acid

\[(RCO)_2O + H_2SO_4 \xrightarrow{\text{fast}} RCO\cdot HS\rightleftharpoons_4 + RCOOH \quad K_1\]

\[2(RCO)_2O + H_2SO_4 \xrightarrow{\text{fast}} (RCO)_2SO_4^- + 2RCOOH \quad K_2\]

\[RCOHSO_4^- + ArOH \xrightarrow{k_1} Ar\cdot CO\cdot R + H_2SO_4\]

\[(RCO)_2SO_4^- + ArOH \xrightarrow{k_2} Ar\cdot CO\cdot R + R\cdot COHSO_4^-\]

The observed rate of reaction was worked out in terms of $K_1$, $K_2$, $k_1$ and $k_2$ and seemed to be in accordance with the above mechanism.

Pyridine has been widely used as a catalyst in acylations. Several explanations for its catalytic ability have been advanced. One theory\(^4\)\(^5\) is that the base removes the acid liberated by acylation. This can not be the reason since acylation is an irreversible process. It has also been suggested\(^4\)\(^9\) that the presence of pyridine aids the ionisation of the anhydride.

\[(CH_3CO)_2 \rightleftharpoons CH_3CO^+ + CH_3COO^-\]

\[CH_3CO^+ + ROH \rightarrow RO\cdot CO\cdot CH_3 + H^+\]

This may be possible at high temperatures and in ionising solvents but pyridine is an effective catalyst when presented in small quantities in non-polar solvents when ionisation is unlikely and so this theory can be rejected.
In their work on the hydrolysis of acetic anhydride Gold and Jefferson\(^{38}\) postulated the formation of acetylpyridinium ions

\[
\begin{align*}
\text{Ac}_2\text{O} + \text{py} & \rightleftharpoons \text{py Ac}^+ + \text{OAc}^- \\
\text{py Ac}^+ + \text{H}_2\text{O} & \rightarrow \text{AcOH} + \text{py} + \text{H}^+
\end{align*}
\]

A similar mechanism can be postulated for the pyridine catalysis of acylation

\[
\begin{align*}
\text{Ac}_2\text{O} + \text{py} & \rightleftharpoons \text{py Ac}^+ + \text{OAc}^- \\
\text{py Ac}^+ + \text{ROH} & \rightarrow \text{ROAc} + \text{py} + \text{H}^+
\end{align*}
\]

Mixtures of acetic anhydride and pyridine have been investigated for evidence of reaction between them. Nelson and Markham\(^{50}\) refluxed acetic anhydride with pyridine for 72 hours, but found that Raoul's Law was closely obeyed. Gold and Jefferson\(^{51}\) studied the ultra-violet spectra of the system in cyclohexane, the infra-red spectra in carbon tetrachloride, the conductivity in dry acetone and the depression of the freezing point in benzene and in none of these could they find any evidence for either ionisation or an association complex between the anhydride and pyridine. A nuclear magnetic resonance study\(^{52}\) in carbon tetrachloride also failed to show any reaction. More recent conductometric work\(^{53}\) on acetic anhydride and pyridine, in the absence of solvent, showed that the conductivity of acetic anhydride increased with increasing pyridine concentration until the pyridine-acetic anhydride ratio was 1:1. Similar results
were obtained with quinoline and \( \alpha \)-picoline except that the increase in conductivity was not as great as in the case of pyridine. This indicates that the reaction
\[
\text{py} + (\text{CH}_3\text{CO})_2\text{O} \rightarrow \text{py}(\text{CH}_3\text{CO})_2\text{O} \rightleftharpoons (\text{py CH}_3\text{CO})^+ + \text{CH}_3\text{COO}^-
\]
probably occurs in the absence of solvent but no evidence for its occurrence has been found in non-polar solvents.

Schenk, Wines and Mojzis\(^5\) investigated the reaction of triethylene diamine (\(N\(\equiv\)N) with acetic anhydride in carbon tetrachloride by infrared and nuclear magnetic resonance spectroscopy. Both methods gave new absorptions which could not be attributed to the solvent or either of the components of the mixture. No evidence of the presence of the acetate ion could be found and so acetic anhydride and triethylene diamine probably form an intermediate complex and are not ionised into an acetate and a triethylene diamine acetylium ion. By the refractive index method of Arshid it was found that the complex consisted of 2 moles of triethylene diamine to 1 mole of acetic anhydride in carbon tetrachloride but in dioxan or 1,2 dimethoxyethane there appeared to be a 1:1 interaction.

An alternative mechanism\(^5\) for pyridine catalysis in acylation is as follows
\[
\text{py} + \text{ROH} \rightleftharpoons \text{py H}^+ + \text{RO}^-
\]
\[
\text{RO}^- + \text{Ac}_2\text{O} \rightarrow \text{ROAc} + \text{OAc}^-
\]
A modification of this mechanism involves hydrogen bonding:

\[ C_5H_5N + ROH \rightleftharpoons HO^- \cdots H \cdots NC_5H_5^+ \]

This mechanism has been rejected by Schenk, Wines, and Mojzis because \( \alpha \)-picoline and 2,6-lutidine, which are stronger bases than pyridine, do not catalyse the reaction to the same extent as pyridine. However, these workers have ignored the steric effect of the methyl groups which may play an important part in a hydrogen-bonded complex even though it would not affect the reaction if it were due to complete ionisation into \( RO^- \) and \( pyH^+ \).

iii) Friedel-Crafts Acylation

The Friedel-Crafts acylation is:

\[ ArH + RCOX \xrightarrow{\text{catalyst}} ArCOR + HX \]

This reaction has been extensively used in synthetic organic chemistry and a wide variety of catalysts have been employed. This subject has been thoroughly surveyed by Olah.

The catalysts originally used were Lewis acids, generally the fluoride or chloride. In the aluminium chloride catalysis of acetic anhydride the best yields of product were obtained when three equivalents of aluminium chloride were used. The mechanism is as shown below:

\[ \text{AlCl}_3 + (\text{CH}_3\text{CO})_2\text{O} \rightarrow \text{CH}_3\text{COCl} + \text{CH}_3\text{COOAlCl}_2 \]

\[ \text{CH}_3\text{COCl} + \text{AlCl}_3 \rightleftharpoons \text{H} - \text{C} = \text{O}:\text{AlCl}_3 \]
This is essentially reaction of an acyl halide catalysed by aluminium chloride. The third equivalent of aluminium chloride is presumably required because some of the catalyst is engaged by the product. Cook investigated the complex RCO\textsubscript{3}Cl\cdot AlCl\textsubscript{3} in the liquid state and found that it consisted of both the donor-acceptor complex \( \text{CH}_3 - \text{C} = \text{O} \cdots \text{AlCl}_3 \) and the ions \( \text{CH}_3\text{CO}^+ \text{AlCl}_4^- \). In a high dielectric constant solvent (nitrobenzene) both species were also present but in a low dielectric constant solvent (chloroform) only the donor-acceptor form was present.

Some Lewis acids, e.g. zinc chloride and stannic chloride, do not decompose in the presence of acid anhydrides and so their catalytic ability is not due to the formation of the acyl halide. In these cases the acylating species is probably the acylium ion

\[
\text{RCO}^+ \rightarrow \text{RCOCl}^+ \quad \text{SnCl}_4^- \rightarrow \text{RCOCl}^+ \text{SnCl}_4^{-}\]

Satchell, however, considered that the complex was more likely to be \( \text{CH}_3\text{CO}_2^0 \rightarrow \text{SnCl}_4^- \) than the acylium ion shown above.

Boron trifluoride has also been used to catalyse the reaction of acetic anhydride. This formed a complex \( \text{Ac}_2\text{O}[\text{BF}_3]_2 \) and on the basis of the infrared spectra the structure shown
More extensively studied, however, is the effect of catalysts such as boron trifluoride on the acyl halide reactions. It was found that boron trifluoride reacts with acyl fluorides yielding stable 1:1 addition compounds

$$\text{RCOF} + \text{BF}_3 \rightleftharpoons \text{RCOBF}_4^+$$

These compounds can be isolated and proved to be very efficient acylating agents. Susz and Wuhmann investigated the structure of this complex and found that it was predominantly the ionic methyl oxocarbonium tetrafluoroborate $\text{CH}_3\text{CO}^+\text{BF}_4^-$ and only a small quantity of the donor-acceptor complex was detected.

Later work utilised the reaction of acyl fluorides with $\text{PF}_5$, $\text{SbF}_5$ and $\text{AsF}_5$ to prepare the 1:1 complexes of these compounds with acetyl, propionyl and benzoyl fluoride. These compounds were also prepared by the metathesis of the acyl halide with the silver salt of the required compound

$$\text{ROCl} + \text{AgMF}_5 \rightarrow \text{ROMF}_5 + \text{AgCl} \text{ where } M = \text{P, Sb, As}$$

Infrared and proton and fluorine magnetic spectroscopy showed that all these compounds in the crystalline state existed in
an ionic form, i.e. $\text{RCO}^+\text{MF}_6^-$, but in solution in liquid sulphur
dioxide or hydrogen fluoride another form, presumably the
polarised co-ordination complex $\text{RCO}^+\cdots\text{MF}_5^-$, was also present.

It is probable that acyl perchlorates also exist in the ionised
form $\text{RCO}^+\text{ClO}_4^-$ in the solid state.

Thus, although there is evidence of acylium ion formation,
it seems highly unlikely that the acylium ion is present in
solvents of low dielectric constant — in these solvents the
complex is more likely to be present in the form of a donor-
acceptor complex.

C. Reactions of Unsymmetrical Anhydrides.

i) General.

Unsymmetrical anhydrides have been widely used as acylating
agents in synthetic organic chemistry because they are more
reactive than the symmetric anhydrides and can be used under
milder reaction conditions. Of these anhydrides the acyl
trifluoroacetates are the most extensively used, especially in
the field of carbohydrate chemistry where acyl groups are
frequently used to block hydroxy groups. This subject has been
reviewed by Bonner.\textsuperscript{61}

Acyl trifluoroacetates have also been used to introduce an
RCO- group into a compound containing a double bond without
removal of the double bond.\textsuperscript{62}

\[ 
\text{RCO} \cdot \text{O} \cdot \text{CO} \cdot \text{H} + \text{R}^2 \text{CO} \cdot \text{O} \cdot \text{CO} \cdot \text{H} \rightarrow \text{R}^2 \text{CO} \cdot \text{CR} \cdot \text{H} \cdot \text{(CF}_3\text{COO)} 
\]

\textit{hydrolysis} \[ \text{R}^2 \text{CO} \cdot \text{CR} \cdot \text{H} + \text{CF}_3\text{COOH} \]

The main interest in asymmetric anhydrides is that, on reaction with substances of the formula \( \text{XH} \), there can be two possible products.

\[ \text{i.e. RCO} \cdot \text{O} \cdot \text{CO} \cdot \text{R}^\prime + \text{XH} \rightarrow \text{RCOX} + \text{R}^\prime \text{COOH} \]

\[ \text{RCO} \cdot \text{O} \cdot \text{CO} \cdot \text{R}^\prime + \text{XH} \rightarrow \text{R}^\prime \text{COX} + \text{RCOOH} \]

where \( \text{XH} \) can be \( \text{OH} \) (alcohol or phenol), \( \text{R}_2\text{NH} \) or \( \text{ArH} \)

\textbf{ii) Reactions with amines and hydroxy compounds.}

Much of the early work on amines, phenols and alcohols was performed by Autenrieth,\textsuperscript{63} Behal,\textsuperscript{3} and Hurd.\textsuperscript{64,65}

On the basis of his work with acetic, isovaleric and acetic benzoic anhydrides Behal concluded that the main product of reactions with asymmetric anhydrides was the derivative of the acid with the smaller number of carbon atoms. However, this postulate did not explain the results obtained using acetic benzoic anhydride by Baroni\textsuperscript{66} et. al. These workers suggested that the main product was the derivative of the stronger of the two acids. In the case of the carboxylic acid anhydrides the stronger acid is that with the smaller number of carbon atoms.
Even this explanation does not cover all the results since, in some cases Kuhn obtained the derivative of the weaker of the two acids.

This early work was probably performed using impure asymmetric anhydrides because there was, at that time, no means available for differentiating between a mixture of symmetric anhydrides and an unsymmetrical anhydride. Furthermore contradictory results were obtained because the importance of the solvent, the temperature, and the specific influence of X in XH were ignored. Due to these facts no mechanistic results can be deduced from the above work.

Emery and Gold prepared fairly pure samples of acetic chloroacetic anhydride by the keten method and investigated their reactions with two primary aromatic amines, aniline and 2,4-dichloroaniline, in benzene. In this solvent it is unlikely that the amines would be ionised and the anhydride is also probably in its molecular form. If the anhydride reacts in the molecular form it would be expected that reactions would take place at the carbonyl carbon which carries the greater relative positive charge i.e. the product which predominates should be that of the more electron attracting group. Due to the electron affinity of the chloro group acetyl chloroacetic anhydrides should be mainly chloroacetylating agents, and as the chlorine
substitution of the methyl group increases, the ratio of chloroaliphatic amide to acetanilide, i.e. the 'chloroacylation ratio', should increase. The 'chloroacylation ratios' found for aniline were

\[
\begin{align*}
\text{Ac}_2\text{O} & \quad \text{ClCH}_2\text{CO.COO.CH}_3 & \quad \text{Cl}_2\text{CHCO.COO.CH}_3 & \quad \text{Cl}_3\text{CO.COO.CH}_3 \\
1 & \quad 6.1 & \quad 2.2 & \quad 0.08
\end{align*}
\]

These results show that, though the substitution of one chlorine group increases the 'chloroacylation ratio', further substitution causes a reduction in the ratio. This is ascribed to the steric effect of the chlorine group which hinders reaction at the carbonyl group adjacent to it. Thus as the chlorine substitution of the methyl group increases both the magnitude of the partial positive charge at the carbonyl group and the steric hindrance at this group increase and the balance between these two effects is shown by the 'chloroacylation ratio'. As can be seen from the results the electronic effect is more important when the number of chlorine groups substituted is small but as the substitution is increased the steric effect predominates over the electronic effect.

These workers also investigated the effect of change of solvent on the system. They found that, whereas the 'chloroacylation ratio' for aniline and acetic monochloroacetic anhydride in benzene was 6.1, in acetone the ratio was 1.6, and
for mixtures of the two solvents intermediate ratios were obtained. This change in ratio with increasing dielectric constant could be due to ionisation of the anhydride. Due to the electron attraction of the chlorine group all the acetic-chloroacetic anhydrides would ionise in the same way giving acetylium and chloroacetate ions.

\[ \text{ClCH}_2\text{CO.O.CO.CH}_3 \quad \rightarrow \quad \text{CH}_3\text{CO}^+ + \text{ClCH}_2\text{COO}^- \]

The amine would then react with the acetylium ion to yield acetonilide. If this were the mechanism the ionisation of the anhydride would be the rate-determining step and the reaction would be zero order in the amine. In practice the rate of the reaction was found to be dependent on the amine concentration. Further, the 'chloroacylation' ratio does not depend strongly on the nature and concentration of the amine as it would do if ionisation took place. For these reasons the ionisation theory was rejected.

Emery and Gold suggested that the change in product with change in solvent was due to solvation of the transition state. In benzene there would be no solvation but in acetone, the solvent could hydrogen-bond with the amine and so the transition state could become sterically strained.
This steric hindrance would be of greater magnitude at the chloromethyl end of the molecule and so the amount of acetate formed would increase.

Formic acetic anhydride has been prepared by van Es et al.\textsuperscript{69} and its reactions with alcohols\textsuperscript{70} and phenols\textsuperscript{71} investigated. They found that phenol reacted with formic acetic anhydride yielding 85\% formate and 15\% acetate. In the presence of catalytic quantities of pyridine, imidazole or sodium formate the product contained only formate but the reaction was much faster than the reaction in the absence of these catalysts. p-Toluene-sulphonic acid also increased the rate of reaction but in this case the product was almost entirely acetate. Reaction with 1-propanol yielded 100\% formate and though the reaction was accelerated by the presence of pyridine or sodium formate there was no change in product. These results are what would be expected if the unsymmetrical anhydride reacted in the molecular as opposed to the ionised form. However, since the primary aim of this work was to establish synthetic routes to pure aryl and alkyl formates it is difficult to draw any mechanistic conclusions from it.

The reactions of hydroxy compounds with acetyl trifluoroacetate have been studied by Bourne, Stacey, Tatlow and Worrall.\textsuperscript{72} These workers proposed that the mixed anhydride exists in an
equilibrium mixture of the molecular and ionised form. Due to the electron attracting power of the trifluoromethyl group, the ionic form will be \( \text{CF}_3\text{COO}^- \) and \( \text{CH}_3\text{CO}^+ \) rather than \( \text{CF}_3\text{CO}^+ \) and \( \text{CH}_3\text{COO}^- \).

i.e. \( \text{CH}_3\text{CO.O.CO.CF}_3 \xrightarrow{\text{⇌}} \text{CF}_3\text{COO}^- + \text{CH}_3\text{CO}^+ \)

Hence reaction can occur with either the molecular form or the acetylium ion. If the hydroxy compound reacts with the acetylium ion the product will be the acetate. If, on the other hand, the molecular form is the reactant the attack will be at the carbonyl group adjacent to the more electron withdrawing group and the trifluoroacetate ester will be formed. Primary and secondary alcohols react forming a mixture of the acetate and the trifluoroacetate, though the acetate production predominates. These results are in agreement with the above theory because, though the acetylium ion is very reactive, it is present in very small quantities in comparison with the molecular form. It was also found that the greater the availability of electrons at the oxygen atom of the hydroxy compound the easier reaction with the molecular form became and so the proportion of trifluoroacetate increased.

The effect of additives on the reaction of alcohols with acetyl trifluoroacetate was investigated. Sodium trifluoroacetate caused a decrease in the acetate production. This was
probably due to suppression of the ionisation by a common ion effect. Similarly addition of carbon tetrachloride to the system reduced the acetate formation by lowering the dielectric constant and so reducing the ionisation. The amount of trifluoroacetate ester formed was increased by the addition of trifluoroacetic acid which probably aids the ionisation by specific solvation of the trifluoroacetate anion.

Phenols and the more acidic alcohols, such as fluoroalcohols, react with acetyl trifluoroacetate forming only the acetate ester. With these compounds the electrons on the oxygen atom of the hydroxy group are less available than those of the primary alcohols, and so they can not react with the molecular forms of the mixed anhydride. Since they can only react with the acetylum ion the product must be entirely acetate. The addition of sodium trifluoroacetate causes some trifluoroacylation to occur but when carried out in a carbon tetrachloride solvent, even with trifluoroacetic acid present, the only product is the acetate ester.

