PROBLEM 1
Propose three fundamentally different mechanisms (other than variations of the same mechanism with different kinds of catalysis) for this reaction. How would (a) D labelling and (b) $^{18}$O labelling help to distinguish the mechanisms? What other experiments would you carry out to rule out some of these mechanisms?

Purpose of the problem
Investigating a reaction where there are several reasonable mechanisms.

Suggested solution
The reaction is an ester hydrolysis so the obvious mechanism is to attack the carbonyl group with hydroxide. Notice that we draw out each stage of the mechanism and do not use any summary or shorthand.

Mechanism 1: Normal ester hydrolysis

But the ester oxygen atom is attached to an aromatic ring with a para nitro group. Nucleophilic aromatic substitution would give the same product.

Mechanism 2: Nucleophilic aromatic substitution
Finally, the ester can be transformed into an enolate, using hydroxide as a base. Elimination gives a ketene that can be attacked by hydroxide as a nucleophile to give the product.

Mechanism 2: Enolate elimination to give a ketene

Mechanism 3 requires the exchange of at least one hydrogen atom with the solvent so, if D₂O were used as the solvent, or better deuterated starting material were used, the exchange of one whole deuterium atom would indicate mechanism 3 while no exchange, or only minor amounts from the inevitable enolization, would show mechanisms 1 or 2. In mechanisms 1 and 3, the added OH group ends up in in CO₂H but in mechanism 2 it ends up as the phenol. Using H₂¹⁸O as solvent, or better labelling the ester oxygen as ¹⁸O would separate mechanisms 1 and 3 from 2.

Other experiments we could do might include trying to trap the ketene intermediate in a [2 + 2] cycloaddition, studying the reaction by UV, hoping to see the release of p-nitrophenolate in mechanism 3, changing the structure of the starting material so that one or other of the mechanisms would be difficult, even measuring the effects of the substituent on the benzene ring on the rate, or looking for a deuterium isotope effect in the labelled lactone.
**PROBLEM 2**

Explain the stereochemistry and labelling pattern in this reaction.

![Reaction diagram]

**Purpose of the problem**

A combination of labelling and stereochemistry reveals the details of a surprisingly interesting rearrangement.

**Suggested solution**

The randomization of the label and the racemisation suggest that the carboxylate falls off the allyl cation and then comes back on again at either end. While they are detached the distinction between the two ends of both cation and anion disappears as they are delocalized.

The product is racemic because the two intermediates each have a plane of symmetry and are achiral. The retention of stereochemistry (formation of the *trans* product from *trans* starting material) could result from stereoselective recombination (the two faces of the allyl cation are not the same) or from the two ions sticking together as an ion pair so that the acetate slides across one face of the cation. An alternative [3,3] sigmatropic rearrangement would not randomize the labels in the same way.
PROBLEM 3

The Hammett $\rho$ value for migrating aryl groups in the acid-catalysed Beckmann rearrangement is $-2.0$. What does that tell us about the rate-determining step?

Purpose of the problem

The Hammett relationship gives an intimate picture of the Beckmann rearrangement.

Suggested solution

The normal mechanism for the Beckmann rearrangement (p. 958-960) involves protonation at OH and migration of the group *anti* to the N–O bond: in this case the substituted benzene ring.

If this mechanism is correct here, we should expect the migration itself to be the slow step. The first step is just a proton transfer to oxygen and must be fast. The steps after the migration involve attack of water on a carbocation and proton transfers to O and N and these must all be fast. The migration breaks a C–C bond, forms a C–N bond and creates an unstable cation. But does this agree with the evidence? Starting material and product in the migration step are cations so the transition state must be a cation too. Any contribution to cation stability made by the migrating group should help and we should therefore expect electron-donating groups to migrate faster. This is what we see:
a \( \rho \) value of \(-2.0\) shows a modest acceleration by electron-donating groups (p. 1041 ff.).

In the Beckmann rearrangement, the \textit{anti} group migrates but in other rearrangements the migrating group is chosen for a very different reason: it is normally the group that is best able to stabilize a positive charge and benzene rings can do this by \( \pi \) participation. This would be the participation mechanism:

\[
\begin{align*}
\text{Me} & \quad \text{N} & \quad \text{OH}_2 \\
\text{X} & \quad \text{N} & \quad \text{Me} \\
\end{align*}
\]

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

The Hammett \( \rho \) value of \(-2.0\) gives very definite evidence that participation does not occur. If it did the closure of the unstable three-membered ring would be the slow step and a positive charge would form on the benzene ring itself. This would give a much larger \( \rho \) value of something like \(-5.0\). One reason that participation does not occur is that the starting material is planar and the \( \pi \) orbitals in the benzene ring cannot point in the right direction to interact with the \( \sigma^* \) orbital of the N–O bond. They are orthogonal to it.

