Solution Guide to the Problems in Physical-Organic Chemistry

PART 1

1.1 a) 

\[
\begin{align*}
\text{Cl} & \quad \text{CO}_2\text{CH}_3 \\
\text{Cl} & \quad \text{CO}_2\text{CH}_3
\end{align*}
\]

Both groups equatorial

b) 

The hydroxyl group less steric demanding, than the t-butyl groups, which becomes equatorial

1.2 a) 

\[
\begin{align*}
\text{H}_a & \quad \text{H}_b \\
\text{Ph} & \quad \text{CH}_3
\end{align*}
\]

\(\text{H}_a\) and \(\text{H}_b\) are diastereotopic

b) Something like:

1.3 a) Azulene is a cyclic conjugated compound with \(4n + 2\) \((n = 2)\) electrons

b) The dipole is directed toward the five membered ring. Structures with a delocalized negative charge in a five membered ring and a delocalized positive charge in a seven membered ring resemble the cyclopentadiene anion and tropylium cation, both of which show some aromatic stability.

1.4 The C-X and C=O dipoles reinforce each other in the equatorial form but cancel to some extent in the axial form. Thus the equatorial form is more polar and should be favored by more polar (higher dielectric constant) solvents. Therefore, 1,4-dioxane has the larger proportion of equatorial-X in each case.

1.5 The rate-determining step must be removal of the secondary proton and this, together with formation of a chromate ester and catalysis by hydrogen ion, suggest the following mechanism.

\[
\begin{align*}
\text{HCrO}_4^- + \text{Me}_2\text{CHOH} + \text{H}^+ & \quad \rightleftharpoons \quad \text{Me}_2\text{CHOCrO}_3\text{H} + \text{H}_2\text{O} \\
\text{H}_2\text{O} + \text{Me}_2\text{CHOCrO}_3\text{H} & \quad \text{Slow} \quad \rightarrow \quad \text{Me}_2\text{C}=\text{O} + \text{H}_3\text{O}^+ + \text{HCrO}_3^- 
\end{align*}
\]

Oxidation of the alcohol results in reduction of the valency state of chromium.

1.6 A negative entropy of activation results from an increase in order on going from the ground state to the transition state of a reaction. Increased order may result from bringing together of previously distinct elements, freezing out of conformational degrees of freedom, or arranging of solvent molecules. Changes in solvation generally occur when charge is separated, created, or destroyed. 

a) The Diels-Alder reaction (i) has the more negative $\Delta S^\#$, since a precise arrangement of both elements in three dimensions is necessary for reaction. The acid-catalysed polymerization of isobutylene, of which only the first step is shown, is also bimolecular but requires alignment in only two dimensions. 

b) The degree to which conformational mobility is frozen out depends on the extent of crowding in the transition state. In these examples of the Williamson synthesis, the nucleophilic substitution of ethoxide ion on methyl iodide is much less crowded than that on neo-pentyl iodide. The additional three methyl groups in the neo-pentyl substrate must arrange themselves as well as possible to minimize crowding ($\Delta S^\# = -19.9$ eu). No such constraints are placed on the methyl substrate; $\Delta S^\#$ becomes more negative. 

c) The charge types in (ii) remain the same during the progress of nucleophilic substitution reaction. Since the charge is less dispersed in the transition state, solvation probably decreases. On the other hand, in (i) charge separation is developing in the transition state, so that solvation is increased and $\Delta S^\#$ becomes more negative.

1.7 a) d) = Diastereomers 
b) c) e) f) g) = Enantiomers 

1.8 Symmetry plane through the molecule makes it racemic. 

1.9 a) b) c) g) h) = Chiral 
d) = Achiral 

1.10 a) 

Charge separation gives two quasi-aromatic structures (The 4n+2 rule) 

b) 

Through-effect increases the dipole sum: 

c) 

Inductive effect is dominating. 
O more electronegative than N. 

1.11A: kinetic product; B: transition state; C: intermediate; D: thermodynamic product.
1.12. This is because the dissolution is an endothermic process, in other words the bonds between the ions within the solid salt are stronger than those between the ions and water, so heat is absorbed from the medium when the bonds between the ions are broken. The reason why this process nevertheless occurs is because there is a large increase in entropy when a solid dissolves, which can often compensate for the unfavourable enthalpy change.

1.13

Imaginary movement in resonance structures: a, c. Real movement in reactions: b, d.

1.14. The alternative four-membered lactone does not form because four-membered rings are thermodynamically less stable than six-membered rings. Under acidic conditions, the formation of lactones is reversible, so the thermodynamic product forms.

PART 2

2.1 Resonance stabilization of the phenoxide requires coplanarity of orbitals of the nitro group, the benzene ring, and the phenoxide oxygen atom. A methyl group ortho to the nitro group sterically inhibits planarity. The nitro group must twist about the C-N bond and thereby the resonance stabilization of the phenoxide is reduced. The steric effect is increased by two methyl groups.

2.2 Resonance between the meta nitrogroup and the electrons on oxygen is not possible. Only an inductive influence can operate and thus the acid strengthening effect of nitro is relatively small in this case.

2.3 Oxazole is more basic than pyrrole. The oxygen can enhance electron density at the nitrogen atom by resonance. Furthermore, the conjugate acid obtained from protonation of aniline loses resonance stabilization.
2.4 a) \( p \)-Cyano phenol: Because of resonance stabilization of the conjugate base.
b) \( CH_3CH=CH-OH \): Because of resonance stabilization of the conjugate base.
c) \( NCCH_2CN \): Because two groups provide resonance stabilization of the conjugate base.

d) \( \text{Because the t-butyl group remains equatorial, the -CO}^-\text{ and the -COOH groups are trans-diaxial in the conformation of d). In the other isomer intramolecular H-bonding between the diequatorial groups decreases acidity (See Fig.).} \)
e) \( CH_3CF_2OH \): Because the inductive electron-withdrawing effect by F falls off with distance.
f) In compound f) the charge of the conjugate base is delocalized over a larger system (See Fig.).
g) Compound g) because of charge delocalization of the conjugate base by carbonyl group (See Fig.).