There is a third group of hydroxy compounds which do not seem to follow any pattern and which yield contradictory results when additives are present. These compounds include tertiary
butyl alcohol and diphenylmethanol. The reason for the unusual behaviour of these compounds is that they are more basic than the primary and secondary alcohols but they are also more sterically hindered. The steric hindrance makes reaction at the trifluoromethyl end of the molecule more difficult while the increased basicity makes reaction at both ends of the molecular form of the anhydride possible. Thus the reaction at the trifluoromethyl end of the molecule, though easier electronically, is sterically hindered while reaction at the other end is less hindered but also slower. Thus the ratio of the products formed depends on the balance between the basicity and the steric hindrance. Further, since these alcohols are so basic, alkyl-oxygen fission can occur in the presence of trifluoroacetic acid.

\[ (\text{CH}_3)_3\text{OH} + \text{CF}_3\text{COOH} \rightarrow (\text{CH}_3)_3\text{C}^+\text{OH}_2 + \text{CF}_3\text{COO}^- \]

\[ (\text{CH}_3)_3\text{C}^+\text{OH}_2 \rightarrow (\text{CH}_3)_3\text{C}^+ + \text{HOH} \]

\[ (\text{CH}_3)_3\text{C}^+ + \text{CF}_3\text{COO}^- \rightarrow (\text{CH}_3)_3\text{COOCOF}_3 \]

A similar mechanism for the formation of acetates can be proposed.

Benzoyl and phenylacetyl anhydrides were also studied by these workers and similar results were obtained though benzoyl trifluoroacetate yielded a greater proportion of trifluoroacetate than acetyl trifluoroacetate. This is probably due to resonance stabilisation of the benzoylium cation \((\text{C}_6\text{H}_5\text{CO}^+)\) which decreases
the positive charge at the carbonyl carbon and so reduces its reactivity and to the fact that it is slightly more electronegative than acetyl trifluoroacetate.

More recently the reaction of hydroxy compounds with acetyl trifluoroacetate in carbon tetrachloride has been investigated by Bonner and Gabb. They found that the reaction was first order in both the p-chlorophenol and acetyl trifluoroacetate and the product was entirely p-chlorophenylacetate. This suggests that the acetate is formed by nucleophilic attack of the phenol on the unionised anhydride and not by reaction with the acetylium ion as had been proposed by previous workers. Ionisation would not be expected to play a large part in a solvent of low dielectric constant. Due to the electron withdrawing nature of the trifluoromethyl group the carbonyl carbon adjacent to it should carry the greater positive charge and so reaction would be expected at this end of the molecule. However, the large size of the trifluoromethyl group prevents the near approach of the phenol and so reaction occurs at the other end and the product contains only the acetate ester. It has also been suggested that the acetate formation is due to the fact that the trifluoroacetate ion is a much better leaving group than the acetate ion. m- and p-substituted phenols satisfied the Hammett equation and so must follow the same mechanism as p-chlorophenol. The reaction of p-chlorophenol
with acetyl trifluoroacetate in the presence of trifluoroacetic acid was investigated and it was found that, although the reaction was faster, it was still first order in the phenol and yielded only acetate. This indicates that, even in the presence of trifluoroacetic acid, reaction takes place through the molecular form of the anhydride and not acetylium ions.

In contrast with the reaction of phenols the reaction of isopropanol was second order in the alcohol and yielded both the acetate and trifluoroacetate esters. The addition of trifluoroacetic acid had little effect on the rate of acetylation but slightly increased the rate of trifluoroacetylation.

On shaking a solution of p-chlorophenol and acetyl trifluoroacetate with saturated aqueous potassium bicarbonate there is rapid and exclusive formation of p-chlorophenyl trifluoroacetate. It was suggested that the phenol is converted into the phenate ion by the bicarbonate solution. When this ion comes into contact with the acetyl trifluoroacetate at the carbon tetrachloride-water interface the trifluoroacetate ester is formed. Since the phenate ion is a powerful nucleophile the importance of bond breaking decreases and reaction takes place at the more electrophilic carbon atom. In the case of nucleophilic reagents whose strengths lie between those of phenol and the phenate ion the product formation will depend on the balance between the ease of bond breaking and bond formation.

Part of this thesis is concerned with the effect of pyridine on the reaction of hydroxy compounds with anhydrides in an inert solvent.
A. Materials.

Carbon Tetrachloride.
"AnalaR" carbon tetrachloride was dried by passage through a "4A" molecular sieve column.

Trifluoroacetic Acid.
Eastman trifluoroacetic acid was redistilled b.p. 73-74°C.

Trifluoroacetic Anhydride.
100 ml of trifluoroacetic acid were added to 120 g of phosphorus pentoxide and heated on a water bath. The distillate b.p. 38-39°C was collected and stored over fresh phosphorus pentoxide.

Acetic Acid.
"AnalaR" acetic acid was redistilled b.p. 117-118°C.

Acetic Anhydride.
"AnalaR" acetic anhydride was redistilled b.p. 137-138°C.

Acetyl trifluoroacetate.
Acetyl trifluoroacetate was prepared by mixing equimolecular solutions of acetic and trifluoroacetic anhydrides in carbon tetrachloride. The acetic anhydride solution was made up in the
normal manner in a "dry box". Trifluoroacetic anhydride is very susceptible to hydrolysis and so was made up under anhydrous conditions. Trifluoroacetic anhydride was distilled on a vacuum line at a pressure of 0.1 mm. mercury from phosphorus pentoxide into a weighed container. The container was closed by a tap, removed from the line and weighed. The container was reconnected to the line and more trifluoroacetic anhydride was distilled into the container or removed from it until the required weight was obtained. Dry carbon tetrachloride was then distilled into the container so forming a concentrated solution. The container was removed from the line and the solution was made up to the desired strength in a dry box.

The equimolecular solutions of acetic and trifluoroacetic anhydrides were mixed in a dry box and left for one week. During this period the infrared absorption bands of acetic anhydride at 1760 and 1820 cm.⁻¹ and of trifluoroacetic anhydride at 1800 and 1850 cm.⁻¹ were replaced by bands at 1780 and 1850 cm.⁻¹ due to acetyl trifluoroacetate. Also the -C-O-C- bands at 1120 and 1040 cm.⁻¹ were replaced by a band at 1080 cm.⁻¹. When these changes were complete the solution was ready for use.

p-Chlorophenol.

B.D.H. "Laboratory Reagent" p-chlorophenol was redistilled b.p. 219°C.
**p-Chlorophenol-d**

*p-Chlorophenol* (4g) was dissolved in deuterium oxide (0.5g.). After some time the *p*-chlorophenol was extracted with dry carbon tetrachloride and the carbon tetrachloride was evaporated off. This was repeated several times. Finally the *p*-chlorophenol was distilled b.p. 217-218°C.

The height of the OH stretching peak of an 0.1M solution of the product in carbon tetrachloride was measured using a Perkin-Elmer Infracord which had been calibrated with known solutions of *p*-chlorophenol. The product was found to be 80% deuterated.

**Phenol-d**

This was prepared in a similar manner b.p. 179-180°C. The product was 90% deuterated.

**p-Cresol.**

B.D.H. "Laboratory Reagent" was redistilled b.p. 201-202°C.

**Pentachlorophenol.**

Aldrich "puriss" pentachlorophenol was used directly.

**Salicylaldehyde.**

B.D.H. "Laboratory Reagent" salicylaldehyde was redistilled b.p. 196°C.

**p-Nitrophenol.**

B.D.H. "Laboratory Reagent", m.p. 45°C, was used directly.

**n-Butanol.**

"AnalaR" butanol was redistilled b.p. 117°C.
Isopropanol.
"AnalaR" isopropanol was redistilled b.p. 81°C.

p-Chlorophenyl acetate.
Ice (44 g.) and acetic anhydride (8 ml.) were added to a solution of p-chlorophenol (8 g.) in 10% aqueous sodium hydroxide (40 ml.). The mixture was shaken for 5 minutes. Carbon tetrachloride (3 ml.) was added, the organic layer separated and washed with saturated aqueous bicarbonate and then water. The solution was distilled and the fraction boiling at 228-230°C collected.

Phenyl acetate.
This was prepared in a similar manner b.p. 192-194°C.

p-Cresyl acetate.
This was prepared in a similar manner b.p. 212-214°C.

n-Butyl acetate.
B.D.H. "Laboratory Reagent" was redistilled b.p. 126-127°C.

p-Chloro phenyl trifluoroacetate.
p-Chlorophenol (14 g.) and trifluoroacetic anhydride (30 g) were refluxed in the presence of a little sodium trifluoroacetate for ½ hour. Carbon tetrachloride (5 ml.) was added and the solution washed with saturated aqueous bicarbonate and then water. The solution was distilled and the fraction boiling at 181-182°C collected.
p-Cresyl trifluoroacetate.
This was prepared in a similar manner b.p. 169-170°C.
Phenyl trifluoroacetate.
This was prepared in a similar manner b.p. 147-148°C.
Pyridine.
B.D.H. "Laboratory Reagent" was refluxed over potassium hydroxide, distilled at 113-115°C and stored over "4A" molecular sieve.

The following substituted pyridines were purified in the same way.

2-Picoline.
Lights 2-picoline, fraction boiling at 128°C collected.

3-Picoline.
Aldrich 3-picoline, fraction boiling at 142°C collected.

4-Picoline.
Lights 4-picoline, fraction boiling at 143-144°C collected.

2,4-Lutidine.
Lights 2,4-lutidine fraction boiling at 157-158°C collected.

2,5-Lutidine.
Lights 2,5-lutidine fraction boiling at 156-7°C collected.

2,6-Lutidine.
Eastman 26-lutidine (300 g.) was warmed with urea (120 g.) and water (40 ml.) to 80°C. The white crystalline complex was filtered off and rapidly washed with water. The crystals were
distilled from water (200 ml.) and the 26-lutidine-water azeotrope collected at 96°C and dried over sodium hydroxide. This process was repeated. The 26-lutidine was then fractionally distilled and the fraction boiling at 143°C collected and stored over "4A" molecular sieve.

The purity was estimated by gas chromatography and there was less than 0.05% pyridine present.

2-Chloropyridine.

B.D.H. "Laboratory Reagent" was used directly.

3-Chloropyridine.

Aldrich 3-chloropyridine was used directly.

Quinoline.

B.D.H. "Laboratory Reagent" was distilled b.p. 237°C and stored over "4A" molecular sieve.

Acetonitrile.

Eastman's 'Spectrograde' acetonitrile was distilled from phosphorus pentoxide several times until the phosphorus pentoxide did not become coloured in its presence. The acetonitrile was then distilled from potassium carbonate and finally distilled above b.p. 81.5°C. The acetonitrile was stored over "4A" molecular sieve.

Dimethyl formamide.

B.D.H. "Laboratory Reagent" dimethyl formamide was distilled from calcium chloride b.p. 152°C and stored over "4A" molecular sieve.
Potassium bicarbonate solution.

Saturated aqueous potassium bicarbonate was made up from B.D.H. "AnalaR" potassium bicarbonate and distilled water.

B. The Reaction of acetic and trifluoroacetic anhydrides in carbon tetrachloride.

i) Infrared Spectra.

All spectra were recorded on a Unicam SP.100 infrared spectrophotometer. Matched 0.1 mm. and 1 mm. potassium bromide cells were used, one cell contained the solution to be examined and the reference cell contained carbon tetrachloride. Before use the cells were evacuated to 0.1 mm. mercury pressure in a vacuum desiccator containing phosphorus pentoxide to ensure dryness.

When used for kinetics the cell was placed in a jacketed cell holder, the temperature of which was maintained by the circulation through the jacket of water from a constant temperature water bath. A platinum resistance thermometer was attached to the cell and the temperature was continuously recorded on an Elliott 6 inch potentiometric chart recorder. The temperature of the cell remained constant to within 0.1°C once thermal equilibrium had been attained.

ii) Kinetic Experiments.

Solutions of acetic anhydride, trifluoroacetic anhydride, acetic acid and trifluoroacetic anhydride in carbon tetrachloride
were made up in a 'dry box' and used the same day. A solution containing equimolecular concentrations of acetic and trifluoroacetic anhydrides and the appropriate amount of acid was prepared and immediately transferred to cell. The cell was removed from the 'dry box' and placed in its jacket which was thermostated at 29.7 ± 0.1°C or 20.2 ± 0.1°C. The absorption of the solution of 661 cm⁻¹ was monitored against time until no further change occurred.

At any time the reaction mixture could contain acetic and trifluoroacetic anhydride, acetyl trifluoroacetate, acetic acid and trifluoroacetic acid. Hence, the infrared absorption spectra of these compounds were recorded (See Table 1). Of these compounds only trifluoroacetic anhydride exhibits absorption at 661 cm⁻¹. This absorption band was sharp and easily recognised.

The spectrometer was calibrated at 661 cm⁻¹ using solutions of trifluoroacetic anhydride in carbon tetrachloride. The concentrations of trifluoroacetic anhydride were found by quantitative hydrolysis followed by titration against N/10 sodium hydroxide using a phenolphthalein indicator. A satisfactory Beer's Law plot was obtained and so the absorption at 661 cm⁻¹ was subsequently used to estimate the concentration of trifluoroacetic anhydride present in the reaction mixture. Due to electronic variations in the SP.100 this instrument had to be calibrated afresh on each occasion that it was used.
A chart speed of $72 \pm 0.02$ cm. hour$^{-1}$ was used and measurement of chart length accurate to $\pm 0.02$ cm. enabled the time to be estimated to $\pm 0.01$ second.

It was found that the time required for the jacketed cell and its contents to reach the reaction temperature was 5 minutes and so all results obtained before the first 10 minutes were ignored.

It was shown that the infrared radiation had no anomalous effect on the reaction by performing two identical reactions except that in one case the reaction was exposed to continuous radiation while the other was only placed in the infrared beam for short periods during the reaction. Since no difference in these two reactions could be detected continuous recording was used for all subsequent experiments.

iii) Position of Equilibrium.

The absorption intensity of trifluoroacetic anhydride at 661 cm.$^{-1}$ was also used to estimate the position of the equilibrium

$$2 \text{ CH}_3 \text{CO.O.CO.CF}_3 \rightleftharpoons \text{ (CH}_3\text{CO)}_2\text{O} + (\text{CF}_3\text{CO})_2\text{O}$$

A solution of known concentration in acetyl trifluoroacetate was prepared and allowed to equilibrate for 7 days. Since the two symmetric anhydrides are present in equimolar proportions the equilibrium constant

$$K = \frac{[\text{CH}_3\text{CO.O.CO.CF}_3]^2}{[(\text{CH}_3\text{CO)}_2\text{O}]([\text{CF}_3\text{CO})_2\text{O}]}$$
may be derived. This procedure was repeated for several different initial concentrations of asymmetric anhydrides and a mean value obtained.

C. Reactions of acetic anhydride, trifluoroacetic anhydride, and acetyl trifluoroacetate with hydroxy compounds.

i) Infrared spectra.

All infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord with the slit override control set at 25°. Matched 1 mm and 5 mm sodium chloride cells, one containing the solution under examination and the other filled with solvent, were used.

ii) Kinetic Procedure.

Reactions were carried out at 0° ± 0.05°C and 25 ± 0.05°C. The temperature of 25°C was obtained by immersing the reaction flask in a thermostatically controlled water bath while 0°C was obtained by immersion in a Dewar vessel containing pure ice in equilibrium with distilled water.

A carbon tetrachloride solution of the hydroxy compound and the reaction flask containing the anhydride solution and any additive were placed in a constant temperature bath. It was found that the time required to reach the temperature of the bath was 15 minutes and so the solutions were left for 30 minutes. After this period the solution of the hydroxy compound was added to the reaction flask and the mixture thoroughly shaken.
2 ml. samples were removed at intervals and shaken with distilled water (20 ml.) to remove the anhydrides and so quench further reaction. In the case of alcohols and ortho substituted phenols (e.g. 2,6-dimethylphenol, o-nitrophenol), a saturated aqueous solution of potassium bicarbonate was used instead. The organic layer was separated, dried with magnesium sulphate, and the Infrared absorption spectrum in 1800-1600 cm$^{-1}$ region recorded in 1 mm. cells.

In the case of acetic anhydride 1 ml. samples were removed, mixed with 0.2M acetyl trifluoroacetate (4 ml.) and immediately shaken with saturated aqueous potassium bicarbonate. The organic layer was separated and treated as before. 5 mm. cells were used.

Short reactions were timed using a calibrated stop clock which was accurate to ± 0.5 seconds. For longer reactions an electric clock was used. Timing was started when half the hydroxy compound had been added to the reaction mixture and the time for the sample was taken as the time when half the solution had been added to the quenching solution.

iii) Analysis of Samples.

In the reaction of trifluoroacetic anhydride with hydroxy compounds a typical reaction sample could contain
unreacted anhydride, unreacted hydroxy compound, trifluoroacetic acid, trifluoroacetic ester and the pyridine base. Shaking with water rapidly hydrolyses the anhydride to the acid and this then goes into the aqueous layer. Shaking with water was found to be sufficient to remove all the anhydride and acid from the organic layer. The pyridine base, in the quantities used in the present work, did not show any absorption in the 1800-1600 cm$^{-1}$ region and in any case most of it was removed from the organic phase by the aqueous layer. Similarly the hydroxy compound did not absorb in this region so no attempt was made to remove it from the organic layer. The only absorption in the 1800-1600 cm$^{-1}$ region was due to the trifluoroacetate ester at 1800 cm$^{-1}$ and since Beer's Law was obeyed in the concentration range used this absorption was utilised to estimate the trifluoroacetate concentration.

A similar procedure was followed for acetyl trifluoroacetate reactions. In this case the reaction mixture contains unreacted acetyl trifluoroacetate, the two parent acids and the two esters in addition to the substances mentioned above. Shaking with water for 1 minute was found to be sufficient to remove all interference in the carbonyl region of the spectrum. This method was tested using gas liquid chromatography to measure the concentration of esters. This procedure obviates the necessity of shaking the sample prior to analysis.
Acetyl trifluoroacetate can bring about the formation of both the acetate and the trifluoroacetate esters. Most acetate esters absorb infrared light at about 1840 cm.$^{-1}$ while the trifluoroacetate absorption is at 1800 cm.$^{-1}$. Thus although the two peaks can be distinguished from one another, the absorption of one ester is slightly affected by the presence of the other. The Infracord was calibrated with the 2 esters in a 1:1 ratio and also with each ester in the absence of the other ester. A plot of transmission against molarity yielded a smooth curve from which the ester concentration was obtained.

The hydrolysis of acetic anhydride by water is slow and so water can not be used to remove it from the reaction mixture. Shaking with saturated aqueous bicarbonate solution brought about acetate formation with the unreacted hydroxy compound. However, it has been found that when acetyl trifluoroacetate and a phenol in carbon tetrachloride are shaken with saturated aqueous bicarbonate there is complete and rapid trifluoroacetate formation.$^{75}$ This was used to quench the reaction of acetic anhydride. Addition of the solution of phenol and acetic anhydride to a solution containing an excess of acetyl trifluoroacetate and immediate shaking with a saturated aqueous bicarbonate resulted in the conversion of all the unreacted phenol to the trifluoroacetate
ester and the organic layer showed no absorption in the carbonyl region apart from those of the 2 esters. This procedure was checked by gas liquid chromatography as before.

The Infracord was calibrated with one ester in the presence of the other, the total ester concentration being equal to that of the hydroxy compound used in the kinetic experiments. A smooth curve of transmission against molarity was obtained and was used to estimate the acetate concentration. The accuracy of this method varied from 16% at low ester concentration to 6% at high ester concentration for the concentration range used in the present work.19

All reactions with alcohols or orthosubstituted phenols were stopped by shaking with aqueous bicarbonate because in these cases bicarbonate does not cause ester formation.

iv) Preliminary Work.

