PROBLEM 1
In the comparison of stability of the last intermediates in the substitution at the carbonyl group of acid chlorides or anhydrides to make esters (chapter 10) we preferred one of these intermediates to the other:

Why is the one more stable than the other? If you were to treat an ester with acid, which of the two would be formed?

Purpose of the problem
Revision of contribution of delocalization to stability, particularly of cations.

Suggested solution
The positive charge on the more stable cation is delocalised over both oxygen atoms making it more stable than the other that has a localised cation on one oxygen atom. Protonation of the ester gives the more stable cation as both oxygens combine to make the carbonyl oxygen more nucleophilic.
PROBLEM 2

This reaction shows third-order kinetics as the rate expression is

$$\text{rate} = [\text{ketone}][\text{HO}^-]^2$$

Suggest a mechanism for the reaction.

Purpose of the problem

Interpretation of unexpected kinetics to find a mechanism

Suggested solution

The hydroxide ion must attack the ketone to form a tetrahedral intermediate. The best leaving group from this intermediate is the hydroxide ion that has just come in ($pK_a$ of H$_2$O is about 15) rather than the alkyne anion. If we use the second hydroxide ion to deprotonate the intermediate, only one leaving group remains, though it is a poor one, and the decomposition of the dianion must be the rate-determining step. This mechanism is found for substitutions at the carbonyl group with very bad leaving groups, as in the hydrolysis of amides (p. 213 in the textbook).
**PROBLEM 3**

Draw an energy profile diagram for this reaction. You will of course need to draw the mechanism first. Suggest which step in this mechanism is likely to be the slow step and what kinetics would be observed.

![Chemical reaction diagram]

**Purpose of the problem**

Practice at drawing energy profile diagrams as one way to present the energetics of mechanisms.

**Suggested solution**

The first thing is to draw the mechanism of the reaction.

![Mechanism diagram]

The first step is bimolecular and forms a new C–C bond. The second step is just a proton transfer between oxygen atoms and is certainly fast. The first step must be the rate-determining step and the intermediate must have a higher energy than the starting material or the product. In this answer we have used the style of energy-profile diagrams used in the book (e.g. p. 252) but there is nothing sacred about this – any similar diagram is fine.

*Insert diagram from chapter 13 problem 7 in old solutions manual*
PROBLEM 4
What would be the effect of solvent changes on these reactions? Would the reactions be accelerated or retarded by a change from a polar to a non-polar solvent?

![Chemical reactions]

**Purpose of the problem**
Practice at assessing the likely effect of solvent polarity in terms of the mechanism of the reaction.

**Suggested solution**
It is essential to draw a mechanism for each reaction and to identify the rate-determining step in each case. The first two reactions are one-step processes so that makes life easier.

Now we need to draw the transition state for each reaction so that we can assess whether it is more or less polar than the starting materials. The way to do this is described on p. 251 of the textbook.

In the first reaction uncharged starting materials form a partly charged transition state. A polar solvent will stabilise the transition state and accelerate the reaction. In the second case a charged (zwitterionic) starting material gives a partly charged transition state. A polar solvent will stabilise both starting material and transition state but it will stabilise the starting material more. The energy gap will increase and the reaction go more slowly.

The third reaction is different as it has more than one step. It is a carbonyl substitution of the kind we met in chapter 10. The nucleophile
(ammonia) attacks the carbonyl group to form a tetrahedral intermediate that decomposes with the loss of the better leaving group.

\[
\begin{align*}
\text{R} & \text{OMe} \quad \xrightarrow{\text{NH}_3} \quad \text{R} & \text{OMe} \\
\text{R} & \text{OMe} \quad \xrightarrow{\text{NH}_3} \quad \text{R} & \text{NH}_2 \quad \xrightarrow{\text{fast}} \quad \text{R} & \text{NH}_2 \\
\text{R} & \text{NH}_2 \quad \xrightarrow{\text{fast}} \quad \text{R} & \text{OH} \\
\text{R} & \text{OH} \quad \xrightarrow{\text{fast}} \quad \text{R} & \text{NH}_2
\end{align*}
\]

We have marked two steps ‘fast’ because they are just proton transfers between nitrogen and oxygen atoms. Either of the other two steps might be rate determining. In this substitution the leaving group is relatively good (compare problem 2) and the rate-determining step is the first: the usual one for carbonyl substitutions. In this step, neutral starting materials turn into charged (zwitterionic) intermediate so the transition state is becoming charged and the reaction is accelerated by more polar solvents.

**PROBLEM 5**

Comment on the effect of acid and base on these equilibria.

**Purpose of the problem**

Practice at assessing how equilibrium constants respond to acid and base.

**Suggested solution**

The first example is cyclic ester (lactone) formation that will go well in acid solution. In base the acidic proton will be removed and cyclisation is no longer possible (see p. 210 in the textbook).

\[
\begin{align*}
\text{HO} & \text{C} \quad \xrightarrow{\text{base}} \quad \text{HO} & \text{C} \\
\text{HO} & \text{C} \quad \xrightarrow{\text{acid}} \quad \text{HO} & \text{C}
\end{align*}
\]

The second example is cyanohydrin formation from a ketone (see p. 127 in the textbook). The reaction is reversible but in basic solution the cyanide anion is more stable than the oxyanion of the cyanohydrin and the carbonyl group is more stable than C–O plus C–C so the reaction
runs backwards. In more acidic solution (pH less than about 12) the oxyanion will be protonated and the reaction driven towards the right.