2.5

\( a) [\text{Ph}-\text{CH}=\text{N}-\text{Ph} \leftrightarrow \text{Ph}-\text{CH}=\text{N}-\text{Ph}] \quad H^+ \rightarrow \text{Ph}-\text{CH}=\text{N}-\text{Ph} \)

\( b) [\text{CH}_3-C-\text{NHCH}_3 \leftrightarrow \text{CH}_3-C-\text{NHCH}_3] \quad H^+ \rightarrow \text{CH}_3-C-\text{NHCH}_3 \)

c) \( \text{d) } \)

\( 2.6 \)

\( a) \) The negative charge in the acetate ion is appreciably localized on the oxygen atoms, whereas the negative charge in the phenoxide ion is delocalized over the oxygen and the aromatic ring. In \( H_2O \), the acetate oxygen’s can be very effectively solvated (a “hard-hard” interaction), the small methyl group offers little steric hindrance to solvation. On the other hand, the larger delocalization of charge in the phenoxide ion decreases solvation by \( H_2O \) (“soft-hard” interaction). The larger overall size of phenoxide also causes less effective solvation. In the gas phase, the extra solvation of acetate is lost, so that the acidities of phenol and acetic acid are comparable. In an aprotic solvent such as dimethyl sulfoxide, the special solvation of acetate should be much less, so that DMSO acidities should more closely resemble gas phase acidities.

\( b) \) The major difference between the two equilibria is the charge types. For \( HOAc \) (a), two (one positive, one negative) must be solvated on dissociation. Water, with a much higher \( \varepsilon \) and the ability to form either the positive or negative end of strong hydrogen bonds, is much better able to stabilize both charge types than \( CH_3OH \). Therefore the acidity of \( HOAc \) is much lower in \( CH_3OH \) than in \( H_2O \). For \( Pyr-H \) (b), the charge type is the same on both sides of the equilibrium. Therefore the change from \( H_2O \) to \( CH_3OH \) has little effect on the acidity constant.
2.7. The strength of an acid depends upon the stability of the anion formed on ionization and this, in turn, depends upon the extent of delocalization of the negative charge.

(i) The methyl group is electron-repelling and (b) is weaker than (a).

(ii) The nitro group is strongly electron-accepting and (d) is stronger than (c).

(iii) The mesomeric effect of the acetyl group is electron-accepting but this cannot be relayed from the \textit{m}-position, so (f) is stronger than (e).

(iv) The second dissociation of malonic acids is much less than the first as it involves separation of a proton from a species which is already negatively charged so that (g) is a stronger acid than (h).

(v) The hydroxy group is electron-attracting so (j) is stronger than (i).

\textit{pK}_a values for all these acids can be found in A. Albert and E.P. Serjeant, \textit{Ionization Constants of Acids and Bases}, Methuen, London, 1962.

2.8. Electron-attracting groups like fluoro delocalize the negative charge on the anion and so (b) is a stronger acid than (a). This is true of \textit{p}-fluorobenzoic acid but the mesomeric effect acts in the opposite sense, so a \textit{p}-fluoro substituent has little effect on the \textit{pK}_a of benzoic acid. There may also be a further important factor known as the \textit{I}_\pi effect: this is discussed by Tedder and Nechvatal (\textit{Basic Organic Chemistry}, Part 2, Wiley, London, p. 70). In the \textit{o}-position the inductive effects is increased because of the reduced distance and (e) is a stronger acid than benzoic acid. There may also be a steric factor, forcing the carboxyl group out of the plane of the ring and reducing the acid-weakening properties of the benzene ring. The inductive effect of the methoxy group is sufficient to make (f) a slightly stronger acid than benzoic. However, an electron-donating mesomeric effect can be relays from the \textit{p}-position and the results is that \textit{p}-methoxybenzoic acid is weaker than benzoic acid.  

2.9. It acts as a Lewis acid, helping the halide to leave.

2.10. Hydroxide is more basic, hydroperoxide is more nucleophilic. The electron-withdrawing effect of the adjacent oxygen stabilizes the negative charge in hydroperoxide, reducing the basicity, but the alpha effect makes it more nucleophilic.

2.11. Propyl bromide will give more O-alkylation because it is a harder electrophile.
PART 3

3.1 Electron-donating substituents have negative sigma values since they decrease the stability of the conjugate base of the substituted acid. The greater the electron donating effect, the greater the magnitude of the negative sigma constant. Similarly, electron-withdrawing substituents stabilize the negative charge on the conjugate base and enhance acidity, thus they have positive values for sigma. The \( \sigma_m \) and \( \sigma_p \) values are expected to differ significantly when direct conjugation between the substituent and conjugate base anion can occur. The para, but not the meta relationship of groups can lead to direct conjugation.

3.2 a) nitration of substituted benzenes \( \rho = -7.29 \)
    b) ionization of substituted benzenthioles \( \rho = +2.45 \),
    c) ionization of substituted benzenephosphonic acids \( \rho = +0.75 \),
    d) reaction of substituted \( N,N \)-dimethylanilines with methyl iodide. \( \rho = -2.39 \)

3.3 The value of \( \rho \) is approximately +1.2

3.4 The value of \( \rho \) is -1.14. The positively charged on nitrogen is decreasing and this will show a negative sign of the reaction constant, when correlated to the Hammett equation.

3.5 A plot of \( \log (k / k_0) \) against \( \sigma \) is linear (as shown in Figure 1). The slope of this line. (the value of \( \rho \)) is 1.0. J. Chem. Soc. (B), 1967, 1084.

3.6 A plot of \( \log k_f \) against \( \sigma^+ \) is linear and \( \rho = -5.95 \). The value of \( k_f \) for \( p \)-flourobenzene is 2.53. The results do not permit the brominating species to be fixed.