In dilute solution phenols exist in the monomeric form but in more concentrated solutions dimers and higher polymers are formed. Maguire and West76 studied solutions of phenols in carbon tetrachloride and found that p-chlorophenol, phenol, and p-cresol obeyed Beer's Law up to concentrations of 0.05M at 0° from which it can be assumed that up to 0.05M the phenols exist as monomers in carbon tetrachloride. In the present work the phenol concentrations used were 0.01M or more dilute still so that dimers and higher forms could be neglected.
The following reactions were carried out to prove that any reaction taking place was due to reaction of the anhydride with the phenol and not due to side reactions:

1) \( p\)-Chlorophenol (0.01M) with acetic acid (0.1M);

2) \( p\)-chlorophenol (0.01M) with trifluoroacetic acid (0.1M);

3) \( p\)-chlorophenyl acetate (0.01M) with acetyl trifluoroacetate (0.1M);

4) \( p\)-chlorophenyl trifluoroacetate (0.01M) with acetyl trifluoroacetate (0.1M);

5) \( p\)-chlorophenyl acetate (0.01M) with trifluoroacetic anhydride (0.1M);

6) \( p\)-chlorophenyl trifluoroacetate (0.01M) with acetic anhydride (0.1M);

7) \( p\)-chlorophenyl acetate (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of pyridine (0.001M);

8) \( p\)-chlorophenyl acetate (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of pyridine (0.005M);

9) \( p\)-chlorophenyl trifluoroacetate (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of pyridine (0.001M);

10) \( p\)-chlorophenyl trifluoroacetate (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of pyridine (0.005M);
11) $p$-chlorophenyl acetate (0.01M) with pyridinium trifluoroacetate (saturated solution);

12) $p$-chlorophenyl acetate (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of pyridine (0.002M).

$p$-Chlorophenyl trifluoroacetate (0.01M) and acetic anhydride (0.1M) in the presence of pyridine (0.001M) was slowly converted into $p$-chlorophenyl acetate.

Several bases e.g. aniline, diethylamine, and benzylamine react with carbon tetrachloride to form the hydrochloride salt. The effect of carbon tetrachloride on the pyridine bases, acetonitrile and dimethyl formamide in the proportions used in the present work was checked. In all cases, except that of triethylene diamine, no reaction was observed. Triethylene diamine reacted with carbon tetrachloride forming a precipitate of triethylenediamine hydrochloride and so it was not used as a catalyst in the present work.
Section III.  

Results 

A. Reaction of acetic and trifluoroacetic anhydrides in carbon tetrachloride to form acetyl trifluoroacetate. 

i) Rate of formation of acetyl trifluoroacetate. 

Newly prepared 0.1 molar solutions of carefully purified acetic and trifluoroacetic anhydrides were mixed and the absorption at 661 cm\(^{-1}\) was monitored for several hours. During the first few minutes the anhydride absorption altered due to change in temperature, but once thermal equilibrium was reached there was no further change in the absorption. The spectrum in the carbonyl region (1900-1600 cm\(^{-1}\)) was obtained and found to be identical to a superimposition of the spectra of the starting materials. This indicates that equimolar mixtures of acetic and trifluoroacetic anhydrides in carbon tetrachloride do not react. Since mixing the two anhydrides in this solvent has been used as a method of preparation of acetyl trifluoroacetate\(^{59}\) reaction must be brought about by the presence of a small amount of impurity. When, instead of freshly prepared solutions of the anhydride, week old solutions were used a regular decrease in the trifluoroacetic anhydride absorption was observed. When no further change in the absorption occurred the infra-red spectrum from 1900-600 cm\(^{-1}\) was obtained. This showed that the absorption peaks for acetic and trifluoroacetic anhydrides
had almost disappeared and had been replaced by absorption peaks attributed to acetyl trifluoroacetate. Small peaks due to acetic and trifluoroacetic acids were also present. The spectra of the original solutions from which this mixture had been prepared were investigated and showed the presence of acids in the solutions.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Infrared absorption frequency (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic Anhydride</td>
<td>1825 1755 1365 1220 1120 990 -</td>
</tr>
<tr>
<td>Trifluoroacetic anhydride</td>
<td>1870 1800 1325 1240 1045 - 661</td>
</tr>
<tr>
<td>Acetyltrifluoroacetic anhydride</td>
<td>1860 1785 - 1230 1075 995 -</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>1715 1360 1290 - - -</td>
</tr>
<tr>
<td>Trifluoroacetic acid</td>
<td>1776 - 1285 - - 685</td>
</tr>
<tr>
<td>Nature of vibration</td>
<td>C=O C=O S(CX₃) - C⁻C C⁻C⁻0</td>
</tr>
</tbody>
</table>

From these results it was concluded that the reaction between the two symmetric anhydrides must be caused by the presence of either acetic or trifluoroacetic acid and so the effect of these acids on the reaction was investigated.

All subsequent anhydride solutions were first checked to see if any reaction occurred in the absence of added acid and if reaction took place the solutions were abandoned.
The reaction was carried out in the presence of a known concentration of acetic acid and the trifluoroacetic anhydride absorption of 661 cm$^{-1}$ continuously recorded. It was found that the trifluoroacetic anhydride concentration decreased linearly with time and the rate was independent of the anhydride concentration, i.e. the acetyl trifluoroacetate formation was zero order in the anhydrides. Since the rate was only time dependent a plot of $\log \frac{I}{I_0}$ (Beer's Law concentration) against time was a straight line. The gradient of this line was found, on multiplication by a proportionality factor, the zero order rate constant was obtained. This procedure was found to be more accurate than working out the concentration every 10 minutes, plotting a graph of concentration against time and then finding the zero order rate constant.

The fact that the reaction was zeroth order in the anhydrides was also verified by performing two reactions each having identical acetic acid concentrations but in one case the anhydride concentration was twice that of the other. The zero order rate constants so obtained were in agreement within the experimental error.
Table 2

Reaction of acetic and trifluoroacetic anhydrides in the presence of acetic acid (0.02M) at 19°C

<table>
<thead>
<tr>
<th>Initial anhydride molarity</th>
<th>Rate constant (mole·liter⁻¹·sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2M</td>
<td>8.0 × 10⁻⁶</td>
</tr>
<tr>
<td>0.1M</td>
<td>8.2 × 10⁻⁶</td>
</tr>
</tbody>
</table>

Results for a typical reaction are shown below and in figure 1.

Table 3

Reaction of 0.1M acetic and trifluoroacetic anhydrides in the presence of 0.05M acetic acid at 20.2°C

<table>
<thead>
<tr>
<th>log I/Io</th>
<th>Time (min.)</th>
<th>log I/Io</th>
<th>Time (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.74</td>
<td>0</td>
<td>0.4</td>
<td>120</td>
</tr>
<tr>
<td>0.69</td>
<td>10</td>
<td>0.375</td>
<td>130</td>
</tr>
<tr>
<td>0.67</td>
<td>20</td>
<td>0.35</td>
<td>140</td>
</tr>
<tr>
<td>0.65</td>
<td>30</td>
<td>0.33</td>
<td>150</td>
</tr>
<tr>
<td>0.62</td>
<td>40</td>
<td>0.3</td>
<td>160</td>
</tr>
<tr>
<td>0.59</td>
<td>50</td>
<td>0.28</td>
<td>170</td>
</tr>
<tr>
<td>0.56</td>
<td>60</td>
<td>0.265</td>
<td>180</td>
</tr>
<tr>
<td>0.53</td>
<td>70</td>
<td>0.25</td>
<td>190</td>
</tr>
<tr>
<td>0.51</td>
<td>80</td>
<td>0.235</td>
<td>200</td>
</tr>
<tr>
<td>0.48</td>
<td>90</td>
<td>0.22</td>
<td>210</td>
</tr>
<tr>
<td>0.46</td>
<td>100</td>
<td>0.21</td>
<td>220</td>
</tr>
<tr>
<td>0.43</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Zeroth order rate constant for above reaction = 19.7 × 10⁻⁶ moles·liter⁻¹·sec⁻¹.
Fig. 1. Reaction of acetic and trifluoroacetic anhydrides (0.1M) in the presence of acetic acid (0.05M) in carbon tetrachloride at 20.2°C.
Fig. 2. Reaction of acetic and trifluoroacetic anhydride (0.1M) in the presence of acetic acid (0.05M) in carbon tetrachloride at 20.2°C.
From Figure 1 it can be seen that most of the reaction was accurately zeroth order in the anhydride and that the concentration of the anhydride depended linearly on time. However, towards the end of the reaction, the rate of formation of acetyl trifluoroacetate decreased and reaction was no longer zeroth order. This change always took place when the trifluoroacetic anhydride concentration became equal to that of the added acid. In the reaction shown this change occurred after three hours, the acid and anhydride concentrations being 0.05M. After this the reaction became first order in the trifluoroacetic anhydride i.e. \( \log c \), where \( c \) is the concentration of trifluoroacetic anhydride, was proportional to the time. This is shown in Figure 2. Since in most reactions the acid concentrations used were small this first order reaction could only be followed in a few cases.

Reactions of acetic and trifluoroacetic anhydrides in the presence of various acetic acid concentrations were carried out and the results obtained are shown in Table 4.
Table 4

Reaction of 0.1M acetic and trifluoroacetic anhydrides in carbon tetrachloride in the presence of acetic acid

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Molarity of Acetic Acid</th>
<th>Zeroth order rate constant x 10^6 (moles litre^-1 sec.^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.2</td>
<td>0.01M</td>
<td>2.9</td>
</tr>
<tr>
<td>20.2</td>
<td>0.03M</td>
<td>12.7</td>
</tr>
<tr>
<td>20.2</td>
<td>0.04M</td>
<td>15.7</td>
</tr>
<tr>
<td>20.2</td>
<td>0.05M</td>
<td>19.4</td>
</tr>
<tr>
<td>29.7</td>
<td>0.0025M</td>
<td>1.7</td>
</tr>
<tr>
<td>29.7</td>
<td>0.005M</td>
<td>3.0</td>
</tr>
<tr>
<td>29.7</td>
<td>0.01M</td>
<td>6.0</td>
</tr>
<tr>
<td>29.7</td>
<td>0.02M</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Similar experiments were carried out using trifluoroacetic acid instead of acetic acid and similar features were observed. The results are shown in Table 5.

Table 5

Reaction of 0.1M acetic and trifluoroacetic anhydrides in the presence of trifluoroacetic acid in carbon tetrachloride solution

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Molarity of trifluoro-</th>
<th>Zeroth order rate constant x 10^6 (moles litre^-1 sec.^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.2</td>
<td>0.0095</td>
<td>3.7</td>
</tr>
<tr>
<td>20.2</td>
<td>0.038</td>
<td>14.9</td>
</tr>
<tr>
<td>20.2</td>
<td>0.057</td>
<td>22.5</td>
</tr>
<tr>
<td>29.7</td>
<td>0.005</td>
<td>3.7</td>
</tr>
<tr>
<td>29.7</td>
<td>0.01</td>
<td>6.4</td>
</tr>
<tr>
<td>29.7</td>
<td>0.02</td>
<td>12.8</td>
</tr>
</tbody>
</table>

A graph of rate of reaction against acid concentration is shown in Figures 3 and 4.
Fig. 3.

Reaction of acetic anhydride (0.1M) with trifluoroacetic anhydride (0.1M) in the presence of acid in carbon tetrachloride at 20.2°C.

- ○ acetic acid.
- x trifluoroacetic acid.
Fig 4.

Reaction of acetic anhydride (0.1 M) with trifluoroacetic anhydride (0.1 M) in the presence of acid at 29.7°C.

Ο acetic acid.
Χ trifluoroacetic acid.
From these graphs it can be seen that the rate of the reaction is directly proportional to the concentration of added acid. It does not appear to matter whether the acid used is acetic or trifluoroacetic acid as both acids catalyse the reaction to the same extent. In some cases the effect of trifluoroacetic acid was slightly greater than that of the acetic acid and the graph, instead of passing through the origin, was vertically displaced. The gradient, however, was unchanged. This was attributed to the hygroscopicity of the trifluoroacetic acid, any water present would hydrolyse the symmetric anhydrides and so the concentration of acid would be greater than that added.

The rate of reaction of trifluoroacetic anhydride and acetic acid was investigated and it was found that the equilibrium

\[
\text{CF}_3\text{CO}_2\text{O} + \text{CH}_3\text{COOH} \rightleftharpoons \text{CF}_3\text{COOH} + \text{CH}_3\text{CO}_2\text{OF}_3
\]

was established within a few minutes. However, the system acetic anhydride-trifluoroacetic acid required several hours before equilibrium was reached, the equilibrium mixture containing 40% acetyltrifluoroacetate and 60% acetic anhydride. These results are similar to those of Randles, Tatlow and Tedder who found that the reaction of trifluoroacetic anhydride and acetic acid was fast but acetic anhydride and trifluoroacetic acid took about 2 hours.
ii) Position of Equilibrium.

The position of the equilibrium

\[ 2 \text{CH}_3\text{CO.O.CO.CF}_3 \rightleftharpoons K \text{(CH}_3\text{CO)}_2\text{O} + \text{(CF}_3\text{CO)}_2\text{O} \]

was determined by mixing equimolar solutions of trifluoroacetic and acetic anhydrides and measuring the quantity of trifluoroacetic anhydride present in the equilibrium mixture. The results obtained are shown in Table 6.

<table>
<thead>
<tr>
<th>Original (CF_3CO)_2O concentration (moles litre^-1)</th>
<th>(CF_3CO)_2O concentration at equilibrium (moles litre^-1)</th>
<th>Equilibrium Constant at 21^\circ (moles litre^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2M</td>
<td>0.0128M</td>
<td>2.14 x 10^2</td>
</tr>
<tr>
<td>0.1M</td>
<td>0.006</td>
<td>2.44 x 10^2</td>
</tr>
<tr>
<td>0.04M</td>
<td>0.0024</td>
<td>2.43 x 10^2</td>
</tr>
<tr>
<td>0.02M</td>
<td>0.0013</td>
<td>2.07 x 10^2</td>
</tr>
</tbody>
</table>

Mean value of \[ K_{210} = (2.23 \pm .2) \times 10^2 \text{ moles litre}^{-1} \]

This shows that though the equilibrium greatly favours the formation of the unsymmetrical anhydride there is some symmetrical anhydride present and this could be of significance in the reactions of acetyl trifluoroacetate.

The position of equilibrium is hardly affected by the presence of small amounts of acetic or trifluoroacetic acid. This could be seen from the fact that, in the kinetic experiments the amount of trifluoroacetic
anhydride present in the equilibrium mixture was small. However, the exact position of the equilibrium was not investigated since the reactions of acetyl trifluoroacetate were carried out in the absence (as near as possible) of any acid.

The spectrum of acetyl trifluoroacetate was obtained at 10 and 50 fold dilution in carbon tetrachloride but no change in the absorption frequencies or in the intensity of the bands could be detected. This indicates that the acetyl trifluoroacetate is a definite compound and not a complex of the type shown below. 30

\[ \text{CF}_3 \quad C = \delta^+ \quad \cdots \cdots \quad O = \delta^- \quad \text{CH}_3 \]

since an oxygen bridged complex of this type would probably break down into the two symmetric anhydrides on dilution with carbon tetrachloride.
8. Reaction of hydroxy compounds with acetic anhydride in carbon tetrachloride.

i) Uncatalysed Reaction.

The reaction of \( p \)-chlorophenol (0.01M) and acetic anhydride (0.05M) was investigated and it was found that no reaction had occurred even after several weeks. This reaction was carried out at two temperatures 0\(^\circ\)C and 25\(^\circ\)C. It was also found that \( p \)-cresol, \( o \)-nitrophenol and salicylaldehyde, under similar conditions, did not react with the acetic anhydride.

Alcohols react with acetic anhydride under these conditions to form acetates. The reaction of iso-propanol was very slow and so it was not further investigated. \( n \)-Butanol reacted at a measurable rate and the reaction was accurately pseudo first order in \( n \)-butanol.

<table>
<thead>
<tr>
<th>Ac(_2)O molarity</th>
<th>First order rate constant ( \times 10^5 ) (sec(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05M</td>
<td>2.79</td>
</tr>
<tr>
<td>0.1M</td>
<td>4.72</td>
</tr>
</tbody>
</table>

ii) Base Catalysis.

The reaction of \( p \)-chlorophenol (0.01M) with acetic anhydride (0.05M) in the presence of pyridine in carbon tetrachloride was investigated. The presence of the pyridine in the reaction mixture brought about complete formation of \( p \)-chlorophenyl acetate from the \( p \)-chlorophenol.
The rate of formation of the acetate was approximately first order with respect to the $p$-chlorophenol but the rate of the reaction tended to decrease slightly as the reaction proceeded. This decrease was within the limits of the experimental error when low concentrations of pyridine were used and was only apparent at higher pyridine concentrations. In order to avoid errors due to this decrease a graph of $\log \frac{a}{a-x}$ where $a$ is the initial phenol concentration and $x$ is the ester concentration, was plotted and the rate constant at $\frac{a}{a-x} = 2$ was estimated. In this way the rate constant was always found at the same concentration of phenol, ester, acid and anhydride.

Reactions were followed between 20 and 80% reaction. A typical reaction is shown below.

**Reaction of $p$-chlorophenol (0.0096M) with acetic anhydride (0.05M) in the presence of pyridine (0.0395M) in carbon tetrachloride at 0°C.**

<table>
<thead>
<tr>
<th>Time (in sec)</th>
<th>Acetate molarity</th>
<th>Rate constant $x 10^2$ (sec$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,600</td>
<td>0.0026</td>
<td>3.42</td>
</tr>
<tr>
<td>16,380</td>
<td>0.00395</td>
<td>3.24</td>
</tr>
<tr>
<td>23,820</td>
<td>0.00485</td>
<td>2.996</td>
</tr>
<tr>
<td>31,020</td>
<td>0.0055</td>
<td>2.745</td>
</tr>
<tr>
<td>38,230</td>
<td>0.0066</td>
<td>3.04</td>
</tr>
<tr>
<td>43,200</td>
<td>0.00755</td>
<td>3.16</td>
</tr>
<tr>
<td>1 week</td>
<td>0.0096</td>
<td></td>
</tr>
</tbody>
</table>

Rate constant at 50% reaction $= (3.15^{±} .4)x 10^{-5}$ sec$^{-1}$

A summary of the results obtained for $p$-chlorophenol is shown in Table 6 and in graphical form in figure 5.
Fig 5. Reaction of \( p \)-chlorophenol with acetic anhydride in the presence of pyridine in carbon tetrachloride at 0°C.

First order rate constant \( \times 10^5 \) (sec\(^{-1}\)).