\section*{PROBLEM 4}

Between pH 2 and 7 the rate of hydrolysis of this ester is independent of pH. At pH 5 the rate is proportional to the concentration of acetate ion (\( \text{AcO}^- \)) in the buffer solution and the reaction goes twice as fast in H\(_2\)O as in D\(_2\)O. Suggest a mechanism for the pH-independent hydrolysis. Above pH 7 the rate increases with pH. What kind of change is this?

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{SEt} \\
\text{O} & \quad \text{NaOAc} \\
\text{H}_2\text{O} & \quad \text{F}_3\text{C} \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{EtSH} & \quad \text{H}_2\text{O} \\
\end{align*}
\]

\section*{Purpose of the problem}

Time for you to try your skill at interpreting pH-rate profiles.

\section*{Suggested solution}

The second part of the question is easily dealt with. In alkaline solution the rate of hydrolysis simply increases with pH and we have the normal
specific base-catalysed reaction in which hydroxide ion attacks the carbonyl group.

![Chemical structure](image)

But this is no ordinary ester. The leaving group is a thiol (pKₐ about 8) not the usual alcohol (pKₐ about 16) and so the thiolate anion is a much better leaving group than EtO⁻. Also the CF₃ group is very electron-withdrawing so nucleophilic attack on the carbonyl group will be unusually fast. This is why there is a region of pH-independent hydrolysis not found with EtOAc. You might have suggested that acetate is a nucleophile or a general base catalyst but the solvent deuterium isotope effect suggests that it is a general base. The change at pH 7 is a change of mechanism as the faster of two mechanisms applies—a sketch of the pH-rate profile will show you the upward curve.

![Chemical structure](image)

**PROBLEM 5**

In acid solution, the hydrolysis of this carbodiimide has a Hammett ρ value of −0.8. What mechanism might account for this?

![Chemical structure](image)

**Purpose of the problem**

Interpretation of a small Hammett ρ value.

**Suggested solution**

The most obvious explanation for a low Hammett ρ value, that the aromatic ring is too far away from the reaction, will not wash here as the aromatic rings are joined directly to the reacting nitrogen atoms of the carbodiimide. The reaction must surely start with the protonation of one of the nitrogens. This cannot be the slow step and it would in any case have a large negative ρ value. The small ρ value observed suggests
that the rate-determining step must have a large positive $\rho$ value that nearly cancels out the large negative value for the first step. Attack by water on the protonated carbodiimide looks about right.

The expected equilibrium Hammett $\rho$ value for the protonation would be about $-2.5$ to $-3$ so the kinetic Hammett $\rho$ value for the attack of water would have to be about $+2$ to give a net Hammett $\rho$ value of $-0.8$. This looks fine. The rest of the mechanism involves proton transfers, hydrolysis of an imide, and decarboxylation.

**PROBLEM 6**

Explain the difference between these Hammett $\rho$ values by mechanisms for the two reactions. In both cases the ring marked with the substituent X is varied. When $R = H$, $\rho = -0.3$ but when $R = Ph$, $\rho = -5.1$.

**Purpose of the problem**

Interpretation of a variation in Hammett $\rho$ value with another structural variation.

**Suggested solution**

The reaction is obviously nucleophilic substitution at the benzylic centre so we are immediately expecting $S_N1$ or $S_N2$. When $R = H$, the reaction occurs at a primary alkyl group and $S_N2$ is expected. When $R = Ph$, the reaction occurs at a secondary benzylic centre and $S_N1$ is expected.
Since $S_N1$ produces a cation delocalized round the benzene ring in the slow step, a large negative Hammett $\rho$ value is reasonable. It is not obvious what sign the Hammett $\rho$ value would have in the $S_N2$ reaction but as there is no build-up of negative charge on the carbon atom in the transition state, a small value is reasonable. The actual value ($-0.3$) is very small indeed but, if we can read anything into it, it suggests a loose $S_N2$ transition state with a small positive charge on carbon.