3.7 At pH = 7.0 the rate-determining step is dehydration. Assuming that the intermediate is present at low steady state, the kinetic equation is the following:

\[
\text{Rate} = \frac{k_2k_1}{k_{-1}} [\text{PhCHO}] [\text{NH}_2\text{NHCONH}_2][\text{H}^+] 
\]

Electron-donating substituents increase the rate of the acid-catalyzed step (\( k_2 \)) but have the opposite effect on the equilibrium (\( k_1/k_{-1} \)), so that at neutral pH the rate is not greatly affected by substitution (\( \rho = 0.2 \)). In acid solution (pH = 1.75) the second step is so fast (because of acid catalysis) that it is no longer rate-determining and the slow step is \( k_1 \), making the overall reaction no longer acid-catalyzed. The value of \( \rho \) at this pH (= 0.91) reflects the effect of substituents on nucleophilic attack of semicarbazide on the carbonyl group of benzaldehyde.


3.8 The Hammett plot shows a distinct break with \( \rho \)-OMe, \( \rho \)-Me, \( m \)-Me, and H on one line
(ρ= -5.5) and the other substituents on another line (ρ= -1.6). This indicates a change of rate-determining step. For anilines with diminished nucleophilicity (i.e. with electron-withdrawing substituents) the slow step is the first \( k_1 \) but, with increased nucleophilicity, this step becomes fast and \( k_2 \) is rate-controlling.

One experimental method of showing this change of rate-determining step would be to demonstrate the transient intermediate spectrophotometrically. This should only be possible in cases where \( k_2 \) is less than \( k_1 \), i.e. the slow step is decomposition of the intermediate. *J. Chem. Soc.* (B), 1971, 18.

3.9 The mechanism of elimination is as shown and what may vary in the transition state is the extent of breaking of the \( C_β - H \) bond or the \( C_α - O \) bond. With a constant substituents

\[
\begin{align*}
  \text{in ring A the magnitude of } \rho \text{ (which depends upon variation of substituents in ring B) reflects the amount of negative charge present on the oxygen of the sulphonate group in the transition state. } \\
  \text{Therefore, with } \rho \text{-OMe in ring A there is more negative charge in the sulphonate group than with } m\text{-Cl. These substituents will also affect the acidity of the hydrogen on the } \beta\text{-carbon atom, the most acidic being substituted } m\text{-Cl. Thus, the more the } C_β - H \text{ bond is weakened in the transition state the less will be the } C_α - O \text{ bond. The } \rho\text{-OMe substituent in ring A will give rise to the least carbanion-like transition state and the } m\text{-Cl the most.} \\
  \text{J. Chem. Soc. (B), 1971, 498. [These results are in conflict with those of H. M. R. Hoffman (*Tetrahedron Letters*, 1967, 4393) who suggest from work on the relative rates of elimination of bromide and tosylate, that increases } C_β - H \text{ bond breaking induces greater } C_α - X \text{ bond breaking.]}
\end{align*}
\]

3.10 Fastest to slowest: c>d>a>b>e>f.

**PART 4**

4.1 Conjugated cyclic compounds with \( 4n + 2 \) electrons: Aromatic; a, c, d, f, g.

Conjugated cyclic compounds with \( 4n \) electrons. Nonaromatic; b, h.

Compounds with \( 4n + 2 \) conjugated electrons, but not having cyclic conjugation. Nonaromatic; e, j.

Compounds with \( 4n \) electrons and noncyclic conjugation. Nonaromatic; i.

4.2 a) The problem is treated as a \([6+2]\) cycloaddition. In the HOMO-LUMO method \( \psi_1 \) of the \( C_2 \) portion can be the HOMO and the \( \psi_4 \) of the \( C_6 \) portion can be the LUMO. The cycloaddition would be a symmetry allowed suprafacial-antarafacial process. The actual reaction is forbidden since the geometry would require a suprafacial-suprafacial process.

b) The azide group can be treated as a \( C_3 \) system with four conjugated electrons, that is as an allyl carbanion (See Fig. above). We can thus use the allyl \( \psi_1 \) as our LUMO and \( \psi_1 \) of a \( C_2 \) system as the HOMO. The reaction is an allowed suprafacial-suprafacial process.
4.3 The initial rearrangement product is an enol. Tautomerism produces the aldehyde which cannot undergo a reverse Cope rearrangement.

\[
\text{HO} \quad \text{HO} \quad \text{O}
\]

4.4 a) 4 electrons $\Rightarrow$ Conrotatory Allowed reaction  
b) 6 electrons $\Rightarrow$ Disrotatory Allowed reaction  
c) 2 electrons $\Rightarrow$ Disrotatory Allowed reaction  
d) 4 electrons $\Rightarrow$ Conrotatory Not allowed reaction  
e) 8 +2 electrons Supra - Supra facial allowed cycloaddition

4.5 a)  

b) $\text{CH}_3\text{CO}_2$  

4.6 This is a $\pi_6^6 + \pi_4^4$ reaction and the number of p electrons involved (q) is ten. As q/2 is odd, the reaction is thermally allowed. Attempt to construct a correlation diagram for this reaction. *Chem, Commun.*, 1966, 15.

4.7 a)  

b) $150^\circ$  

8 e$^-$ Conrotatory  

6 e$^-$ Disrotatory
4.8  a) \( \text{(2+2) Cycloaddition (supra-antra)} \)

4.8  b) \( \text{[3,3]-Sigmatropic rearr.} \)

c) \( \text{[3,3]-Sigmatropic rearr.} \)

d) \( \text{6 e\textsuperscript{-} Disrotatory} \)
4.9 a) 

\[
\begin{align*}
\text{Retro-Diels Alder} & \quad \Delta \quad \text{Diels Alder} \\
\end{align*}
\]

b) 

\[
\begin{align*}
\text{Electrocyclic Opening (2 e\text{-}^\text{\textcircled{\textbullet}})}
\end{align*}
\]

c) 

4.10 a) 

\[
\begin{align*}
\text{Electrocyclization 6 e\text{-}^{-}} & \quad \text{disrotatory} \\
\text{4+2 e\text{-}^{-}} & \quad \text{Cycloaddition}
\end{align*}
\]

b) 

\[
\begin{align*}
\text{Electrocyclization 4 e\text{-}^{-}} & \quad \text{conrotatory} \\
\text{4+2 e\text{-}^{-}} & \quad \text{Cycloaddition}
\end{align*}
\]

4.11 Two successive [3,3] shifts occur. The first is an ortho-Claisen rearrangement and the second a Cope rearrangement.

4.12 The general rule for an electrocyclic reaction of q \(\pi\)-electrons in the ground state is that it will be disrotatory if \(q/2\) is odd and conrotatory if \(q/2\) is even. In this example \(q = 8\), so the reaction is thermally conrotatory. In the first excited state the criteria are reversed and the reaction is photochemically disrotatory. 