- Acetic anhydride (0.054 M)
- \( p \)-chlorophenol (0.0096 M)
- Acetic anhydride (0.025 M)
- \( p \)-chlorophenol (0.005 M)

Pyridine molarity.
<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>p-chlorophenol molarity</th>
<th>acetic anhydride molarity</th>
<th>pyridine molarity</th>
<th>Rate constant $x 10^5$ (sec. $^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°C</td>
<td>0.0096</td>
<td>0.054</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>2.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td>2.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
<td>3.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
<td>3.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0796</td>
<td>3.30</td>
</tr>
<tr>
<td>0°C</td>
<td>0.005</td>
<td>0.025</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.025</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>2.35</td>
</tr>
</tbody>
</table>

From this graph it can be seen that the addition of pyridine brings about acetate formation, the rate of formation depending on the pyridine concentration. After a certain concentration of pyridine was reached there was no further increase in rate when more pyridine was added. Further, from the results shown above, the rate stops increasing when the pyridine concentration is equal to that of the anhydride.
This suggests that there is complete reaction between the pyridine and acetic anhydride to form a complex which then reacts with the \( p \)-chlorophenol forming the acetate ester. To test this possibility two similar reactions were carried out except that in one case the reaction mixture contained 0.05M acetic anhydride, and in the other case only 0.025M acetic anhydride was present. If the reaction proceeded by the complete formation of the acetic anhydride-pyridine complex the rates of these two reactions would be the same. In practice the rates were different as shown below.

**Reaction of \( p \)-chlorophenol (0.005M) with acetic anhydride in the presence of pyridine (0.02M) at 0°C.**

<table>
<thead>
<tr>
<th>Acetic anhydride</th>
<th>Rate constant ( \times 10^5 ) (sec.(^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025M</td>
<td>1.8</td>
</tr>
<tr>
<td>0.05M</td>
<td>2.9</td>
</tr>
</tbody>
</table>

This implies that there is not complete formation of the complex. Further evidence against complete formation is the fact that the rate of the reaction does not increase linearly with pyridine concentration but is a curve. Therefore if the complex is formed it must be in equilibrium with the pyridine and acetic anhydride i.e.

\[
\text{Ac}_2\text{O} + \text{py} \leftrightarrow [\text{Ac}^+\text{py AcO}^-]
\]

The rates of reaction of \( p \)-chlorophenol (0.01M) with acetic anhydride (0.05M) in the presence of pyridine at 25°C were found and the results shown in Table 7 and figure 6.
Figure 6  Reaction of $p$-chlorophenol (0.01 M) with acetic anhydride (0.05 M) in the presence of pyridine at 25°C.
Table 7

Reaction of p-chlorophenol (0.01M) with acetic anhydride (0.05M) in the presence of pyridine at 25°C

<table>
<thead>
<tr>
<th>Pyridine molarity</th>
<th>Rate Constant x 10^5 (sec.^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.02</td>
<td>6.6</td>
</tr>
<tr>
<td>0.05</td>
<td>12.2</td>
</tr>
<tr>
<td>0.08</td>
<td>16.3</td>
</tr>
</tbody>
</table>

As would be expected the rate of the reaction at 25°C was higher than the corresponding rate at 0°C. However at 0°C increase in pyridine concentration above 0.05M had a negligible effect on the rate of the reaction but at 25°C the reaction rate continued increasing up to 0.08M pyridine. Further the temperature coefficient for 0.02M pyridine is \( \frac{6.6}{2.65} = 2.5 \). This is a very low ratio for a temperature increase of 25°C. Above 0.08M pyridine the reaction was not followed due to the possibility of acetate formation by the quenching procedure. This indicates that if reaction occurs through an acetic anhydride pyridine complex a decrease in temperature favours complex formation. Alternatively, reaction could occur through hydrogen bonding of the pyridine to the phenol and increase in temperature is known to decrease the proportion of hydrogen-bonded complex.

Pyridine was replaced by other pyridine bases and it was found that pyridines with methyl groups substituted in
the β and γ positions, i.e., β- and γ-picolines and lutidines, were more effective catalysts than pyridine. α-Picoline and 2,6-lutidine, however, did not have any catalytic effect on the reaction. Reaction in the presence of 3-chloropyridine was very slow.

The reaction was carried out in the presence of 0.02M pyridine and a similar reaction was carried out in the presence of 0.02M pyridine in addition to 0.025M 2,6-lutidine. The lutidine decreased the rate of the reaction.

Reaction of p-chlorophenol (0.01M) with acetic anhydride (0.05M) at 0°C.

<table>
<thead>
<tr>
<th>Pyridine molarity</th>
<th>2,6-Lutidine molarity</th>
<th>Rate Constant x 10^5 (sec.⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02M</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td>0.02M</td>
<td>0.025M</td>
<td>1.4</td>
</tr>
</tbody>
</table>

The reaction of p-chlorophenol was also carried out in the presence of either dimethylformamide or acetonitrile. These compounds are known to form hydrogen bonds with phenols. Neither of these compounds promoted the reaction of the phenol with the acetic anhydride. Dimethylformamide reduced the catalytic effect of pyridine in the same manner as 2,6-lutidine.

The effect of acetic acid on the catalysis by pyridine was investigated but no change in rate could be detected.
p-Cresol (0.01M) was treated with acetic anhydride (0.1M) in a carbon tetrachloride and, as in the case of p-chlorophenol, there was no reaction in the absence of pyridine but in the presence of pyridine complete acetylation occurred. The results are shown in Table 8 and figure 7.

**Table 8**

Reaction of p-cresol (0.01M) with acetic anhydride (0.05M) in the presence of pyridine at 0°C

<table>
<thead>
<tr>
<th>Pyridine molarity</th>
<th>Rate constant x 10⁵ (sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.01</td>
<td>0.45</td>
</tr>
<tr>
<td>0.02</td>
<td>0.7</td>
</tr>
<tr>
<td>0.05</td>
<td>1.2</td>
</tr>
<tr>
<td>0.08</td>
<td>1.6</td>
</tr>
</tbody>
</table>

From these results it can be seen that the reaction is much slower than the corresponding reaction of p-chlorophenol. Another difference between these two phenols is that, in the case of p-chlorophenol, the rate of the reaction does not increase above 0.05M pyridine, but the rate of reaction of p-cresol continues increasing within the range of pyridine concentrations studied.

Also investigated were o-nitrophenol and salicylaldehyde and these exhibited the same features as p-chlorophenol i.e. there was no reaction in the absence of pyridine and reaction,
Figure 7. Reaction of $p$-cresol (0.01M) with acetic anhydride (0.05M) in the presence of pyridine at 0°C.
though slow reaction took place in the presence of pyridine. As before, the presence of 2,6-lutidine reduced the catalytic effect of pyridine while acetic acid had no effect.

The effect of replacement of the hydrogen atom of the hydroxyl group of several phenols by deuterium was investigated. The experiments were performed using either 90% deuterated phenol or 80% deuterated \( p \)-chlorophenol. The rate constant for the reaction of undeuterated phenol under identical conditions was first found. This was then used to calculate the molarity of acetate which had been formed from the undeuterated phenol present and, by subtraction of this from the total acetate, the acetate formed from deuterated phenol was found. The rate constant was then calculated in the normal manner for first order reactions. The results are shown below.

<table>
<thead>
<tr>
<th>phenol</th>
<th>pyridine</th>
<th>Deuterium isotope effect ( \frac{K_H}{K_D} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenol (d)</td>
<td>0.01M</td>
<td>1.51</td>
</tr>
<tr>
<td>( p )-chlorophenol (d)</td>
<td>0.02M</td>
<td>1.40</td>
</tr>
</tbody>
</table>

The reaction of \( n \)-butanol (0.01M) with acetic anhydride was studied. As mentioned above complete acetylation occurs in the absence of pyridine. Pyridine exerts a slight catalytic effect and the rate in the presence of pyridine was accurately first order in the butanol. The results are shown in Table 9 and figure 8.
Figure 8: Reaction of o-butanol (0.01M) with acetic anhydride in the presence of pyridine at 25°C.

- ○ 0.05M acetic anhydride.
- ○ 0.1M acetic anhydride.
Table 9

Reaction of n-butanol (0.01M) with acetic anhydride at 25°C

<table>
<thead>
<tr>
<th>Acetic anhydride molarity</th>
<th>Pyridine molarity</th>
<th>Rate constant x 10^5 (sec.⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05M</td>
<td>0</td>
<td>2.79</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.02</td>
<td>3.22</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.04</td>
<td>3.72</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.06</td>
<td>4.16</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.08</td>
<td>4.58</td>
</tr>
<tr>
<td>0.1M</td>
<td>0</td>
<td>4.72</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.02</td>
<td>7.23</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.04</td>
<td>9.15</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.06</td>
<td>10.5</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.08</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Acetic acid and pyridine had a greater catalytic effect on the reaction than had pyridine alone and the rate was no longer first order in n-butanol. In the absence of pyridine acetic acid had no effect on the rate of reaction. Further, acetic acid and pyridine, in the absence of acetic anhydride did not bring about acetylation of n-butanol.
C. Reaction of hydroxy compounds with acetyl trifluoroacetate in carbon tetrachloride.

i) Uncatalysed Reaction.

The product from the reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in carbon tetrachloride was mainly the acetate ester but a small amount (3%) of p-chlorophenyl trifluoroacetate was detected. The presence of the trifluoroacetate ester was shown by both infrared spectroscopy (for this method the sample had to be washed with distilled water to remove the anhydrides and acids present) and vapour phase chromatography for which no treatment prior to analysis was required. Previous workers do not mention the trifluoroacetate formation.

The trifluoroacetate ester could have been formed by the acetyl trifluoroacetate (0.1M) or by the trifluoroacetic anhydride (0.006M) present in the equilibrium mixture (See Section III A). To decide which anhydride was responsible for the trifluoroacetylation the reaction was repeated except that in addition 0.006M trifluoroacetic anhydride was present. This trifluoroacetic anhydride would cause the equilibrium to shift towards the formation of more acetyltrifluoroacetate but, while the increase in acetyl trifluoroacetate would be negligible there would be an appreciable increase in the
trifluoroacetic anhydride present. Since the equilibrium constant was found to be $2.5 \times 10^{-4}$ moles litre$^{-1}$, addition of 0.006 M trifluoroacetic anhydride would cause the concentration of this anhydride to rise to 0.009 M in the equilibrium mixture. Consequently, if the trifluoroacylating agent is the trifluoroacetic anhydride, the proportion of trifluoroacetate ester in the product would increase but no change in ratio would be expected for reaction with acetyl trifluoroacetate. No change in the ester ratio was observed and hence it was concluded that the trifluoroacetate ester is formed from the unsymmetrical anhydride. Similarly, addition of acetic anhydride to the equilibrium mixture would reduce the concentration of trifluoroacetic anhydride and, if this brought about trifluoroacylation, the proportion of trifluoroacetate ester would decrease. In practice it was found that the addition of acetic anhydride slightly increased the concentration of trifluoroacetate so confirming the conclusion that acetyl trifluoroacetate brings about the formation of both esters.

The reaction of alcohols with the unsymmetrical anhydride was also investigated, and it was found that with $n$-butanol the product was entirely the trifluoroacetate ester but isopropanol yielded a mixture of the two esters. No kinetic experiments with these alcohols were performed.
ii) Base-Catalysed reaction.

The reaction of p-chlorophenol with acetyl trifluoroacetate was performed in the presence of small quantities of pyridine. The pyridine caused a change in the ratio of the esters formed. The results are shown in table 10 and figure 9. From the graph it can be seen that the presence of a small amount of pyridine brings about the formation of some p-chlorophenyl trifluoroacetate. The proportion of trifluoroacetate ester increased with increase in pyridine concentration until a maximum value was reached, further addition of pyridine beyond this point caused an increase in the acetate formation.

The effect of the related pyridine bases, α-picoline, 2,6-lutidine, quinoline and quinaldine, on the reaction with acetyl trifluoroacetate with p-chlorophenol was also investigated. Similar results were obtained with all these bases except that the concentration of the bases required to produce the same effect varied (See table 10). In the case of α-picoline and quinoline addition of base after the maximum concentration of trifluoroacetate had been reached did not cause a change in the ratio of the two esters.
Figure 9. Reaction of p-chlorophenol with acetyl trifluoroacetate in the presence of pyridine at 25°C.
Figure 10: Reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of bases at 25°C.

- 2-picoline
- 2,6-lutidine
- Dimethyl formamide
Table 10. Reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of various bases in carbon tetrachloride at 0°C.

<table>
<thead>
<tr>
<th></th>
<th>Base molarity</th>
<th>% trifluoroacetate</th>
<th>Base molarity</th>
<th>% trifluoroacetate</th>
<th>Base molarity</th>
<th>% trifluoroacetate</th>
<th>Base molarity</th>
<th>% trifluoroacetate</th>
<th>Base molarity</th>
<th>% trifluoroacetate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) Pyridine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0.00009</td>
<td>0.00045</td>
<td>0.0009</td>
<td>0.0013</td>
<td>0.0027</td>
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<tr>
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<td>3.85</td>
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<td></td>
<td>0.0036</td>
<td>0.0072</td>
<td>0.009*</td>
<td>0.0109</td>
<td>0.0125*</td>
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<tr>
<td></td>
<td>0.0074</td>
<td>0.0375</td>
<td>0.0741</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>b) α-picoline</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.00038</td>
<td>0.00076</td>
<td>0.00102</td>
<td>0.00152</td>
<td>0.00226</td>
<td>0.00375</td>
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<td>38.2</td>
<td>47.9</td>
<td>56.6</td>
<td>73.5</td>
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<tr>
<td></td>
<td>0.0074</td>
<td>0.0152</td>
<td>0.0375</td>
<td>0.0741</td>
<td></td>
<td></td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>c) 2,6-lutidine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>0.00148</td>
<td>0.0027</td>
<td>0.00296</td>
<td>0.0039</td>
<td>0.00494</td>
<td>0.0074</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>4.5</td>
<td>23.4</td>
<td>45</td>
<td>61.9</td>
<td>66.3</td>
<td>85.0</td>
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<td></td>
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<tr>
<td></td>
<td>0.0148</td>
<td>0.029+*</td>
<td>0.039+*</td>
<td>0.0494+*</td>
<td>0.074+*</td>
<td>0.148+*</td>
<td></td>
<td></td>
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<td></td>
<td>90.2</td>
<td>90.2</td>
<td>88.8</td>
<td>87.5</td>
<td>85.5</td>
<td>81.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>d) Quinoline</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.000186</td>
<td>0.000223</td>
<td>0.000371</td>
<td>0.000557</td>
<td>0.001150</td>
<td>0.00139</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>16.5</td>
<td>32</td>
<td>39.5</td>
<td>51</td>
<td>83</td>
<td>85.5</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.00223</td>
<td>0.0037</td>
<td>0.0112</td>
<td>0.013</td>
<td>0.1115+*</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
brought about the slow conversion of the trifluoroacetate to the acetate ester. However, the reaction of p-chlorophenol with acetyl trifluoroacetate in the presence of high pyridine concentrations was very fast (complete within 2 minutes) and the ratio of the two esters remained constant after this time. Further the equilibrium concentration of acetic anhydride in acetyl trifluoroacetate is only 0.006M so it is unlikely that the acetate was formed by the conversion of the trifluoroacetate to the acetate.

It was observed that when some bases were added to the acetyl trifluoroacetate a white precipitate was formed. In the case of pyridine and 2,6-lutidine this precipitate was isolated and investigated. The infrared spectra, in potassium bromide discs and in nujol mulls, were similar to those of pyridinium and lutidinium trifluoroacetate. Melting points and mixed melting points also indicated that the white precipitates were the pyridine and lutidine salts of trifluoroacetic acid.

Melting point of solid formed by acetyl trifluoroacetate and pyridine = 73°C (lit. m.p. for pyridinium trifluoroacetate = 78.5°C).

Melting point of solid formed from acetyl trifluoroacetate and 2,6-lutidine = 38°C.
Melting point for 2,6-lutidinium trifluoroacetate (formed from 2,6-lutidine and trifluoroacetic acid) = 38°C.

When these precipitates were present the proportion of acetate ester increased but when bases such as α-picoline and quinoline were used no precipitate was visible, and the product of the reaction was nearly 100% trifluoroacetate ester and this ratio was unaffected by addition of more base.

Pyridine was added to two similar samples of acetyl trifluoroacetate and a fine but uniformly distributed precipitate was formed. One sample was then allowed to react with p-chlorophenol while the other was left for several hours until the precipitate settled out leaving a clear supernatant solution, and then the reaction was performed. It was found that the reaction in which pyridinium trifluoroacetate was uniformly distributed yielded more acetate ester than the other reaction.

The effect of pyridine on the rate of acetylation (see fig.11) was small until a precipitate of pyridinium trifluoroacetate had been formed and then there was a rapid increase in the rate of acetylation. This indicates that heterogeneous catalysis, possibly on the surface of the trifluoroacetate salt, is responsible for the increase in the acetate formation.
b) Reaction at lower base concentrations.

At the lower base concentrations the addition of pyridine to the reaction mixture resulted in a change from acetate to trifluoroacetate ester formation. The reaction of $\mathbf{p}$-chlorophenol with trifluoroacetic anhydride in the presence of pyridine is very rapid, (see Section III D) and so it is possible that the $\mathbf{p}$-chlorophenol was reacting with the 0.006M trifluoroacetic anhydride present in equilibrium with the acetyl trifluoroacetate and so causing the change from the acetate to the trifluoroacetate ester. An additional 0.006M trifluoroacetic anhydride was mixed with the acetyl trifluoroacetate and pyridine and, as discussed before, this results in the trifluoroacetic anhydride concentration present in the equilibrium mixture being raised to 0.009M. Consequently if the trifluoroacetylation is due to the presence of trifluoroacetic anhydride and pyridine the ratio of trifluoroacetate to acetate would increase when the extra trifluoroacetic anhydride is present. However, no change in the ratio of products was obtained and so the trifluoroacylating agent must be the acetyl trifluoroacetate.

Another possibility is that the pyridine splits the acetyl-trifluoroacetate into the two symmetrical anhydrides and the trifluoroacetic anhydride so formed reacts with the $\mathbf{p}$-chlorophenol in the presence of pyridine, to produce the
trifluoroacetate ester. The infrared spectrum of acetyl trifluoroacetate was examined in the presence and absence of pyridine and no change in the spectrum was observed. This indicates that pyridine does not have any effect on the position of equilibrium and so the above explanation does not account for the change in product.

*p-Nitrophenyl acetate* and acetic anhydride, in the presence of pyridine, exchange acetate groups and so in the reaction under consideration the change from acetate to trifluoroacetate formation may be due to the initial formation of the acetate ester and subsequent exchange of acyl groups between this ester and the acetyl|trifluoroacetate or trifluoro-

acetic anhydride i.e.

\[
\text{Cl} \ \phi \ \text{COOCH}_3 + \text{CH}_3\text{CO}_2\text{O} \rightarrow \text{Cl} \ \phi \ \text{CO}_2\text{CF}_3 + (\text{CH}_3\text{CO})_2\text{O}.
\]

*p-Chlorophenylacetate* (0.01M) was treated with acetyl|trifluoroacetate (0.1M) and pyridine (0.001M to 0.01M). No trifluoroacetate was formed and the acetate concentration was unchanged. Therefore the trifluoroacetate formation is not due to exchange reactions by the acetate ester.