**PROBLEM 7**

Explain how chloride catalyses this reaction.

**Purpose of the problem**

An extreme example of surprising catalysis.

**Suggested solution**

At first you might ask how chloride can catalyse anything at all. It is a weak base and not a very good nucleophile for the carbonyl group. However, in polar aprotic solvents like acetonitrile (MeCN), chloride is not solvated and is both more basic and more nucleophilic. In this reaction it cannot be a nucleophilic catalyst as attack on the carbonyl
group simply regenerates starting material. It cannot be a specific base as it is too weak, even in acetonitrile, to remove a proton from methanol. But it can act as a general base. As methanol attacks the carbonyl group its proton becomes more acidic and, in the transition state, chloride is at last able to act.

\[
\begin{align*}
\text{O}_2N &\quad \text{O}_2N \\
\text{Cl} &\quad \text{Cl} \\
\text{Me} &\quad \text{Me} \\
\text{O} &\quad \text{O} \\
\text{H} &\quad \text{H} \\
\text{Cl} &\quad \text{Cl} \\
\text{OMe} &\quad \text{OMe} \\
\end{align*}
\]

**PROBLEM 8**

The hydrolysis of this oxaziridine in 0.1M sulfuric acid has \(k(H_2O)/k(D_2O) = 0.7\) and an entropy of activation of \(\Delta S = -76 \text{ J mol}^{-1}\text{K}^{-1}\). Suggest a mechanism.

\[
\begin{align*}
\text{Ph} &\xrightarrow{\text{H}^+} \text{H}_2\text{O} \quad \text{PhCHO} + \text{t-BuNHOH}
\end{align*}
\]

**Purpose of the problem**

Deducing a mechanism from isotope effects and entropy of activation.

**Suggested solution**

The inverse solvent deuterium isotope effect indicates specific acid catalysis and the modest negative entropy of activation suggests some bimolecular involvement. There are various mechanisms you might have proposed and a likely one involves cleavage of the three-membered ring in the protonated amine. The second or possibly the third step could be rate-determining.

\[
\begin{align*}
\text{Ph} &\xrightarrow{\text{fast}} \text{H}_2\text{O} \quad \text{Ph}\text{CHO} + \text{t-BuNHOH}
\end{align*}
\]

Once the three-membered ring is opened, the rest of the mechanism amounts to acid-catalysed hemiacetal hydrolysis. The original workers
favoured an alternative mechanism that starts with protonation of the oxygen atom and ends up with the hydrolysis of an imine. Again, the second or third step could be rate-determining.

PROBLEM 9
Explain how both methyl groups in the product of this reaction come to be labelled. If the starting material is reisolated at 50% reaction, its methyl group is also labelled.

Purpose of the problem
Exploring a mechanism through labelling.

Suggested solution
The role of silver ion (Ag⁺) is the removal of the halide to give an acylium ion that reacts, not at the carbonyl group, but at the methyl group to give CO₂ and a methylated benzene ring. The simple Friedel-Crafts route cannot be the whole story: it explains how the added methyl group is labelled, but not why it is only partly labelled and how label gets into the other methyl group.

The only way in which we can explain those extra features is to suggest that methylation initially occurs on the oxygen atom and that a
methyl group is transferred from there to the benzene ring. We should never have detected this detail without the labelling experiment. Alkylation on oxygen provides an alkylation agent that can transfer either CH₃ or CD₃ and also explains the formation of trideuterotoluene.

PROBLEM 10
The pKa values of some protonated pyridines are as follows:

<table>
<thead>
<tr>
<th>X</th>
<th>H</th>
<th>3-Cl</th>
<th>3-Me</th>
<th>4-Me</th>
<th>3-MeO</th>
<th>4-MeO</th>
<th>3-NO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKₐ</td>
<td>5.2</td>
<td>2.84</td>
<td>5.68</td>
<td>6.02</td>
<td>4.88</td>
<td>6.62</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Can the Hammett correlation be applied to pyridines using the σ values for benzene? What equilibrium ρ value does it give and how do you interpret it? Why are no 2-substituted pyridines included in the list?

Purpose of the problem
Making sure you understand the ideas behind the Hammett relationship.