\textit{J. Amer. Chem. Soc., 89, 7130 (1967).}

4.13 A series of reversible [1,3] sigmatropic shifts would results in distributing the
deuterium statistically around the ring. However, a sequence of [1,5] shifts would place the deuterium in positions 3, 4, 7 and 8 only. The latter was found to be experimentally observed, thus confirming the prediction. Anm., 671, 25 (1964).

4.14 Such an isomerization involves a symmetry forbidden [1,3] shift.

4.15 The first step is a [1,5 s]-sigmatropic shift to give 4, the trans form of which exhibits a disrotatory ring closure to give 2 and the cis form undergoes a [1,7 a]-sigmatropic H-shift to give 3.

4.16 Fastest to slowest: c>d>e>b>a.
PART 5

5.1 The rate-controlling step for the SN1 reaction is a dissociation. The position of the equilibrium can be shifted back to undissociated starting material by increasing the concentration of one of the products, in this case X⁻ (mass law effect). The leaving group X⁻, and the added nucleophile both compete for the intermediate carbocation.

5.2 The reaction proceeds by an SN1 mechanism. The reaction rate depends on the formation of the carbocation, not on the nature of the nucleophile.

5.3 Hydroxide is a poor leaving group. However, in the presence of an acid the hydroxyl group is protonated and the good leaving group, water, departs.

5.4 Substitution on this secondary benzylic substrate can proceed by an SN1 or an SN2 pathway. Solvolysis by methanol proceeds by the SN1 mechanism and gives a mixture of inversion and racemization. With the good nucleophile methoxide, an SN2 reaction takes place with inversion.

5.5 The rate of reaction is the rate of carbocation formation and is independent of the nucleophile. However, the product mixture will depend on the nucleophilicity of Br⁻ and Cl⁻ even though the addition occurs after the slow step of the overall reaction. Br⁻ is a better nucleophile than Cl⁻ in this reaction.

5.6 a) In the highly polar solvent formic acid, the benzylic alcohol solvolyses by an SN1 pathway with racemization stereochemistry.

b) In this case bromide replaces bromide in an SN2 reaction. Each substituent gives an inverted molecule which cancels the rotation of an unreacted molecule.

c) The moderately nucleophilic acetic acid results in SN1 solvolysis. The good nucleophilic acetate in the aprotic solvent acetone leads to an SN2 reaction.
d) In azide the negative charge is more delocalized than in the amide anion. Charge is spread over three atoms.

\[
\text{\[
\begin{array}{c}
\text{IN} \equiv \text{N} \equiv \text{N} \\
\text{IN} \equiv \text{N} \equiv \text{N}
\end{array}
\]}
\]

\[
\text{\[
\begin{array}{c}
\text{IN} \equiv \text{N} \equiv \text{N} \\
\text{IN} \equiv \text{N} \equiv \text{N}
\end{array}
\]}
\]

\[
\text{\[
\begin{array}{c}
\text{IN} \equiv \text{N} \equiv \text{N} \\
\text{IN} \equiv \text{N} \equiv \text{N}
\end{array}
\]}
\]

e) The structure of the rigid bicyclic molecule inhibits backsided attack of a nucleophile by an SN2 pathway. Formation of a carbocation in an SN1 processes inhibited because the bridgehead carbon atom cannot become planar.

f) Only the trans isomer can undergo a backside SN2 cyclization.

\[
\begin{array}{c}
\text{OH} \\
\text{Cl}
\end{array} \xrightarrow{\text{OH}^-} \begin{array}{c}
\text{O} \equiv \\
\text{Cl}
\end{array} \xrightarrow{\text{Cl}^-} \begin{array}{c}
\text{O} \equiv \\
\text{Cl}
\end{array}
\]

5.7a) Reaction of each of the tertiary haloalkanes proceeds by an SN1 mechanism. They form the same carbocation in their rate controlling steps, thus give the same mixture of alcohol and ether products on subsequent substitution by water and methanol.

b) The rate controlling step depends on relative leaving group abilities of the halide. It is found that I > Br > Cl.

5.8 A is a very crowded molecule. Dissociation into a carbocation relieves strain as the molecule changes from a tetrahedral to a trigonal geometry. The rate controlling step is favored by "steric acceleration".

5.9 Iodine is a better nucleophile than water and a better leaving group than chloride. Iodine substitutes for chloride, then water displaces iodine. Only a catalytic amount of iodine is added since it is generated as the alcohol product forms.

5.10 The first methyl group increases the electron density at the nitrogen atom to which it is attached. That nitrogen atom is the better nucleophile in the second alkylation step.

5.11 Hydoxide attacks the less hindered carbon atom.

\[
\text{\[
\begin{array}{c}
\text{(C}_2\text{H}_5\text{)}_2\text{N} \equiv \text{N} \equiv \text{N} \\
\text{(C}_2\text{H}_5\text{)}_2\text{N} \equiv \text{N} \equiv \text{N}
\end{array}
\]}
\]

\[
\text{\[
\begin{array}{c}
\text{(C}_2\text{H}_5\text{)}_2\text{N} \equiv \text{N} \equiv \text{N} \\
\text{(C}_2\text{H}_5\text{)}_2\text{N} \equiv \text{N} \equiv \text{N}
\end{array}
\]}
\]

\[
\text{\[
\begin{array}{c}
\text{(C}_2\text{H}_5\text{)}_2\text{N} \equiv \text{N} \equiv \text{N} \\
\text{(C}_2\text{H}_5\text{)}_2\text{N} \equiv \text{N} \equiv \text{N}
\end{array}
\]}
\]
5.12 Solvation of the cyanide ion through hydrogen bonding to ethanol increases the effective nucleophilicity of the anion. Aprotic solvents minimize such anion solvation.