The kinetics of the reaction of *p*-chlorophenol with acetyl trifluoroacetate in the presence of pyridine in carbon tetrachloride were studied. A typical reaction is shown below. The method of calculation assumed that both the acetylation and
the trifluoroacetylation were first order in p-chlorophenol and since the rate constants calculated on this basis were constant throughout the reaction this assumption was justified.

Reaction of p-chlorophenol (0.01M) with acetyl|trifluoroacetate (0.1M) in the presence of pyridine (0.001M) at 0°C.

<table>
<thead>
<tr>
<th>Time (sec.)</th>
<th>486</th>
<th>2280</th>
<th>3040</th>
<th>4142</th>
<th>5905</th>
<th>7200</th>
<th>8250</th>
<th>10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetate</td>
<td>0.00095 0.00165 0.0024 0.00266 0.0028 0.0035 0.00395 0.00525</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trifluoroacetate</td>
<td>0.0013 0.0024 0.00295 0.00315 0.0035 0.00425 0.0044 0.00625</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of ester molarities</td>
<td>0.73 0.69 0.81 0.83 0.80 0.83 0.87 0.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First order rate constant (sec.−1)</td>
<td>1.73 1.69 1.81 1.76 1.8 1.83 1.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

First order rate constant (estimated by graphical method) = 1.8 x 10⁻⁴ sec.⁻¹.
First order rate constant for acetylation = 0.8 x 10⁻⁴ sec.⁻¹
First order rate constant for trifluoroacetylation = 1.0 x 10⁻⁴ sec.⁻¹

The effect of variation of the pyridine concentration is shown in Table 11 and Figure 11. As can be seen from fig. 11 the
Figure 11. Reaction of chlorophenol (0.01 M) with acetyl trifluoroacetate (0.1 M) in the presence of pyridine at 0°C.
Figure 12. Reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of bases at 0°C.

- x, 2,6-lutidine.
- O, pyridine.

First order rate constant \( \times 10^4 \):

\[ \text{[Pyridine]} \times 10^6 \]
rate of trifluoroacetylation increases rapidly with increase in pyridine concentration and if a graph of rate against $py^2$, where $py$ is the pyridine concentration, is plotted the points fall on or near a straight line, Fig. 12. The rate of acetylation, however, shows no such simple relation to the pyridine concentration. When the acetyl trifluoroacetate is 0.1M addition of pyridine causes an initial small decrease in the rate of acetylation and then the rate slowly increases. When pyridinium trifluoroacetate was precipitated from the solution there was a sudden large increase in the rate of acetylation suggesting that heterogeneous catalysis had occurred (this has already been discussed). However, when an acetyl trifluoroacetate concentration of 0.02M was utilised there was a slow, but steady, increase in the rate of acetylation.

The reaction of $\beta$-chlorophenol with acetyltrifluoroacetate in the presence of both acetic acid and pyridine was investigated and it was found that the rates and ratio of products was the same whether the acetic acid was present or absent. When the reaction was performed in the absence of pyridine the addition of acetic acid slightly decreased the rate of acetylation.
Table 11. Reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of pyridine at 0°C.

<table>
<thead>
<tr>
<th>Pyridine molarity x 10^{-4}</th>
<th>$k_{acetate} \times 10^4$ (sec^{-1})</th>
<th>$k_{trifluoroacetate} \times 10^5$ (sec^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.1</td>
<td>-</td>
</tr>
<tr>
<td>2.5</td>
<td>0.975</td>
<td>0.365</td>
</tr>
<tr>
<td>5</td>
<td>0.84</td>
<td>0.563</td>
</tr>
<tr>
<td>7.5</td>
<td>0.8</td>
<td>0.763</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>12.5</td>
<td>0.84</td>
<td>1.5</td>
</tr>
<tr>
<td>15</td>
<td>1.0</td>
<td>2.29</td>
</tr>
<tr>
<td>17.5</td>
<td>0.98</td>
<td>3.0</td>
</tr>
<tr>
<td>20</td>
<td>1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>30</td>
<td>-</td>
<td>8.7</td>
</tr>
<tr>
<td>50*</td>
<td>9</td>
<td>38.0</td>
</tr>
</tbody>
</table>

Reaction of p-chlorophenol (0.002M) with acetyl trifluoroacetate (0.02M) at 0°C

<table>
<thead>
<tr>
<th>Pyridine molarity x 10^{-4}</th>
<th>$k_{ac} \times 10^4$ (sec^{-1})</th>
<th>$k_{TFAc} \times 10^4$ (sec^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.08</td>
<td>-</td>
</tr>
<tr>
<td>4.99</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>19.9</td>
<td>-</td>
<td>1.0</td>
</tr>
<tr>
<td>39.8</td>
<td>0.57</td>
<td>1.75</td>
</tr>
<tr>
<td>99.5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>126.9*</td>
<td>59.0</td>
<td>12.6</td>
</tr>
<tr>
<td>149.2*</td>
<td>105.1</td>
<td>15.6</td>
</tr>
</tbody>
</table>
Table 11. (continued).

Reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of 2,6-lutidine at 0°C.

<table>
<thead>
<tr>
<th>2,6-lutidine molarity</th>
<th>$k_{ac} \times 10^4$ (sec.⁻¹)</th>
<th>$k_{TPAC} \times 10^4$ (sec.⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.1</td>
<td>-</td>
</tr>
<tr>
<td>0.00122</td>
<td>0.8</td>
<td>0.27</td>
</tr>
<tr>
<td>0.00245</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>0.00365</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>0.0048</td>
<td>-</td>
<td>3.0</td>
</tr>
<tr>
<td>0.0049</td>
<td>-</td>
<td>4.0</td>
</tr>
</tbody>
</table>

* white precipitate present.

Reaction of p-chlorophenol (0.01M) with acetyl trifluoroacetate (0.1M) in the presence of acetic acid at 25°C

<table>
<thead>
<tr>
<th>Acetic Acid molarity</th>
<th>First order rate constant for acetylation (sec.⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$3 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.05M</td>
<td>$2.5 \times 10^{-4}$</td>
</tr>
<tr>
<td>0.075M</td>
<td>$1.4 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

The effect of trifluoroacetic acid on the reaction of p-chlorophenol with acetyl trifluoroacetate was also studied. However, in this case, pyridinium trifluoroacetate formed and...
precipitated out of the solution so the rate of trifluoroacetylation was reduced.

Isopropanol reacts with acetyltrifluoroacetate yielding a mixture of the acetate and trifluoroacetate esters. The effect of pyridine on this system was investigated but no change in the ratio of the products or the rate of the reactions could be detected. Similar results were obtained with 4-chlorophenylmethyl carbinol.

D. Reaction of hydroxy compounds with trifluoroacetic anhydride in carbon tetrachloride.

i) Uncatalysed Reaction.

p-Chlorophenol (0.01M) was reacted with trifluoroacetic anhydride (0.1M) in carbon tetrachloride and the rate of the reaction was found to be first order in p-chlorophenol. However 4-chloro-2,6-dimethylphenol did not react with trifluoroacetic anhydride - presumably the steric effect of the two methyl groups was sufficient to prevent the approach to the anhydride molecule and so no reaction took place.

Alcohols react very rapidly with trifluoroacetic anhydride, the reactions of n-butanol (0.002M) and isopropanol (0.002M) with 0.02M anhydride being too fast for any measurements to be performed. In the case of 4-chlorophenylmethyl carbinol the reaction was slower and the rate constant could be calculated.
Reaction of hydroxy compounds with trifluoroacetic anhydride at 0°C

<table>
<thead>
<tr>
<th>Hydroxy Compound</th>
<th>Molarity of hydroxy compound</th>
<th>Molarity of (CF$_3$CO)$_2$O</th>
<th>First order rate constant (sec.$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-butanol</td>
<td>0.002M</td>
<td>0.02M</td>
<td>$&gt;10^{-2}$</td>
</tr>
<tr>
<td>iso propanol</td>
<td>&quot;</td>
<td>&quot;</td>
<td>$&gt;10^{-2}$</td>
</tr>
<tr>
<td>4-chlorophenyl methyl carbinol</td>
<td>0.01M</td>
<td>0.1M</td>
<td>103 x $10^{-4}$</td>
</tr>
<tr>
<td></td>
<td>0.002M</td>
<td>0.02M</td>
<td>$10 x 10^{-4}$</td>
</tr>
<tr>
<td>p-chlorophenol</td>
<td>0.01M</td>
<td>0.1M</td>
<td>$0.9 x 10^{-4}$</td>
</tr>
<tr>
<td>p-cresol</td>
<td>0.01M</td>
<td>0.1M</td>
<td>$4.5 x 10^{-4}$</td>
</tr>
<tr>
<td>4-chloro 2,6-dimethyl phenol</td>
<td>0.01M</td>
<td>0.1M</td>
<td>0</td>
</tr>
</tbody>
</table>

ii) Base-Catalysed Reaction.

The reaction of p-chlorophenol (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of pyridine in carbon tetrachloride was performed and it was found that the rate was approximately first order in p-chlorophenol. The variation of the first order rate constant with pyridine concentration is shown in Table 12 and Figure 13. As can be seen from Figure 12 the rate of the reaction appeared to be directly proportional to the pyridine concentration up to 0.0005M pyridine and above this value the rate was proportional to the square of the pyridine concentration (See Figure 14).
Figure 13: Reaction of p-chlorophenol (0.01 M) with acetyl trifluoroacetate (0.1 M) in the presence of bases at 0°C.

- x pyridine
- O 2,6-lutidine
- △ dimethyl formamide
Figure 11: Reaction of p-chlorophenol (0.01 M) with trifluoroacetic anhydride in the presence of various bases at 0°C.
Unfortunately the reaction could only be followed up to 0.001M pyridine, beyond this value the reaction was too fast for measurements to be made with any accuracy, and so no great reliance can be placed on this result.

The effect of 2,6-lutidine on the reaction of p-chlorophenol and trifluoroacetic anhydride was also investigated and it was found that the rate of the reaction was proportional to the square of the lutidine concentration over the entire range of concentrations studied. Similarly dimethylformamide increased the rate of the reaction and, although its catalytic effect was not nearly as great as that of pyridine, it could be studied over a wider range. Once again the rate of the reaction was proportional to (molarity)² of dimethylformamide. Acetonitrile, however, decreased the rate of the reaction.

Substituted pyridines were used as catalysts in the reaction and the rates of reaction for identical concentrations found. A Brönsted plot of log₁₀ rate against pKₐ of the base was obtained (Figure 15 and Table 13) and the results were similar to the results obtained by Feather and Gold. The 3- and 4-substituted pyridines and pyridine all lay on a straight line but 3-picoline and 2,6-lutidine fell below this line. 3-chloropyridine was exceptional since it has a
Figure 15. Reaction of p-chlorophenol (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of pyridine bases at 0°C.

1. pyridine.
2. 3-picoline.
3. 4-picoline.
4. 3,5-lutidine.
5. 2-picoline.
6. 2,6-lutidine.
7. 3-chloropyridine.
Table 12. Reaction of p-chlorophenol (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of various bases at 0°C.

<table>
<thead>
<tr>
<th>Base</th>
<th>Base molarity x $10^4$</th>
<th>First order rate constant x $10^4$ (sec.$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Pyridine</td>
<td>0.05 0.95 1.25 2.5 4.95 7.5 9.9</td>
<td>2.5 3.5 4.5 7.5 15 25 41</td>
</tr>
<tr>
<td>b) 2,6-lutidine</td>
<td>5.2 9.5 16.5 19.5 24.5</td>
<td>4 7.5 12.7 17 24</td>
</tr>
<tr>
<td>c) Dimethylformamide</td>
<td>30 50 100 300</td>
<td>8.3 14.7 36.4 300</td>
</tr>
<tr>
<td>d) Acetonitrile</td>
<td>0 1 200 400</td>
<td>0.9 0.7 0.01 0.09</td>
</tr>
</tbody>
</table>
Table 13. Reaction of \( p \)-chlorophenol (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of various bases (0.001M) at 0°C.

<table>
<thead>
<tr>
<th>Base</th>
<th>( \text{pK}_a )</th>
<th>First order rate constant ( \times 10^4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyridine</td>
<td>5.20</td>
<td>50</td>
</tr>
<tr>
<td>2-picoline</td>
<td>5.96</td>
<td>49.8</td>
</tr>
<tr>
<td>3-picoline</td>
<td>5.65</td>
<td>79.4</td>
</tr>
<tr>
<td>4-picoline</td>
<td>6.0</td>
<td>89.1</td>
</tr>
<tr>
<td>3,5-lutidine</td>
<td>6.15</td>
<td>100</td>
</tr>
<tr>
<td>2,6-lutidine</td>
<td>6.73</td>
<td>7.08</td>
</tr>
<tr>
<td>3-chloropyridine</td>
<td>2.85(^{85})</td>
<td>49.8</td>
</tr>
</tbody>
</table>

low \( \text{pK}_a \) value but a catalytic ability equal to that of pyridine.

The presence of \( p \)-chlorophenyl acetate (0.02M) in addition to pyridine caused an increase in the rate of the reaction. The catalytic effect of this ester was the same in the absence of pyridine.

Reaction of \( p \)-chlorophenol (0.01M) with trifluoroacetic anhydride (0.1M) at 0°C.

a) No pyridine present.

Rate of reaction is \( 0.9 \times 10^{-4} \text{ sec}^{-1} \)

Rate of reaction in the presence of p-chlorophenyl acetate = \( 1.30 \times 10^{-4} \text{ sec}^{-1} \)  

\( \text{ratio} = 1:1.45 \)
b) 0.00025M pyridine present.

Rate of reaction is $1.5 \times 10^{-5} \text{ sec.}^{-1}$

Rate of reaction in the presence of $p$-chlorophenyl acetate is $2.0 \times 10^{-5} \text{ sec.}^{-1}$

The ratio = $1:1.33$

The effect of pentachlorophenol on the reaction of $p$-chlorophenol and trifluoroacetic anhydride in the presence of pyridine was also investigated but no change in the rate of the reaction could be found. The reaction of pentachlorophenol with trifluoroacetic anhydride is very slow and so there is no pentachlorophenyl acetate formed during the time required for reaction of the $p$-chlorophenol.

The deuterium isotope effect on the reaction was investigated and was found to be 1.2 for phenol and 1.3 for $p$-chlorophenol at 0.001M pyridine.

When the reaction was carried out using $p$-cresol instead of $p$-chlorophenol it was found that, although the uncatalysed reaction was faster than that of $p$-chlorophenol, the catalytic effect of pyridine on the reaction was less. The ratio of the rates of reaction of $p$-cresol to $p$-chlorophenol are shown in Table 14 and Figure 16. Initially the rate of reaction of $p$-cresol is greater than that of $p$-chlorophenol but as the pyridine concentration is increased, the rate of reaction of $p$-cresol does not increase as much as that for $p$-chlorophenol.
Figure 16. Reaction of phenols (0.01 M) with trifluoroacetic anhydride (0.1 M) in the presence of pyridine at 0°C.
and so at about 0.000215M pyridine both rates are equal and at higher pyridine concentrations the rate of reaction of p-chlorophenol exceeds that of phenol. Eventually a pyridine concentration is reached such that both rates of reaction increase to a similar extent with increase in pyridine concentration and so the ratio of the rates becomes constant. Similar results were obtained when the catalyst was 2,6-lutidine except that in this case the rate of reaction of p-chlorophenol never exceeded that of p-cresol. These results were verified by gas liquid chromatographic analysis of the products of reaction of competitive reactions between p-chlorophenol and p-cresol with trifluoroacetic anhydride in the presence of pyridine.

Table 14. Reaction of phenols (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of pyridine at 0°C.

<table>
<thead>
<tr>
<th>Pyridine molarity x 10^4</th>
<th>0</th>
<th>1.25</th>
<th>2.5</th>
<th>5</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of rates (p-cresol/p-chlorophenol)</td>
<td>5</td>
<td>1.8</td>
<td>1</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>2,6-lutidine molarity</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Ratio of rates</td>
<td>5</td>
<td>1.22</td>
<td>1.02</td>
<td>1.02</td>
<td></td>
</tr>
</tbody>
</table>

4-chloro-2,6-dimethylphenol does not react with trifluoroacetic anhydride in the absence of pyridine and the
system was investigated. It was found that at low phenol and anhydride concentrations (0.002M phenol 0.02M anhydride) low concentrations of 2-chloropyridine brought about trifluoroacetylation but the reaction did not go to completion. If either the phenol or the anhydride concentration was increased the reaction went to completion. At higher 2-chloropyridine concentrations 100% reaction was obtained but the rate was not first order in the 4-chloro-2,6-dimethylphenol.

\[ \text{e.g. Reaction of 4-chloro-2,6-dimethylphenol (0.01M) with} \]
\[ \text{trifluoroacetic anhydride (0.1M) in the presence of} \]
\[ \text{pyridine (0.002M) at 0°C.} \]

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>670</th>
<th>1870</th>
<th>2480</th>
<th>4037</th>
<th>6720</th>
<th>9615</th>
<th>17460</th>
<th>29820</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated first order rate constant (sec.(^{-1}))</td>
<td>1.95, 1.32, 1.42, 1.05, 0.905, 0.751, 0.420, 0.420</td>
<td>(\times 10^{-4})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The effect of pyridine on the reaction of alcohols such as \(\text{n-butanol and isopropanol, with trifluoroacetic anhydride could not be studied but the reaction of 4-chlorophenylmethy} \]
carbinol was investigated.

Rate of reaction of 4-chlorophenyl methyl carbinol (0.002M) with trifluoroacetic anhydride (0.02M) at 0°C = \(10 \times 10^{-4}\) sec.\(^{-1}\).

Rate in the presence of 0.001M pyridine = \(12.5 \times 10^{-4}\) sec.\(^{-1}\).
This result should be compared with the results for p-chlorophenol (0.002M) for which the uncatalysed rate is $0.1 \times 10^{-4}$ sec.$^{-1}$ and the catalysed rate is $10 \times 10^{-4}$ sec.$^{-1}$).

The reaction of thiophenol with trifluoroacetic anhydride is accurately first order in the thiophenol in both the presence, and absence, of pyridine. Pyridine has a very small catalytic effect on this reaction.

**Reaction of thiophenol (0.01M) with trifluoroacetic anhydride (0.1M) in the presence of pyridine at 0°C.**

<table>
<thead>
<tr>
<th>Pyridine molarity</th>
<th>First order rate constant (sec.$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.6 $\times 10^{-5}$</td>
</tr>
<tr>
<td>0.001M</td>
<td>4.13 $\times 10^{-5}$</td>
</tr>
<tr>
<td>0.002M</td>
<td>4.6 $\times 10^{-5}$</td>
</tr>
</tbody>
</table>

iii) Reaction of pyridine with trifluoroacetic anhydride.

A large excess of trifluoroacetic anhydride was distilled onto a known quantity of pyridine on a vacuum line and the mixture was allowed to warm up to the melting point of the mixture. The excess of trifluoroacetic anhydride was then distilled off leaving a white solid. This solid was weighed and the amount of trifluoroacetic anhydride contained in it calculated.
No. of moles of pyridine = 0.8390
No. of moles of trifluoroacetic anhydride = 0.380
Ratio of pyridine to trifluoroacetic anhydride = 2.2:1.
\[\therefore\] complex is probably 2 moles of pyridine to 1 mole of trifluoroacetic anhydride.