Suggested solution
The obvious thing to do is to plot the pKₐ values against the σ values for the substituents using the meta values for the 3-substituted and para values for the 4-substituted compounds (see table on p. 1042 of the textbook). This gives quite a good straight line and we get a slope (Hammett ρ value) of +5.9. The sign is of course positive as the same electronic effects that make benzoic acids more acidic will also make pyridinium ions more acidic. The large ρ value may have surprised you, but reflect: ionization of benzoic acids occurs outside the ring and the charge isn’t deocalized round the ring. Deprotonation of pyridinium
ions occurs on the ring and the charge (positive this time) is delocalized round the ring.

\[
\text{X} \quad \text{OH} \quad \leftrightarrow \quad \text{X} \quad \text{O}^{-}\n\]

There are no 2-substituted pyridines on the list since, like ortho-substituted benzenes, they cannot be expected to give a good correlation because of steric effects.

**PROBLEM 11**

These two reactions of diazo compounds with carboxylic acids give gaseous nitrogen and esters as products. In both cases the rate of reaction is proportional to [diazo compound][RCO₂H]. Use the data for each reaction to suggest mechanisms and comment on the difference between them.

\[
\begin{align*}
\text{Ar} & \quad \text{N}^+ \quad \text{N}^- \\
\text{RCO}_2\text{H} & \quad \rightarrow \quad \text{Ar} \quad \text{O} \quad \text{R} \quad \text{N}_2
\end{align*}
\]

\[\rho = 1.6 \quad \frac{k(\text{RCO}_2\text{H})}{k(\text{RCO}_2\text{D})} = 3.5\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{N}^+ \quad \text{N}^- \\
\text{RCO}_2\text{H} & \quad \rightarrow \quad \text{EtO}_2\text{C} \quad \text{O} \quad \text{R} \quad \text{N}_2
\end{align*}
\]

\[\frac{k(\text{RCO}_2\text{D})}{k(\text{RCO}_2\text{H})} = 2.9\]

**Purpose of the problem**

Application of contrasting isotope effects to detailed mechanistic analysis.

**Suggested solution**

The first reaction has a normal kinetic isotope effect (RCO₂H reacts faster than RCO₂D) while the second has an inverse deuterium isotope effect (RCO₂H reacts slower than RCO₂D). This suggests that there is a rate-determining proton transfer in the first reaction but specific acid catalysis in the second (i.e. fast equilibrium proton transfer followed by slow reaction of the protonated species). Protonation occurs at carbon in both reactions, and this can be a slow step.
The second reaction follows much the same pathway except that loss of nitrogen is now difficult because the cation would be very unstable (primary and next to a CO₂Et group) so the second step is S₉₂ and rate determining. 

PROBLEM 12
Suggest mechanisms for these reactions and comment on their relevance to the Favorskii family of mechanisms.

Purpose of the problem
Extension of a section of the chapter (p. 1061-3) into new reactions with internal trapping of intermediates.

Suggested solution
In the first reaction the bromination must occur on the alkene to give a dibromide. We cannot suggest stereochemistry at this stage and it is better to continue with the standard Favorskii mechanism and see what happens. Everything follows until the very last step when the opening of the cyclopropane provides electrons in just the right place to eliminate the second bromide and put the alkene back where it was.
This alternative behaviour of a proposed intermediate gives us confidence that the intermediate really is involved.

The stereochemistry of the initial bromination turns out to be irrelevant as it disappears when the oxyallyl cation is formed. We know the stereochemistry of the final product so we know the stereochemistry of the cyclopropanone: it must be on the opposite face of the five-membered ring to the methyl group. The disrotatory closure of the oxyallyl cation evidently goes preferentially one way with the H and the CMe₂Br substituents going upwards and the carbonyl group going down.

The second reaction to the right is a normal Favorskii. The only point of interest is the way the three-membered ring breaks up. The more stable carbanion is the doubly benzylic one so that leaves.

The reaction with excess bromoketone starts the same way but the oxyallyl cation is intercepted by one of the benzene rings in a four-
electron conrotatory electrocyclic reaction like the Nazarov reaction (p. 927).

You may wonder how excess MeO\(^{-}\) stops this from happening. It doesn’t. The oxyallyl cation and the cyclopropanone are in equilibrium and excess MeO\(^{-}\) captures the cyclopropanone and drives the normal Favorskii onwards. If there is no excess MeO\(^{-}\) the oxyallyl cation lasts long enough for the five-membered ring to be the main product.