5.13 The solvent theory developed by Hughes and Ingold states that an increase in $\varepsilon$ causes an increase in rate when the transition state is more polar than the ground state and causes a decrease in rate when it is less polar. Thus in many instances the effect of solvent $\varepsilon$ on the rate can be predicted simply from the relative polarity of the ground and transition states.

a) In this displacement reaction, two oppositely charged species are brought together. The transition state should be less polar than the ground state, so an increase in $\varepsilon$ will slow the reaction.

b) If the reactions is concerted or passes through a diradical (A), a change in $\varepsilon$ will have little effect on the rate. A dipolar intermediate (B) would be indicated by an increase in rate. The observed rate shows little solvent sensitivity (relative rates, C$_6$H$_6$ 1.45, CH$_3$CH$_2$OAc 1.00, CH$_3$CN 1.85), so the dipolar specie B can be eliminated.

\[
\text{A': } \begin{array}{c}
\text{B: } \end{array}
\]

5.14 The normal mechanism for the hydrolysis of an alkyl halide is $S_N2$ but with $t$-butyl chloride the reaction is $S_N1$, where the rate-determining step is heterolysis of the carbon chloride bond, to give a carbonium ion.

\[
\text{Me}_3C-\text{Cl} \xrightarrow{\text{Slow}} \text{Me}_3\text{C}^+ + \text{Cl}^- \\
\text{Me}_3\text{C}^+ + \text{OH}^- \xrightarrow{\text{Fast}} \text{Me}_3\text{C}-\text{OH}
\]

As reaction with hydroxide occurs after the slow step, addition of potassium hydroxide has no effect on the rate of reaction. The $t$-butyl carbonium is more stable than similar ions formed from secondary or primary alkyl halides and this is why the effect is observed only with a $t$-butyl compound. Stabilization is probably due to hyperconjugation (see Figure). J. Chem. Soc., 1935, 255.

5.15 With $n = 4$ and 5 there is neighbouring participation by the hydroxyl group which facilitates loss of chloride ion.

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{OH} \quad \text{CH}_2-\text{Cl} \quad \text{H}_3\text{C} \quad \text{OH} \\
\text{H}_3\text{C} \quad \text{CH}_2 \quad \text{CH}_2-\text{Cl} \quad \text{H}_3\text{C} \quad \text{CH}_2 \quad \text{CH}_2 - \text{HCl}
\end{array}
\]

The cyclic transition state in these cases is a five- or six-membered ring. J. Amer. Chem. Soc., F75, 4778 (1953)

5.16 Racemization occurs when an iodide ion attacks an iodoctane molecule and displaces the iodide already present with inversion of configuration (i.e. the Walden inversion). When half the iodoctane molecules have undergone this displacement reaction, racemization will be complete, and there will be a mixture of equal parts (+)-2-iodooctane and (-)-2-iodooctane. J. Chem. Soc., 1935, 1525.
5.18 Most stable to least stable: b\(\succ\)g\(\succ\)f\(\succ\)d\(\succ\)e\(\succ\)c\(\succ\)a.

5.19 Ethyl bromide is converted to ethanol in base; ethyl bromide can then react with hydroxide ion, which is more nucleophilic than water. The reverse reaction takes place in acid, because the hydroxyl group can then be protonated, making it into a better leaving group.

5.20 The first step in this reaction is rate-determining, and is faster with fluoride than with other halogens, because fluoride is more electron-withdrawing, thus making the ring more reactive towards nucleophiles. Although the second step is slower with fluoride than with other halogens, this is immaterial because it is not rate-determining.

PART 6

6.1 Acetate is a stronger base than chloride. (acetate is the conjugate base of a weaker acid) Elimination is favored relative substitution with the stronger base.

6.2 The 1-alkene product increases as the size of the base increases because approach by base to the hydrogen at number three carbon (to give the 2-alkene) becomes more crowded.

6.3 The exchange of deuterium for proton takes place via the initially formed carbanion intermediate. Since departure of a fluoride ion is the rate controlling step, hydrogen-deuterium exchange occurs during an initial pre-equilibrium step.

6.4 The carbonyl group and the chloride atom enhance the acidity of the adjacent hydrogen atom. Carbanion formation should be rapid.

6.5 As the size of the leaving group increases, more product of Hofmann orientation is observed. Note that the tosylate is effectively smaller than the \(-\text{S(CH}_3\text{)}_2\) or \(-\text{SO}_2\text{CH}_3\) groups. Though tosylate is large group, attachment to the carbon atom at which reaction occurs involves a single C-O-S bond. The largeness of OTs is further away from the reaction center.

6.6 We expect loss of the benzylic \(\beta\)-hydrogen atom to be most favorable. Only cis isomer has the benzylic H atom and OTs group antiperiplanar. The trans isomer must change to an unfavorable diaxial conformation for anti-E2 elimination to occur, and then a less acidic \(\beta\)-hydrogen atom removed. An E1 process is more likely to take place from the trans diequatorial conformation.

6.7

6.8 The H and Cl atoms are coplanar in A, but in B their dihedral angle is about 60°. The E2 process is favored in the coplanar system A.
The first-order dependence on ethoxide ion concentration shows the reaction cannot be E1. Reversible proton abstraction to form a carbanion ion (E1cB mechanism) should lead to incorporation of tritium from the solvent into unreacted DDT but, as this does not occur, an E2 mechanism is indicated.

\[
(C\text{IC}_6\text{H}_4)_2\text{CH-CCl}_3 \leftrightarrow (C\text{IC}_6\text{H}_4)_2\text{C}^\ominus \text{-CCl}_3 + \text{H}^+ \\
(C\text{IC}_6\text{H}_4)_2\text{C}^\ominus \text{-C}^\ominus \text{CCl}_2\text{-Cl} \rightarrow (C\text{IC}_6\text{H}_4)_2\text{C}^\ominus \text{-CCl}_2 + \text{Cl}^- + \text{HOEt}
\]

An isotope effect of 3.8 is consistent with this as an E2 mechanism involves breaking a C-H or C-D bond in the rate determining step and, as the latter is a stronger bond, the rate is consequently reduced. *J. Chem. Soc. (B), 1966*, 696.