Prolonged pumping caused the solid to decompose yielding trifluoroacetic anhydride and pyridine. If left at room temperature for any length of time blackening occurred. On exposure to the atmosphere pyridinium trifluoroacetate was formed.

The solid was dissolved in carbon tetrachloride and the yellow solution so obtained was investigated by both infrared and proton magnetic resonance spectroscopy but no peaks, other than those due to trifluoroacetic anhydride and pyridine could be found. If a concentrated solution was left for about 1 day a black precipitate formed. This behaviour is similar to that of the complex and so the complex probably exists in carbon tetrachloride solution.

A phase diagram for the system pyridine–trifluoroacetic anhydride was attempted but the complex was not sufficiently soluble in either pyridine or trifluoroacetic anhydride for any results to be obtained.
SECTION IV. DISCUSSION

A. Reaction of acetic anhydride and trifluoroacetic anhydride in carbon tetrachloride to form acetyl/trifluoroacetate.

It has been shown that acetic anhydride does not react with trifluoroacetic anhydride to form acetyl/trifluoroacetate unless catalytic quantities of either acetic or trifluoroacetic acid are present, both acids being equally effective. Acetic acid reacts rapidly with trifluoroacetic anhydride to form the unsymmetrical anhydride but the corresponding reaction between trifluoroacetic acid and acetic anhydride is relatively slow.

From these results it is clear that the formation of the mixed anhydride is due to reaction of the acid with the anhydride of the other acid. Consider the addition of a small quantity of acetic acid to a mixture of acetic and trifluoroacetic anhydrides. The acetic acid rapidly reacts with the trifluoroacetic anhydride forming acetyl/trifluoroacetate and trifluoroacetic acid. This trifluoroacetic acid slowly reacts with the acetic anhydride present once again forming acetyl/trifluoroacetate and acetic acid. Since the reaction between acetic acid and trifluoroacetic anhydride is very fast, the acetic acid will immediately be converted back into trifluoroacetic acid. Consequently this acid will be present throughout the reaction and its
concentration will always be equal to that of the added acid, irrespective of which acid was originally added. The rate controlling step will be the reaction of the acetic anhydride with the trifluoroacetic acid.

\[ \text{rate of formation of CH}_2\text{CO}_2\text{O} \cdot \text{COCF}_3 = \]
\[ k_2 \frac{[\text{CH}_3\text{COOH}]}{[\text{ATP}]} \]
\[ \text{rate of formation of ATP} = k_2 \frac{[\text{CF}_3\text{COOH}]}{[\text{CH}_2\text{COOH}]} \]

Since \([\text{CH}_3\text{COOH}] = 0\) this reduces to

Rate of formation of \(\text{ATF} = k_2[\text{CF}_3\text{COOH}][(\text{CH}_3\text{CO})_2\text{O}] - k_1[\text{ATP}] \]

However \(k_1\) is small since in equilibrium (2) 95% of the anhydride is present as \(\text{ATF}\)

\[ \text{rate of formation of \text{ATF} = k}_2[\text{CF}_3\text{COOH}][(\text{CH}_3\text{CO})_2\text{O}] \]

\[ = k_2C[(\text{CH}_3\text{CO})_2\text{O}] \text{ where } C \text{ is constant} \]

From this one would expect the rate of formation of acetyltrifluoroacetate to be first order in the anhydride.
In practice it was found that the rate of formation of acetyl trifluoroacetate was only first order in the trifluoroacetic anhydride when the anhydride concentration was less than that of the acid. When the acid concentration was less than that of the anhydride the reaction was zero order in the anhydride. This can be explained if it is assumed that acetic anhydride and trifluoroacetic acid rapidly and completely form a complex which then slowly forms acetyl trifluoroacetate. This means that the concentration of the complex will be equal to that of the anhydride when there is less anhydride than acid and so the reaction will be first order in the anhydride. And when there is more anhydride than acid present the rate will constant and depend only on the concentration of added acid.

Evidence for complex formation came from the work of Randles, Tatlow, and Tedder\textsuperscript{15} who found that when acetic anhydride and trifluoroacetic acid were mixed there was an immediate rise in conductivity and then the conductivity slowly decreased until after about 2 hours a constant value was obtained. This indicates that a complex is formed and that it has a greater conductivity than either the starting materials or the products. Bel'skii and Vinnik\textsuperscript{86} investigated
the conductivity and dielectric permeability of the system acetic acid-acetic anhydride. From this work it appeared that a complex of the formula \( \text{Ac}_2\text{O} (\text{AcOH})_2 \) was formed and these workers considered that the complex was either \([\text{CH}_3\text{CO}^+ (\text{AcOH})_2 \quad \text{COOH}_2]\) or \([\text{CH}_3\text{CO}_2\text{O} \quad \text{H}^+ \quad \text{AcOH}]\text{AcO}^-\).

Recent work on the acylation of phenols with acetyltrifluoroacetate and trifluoroacetic acid in carbon tetrachloride shows that the presence of trifluoroacetic acid does not bring about the formation of acetylium ion and so the complex observed by Bel'skii and Vinnik is probably of the form \([\text{CH}_3\text{CO}_2\text{OH}^+ \quad \text{AcOH}]\text{AcO}^-\).

By analogy acetic anhydride and trifluoroacetic acid could form a complex of the type shown below.

\[
\begin{align*}
(\text{CH}_3\text{CO})_2\text{O} + (\text{CF}_3\text{COOH})_2 &\rightarrow \begin{bmatrix}
\text{O} & \text{CH}_3 \\
\text{C} & \text{H} \\
\text{O} & \text{C} = \text{O} & \text{CF}_3 \\
\text{C} & \text{O} & \text{H} \\
\text{CH}_3 & & \\
\end{bmatrix} + \text{CF}_3\text{COOH} \quad \text{I}
\end{align*}
\]

\[
\begin{align*}
\rightarrow \text{CH}_3 & - \text{C}^0 \quad \text{C} - \text{CF}_3 \\
\text{0} & - \text{H} \cdots \text{O} \\
\end{align*}
\]

A similar complex to I is formed by trifluoroacetic anhydride and acetic acid but the electron withdrawing effect
of the trifluoromethyl group makes this complex more reactive than I and so the products are almost instantaneously formed.

As shown above the rate of formation of acetyl|trifluoroacetate depends only on the concentration of the acetic anhydride-trifluoroacetic acid complex i.e. Rate = k [complex] where k = velocity constant. When the anhydride concentration is greater than that of the acid the complex concentration is equal to that of the acid and so k can be found by dividing the zero order rate constant by the acid concentration.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Acid</th>
<th>Zero order rate constant</th>
<th>k x 10^4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x 10^5 (sec.(^{-1}))</td>
<td>(sec.(^{-1}))</td>
</tr>
<tr>
<td>20.2</td>
<td>0.01 M CH(_3)COOH</td>
<td>2.9</td>
<td>2.9</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.03 M &quot;</td>
<td>12.7</td>
<td>4.2</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.04 M &quot;</td>
<td>15.7</td>
<td>3.9</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.05 M &quot;</td>
<td>19.4</td>
<td>3.9</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.0095 M CF(_3)COOH</td>
<td>3.7</td>
<td>3.9</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.038 M &quot;</td>
<td>14.9</td>
<td>3.9</td>
</tr>
<tr>
<td>&quot;</td>
<td>0.057 M &quot;</td>
<td>22.5</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Mean value of \( k_{20°C} = (3.8 \pm .4) \times 10^{-4} \) sec.\(^{-1}\)

When the acid is present in greater concentration than the anhydride, [complex] is equal to [anhydride] and so k is the first order rate constant found in figure 3. The value
of $k$ found was $(4.1 \pm 0.4) \times 10^{-4}$ sec.\(^{-1}\) at 20.2\(^{\circ}\)C. This is in agreement with the value found in Table 15.

The rate at which the complex I decomposes giving acetyltrifluoroacetate was also found at 29.7\(^{\circ}\)C.

Table 16.

<table>
<thead>
<tr>
<th>Temperature ((^{\circ})C)</th>
<th>Acid</th>
<th>Zero order rate constant $\times 10^{-6}$ (mole$^{-1}$ litre$^{-1}$ sec.(^{-1}))</th>
<th>$k \times 10^4$ (sec.$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.7</td>
<td>0.0025M CH$_3$COOH</td>
<td>1.7</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>0.005M</td>
<td>3.0</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>0.01M</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>0.02M</td>
<td>12.3</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>0.005M CF$_3$COOH</td>
<td>3.6</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>0.01M</td>
<td>6.4</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>0.02M</td>
<td>12.8</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Mean value of $k_{29.7^{\circ}\text{C}} = (6.4 \pm 0.8) \times 10^{-4}$ sec.$^{-1}$

From these values of $k$ found at 29.7\(^{\circ}\)C and 20.2\(^{\circ}\)C the energy of activation was calculated. The value obtained was 10.4 \(\pm\) 3 kcal$\cdot$ mole$^{-1}$ however this value is not very accurate due to the fact that the rate constant was only obtained at two temperatures, and the two temperatures were not far apart.
B. Effect of pyridine catalysis on the acylation of hydroxy compounds by acetic anhydride in carbon tetrachloride.

The purpose of this part of the work was to determine the mechanism of the pyridine catalysis of esterification by acetic anhydride. This was discussed in the introduction and the suggested mechanisms were critically evaluated. The mechanisms for which there are no serious objections are:

a) Reaction of the pyridine with the phenol so enhancing the nucleophilicity of the phenol.

\[ \text{ROH} + \text{py} \rightleftharpoons \text{RO}^- + \text{Hpy} \]

b) Reaction of pyridine with acetic anhydride to form acetylium ions

\[ \text{CH}_3\text{CO.O.CO.CH}_3 + \text{py} \rightleftharpoons [\text{CH}_3\text{CO}^+\text{py}] + \text{CH}_3\text{COO}^- \]

The larger part of the published work was performed in the absence of solvent and since the present work was performed in carbon tetrachloride, the possibility of these two reactions occurring in this solvent will be considered. Cook's work on the complex "\text{CH}_3\text{COAlCl}_4" showed that in low dielectric solvents the complex exists entirely in the polarised form although in high dielectric solvents it also exists in the ionised form \( \text{CH}_3\text{CO}^+\text{AlCl}_4^- \). Gold postulated that the formation of the complex \( (\text{pyCH}_3\text{CO})^+\text{CH}_3\text{COO}^- \) to explain the
results obtained in the pyridine-catalysed decomposition of formic acetic anhydride in toluene but there was no evidence to show that the complex was in the ionic rather than the polarised form. The above evidence suggests that if a pyridine-acetic anhydride complex is formed in carbon tetrachloride it would be $\text{CH}_3\text{CO-OCOCH}_3$ rather than $\text{CH}_3\text{COO}^-$ $\py$. There is no physical evidence for complex formation in solution.

The interaction between phenols (and alcohols) and pyridine has been widely studied and there is an extensive literature on the position of the equilibrium, $K$. However, there is very little work on the structure of the complex formed by such a reaction. The system could be $\text{OH} + \py \rightleftharpoons \text{O-\cdots-H-\cdots-py}$ $\rightleftharpoons \text{O}^\cdots+\py^\text{H}$

Bell and Barrow investigated systems of this type and decided that the potential barrier to proton transfer in the case of alcohols was too great for an alcoholate ion to be formed. Therefore alcohols exist in the hydrogen-bonded form. These workers also studied the reaction of $p$-nitrophenol with triethylamine in chloroform and found that in this case proton transfer did occur.
Table 17. Hydrogen bonding between various donor and acceptor molecules in carbon tetrachloride

<table>
<thead>
<tr>
<th>Donor</th>
<th>Acceptor</th>
<th>$K_{association}$ (litres mole$^{-1}$)</th>
<th>$\Delta H$ (Kcal.mole$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$-chlorophenol</td>
<td>pyridine</td>
<td>126.210 88</td>
<td>-</td>
</tr>
<tr>
<td>$p$-cresol</td>
<td>pyridine</td>
<td>42.210 88</td>
<td>-</td>
</tr>
<tr>
<td>phenol</td>
<td>pyridine</td>
<td>59.200 89</td>
<td>-7.89, -6.5</td>
</tr>
<tr>
<td>phenol</td>
<td>2-picoline</td>
<td>74.7200 89</td>
<td>-6.989</td>
</tr>
<tr>
<td>phenol</td>
<td>2,6-lutidine</td>
<td>93.5200 89</td>
<td>-6.9 89</td>
</tr>
<tr>
<td>phenol</td>
<td>3-chloropyridine</td>
<td>14.7 94</td>
<td>-</td>
</tr>
<tr>
<td>phenol</td>
<td>quinoline</td>
<td>57.4200 89</td>
<td>-7.2 89</td>
</tr>
<tr>
<td>phenol</td>
<td>quinaldine</td>
<td>79.9200 89</td>
<td>-7.1 89</td>
</tr>
<tr>
<td>phenol</td>
<td>dimethylformamide</td>
<td>63.2250 90</td>
<td>-6.4 87, -6.1 90</td>
</tr>
<tr>
<td>phenol</td>
<td>acetonitrile</td>
<td>30.230 87</td>
<td>-4.2 87</td>
</tr>
<tr>
<td>$\alpha$-butanol</td>
<td>pyridine</td>
<td>2.32230 93</td>
<td>-3.2, -5</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>pyridine</td>
<td>5.24 94</td>
<td>-</td>
</tr>
<tr>
<td>pentachlorophenol</td>
<td>pyridine</td>
<td>111.4200 89</td>
<td>-5.8 89</td>
</tr>
<tr>
<td>thiophenol</td>
<td>pyridine</td>
<td>0.22 96</td>
<td>-2.4 96</td>
</tr>
<tr>
<td>acetic acid</td>
<td>pyridine</td>
<td>220.95</td>
<td>-</td>
</tr>
</tbody>
</table>
Similarly phenol and pyridine in chloroform showed proton transfer but in carbon tetrachloride, though there was no evidence, was just possible that proton transfer could occur. Therefore pyridine catalysis could be due to the formation of either $\text{O} \cdot \cdot \cdot \text{py}$ or $\text{O}^{-} \cdot \text{Hpy}$ in the case of phenols. However, the extent of hydrogen bonding and of phenate ion formation will both be dependent on the same factors i.e. the strength of the donor and acceptor molecules and the solvent and so initially both species will be considered together.

When $p$-chloro-phenol reacts with acetic anhydride the variation in the first order rate constant with pyridine concentration was found to be a smooth curve (Fig. 5). For a fixed acetic anhydride concentration there was a certain pyridine concentration above which further addition of pyridine caused no increase in the rate. Preliminary experiments indicated that if the catalysis was due to interaction with the acetic anhydride, there must be complete formation of a pyridine–acetic anhydride complex but when reactions with the same phenol and pyridine concentrations but different acetic anhydride concentrations were performed different rates were obtained so complete reaction between the pyridine and the acetic anhydride can be dismissed. If, however the complex exists in equilibrium with its
components it is difficult to explain why concentrations of pyridine above 0.05M do not cause any further increase in the rate of reaction of 0.05M acetic anhydride and 0.01M p-chlorophenol.

The variation in the first order rate constant must also be considered from the hydrogen-bonding point of view. When pyridine is added to a fixed concentration of p-chlorophenol it brings about the formation of the hydrogen-bonded complex and the concentration of complex increases with increasing pyridine concentration. This continues until the concentration of complex equals that of the phenol and after this no further complex can be formed and so the rate of reaction could not be increased by the addition of more pyridine. If a graph of hydrogen-bonded p-chlorophenol against pyridine molarity is plotted a smooth curve similar to Fig. 5 is obtained. Unfortunately, although the value of the association constant of p-chlorophenol with pyridine in carbon tetrachloride at 21°C has been determined, the value at 0°C is unknown. However a rough estimate at 0°C can be obtained by using the value at 21°C and the known enthalpy of hydrogen bonding between phenol and pyridine under similar conditions. (The values used were $K_{21°C} = 126^{38}$ litres mole$^{-1}$ and $ΔH^{38} = 7$ Kcals.mole$^{-1}$).
From this the value of the association constant at 0°C must be approximately 253 litres mole\(^{-1}\). Using this value it was calculated that at 0.01M \(p\)-chlorophenol and 0.05M pyridine 92% of the \(p\)-chlorophenol was hydrogen-bonded to the pyridine and at 0.005M \(p\)-chlorophenol and 0.03M pyridine about 95% of the \(p\)-chlorophenol is hydrogen bonded. Therefore increasing the pyridine concentrations above these values will not cause much increase in the rate of the reaction. This indicates that the pyridine catalysis is probably due to interaction of the pyridine with the phenol rather than with the anhydride.

The above work does not enable one to decide whether the species undergoing acetylation is the \(p\)-chlorophenate ion or the hydrogen-bonded complex. This is because the \(p\)-chlorophenate ion, if present, would have been formed from the hydrogen-bonded complex:

\[
\text{Cl} \underbrace{\text{O}}_{\text{H\cdots py}} \rightleftharpoons \text{Cl} \underbrace{\text{O}^-}_{\text{py}^+H}
\]

i.e. the concentration of \(p\)-chlorophenate ion is proportional to the concentration of hydrogen-bonded complex. Consequently as the concentration of hydrogen-bonded complex increases the concentration of the ion would increase until all the \(p\)-chlorophenol was hydrogen bonded and after this there would be no further increase in \(p\)-chlorophenate ion caused by increasing the pyridine concentration.
The effect of temperature on the rate of the reaction also supports the pyridine-phenol interaction theory. The rate of reaction of 0.01M \( p \)-chlorophenol with 0.05M acetic anhydride at 25\(^\circ\)C is greater than that at 0\(^\circ\)C but the rate is still increasing at 0.08M pyridine while at 0\(^\circ\)C the rate was constant above 0.05M pyridine. This is in accordance with the fact that the extent of hydrogen-bonding decreases with increase in temperature. However, this is not conclusive evidence in favour of hydrogen-bonding since increase in temperature could cause the decomposition of the acetic anhydride-pyridine complex into its components and so produce the same effect on the rate.

\( p \)-Cresol is more nucleophilic than \( p \)-chlorophenol and would be expected to react faster with an acylating agent than \( p \)-chlorophenol. However, the extent of hydrogen-bonding of \( p \)-cresol with pyridine is less than that for \( p \)-chlorophenol and the bonds formed are weaker. (Table 17). Therefore if pyridine catalysis is due to complex formation with acetic anhydride the reaction of \( p \)-cresol would be faster, or at least as fast as that of \( p \)-chlorophenol and the maximum rate would occur at the same pyridine concentration in both cases. Alternatively, if the catalysis is due to hydrogen bonding
the maximum rate would be reached at a higher pyridine concentration. In practice it was found that the reaction rate for p-cresol was less than that of p-chlorophenol at the same pyridine concentration and the rate of the reaction continued to increase within the range of pyridine concentrations studied (up to 0.08M pyridine). This is fairly strong evidence in favour of the pyridine-phenol interaction theory.