**PROBLEM 13**

A typical Darzens reaction involves the base-catalysed formation of an epoxide from an α-haloketone and an aldehyde. Suggest a mechanism consistent with the data below.

\[
\text{Ph\text{-}CHClCOCH}_2\text{Cl} + \text{ArCHO} \xrightarrow{\text{EtO}^-, \text{EtOH}} \text{Ph\text{-}CHClCOCH}_2\text{Ar}
\]

(a) The rate expression is: \(\text{rate} = k_3[^{\text{PhCOCH}_2\text{Cl}}][\text{ArCHO}][\text{EtO}^-]\)

(b) When Ar is varied, the Hammett \(\rho\) value is +2.5.

(c) The following attempted Darzens reactions produced unexpected results:

\[
\begin{align*}
\text{Ph\text{-}CHClCOCH}_2\text{Cl} + \text{OHC\text{-}H}_2\text{CMe}_3 \xrightarrow{\text{EtO}^-, \text{EtOH}} & \text{Ph}\text{-}CHClCOCH}_2\text{H}_2\text{CMe}_3 \\
\text{Ph\text{-}CHClCOCH}_2\text{Cl} + \text{OHC\text{-}H}_2\text{CMeO}_2\text{H} \xrightarrow{\text{EtO}^-, \text{EtOH}} & \text{Ph}\text{-}CHClCOCH}_2\text{H}_2\text{CMeO}_2\text{H}
\end{align*}
\]

**Purpose of the problem**

Trying to get a complete picture of a reaction using physical data and structural variation.
Suggested solution

The ethoxide is not incorporated into the product but appears in the rate expression. Its role must be as a base and there is only one set of enolvable protons. We start by making the enolate of the chloroketone. This cannot be the slow step as the aldehyde appears in the rate expression. Then we can attack the aldehyde with the enolate and finally close the epoxide ring by nucleophilic displacement of chloride ion.

If this mechanism is right, the kinetic data show that the second step is rate-determining (a reasonable deduction as it is a bimolecular step) and that the first step is a pre-equilibrium. We can write:

\[
\text{rate} = k_2[\text{enolate}][\text{ArCHO}]
\]

And we know from the pre-equilibrium that

\[
K_1 = \frac{[\text{enolate}]}{[\text{PhCOCH}_2\text{Cl}][\text{EtO}^-]}
\]

So the rate expression becomes when we substitute for [enolate]:

\[
\text{rate} = K_1k_2[\text{PhCOCH}_2\text{Cl}][\text{EtO}^-][\text{ArCHO}]
\]

and this matches the observed rate expression though the apparently third order rate constant is revealed as the product of an equilibrium constant and a second order rate constant.

The Hammett $\rho$ value shows a modest gain of electrons near the Ar group in the rate-determining step. We must not take the pre-equilibrium into account as ArCHO is not involved in this step. In fact a Hammett $\rho$ value of +2.5 is typical of nucleophilic attack on a carbonyl group conjugated to the benzene ring.

The unexpected products come from variations in this mechanism. para-Methoxybenzaldehyde is conjugated and unreactive so the enolate ignores it and reacts with the unenolised version of itself.
With salicylaldehyde, the second example, the phenolic OH group will exist as an anion under the reaction conditions. Alkylation by the chloroketone allows enolate formation leading to an intramolecular aldol reaction.

**PROBLEM 14**

If you believed that this reaction went by elimination followed by conjugate addition, what experiments would you carry out to try and prove that the enone is an intermediate?

**Purpose of the problem**

Turning the usual question backwards: what evidence do you want, rather than how to interpret what you are given.

**Suggested solution**

The suggested mechanism of elimination followed by conjugate addition might be contrasted with direct $S_N2$ to see what evidence is needed.
mechanism 1:
simple $S_n^2$ displacement

mechanism 2:
elimination - addition

(a) elimination

(b) addition

There are many types of evidence you might suggest: here are some of them.

- Exchange of protons in $D_2O/EtOD$ would suggest elimination/addition.
- Kinetic evidence (tricky as you cannot be sure which is the slow step.
- A Hammett plot with substituted benzene rings. The $S_n^2$ mechanism would have a small $\rho$ as the benzene ring is a long way from the action.
- Base catalysis: mechanism 2 is base catalysed, mechanism 1 isn’t.
- Kinetic isotope effect might be found in mechanism 2.
- Stereochemistry. If a substituent were added to make the terminal carbon chiral, inversion would be expected for mechanism 1 and racemization for mechanism 2. But choose a small substituent otherwise it would be a very different compound.