The reaction is under kinetic control, because it is irreversible; the base will remove the most kinetically accessible proton, this determines which product forms.

On treatment with base, a will give an allene and b an alkyne. In b, the bromine is fixed in an antiperiplanar conformation to hydrogen across the double bond, so this elimination will be efficient. In a, elimination across the double bond must take place from a synperiplanar conformation, which is less efficient, so elimination across the single bond to give the allene will predominate.

a will give more elimination, because of the enhanced acidity of the proton a to the carbonyl group. The use of potassium t-butoxide would increase the proportion of elimination from both compounds.

**PART 7**

The aromatic aldehyde is stabilized more than the aliphatic aldehyde because of resonance with the benzene ring.

At the transition state leading to product, the unsaturated carbonyl group is becoming saturated. The extra resonance stabilization is lost. The result is that the activation energy for reaction of the aromatic compound is relatively greater because the aliphatic compound never had a significant resonance energy to lose.

The major difference between the two resonance hybrids is that the charge separated resonance structures of the ketone involves a secondary carbocation and that of the aldehyde a primary carbocation. Secondary carbocations are the more stable.
7.3

7.4 If water is involved in the rate-determining step then it will suffer loss of translational and rotational freedom and lead to a more negative entropy of activation than in an A-1 reaction (i.e. monomolecular decomposition of the protonated substrate). A value of -26 e.u. is typical of a reaction involving water in the rate-determining step. *J. Chem. Soc.*, **91**, 3594 (1969).

\[
\begin{align*}
\text{MeOCH} = \text{CH} & \quad \text{C} - \text{Me} + \text{H}^+ \\
\text{MeOCH} = \text{CH} & \quad \text{C} - \text{Me} \\
\text{MeOCH} & \quad \text{= CH} = \text{C} - \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{O} & \quad \text{Slow} \\
\text{HO} & \quad \text{MeOCH} = \text{CH} = \text{C} - \text{Me} + \text{H}^+ \\
\text{MeOCH} & \quad \text{= CH} = \text{C} - \text{Me} \\
\text{MeOCH} & \quad \text{= CH} = \text{C} - \text{Me} + \text{MeOH}
\end{align*}
\]

7.5 Above pH = 4.5 the slow step is dehydration which, as it is acid catalyzed, decreases with increasing pH. Below that pH, dehydration is so fast it is no longer rate-determining and the slow step is attack of free hydroxyl amine on the carbonyl double bond. However, with increasing acidity more of the hydroxyl amine becomes protonated and, therefore, unreactive and there is consequent decrease in rate. *J. Amer. Chem. Soc.*, **81**, 475 (1959).

7.6 The large change in $\Delta S$ in going from $t$-butyl to methyl indicates a change in mechanism. The large negative entropy of activation suggests that a water molecule is involved in the rate-determining step (see previous solution) and the mechanism for the methyl ester must be $S_{N} 1$ mechanism but it is difficult to give an interpretation to the positive entropy of activation. *Chem. Ind. (London)*, **1967**, 665.

7.7

Method B is the matter of choise: Threo
7.8 The intermediate phenonium ion forms by a stereospecific back side displacement by tosylate. Back side displacement by tosylate anion generated in that first step reforms starting material. Since formation of the phenonium ion is stereospecific, the intermediate from *erthro* reactant retains chirality and returns to optically active starting material. In the case of *threo*, the phenonium ion is symmetrical and leads back to racemic starting material.

\[
\text{threo-3-Phenyl-2-butyl tosylate} \rightarrow \begin{array}{c}
\text{Achiral} \\
\text{CH}_3 \text{CH}_3
\end{array}
\]

\[
\text{erythro-3-Phenyl-2-butyl tosylate} \rightarrow \begin{array}{c}
\text{Chiral} \\
\text{CH}_3 \text{CH}_3
\end{array}
\]

7.9 If alkyl-oxygen cleavage takes place, the oxygen atom of the alcohol product must come from the water.

\[
\begin{align*}
\text{CH}_3 \text{C} \text{OC(CH}_3)_3 + \text{H} & \iff \text{CH}_3 \text{C} \text{O} \text{O} \text{C(CH}_3)_3 \\
\text{H}_2\text{O} + \text{C(CH}_3)_3 & \iff \text{HO} \text{C(CH}_3)_3 + \text{H}^+
\end{align*}
\]

7.10 Most reactive to least reactive: b>a>d>e>c

7.11 The bromonium ion can be written as the following combination of resonance structures. The resonance form with the secondary carbocation will contribute more to the resonance hybrid than the form with the primary carbocation, so the secondary position will carry the greater positive charge, and hence will react more readily with the chloride.
PART 8

8.1 The second Br₂ molecule acts as a catalyst to enhance the displacement of Br⁻.

\[
\begin{align*}
\text{OCH}_3 \quad \text{Br} - \text{Br} \quad \ldots \quad \text{Br}_2 & \rightarrow \text{OCH}_3 \quad \text{Br} \quad \text{H} \quad \ldots \quad \text{Br}_3 \\
+ & \rightarrow \text{OCH}_3 \quad \text{Br} \quad \text{H} \quad \ldots \quad \text{Br}_2 \\
+ & \quad \text{HBr} \quad \text{Br}_2
\end{align*}
\]

8.2 An \(\alpha\)-substituent is close to the hydrogen atom on the 8-position (a peri relationship). There is less steric hindrance between the \(\beta\)-substituent and the adjacent hydrogen atoms since the groups point away from each other.

\[
\text{peri interaction}
\]

8.3 The alternative to formation of phthalic anyhydride is direct attack of water on the amide group [path (a)]. This would result in all the \(^{18}\text{O}\) occupying the carboxylic group labelled with \(^{13}\text{C}\). However, formation of the symmetrical anhydride leads to equal distribution of \(^{18}\text{O}\) between the two carboxylic groups.

\[
\begin{align*}
\text{H}_2^{18}\text{O} & \rightarrow \text{H}_2\text{O} \\
(a) & \rightarrow \text{H}_2\text{O} \\
(b) & \rightarrow \text{H}_2\text{O}
\end{align*}
\]

The product of reaction was analyzed by mass spectroscopy. The phthalic acid was decarboxylated and the amount of CO₂ of mass 47 determined. Pathway (b) should produce half of the amount of (a) and by knowing the isotopic composition of the reactants, the pathway (b) was shown to be the correct one.