A similar situation arises in the case of n-butanol. This alcohol is far more nucleophilic than the phenols as shown by the fact that it is acetylated by acetic anhydride under conditions where phenols remain unchanged. However, the extent of hydrogen bonding of n-butanol with pyridine is nearly negligible in comparison with that of phenols (Table 17). Thus, if catalysis by pyridine is due to acetic anhydride-pyridine interaction, one would expect a considerable change in reaction rate on addition of pyridine while a hydrogen-bonding mechanism would cause very little change in the rate. As can be seen from Fig.8 the catalytic effect of pyridine on the reaction was very slight. These results seem to prove quite conclusively that pyridine catalysis is due to pyridine-hydroxy compound interaction.
When pyridine was replaced by \( \beta \)-or \( \gamma \) substituted pyridine the catalysis exhibited the same features as that of pyridine but when \( \alpha \)-picoline or 2,6-lutidine were used there was no catalysis at all. This lack of catalysis cannot be due to prevention of hydrogen bonding caused by steric hindrance at the ortho position as it has been shown that the hydrogen bonding between ortho-methyl substituted pyridines is more extensive than that with pyridine itself (Table 17). Similarly dimethylformamide, \( \beta \), triethyl phosphate, and acetonitrile are known to form hydrogen bonds with phenols (Table 17), but were unable to bring about acetylation of \( p \)-chlorophenol.

The reaction of \( p \)-chlorophenol with acetic anhydride was carried out in the presence of both pyridine (0.01M) and 2,6-lutidine (0.04M) and was found to be slower than the reaction in the presence of pyridine (0.01M) alone. Dimethyl formamide also reduced the rate of the reaction. This reduction in the rate could be due to the fact that the hydrogen-bonded complex does not form the \( p \)-chlorophenate ion.

\[
\text{Cl} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{CH}_3
\]

\[
\text{Cl} \quad \text{O}^- \quad \text{H}^+ \quad \text{N} \quad \text{CH}_3
\]
i.e. the above reaction cannot take place due to steric hindrance to proton transfer. Since some of the phenol is hydrogen bonded to the 2,6-lutidine the amount of phenol available to hydrogen-bond with the pyridine is reduced and so the rate of the reaction is reduced. However it seems unlikely that the presence of one ortho methyl group as in α-picoline could prevent the formation of a picolinium ion. Also the reaction of p-chlorophenol with trifluoroacetic anhydride is catalysed by α-picoline and 2,6-lutidine and the catalysis in this case is probably due to a pyridine-phenol interaction (this is discussed fully in Section IV C). Therefore the species undergoing acylation is probably not the p-chlorophenate ion.

The fact that 2,6-lutidine is unable to catalyse the reaction of p-chlorophenol with acetic anhydride is because the ortho-substituted methyl groups prevent the near approach of the anhydride to the hydrogen-bonded complex. This becomes clear using molecular models.
In the case of dimethyl formamide the lack of catalysis is also due to steric hindrance to the approaching acetic anhydride molecule. It has been shown by nuclear magnetic resonance spectroscopy that all the atoms except for the methyl protons in the dimethyl formamide molecule lie in one plane, and that hydrogen bonding occurs through the oxygen atom. Therefore one of the methyl groups will prevent the approach of the acetic anhydride.
A deuterium isotope effect $K_H/K_D$ of 1.5 and 1.4 has been found for the reactions of phenol(d) and $p$-chlorophenol(d) with acetic anhydride in the presence of pyridine. This effect is small (the largest effect for the hydroxyl group reaction is $11.5^{99}$) and suggests that there is no change in the hydrogen-oxygen bond in the rate controlling step of the reaction. This result is what would be expected for the mechanism,

$$\text{Ac}_2\text{O} + \text{py.} \rightarrow \text{pyAc}^+ + \text{AcO}^- \quad \text{slow}$$

$$\text{pyAc}^+ + \text{phenol} \rightarrow \text{phenyl acetate} + \text{py.} \quad \text{fast}$$

since the first step is the rate controlling step. However there is a great deal of other evidence against this mechanism and so it will not be considered further.

The deuterium isotope effect is difficult to explain on the basis of the hydrogen-bonding theory due to insufficient information on the hydrogen bonding of the phenol(d) with pyridine being available i.e. the strength and extent of bonding are unknown. However it has been found that the ratio of the association constants of phenol(d) and phenol with hexamethylbenzene is $1.36^{97}$, and so it seems possible that the phenol(d) is more extensively hydrogen bonded to pyridine than is phenol. This means that, had the extent of hydrogen bonding been the same in both cases, the deuterium isotope
The addition of acetic acid to a reaction of p-chlorophenol with acetic anhydride in the presence of pyridine had no effect on the rate of the reaction. The extent of hydrogen bonding between pyridine and acetic acid is much greater than that between pyridine and p-chlorophenol and so one would expect the addition of acetic acid to reduce the rate of the reaction. The effect of acetic acid on the reaction of n-butanol in the presence of pyridine is even more complicated since here acetic acid increases the rate.
of the reaction. Trifluoroacetic acid catalyses the acetylation of \( p \)-chlorophenol by acetyltribromoacetate\(^{19} \) and so acetic acid would probably catalyse the reaction of \( p \)-chlorophenol with acetic anhydride. Thus the effect of addition of acetic acid to the reaction of \( p \)-chlorophenol with acetic anhydride in the presence of pyridine is twofold. The acetic acid forms hydrogen bonds with the pyridine (\( K = 220 \)) and so reduces the amount of pyridine available for hydrogen bonding with the \( p \)-chlorophenol and so the rate of the reaction is decreased but at the same time the acetic acid exerts its own catalytic effect on the system. It is probable that, in the case of \( p \)-chlorophenol these two effects cancel out and so there is no overall change in the rate. In the case of \( n \)-butanol the catalysis by pyridine is negligible and so the presence of the acetic acid results in an increase in the rate of the reaction.

The acid catalysis of acylation is probably due to the formation of a complex of the type proposed in Section IV A which makes bond-breaking easier.

\[
\begin{align*}
\text{CH}_3 & \quad \text{O=O} \quad \text{O} \\
\text{O} & \quad \text{C} \quad \text{CH}_3 \\
\text{C} & \quad \text{O} \quad \text{H} \quad \text{O} \\
\text{CH}_3 &
\end{align*}
\]
C. Reaction of hydroxy compounds with trifluoroacetic anhydride in the presence of pyridine in carbon tetrachloride.

In the section on acetic anhydride it was concluded that pyridine reacts with phenols in carbon tetrachloride to form hydrogen bonded complexes,

\[
\text{OH} + \text{py} \rightleftharpoons \text{O} = \text{H} \cdots \text{py}
\]

and that the phenate ions are not formed under the conditions used for reaction. In the case of trifluoroacetic anhydride the conditions are the same as those used for acetic anhydride and so it will be assumed that phenate ions are not present.

It is more difficult to come to any conclusions as to the mechanism of pyridine catalysis in the case of trifluoroacetic anhydride than in the case of acetic anhydride. This is because the reactions are so fast that only a small range of pyridine concentrations can be studied.

There are several factors which make it seem likely that the pyridine catalysis occurs via hydrogen bonding to the hydroxy compound. The hydrogen bonding of thiophenol to pyridine is slight \((K = 0.22^{96} \text{ litres mole}^{-1})\) and so if the catalysis is due to the formation of a complex between the trifluoroacetic anhydride and pyridine there should be a
large increase in the rate of trifluoroacetylation of thiophenol. If, however, the catalysis is due to hydrogen bonding pyridine will not have much catalytic effect on the trifluoroacetylation. In practice it was found that there was very little increase in rate when pyridine was present.

As was discussed in Section 103, p-cresol is more nucleophilic than p-chlorophenol and so, in the absence of pyridine, it reacts with trifluoroacetic anhydride more rapidly than p-chlorophenol. If the catalysis is due to complex formation between the anhydride and the pyridine the reaction of p-cresol should always be greater than, or equal to that of p-chlorophenol. The two rates would be equal if the acylating agent is so reactive that the nature of the nucleophile becomes unimportant. If the catalysis is due to hydrogen bonding pyridine would be a much better catalyst for p-chlorophenol than for p-cresol.

Figure 16 shows that in the absence of pyridine the rate of reaction of p-cresol is greater than that for p-chlorophenol but as the pyridine concentration is increased the ratio of the rates decreases until eventually the rate of reaction of p-chlorophenol exceeds that of p-cresol. This indicates that the catalytic effect of pyridine is due to its hydrogen-bonding ability.
If hydrogen bonding is the mechanism of the pyridine catalysis the variation in the ratio of the rates of reaction of p-cresol to p-chlorophenol can be explained. Consider the case of p-cresol. At any pyridine concentration there are two species present which may be acylated, the hydrogen-bonded and the non-hydrogen-bonded phenol. These two species react at different rates.

Rate of trifluoroacetylation = \( k_e [\text{total p-cresol}] [\text{trifluoroacetic anhydride}] = k_1 [\text{free p-cresol}] [\text{trifluoroacetic anhydride}] + k_2 [\text{hydrogen-bonded p-cresol}] [\text{trifluoroacetic anhydride}] \)

where \( k_e \) = experimentally determined rate constant

\( k_1 \) = rate constant for non-hydrogen-bonded species

\( k_2 \) = rate constant for hydrogen-bonded species

\[ k_e [a_o] = k_1 [a] + k_2 [x] \]

\[ = k_1 [a] + k_2 [a] [p] \]

\[ \text{or } k_e = k_1 [\frac{a}{a_o}] + k_2 [\frac{a}{a_o}] [p] \]

Since pyridine concentration is small (< 10^{-3}) \( \frac{a}{a_o} \approx 1 \)

\[ k_e = k_1 + k_2 [p] \]

Similarly for p-chlorophenol \( k_e = k_1 + k_2 [p] \)
\[ \dot{\kappa}_e = \kappa_1 + \kappa_2 \kappa [P] \]
\[ \frac{\dot{\kappa}_e}{\kappa_1} = \frac{\kappa_1 - \kappa_2 \kappa [P]}{\kappa_1 + \kappa_2 \kappa [P]} \]

In the absence of pyridine this equation reduces to
\[ \frac{\dot{\kappa}_e}{\kappa_1} = \frac{\kappa_1}{\kappa_1} \]

The rate of reaction of the hydrogen-bonded species is much greater than that of the non-hydrogen-bonded species and so the rate of the reaction when pyridine is present will be almost entirely due to reaction with the hydrogen bonded species
\[ \frac{\dot{\kappa}_e}{\kappa_1} = \frac{\kappa_2 \kappa [P]}{\kappa_1 \kappa [P]} \]

In the competitive reaction between \( p \)-chlorophenol and \( p \)-cresol with trifluoroacetic anhydride and pyridine \([P] = [P^1]\) and the equation reduces to \[ \frac{\dot{\kappa}_e}{\kappa_1} = \frac{\kappa_2 \kappa}{\kappa_1 \kappa} \]

i.e. the ratio of rates is independent of the pyridine concentration and so increase in the pyridine concentration does not cause a change in the ratio.

The values of \( \kappa \) and \( \kappa_1 \) have been determined at 21°C and since the value of \( \Delta H \) for hydrogen bonding of phenol and pyridine is known an estimate of the value of \( \kappa \) and \( \kappa_1 \) can be obtained. The values calculated in this way are
\[ K = 93 \text{ litre mole}^{-1} \text{ and } K^1 = 253 \text{ litre mole}^{-1}. \]

\[ \frac{k}{k^1} \]

\[ \therefore \frac{k_2}{k^1_2} = \frac{0.7 \times 253}{93} = 1.93 \]

\( k_2/k_2^1 \) has also been calculated from the ratio of the rates of trifluoroacetylation of the two phenols when the reactions were carried out separately and a value of 2.5 was obtained. This means that the hydrogen-bonded p-cresol is more reactive than the non-hydrogen-bonded p-chlorophenol. p-Cresol itself is 5 times more reactive than the non-hydrogen-bonded form of p-chlorophenol. Thus, although hydrogen bonding increases the reactivity of p-chlorophenol more than that of p-cresol the hydrogen-bonded form of p-cresol remains more reactive than that of p-chlorophenol.

When the catalyst is 2,6-lutidine the constant ratio of rates is approximately unity. This indicates that the difference in the extent of hydrogen bonding is exactly cancelled out by the difference in reactivity. Unfortunately there is no data available on the strength or extent of hydrogen bonding of 2,6-lutidine with either p-cresol or p-chlorophenol.
Using the equation $k_2 \left[ a \right] + k_1 \left[ a \right] P = k_1 \left[ a \right] + k_2 \left[ a \right] P$ the value of $k_2$ can be calculated and is found to be $4.4 \times 10^{-2}$ sec$^{-1}$. This means that the rate constant for the hydrogen-bonded $p$-chlorophenol is $4.4 \times 10^{-2}$ sec$^{-1}$ and for the non-hydrogen-bonded species is $1 \times 10^{-4}$ sec$^{-1}$ i.e. the hydrogen bonding increases the reactivity approximately 440 times.

Since the addition of pyridine to the reactions of isopropylalcohol and thiophenol with trifluoroacetic anhydride has very little catalytic effect on the rate it does not appear that complex formation between the anhydride and pyridine is responsible for the catalysis in the case of $p$-chlorophenol. Also the effect of pyridine on a carbon tetrachloride solution of trifluoroacetic anhydride has been studied by both infrared and nuclear magnetic resonance spectroscopy and no evidence of complex formation in this solvent has been observed. From these results it was concluded that the pyridine catalysis must be due to its hydrogen-bonding ability.

The reaction of $p$-chlorophenol with trifluoroacetic anhydride was proportional to the pyridine concentration (see figure 13) at very low pyridine concentrations ($< 5 \times 10^{-4}$ M) but above this the rate of the reaction
appeared to be proportional to \([\text{pyridine}]^2\). This could be due to the formation of hydrogen-bonded complexes containing pyridine and phenol in a 2:1 ratio. Hydrogen bonding of this type has been observed for phenol and acetates. However Granstad has investigated the hydrogen bonding between pentachlorophenol and pyridine in carbon tetrachloride and obtained no evidence for 2:1 complexes. The explanation for the reaction being second order in the pyridine could be that very small quantities of the 2:1 complexes are present and so no direct evidence for their existence has been found but that they are very much more reactive than the 1:1 complexes. A more likely explanation is that 1:1 complexes are formed and these are then solvated by a second pyridine molecule and it is this entity which undergoes acylation.

The reaction of \(\text{p-}\)chlorophenol with trifluoroacetic anhydride is catalysed by the presence of \(\text{p-}\)chlorophenyl acetate and this catalysis persists even in the presence of pyridine. In this case there is no possibility of complex formation with the trifluoroacetic anhydride and so it seems very probable that catalysis is due to hydrogen-bond formation between this phenol and the acetate. The association constant for hydrogen bonding between \(\text{o-}\)cresol and phenyl acetate is 6.5 litre mole\(^{-1}\) and the hydrogen
bonding between \( p \)-chlorophenol and \( p \)-chlorophenyl acetate will be of the same order. Therefore the hydrogen bonding is much less than in the case of pyridine and \( p \)-chlorophenol and the catalysis is not as great as that of pyridine.

The fact that 3-chloropyridine catalyses the reaction of \( p \)-chlorophenol with trifluoroacetic anhydride to the same extent as pyridine does, cannot be explained. The hydrogen bonding of pyridine to phenol is much reduced by the substitution of a chloro group in the meta position of the pyridine (association constant for pyridine and phenol = 46.3, \(^8\) association constant for 3-chloropyridine and phenol = 14.7 \(^9\) litres mole\(^{-1}\)) and so catalysis due to hydrogen bonding should be much less than that for pyridine. 3-Chloropyridine is also very much less basic than pyridine (\( pK_a \) pyridine = 5.17, \(^9\)4 \( pK_a \) 3-chloropyridine 2.84 \(^9\)4) and so its ability to form a complex with trifluoroacetic anhydride would also be less than that of pyridine.

The extent of hydrogen bonding of pentachlorophenol to pyridine is approximately the same as that between pyridine and \( p \)-chlorophenol and so when the reaction of \( p \)-chlorophenol with trifluoroacetic anhydride is carried out in the presence of both pyridine and pentachlorophenol the pentachlorophenol
would reduce the amount of pyridine available for hydrogen bonding with the \( p \)-chlorophenol and so reduce the rate of the reaction. However, 0.01M pentachlorophenol did not cause any appreciable decrease in rate. This is presumably because pentachlorophenol is fairly acidic and may have exerted a catalytic effect on the reaction and so compensated for the reduction in hydrogen bonding.

4-Chloro-2,6-dimethyl phenol does not react with trifluoroacetic anhydride in the absence of pyridine. When 2-chloropyridine was used as a catalyst it was found that at low concentrations of phenol, catalyst, and trifluoroacetic anhydride the reaction did not go to completion although the reaction was irreversible. If, however the concentration of one of the three substances present was increased 100\% reaction was achieved. In this case hydrogen bonding between the phenol and 2-chloropyridine is small \( (K = 9 \text{ litre mole}^{-1}) \) and there are large groups attached to both the catalyst and the phenol which hinder reaction. Further work on this system is necessary before the fact that the reaction does not go to completion can be explained.

From the above discussion it is concluded that the pyridine catalysis of trifluoroacetylation by trifluoroacetic anhydride is due to the formation of hydrogen bonds between the pyridine and the phenol and not to complex formation between the anhydride and the pyridine.
D. Reaction of hydroxy compounds with acetyl trifluoroacetate in the presence of pyridine in carbon tetrachloride.

The reaction of an hydroxy compound with an anhydride can be written

\[
\begin{align*}
\text{H} & \quad \text{C} \quad \text{O} \\
\text{R} & \quad \text{O} \quad \text{C}^{\text{b}} \quad \text{C} \quad \text{R}_3
\end{align*}
\]

where arrow "a" represents the bond-forming process and arrow "b" the bond-breaking process. When the bond-forming process occurs energy is released and if this energy is sufficient to bring about the bond breaking process acylation of the hydroxy compound will take place. In the case of acetyl trifluoroacetate the carbonyl carbon atom adjacent to the trifluoromethyl group carries the greater positive charge and so more energy will be released during bond formation at this carbon atom than at the acetyl carbon atom. However the trifluoroacetate ion is a better leaving group than the acetate ion and so bond breaking at the trifluoromethyl carbonyl atom requires more energy than that at the methyl carbonyl atom.

When phenols react with acetyl/trifluoroacetate a small amount of trifluoroacetate is formed but 97% of the reaction product is the acetate ester. This indicates that although the energy released by bond formation at the trifluoromethyl
end is greater than that at the other end. The energy required for bond breaking at the acetyl end is so much less than that at the trifluoromethyl end that the overall energy barrier to acetate formation is less than that of trifluoroacetate. However, steric hindrance to trifluoroacetylation by the trifluoromethyl group also plays a part in determining the nature of the product since n-butanol reacts with acetyl trifluoroacetate forming only the trifluoroacetate ester but isopropanol forms a mixture of the two possible esters.

Similarly, although p-chlorophenol forms a small quantity of the trifluoroacetate ester, 4-chloro-2,6-dimethylphenol, a stronger nucleophile, does not form any trifluoroacetate ester at all.