8.4 a) The isomer with nitrogen in the equatorial position (right one) is more free to react.

b) The electron pair from the ring oxygen can participate (by diaxial interaction) when the phenolate group is leaving from the left compound. For the other compound the hydrolysis is slower as the ring oxygen is not in an good orientation for participation.

c) Both compound gives the same product. The ground state energy for the right compound is higher than for the isomer with equatorial hydroxyl group. As the energy differences are larger in the ground state than at transition state, the isomer with axial hydroxyl group will react faster than the equatorial isomer.
8.5 The appearance of $^{18}$O in the hydroxyl group indicates alkyl oxygen fission and inversion of configuration.

\[
\begin{align*}
\text{CH}_3\text{CH} & \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}O \xleftarrow{\text{OH}_2} \\
\text{CH} & \xrightarrow{} \text{CH}O
\end{align*}
\]

Therefore (+)-butyrolactone and (+)-β-hydroxybutyric acid must have opposite configurations. \textit{J. Amer. Chem. Soc.}, 60, 2687 (1938), \textit{J. Chem. Soc.}, 53, 2459 (1941)

8.6a) The conjugate base of 4-methylpyridine is stabilized by delocalization of charge by the nitrogen atom.

\[
\text{CH}_3\text{N} \xrightarrow{\text{BH}} \text{CH}_2\text{N} + \text{H}^+ + \text{BH}^-
\]

Direct conjugation of the negative charge with the nitrogen atom of 3-methylpyridine is not possible.

b) The decarboxylation of A leads by a favorable cyclic pathway, to a conjugated intermediate. Decarboxylation of B leads to an unstable aryl anion.

8.7 General acid-catalysis and the size of the $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$ ratio indicate a slow proton transfer as the rate-determining step. The proton will add to the CH$_2$ group, giving the following carbonium ion.

\[
\text{EtO}--\text{CH}==\text{CH}_2 + \text{HA} \xrightarrow{\text{Slow}} \text{EtO}--\text{CH}==\text{CH}_3 + \text{A}^-
\]

Subsequent reaction with water, a fast step, must involve fission of the C-OEt bond and not alkyl-oxygen fission as no $^{18}$O appears in the ethanol. The appearance of only one deuterium in acetaldehyde indicates that protonation cannot be an equilibrium process as this would lead to replacement of H by D in the vinyl ether and, after attack of D$_2$O, would give acetaldehyde containing more than one deuterium.

Kresge and Chiang, J.Chem. Soc. (B) 1967, 53

8.8 The inversion of the kinetic isotope effect indicates a change of mechanism.

In dilute acid the mechanism is the same as that for normal ester hydrolysis, i.e. attack of water on the protonated form of the ester. D$_3$O$^+$ is a stronger acid than H$_3$O$^+$ and there will be a higher concentration of protonated ester in D$_2$O than H$_2$O, so the rate will be faster in the D$_2$O.

In more concentrated acid the rate is \textit{slower} in D$_2$O than H$_2$O. This indicates that the rate-determining step is protonation of the ester go give a carbenium ion, followed by rapid attack of water.
In this case the slow step involves fission of an O-H or O-D bond and, as the latter is stronger, the rate will be slower in D$_2$O. *J. Amer. Chem. Soc.* 91, 119 (1969).

8.9 Clearly the C-H or C-D bond is broken in the rate-determining step and, as the C-D bond is stronger, the deuteriated compound reacts more slowly. The slow step is ionization of the nitromethane, catalyzed by the acetate ion acting as a base, and the anion of nitromethane reacts rapidly with bromine. *Physik. Chem. Frankfurt,* 176, 363 (1936).

\[
\begin{align*}
O_2N\text{CH}_3 + \text{CH}_3\text{COO}^- & \quad \text{Slow} \quad \rightarrow \quad O_2N\text{CH}_2^- + \text{CH}_3\text{COOH} \\
O_2N\text{CH}_2^- + \text{Br}_2 & \quad \text{Fast} \quad \rightarrow \quad O_2N\text{CH}_2\text{Br} + \text{Br}^-
\end{align*}
\]

8.10 A plot of log k/k$_O$ versus $\sigma$ is linear and the slope of this line (i.e. $\rho$ is -3.4).

From the known value of $\sigma$ for fluorine the ratio k$_F$/k$_O$ = 0.62 and this gives k$_F$ = 4.0 x 10$^{-5}$ sec$^{-1}$. The value for methyl o-methoxybenzoate is much greater than that of the m- or p-isomers showing that, as expected for an o-substituent, it does not fit a simple Hammett $\alpha$ $\rho$ plot. There is no obvious reason why the p-methoxy compound should not lie on the line obtained for the other compounds, but, by using the value of $\sigma$ for methoxy, the rate is found to be enhanced.

Hydrolysis in concentrated sulphuric acid involves formation of a carbonion (1)

\[
O_2N\text{C}\text{OMe}\text{O} \quad + \quad \text{H}^+ \quad \leftrightarrow \quad \text{HO}\text{C}\text{OMe}\text{O} \quad + \quad \text{MeOH} \quad \text{Fast} \quad \rightarrow \quad \text{COOH} \quad + \quad \text{H}^+ \quad + \quad \text{MeOH}
\]

and substitution will greatly affect the case with which 1 forms. In dilute acid however, the slow step is attack of water on the protonated ester:

\[
\text{H}_2\text{O} + \quad \text{HO}\text{C}\text{OMe}\text{O} \quad \rightarrow \quad \text{COOH} \quad + \quad \text{H}^+ \quad + \quad \text{MeOH}
\]

and this reaction is much less sensitive to substituents. The enhanced rate for the p-methoxy compound is not easy to understand, but the system must gain some con-jugative energy in going from the protonated ester to the transition state for hydro-lysis. With the o-methyl compound steric strain will be lost on going to the transition state as it is less space-demanding than the protonated ester, leading to an enhanced rate of reaction. *Rec. Trav.Chim.* 88, 301 (1969) and *J.Chem. Soc.*, 1938, 862

8.11a) In gas phase is the COO$^-$ group less stabilized than in water.

Substituent stabilizing the anion will therefore have larger effect.

b) The anion of benzoic acid have it's charge more spread over the phenyl ring.

c) In water the solvent is organizedby solvation.
8.12 The fact that 2 and 3 have similar pH rate profiles with rates which increase as the pH is increased, suggests that the reaction is simple hydrolysis of the carbonate group by hydroxide ion. The elected rate for 1 at lower pH indicates involvement of the o-hydroxy group. The most obvious possibility is rate-determining attack by the ionized hydroxy group on the carbonyl group.

\[ \text{(i) } \begin{array}{c} \text{O} \\ \text{C} \\ \text{OEt} \\ \text{O} \end{array} \quad \text{(ii) } \begin{array}{c} \text{O} \\ \text{C} \\ \text{OEt} \\ \text{O} \end{array} \] 

However, this cyclic mechanism should be associated with a small entropy of activation, as it requires very little ordering of the molecules. A more likely mechanism is assisted of a water molecule, which should have a negative entropy of activation. Tetrahedron Letters, 1971, 911.

8.13 a) Hyperconjugation \( k_H/k_D > 1 \) (but < 2) Normal secondary K.I.E..
 b) \( \text{Sp}^2 \) to \( \text{sp}^3 \) Inverse secondary K.I.E. \( k_H/k_D < 1 \).
 c) \( \text{Sp}^3 \) to \( \text{sp}^2 \) Normal secondary K.I.E. \( k_H/k_D > 1 \).

8.14 In the base-catalysed iodination of acetone the rate-determining step is proton removal to give a carbanion. The rate maximum with \( n = 2 \) suggest that the ionized carboxylate group may assist in the removal of a proton. This results in a six-membered cyclic transition state. There is then rapid attack of iodine on the resulting carbanion. With \( n = 3 \) or more a more strained transition state results.

\[ \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{OH} \quad + \quad \text{I}_2 \quad \text{H}_2\text{C} \quad \text{CHI} \quad \text{OH} \] 

When there is no ionizable group (i.e. the ethyl ester) the compound with \( n = 2 \) does not show the same rate enhancement. Trans. Faraday Soc., 66, 930 (1970).

8.15. c will react only by protonating the Grignard reagent to give benzene. a will not react. b, d, and e will react as follows:

b

\[ \text{O} \quad \text{PhMgBr} \quad \text{HO} \quad \text{Ph} \] 

d

\[ \text{OEt} \quad \text{PhMgBr} \quad \text{HO} \quad \text{Ph} \] 

e

\[ \text{PhMgBr} \quad \text{F} \quad \text{Ph} \]
8.16. The mechanism is shown below. In the sequence leading to the other isomer, the methoxy group would be adjacent to the negative charge in the intermediates, which is unfavourable because of the interaction between the negative charge and the oxygen lone pair.

8.17 The carbene must have been in the triplet configuration. A singlet carbene would give a concerted reaction, conserving the stereochemistry of the olefin.

8.18 In the first pair, either compound can form an enolate, and this can react with either compound, giving four possible products. In the second pair, the aromatic aldehyde cannot form an enolate, but is much more electrophilic than the ketone, so the only product that forms is from the enolate of the ketone reacting with the aldehyde.

8.19

A: \[ \text{N} \quad \text{OH} \]

B: \[ \text{N} \quad \text{OH} \]

8.20
8.21 The stereochemistry of the intermediate is determined by the trans addition of bromine. This intermediate must adopt a conformation in which a bromine is antiperiplanar to a hydrogen to eliminate HBr, leading to the geometry of the product as shown.

8.22 The intermediate \( \alpha \)-lactone can be opened intramolecularly by the hydroxyl group to give a protonated epoxide that can be opened by chloride at either end.

8.23a) The hydrolysis reaction could be carried out in \(^{18}\)O-labelled water. The label would end up in the carboxylic acid if the acyl-oxygen bond were cleaved (as it normally is) and in the alcohol if the alkyl-oxygen bond were cleaved.

b). Although the rate laws are different, in practice it would not be possible to distinguish between the mechanisms directly. The rate law for normal acid hydrolysis is rate = \( k [H^+] [\text{Ester}] [H_2O] \), and that for hydrolysis of a tertiary ester with cleavage of the alkyl-oxygen bond is rate = \( k [H^+] [\text{Ester}] \). Since water is present in large excess in such reactions, we will not see the effect of it when measuring the rate. Another piece of evidence that could be used to verify this mechanism is to look at the stereochemistry if a chiral tertiary alkyl group is used. If the alkyl-oxygen bond remains intact, then the stereochemistry of this group must be conserved. If the reaction takes place with inversion or racemization at this group, then this shows that the alkyl-oxygen bond must be cleaved at some point during the reaction.

8.24 The products of the reaction could be subjected to the reaction conditions for extended periods of time. If the ratio of products is unchanged, then this would show that the hydrazino compound could not be an intermediate in the formation of the reduced product.
This tells us that the rate-determining step (RDS) does not involve bromine, but that acetone is deprotonated in this step. We can postulate a mechanism in which the RDS is enolization, which is followed by fast reaction with bromine.