If the reaction of p-chlorophenol with acetyl trifluoroacetate is carried out in the presence of pyridine ($\geq 10^{-3} M$) the proportion of trifluoroacetate in the final product is greatly increased and increases still further on addition of more pyridine. Above $3 \times 10^{-3} M$ pyridine the acetate production once again increases (see fig. 10). The explanation of the reaction above $3 \times 10^{-3} M$ pyridine was dealt with in Section III and will not be discussed here. Pyridine can bring about trifluoroacetate formation by increasing the nucleophilicity of the phenol, by the formation of hydrogen bonds, so enabling the phenol to overcome the steric effect.
of the trifluoromethyl group and making the energy released on bond formation greater than that required for bond fission. Alternatively the possibility of the pyridine reacting with the unsymmetrical anhydride to form a complex which brings about trifluoroacetylation should also be considered.

Isopropanol forms hydrogen bonds with pyridine to a much smaller extent than p-chlorophenol (association constant for isopropanol at 33°C = 1.3 litre mole⁻¹, association constant for p-chlorophenol at 21°C = 126 litre mole⁻¹) and therefore if the change in product is due to hydrogen bonding there should be little change in the ratio of esters formed by isopropanol. If, however, the trifluoroacetylation is due to complex formation between pyridine and the anhydride the amount of isopropyl trifluoroacetate would be expected to increase. By experiment it was found that pyridine had no effect on either the rate or the ratio of the esters formed by reaction of isopropanol with acetyl trifluoroacetate and so it appears that hydrogen bonding is responsible for the change to trifluoroacetylation. It was similarly concluded that hydrogen bonding was responsible for the catalytic ability of pyridine in the acylating reactions of acetic anhydride and acetyl trifluoroacetate.
The reaction of p-chlorophenol with acetyltrifluoroacetate was investigated in the presence of dimethyl formamide and various pyridine bases and all these substances brought about trifluoroacetylation in the same way as pyridine and to the same extent as would be expected from their hydrogen-bonding ability except for 2-picoline, 2,6-lutidine and dimethylformamide whose effects were less than anticipated. In section III it has been shown that in the 4-substituted pyridines and dimethyl formamide there is steric hindrance to the approach of the hydrogen-bonded phenol to the anhydride.

The rate of trifluoroacetylation of p-chlorophenol by acetyltrifluoroacetate in the presence of pyridine was approximately proportional to \([\text{pyridine}]^2\). A similar result was obtained using 2,6-lutidine and dimethylformamide. In the case of trifluoroacetic anhydride it was concluded that this was due to solvation of the hydrogen-bonded complex by a second pyridine molecule.

At 0.001M pyridine the rate of trifluoroacetylation of p-chlorophenol by trifluoroacetic anhydride is \(50 \times 10^{-4}\text{ sec.}^{-1}\) and by acetyl/trifluoroacetate is \(1 \times 10^{-4}\text{ sec.}^{-1}\). The concentration of hydrogen-bonded phenol will be the same in both cases and so the difference in the rate must be due to the difference in leaving groups. In trifluoroacetic
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THE INTERACTION OF ACETIC AND TRIFLUOROACETIC ANHYDRIDES IN CARBON TETRACHLORIDE

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Abstract—The reaction of acetic and trifluoroacetic anhydrides in carbon tetrachloride to form acetyl trifluoroacetate does not proceed at a measurable rate under anhydrous conditions. Small quantities of either acetic or trifluoroacetic acid catalyse the reaction equally effectively and with both a zeroth order kinetic rate law is found. An interpretation of these results is given.

The preparation of acetyl trifluoroacetate by distillation methods based on the reaction of acetic acid or anhydride with trifluoroacetic anhydride is unreliable. Wherever possible it is preferable to use equimolecular quantities of the simple anhydrides in situ and to follow the formation of the unsymmetrical anhydride by the changing IR absorption spectrum. The time required to reach equilibrium (corresponding to 95% reaction) is however unpredictable and in carbon tetrachloride has been found to vary from a few hours to several days. The presence of small catalytic quantities of acetic or trifluoroacetic acid has now been shown to be a time controlling factor for the reaction.

Solutions (0·10–0·20 M) of the simple anhydrides in dry carbon tetrachloride were mixed and introduced into a suitable cell in a 'drybox'. The cell was immediately transferred to an IR spectrometer set to a frequency of 661 cm⁻¹, at which a sharp band has been found characteristic of trifluoroacetic anhydride. No significant change in absorbance was observed over a period of some hours with the anhydrous solutions; the addition of either acetic or trifluoroacetic acid (0·005–0·05 M in the reaction solution) however resulted in a gradual decrease in absorbance at 661 cm⁻¹ recorded continuously as reaction proceeded.

Measurements of the absorbance of standard solutions of different known concentrations of trifluoroacetic anhydride in carbon tetrachloride at 661 cm⁻¹ showed a reasonably linear correspondence with concentration in accordance with Beer's law, which made possible the evaluation of rate constants from the absorption data on the reacting solutions. The rate of fall of concentration of trifluoroacetic anhydride in either acid-catalysed reaction consistently showed a zeroth order form. A typical plot is shown in Fig. 1. A straight line dependence of the zeroth order rate constant on the concentration of added carboxylic acid was found with closely similar gradients for the two acids (Fig. 2). The rate constants for a fixed concentration of added acid had the same value for either 0·1 M or 0·2 M initial anhydride

concentrations and the rate constants were also found to be closely similar for the same concentration of either acid (Table 1). The higher rate constants for trifluoroacetic acid catalysis at 190° compared with those at 20-2° are attributed to the considerable hygroscopicity of trifluoroacetic acid. Any water present in a particular specimen would be rapidly converted on mixing with the anhydrides into an additional amount of acid with a consequent enhanced catalytic effect. The rate of change of rate constant with concentration of added acid should however not be affected by the acid increment introduced by the water present. In accordance with this conclusion the gradients of the plots of the rate constant $k$ against molarity of initially added acid were found to be practically the same for the results at two temperatures.

Since acetyl trifluoroacetate is formed readily from either acetic acid and trifluoroacetic anhydride (2) or trifluoroacetic acid and acetic anhydride (3) in carbon tetrachloride, the rate at which these equilibria were established was measured approximately. Using 0.1–0.2 M concentrations of the reactants it was found that
The interaction of acetic and trifluoroacetic anhydrides in carbon tetrachloride

reaction (2) was too rapid for measurement while reaction (3) required 1–2 hr to attain equilibrium.

\[
\begin{align*}
(\text{CH}_3\text{CO})_2\text{O} + (\text{CF}_3\text{CO})_2\text{O} &= 2\text{CH}_3\text{COOCOCF}_3 \quad (1) \\
(\text{CF}_3\text{CO})_2\text{O} + \text{CH}_3\text{CO}_2\text{H} &= \text{CH}_3\text{COOCOCF}_3 + \text{CF}_3\text{CO}_2\text{H} \quad (2) \\
(\text{CH}_3\text{CO})_2\text{O} + \text{CF}_3\text{CO}_2\text{H} &= \text{CH}_3\text{COOCOCF}_3 + \text{CH}_3\text{CO}_2\text{H} \quad (3)
\end{align*}
\]

The formation of acetyl trifluoroacetate from the symmetrical anhydrides can therefore be interpreted in the following way: in catalysing reaction (1) either acid probably reacts with its appropriate anhydride to form the unsymmetrical anhydride and the other acid. The rate-limiting step will be reaction (3) and this could result in a zeroth order reaction if reaction (3) proceeds through a complex formed rapidly and completely by trifluoroacetic acid and acetic anhydride. Since the rapidity of reaction (2) ensures that the free acid present is always trifluoroacetic acid (even when the added catalyst is acetic acid), the amount of either anhydride undergoing change in unit time will be constant.

The formation of acetyl trifluoroacetate from the simple anhydrides accordingly proceeds by reactions (2) and (3) only and not by (1). In the absence of added acids reaction can presumably only occur by ingress of extraneous moisture. Hydrolysis of trifluoroacetic anhydride by water is extremely rapid and the trifluoroacetic acid formed would then initiate the cycle of alternating acid-anhydride reactions as described above.

The mechanism is one which probably operates in other similar equilibria involving acylating species.\(^5\)

\[^5\] D. P. N. Satchell, Quart. Rev. 17, 178 (1963).
EXPERIMENTAL

Materials. "AnalR" CCl₄ was dried by treatment with CaH₂ followed by passage through a molecular sieve column. Trifluoroacetic anhydride (b.p. 38-39°) was dried with P₂O₅ and distilled in a vacuum line as required. Trifluoroacetic acid (b.p. 72-74°) and "AnalR" acetic anhydride (b.p. 139-140°) were both redistilled. All solutions were made up in a dry box. The trifluoroacetic anhydride solution was stored at 0° over a drying agent.

IR absorption spectra. The two single anhydrides and acetyl trifluoroacetate have readily distinguishable absorption spectra. Very strong absorptions occur between 990 cm⁻¹ and 1900 cm⁻¹ and the six strongest absorptions for each anhydride (0-1 M to 0-2 M) in this range are set out in Table 2. Trifluoroacetic anhydride alone had a less intense but sharp and characteristic peak at 661 cm⁻¹ which was used for preparing a calibration curve of the variation of absorbance with concentration for this anhydride.

Table 2. Strongest absorptions in the range 990-1900 cm⁻¹ in CCl₄ solution

<table>
<thead>
<tr>
<th>Compound</th>
<th>Frequency (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃CO)₂O</td>
<td>1825² 1755² 1365² 1220² 1120² 990²</td>
</tr>
<tr>
<td>(CF₂CO)₂O</td>
<td>1870³ 1800³ 1240³ 1190³ 1045³</td>
</tr>
<tr>
<td>CH₃COOCOCF₃</td>
<td>1860³ 1785³ 1230³ 1180³ 1075³ 995³</td>
</tr>
</tbody>
</table>

The superscripts indicate the order of intensity of the absorbance for each anhydride.

Rate measurements. Mixtures of the reactants giving solutions always equimolecular in concentrations of the two anhydrides were prepared and transferred to a KBr cell (0.2 mm) in the dry box. The cell was transferred to the jacketed cell-holder in a SP 100 IR spectrometer set to a frequency of 661 cm⁻¹. Temp control was maintained by circulating water from a constant temp bath. The temp was continuously recorded by means of a Pt resistance thermometer and apart from the time required to attain thermal equilibrium (ca. 10 min) the temp remained constant to within 0.1°.

In the experiments in which an acid catalyst was present, the gradual decrease in absorbance at 661 cm⁻¹ was continuously recorded until no further change occurred. The same rate of change of absorbance at 661 cm⁻¹ was evident when measurements were made with brief exposure to the IR beam at 10 min intervals: this demonstrated that no initiation of reaction or rate variation occurred as a result of continuous exposure to the radiation.

The plot of absorbance at 661 cm⁻¹ against time showed a constant rate of disappearance of trifluoroacetic anhydride throughout the reaction (Fig. 1). Rate constants were evaluated from the gradients of these graphs and the calibration curve obtained for trifluoroacetic anhydride.

Acknowledgement—The Department of Scientific and Industrial Research is thanked for studentships (to E. G. G. and P. M.) and for a grant for the purchase of the SP 100 spectrometer.
BASE-CATALYSED ACYLATION OF PHENOLS IN CARBON TETRACHLORIDE

BY

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Acetylation of phenols by acetyl trifluoroacetate is superseded by more rapid trifluoroacetylation in the presence of low concentrations of pyridine bases.

The predominant formation of phenyl formate in the reaction of formic acid/acetic anhydride reaction mixture (F.A.M.) with phenol which has been recently reported \(^1\) is closely paralleled by the exclusive formation of the acetate ester in the acylation of phenols by acetyl trifluoroacetate (ATF) in carbon tetrachloride.\(^2,3\) Factors which may be significant in preventing the formation of the trifluoroacetate ester are (i) the nature of the leaving group \(^4\) (ii) the different steric environment at the two acylating centres of the unsymmetrical anhydride \(^5\) and (iii) the lower nucleophilicity of the hydroxyl oxygen atom in phenols compared with alcohols (which in general form both esters).

The importance of (i) is shown by the values of the rate constants of acylation of p-chlorophenol (PCP) in carbon tetrachloride by three different acid anhydrides (see Table 1). The similarity of rate constants for acylation by ATF (a) and trifluoroacetate anhydride (b) and the failure to obtain any detectable amount of ester with acetic anhydride (d) is characteristic of control of reaction rate by the leaving group which in both (a) and (b) is the trifluoroacetate anion. In (d) and in any trifluoroacylation in (a) the leaving group would be the less stable acetate ion.

\(^3\) T. G. Bonner and E. G. Gabb, Ibid. 1963, 3291.
Table I

Rates of acylation of \( p \)-chlorophenol (0.01 M) with acid anhydrides (0.1 M) in CCl\(_4\) at 0°.

<table>
<thead>
<tr>
<th>Anhydride</th>
<th>Pyridine (M)</th>
<th>Acetylation</th>
<th>Trifluoroacetylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) CH(_3)COOCOCF(_3)</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>(b) (CF(_3)CO)(_2)O</td>
<td>0</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>(c) (CF(_3)CO)(_2)O</td>
<td>0.001</td>
<td>—</td>
<td>48</td>
</tr>
<tr>
<td>(d) (CH(_3)CO)(_2)O (0.05 M)</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>(e) (CH(_3)CO)(_2)O</td>
<td>0.01</td>
<td>0.20</td>
<td>—</td>
</tr>
<tr>
<td>(f) (CH(_3)CO)(_2)O</td>
<td>[0.04 Lutidine]</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

The addition of pyridine, however, transforms the acylation of phenols by acetyl trifluoroacetate into a predominating trifluoroacetylation. The variation of product ratio of the two esters with concentration of added base is shown in Table II. The position of the maximum is dependent on the concentration ratio \([ATF]/[PCP]\) — at a ratio of molarity 0.10/0.01 it occurs at about 0.0035 \( M \) pyridine while at 0.02/0.01 it is at about 0.002 \( M \) pyridine. The subsequent reversion to increasing acetate formation beyond the maximum is complicated at the higher ATF concentration by the visible separation of a white solid, identified as pyridinium trifluoroacetate at pyridine concentrations just beyond the maximum.

The same type of variation in Table II has been obtained when pyridine is replaced by quinoline, 2-quinidine and lutidine. The first two bases were of similar efficacy to pyridine, while lutidine was only as effective as

Table II

Product ratio (moles trifluoroacetate/acetate) of esters formed by \( p \)-chlorophenol (0.0095 \( M \)) and acetyl trifluoroacetate (0.097 \( M \)) in carbon tetrachloride at 25° in the presence of pyridine.

<table>
<thead>
<tr>
<th>Pyridine (10(^{-4}) M)</th>
<th>Product ratio</th>
<th>Pyridine (10(^{-4}) M)</th>
<th>Product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>54 *</td>
<td>4.0</td>
</tr>
<tr>
<td>0.9</td>
<td>0.10</td>
<td>72 *</td>
<td>2.7</td>
</tr>
<tr>
<td>4.5</td>
<td>0.35</td>
<td>90 *</td>
<td>1.9</td>
</tr>
<tr>
<td>9</td>
<td>0.89</td>
<td>109 *</td>
<td>1.1</td>
</tr>
<tr>
<td>18</td>
<td>3.0</td>
<td>125 *</td>
<td>1.0</td>
</tr>
<tr>
<td>27</td>
<td>5.3</td>
<td>141 *</td>
<td>0.73</td>
</tr>
<tr>
<td>36</td>
<td>6.1</td>
<td>156 *</td>
<td>0.70</td>
</tr>
</tbody>
</table>

* White solid visibly present.
pyridine at about a ten fold higher concentration. This feature contrasts strongly with the complete absence of a catalytic effect by 2-methylsubsti­tuted pyridine bases both in the acetylation of water by acetic anhydride and in the acylation of p-chlorophenol in carbon tetrachloride by acetic anhydride [see Table I (d), (e), (f)].

The rate of disappearance of p-chlorophenol in the pyridine catalysed acylations of PCP was found to be first order in the phenol and the composite rate constant for acylation was evaluated. Assuming that the ester product ratio corresponded to the ratio of the individual rate constants for trifluoroacetylation ($k_f$) and acetylation ($k_a$), $k_f$ and $k_a$ could be obtained. Their variation with pyridine concentration is shown in Table III. Up to a concentration of 0.002 M pyridine $k_a$ remains virtually constant and equal to its value in the absence of pyridine while $k_f$ increases rapidly. Over the range of pyridine concentration to 0.003 M it is found that $k_f = \text{constant} \times [\text{pyridine}]^2$. This suggests that the active trifluoroacetylation species might be a pyridine solvated $N$-trifluoroacetylpyridinium ion.

Hydrogen bonding between the pyridine bases and PCP is evident from infrared spectrum studies but no indication has been obtained that this feature favours exclusive trifluoroacetylation with ATF. Infrared studies of mixtures of ATF and the pyridine bases in carbon tetrachloride have not yet revealed that detectable disproportionation of the mixed anhydride occurs although this does not exclude the possible formation of kinetically significant concentrations of trifluoroacetic anhydride which is a rapid acylating agent in the presence of pyridine [see Table I (c)].

### Table III

Rates of acetylation ($k_a$) and trifluoroacetylation ($k_f$) of p-chlorophenol (0.01 M) with acetyl trifluoroacetate (0.1 M) in carbon tetrachloride at 25°C in the presence of pyridine.

<table>
<thead>
<tr>
<th>Pyridine (10^-4 M)</th>
<th>10^3$k_a$ (sec^-1)</th>
<th>10^3$k_f$ (sec^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>2.5</td>
<td>9.75</td>
<td>3.65</td>
</tr>
<tr>
<td>5</td>
<td>8.4</td>
<td>5.63</td>
</tr>
<tr>
<td>7.5</td>
<td>8</td>
<td>7.63</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>10.5</td>
</tr>
<tr>
<td>12.5</td>
<td>8.4</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>22.9</td>
</tr>
<tr>
<td>17.5</td>
<td>9.8</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>—</td>
<td>87</td>
</tr>
<tr>
<td>50 *</td>
<td>90</td>
<td>380</td>
</tr>
</tbody>
</table>

* White solid visibly present.

Experimental

Kinetic analysis of the reaction mixture was similar to the method previously reported. Reactions were carried out at 0° ± .05°C. The ATF and pyridine solutions were made up in carbon tetrachloride, mixed together and left for 1-hour to equilibrate. The phenol solution was then added to initiate the reaction. Samples (ca. 2 ml.) were removed at fixed intervals and immediately shaken with water (ca. 20 ml). The organic layer was separated, dried with anhydrous magnesium sulphate and its infrared spectrum recorded in the carbonyl absorption region. The intensity of the carbonyl peak was noted and the corresponding concentration of ester read off from a calibration curve obtained from known concentrations of the ester.

Acylations with trifluoroacetic anhydride were similarly performed. In the case of acetic anhydride 1 ml samples were removed and immediately shaken with 4 ml ATF (.2 M) in carbon tetrachloride and saturated aqueous potassium hydrogen carbonate. This procedure ensured that any unreacted phenol was completely converted to its trifluoroacetate ester. The solution of the two esters was dried and analysed as above.

Acknowledgements

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