Organic Chemistry-2
Semester-2, CBCS
Course: CEMA CC-2-3-TH

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Recommended texts:
Elimination reactions:

Pyrolytic syn-elimination (E1):

There are certain substrates that, when heated strongly, undergo spontaneous elimination. These reactions are called pyrolytic eliminations (pyro from the Greek *pyr* meaning fire, i.e. heat) and they are usually carried out in gas phase, although, there are examples of such reactions in solution phase as well.

When carried out in the gas phase, these reactions are *not affected by solvent, counterions, or other species that can affect reactions in solution*. These eliminations occur without the presence of any external base, implying that the mechanism must be fundamentally different from those (E2, E1cB and E1) we have discussed so far.

These reactions are *intramolecular in nature with the mechanistic descriptor of E1 (elimination, intramolecular) assigned to them*. Experimental evidences strongly point to a syn elimination mechanism for most of the cases. We will discuss three substrate class for these reactions, but there are many more examples.

A) Pyrolysis of carboxylic acid esters:

*Esters that have at least one β-hydrogen* are capable of undergoing E1 when heated strongly at 300-500°C, yielding an olefin and a carboxylic acid:

\[
\text{alcohol} + \text{ester} \xrightarrow{\text{Et}_3\text{N}, \text{heat}} \text{alkene} + \text{carboxylic acid}
\]

At this temperature range, *only vapour phase pyrolysis can happen*, so this reaction is carried out in gas phase. The mechanism is believed to proceed by a single-step, intramolecular process, through the involvement of a *six-membered cyclic TS*:

*Intermolecular reactions are very unlikely to happen in the vapour phase.*

The carbonyl oxygen of the ester group thus acts as the base here. For this to happen, the high-energy, eclipsed, syn-periplanar conformation must be accessed. The *anti*-periplanar or gauche conformers are undoubtedly more populated but the larger distance between the β-H(s) and the ester group won't permit any intramolecular proton abstraction there. As the population of the reactive conformation is intrinsically low, very high temperatures are required to carry out the reaction.

The cyclic, ordered TS implies that the *entropy of activation (ΔS^‡)* should be *largely negative* and that is indeed found to be the case.
Elimination reactions:

Pyrolytic syn-elimination (E1):

A] Pyrolysis of carboxylic acid esters:

The syn-elimination was experimentally proved by the pyrolysis of the erythro and threo-2-deuterio-1,2-diphenylethyl acetate.

Although the product of both reactions is trans-stilbene, the product from the erythro-isomer retains almost all of the deuterium label, while the olefinic product from the threo isomer loses most of the deuterium label.

These observations can be explained by considering the reactive conformation for each of the diastereoisomer from where the syn-elimination of the acetoxy group and the hydrogen or the deuterium atom ensues. That eclipsed conformation is more accessible where the two phenyl groups are as far apart as possible and this is what determines the fate of the deuterium label in the respective products.

The TSs where the two phenyls are eclipsed are less accessible compared to those where those phenyls are far apart.

These acetate pyrolysis reactions are stereospecific (why?). Also notice that if anti-elimination were to occur, we would have had the non-deuterated trans-stilbene form the erythro and the deuterated trans-stilbene from the threo isomer as the major product respectively. But that doesn’t happen. So anti-elimination can be ruled out.
Elimination reactions:

Pyrolytic syn-elimination (Ei):

A] Pyrolysis of carboxylic acid esters:

The syn-elimination is also evident from the following series of experiments with the two diastereoisomeric esters:

\[
\begin{align*}
\text{Me} & \quad \text{OAc} & \quad \text{Me} & \quad \text{OAc} \\
\text{Me} & \quad \text{Me} & \quad \text{heat} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{CH}_2 & \quad \text{Me}
\end{align*}
\]

This can be explained in the following way:

for

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{OAc} \\
\text{Me} & \quad \text{Me} & \quad \text{H}_2 \quad \text{Me} & \quad \text{H}_2 \quad \text{Me}
\end{align*}
\]

C-6 H and C-1 OAc can be syn

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

one of the C-5 H and C-1 OAc can be syn

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

no syn-elimination b/w C-1 and C-2 possible

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

the C-2 H and C-1 OAc are anti
Elimination reactions:

Pyrolytic syn-elimination (E1):

A] Pyrolysis of carboxylic acid esters:

The regioselectivity of acetate pyrolysis is rather modest and is affected by several factors, in particular the stability of the alkene produced (actually the stability of the respective TSs leading to those alkenes) and the number of \( \beta \)-hydrogens available.

When these two factors oppose each other, the regioselectivity is modest, e.g. the following reaction affords a 1:1 mixture of two alkenes:

\[
\begin{align*}
\text{six such primary hydrogens} & \quad \text{Ph} \quad \beta' \quad \beta' \quad \text{H} \\
\text{two such secondary hydrogens} & \quad \text{OAc} \\
\text{300-575°C} & \quad \text{Ph} \quad \text{Me} + \text{Ph} \quad \text{Me} \\
\end{align*}
\]

less stable alkene - non-conjugated

more stable alkene - conjugated

OTOH, if the stability difference between the two alkenes is not as great as seen in the previous example, the statistical factor may solely guide the regioselectivity:

\[
\begin{align*}
\text{two such secondary hydrogens} & \quad \text{Me} \quad \text{H} \quad \text{H} \\
\text{three such primary hydrogens} & \quad \text{OAc} \\
\text{heat} & \quad \text{Me} \quad \text{Me} + \text{Me} \\
\end{align*}
\]

2-butene (38-45%) (mainly E-isomer)

1-butene (55-62%)

product ratio approximately 2:3

This is a good opportunity for you to draw the two conformations of 2-butyl acetate that are responsible for generating the E- and Z-2-butene and convince yourself that the E-alkene should indeed be the major product. The starting ester is chiral here, but you can start from any enantiomer, that won’t make any difference in this analysis.

The rate of acetate fragmentation depends upon the nature of the alkyl group, with the relative rates of elimination of ethyl, isopropyl and isobutyl acetates being 1: 26 : 1660. Notice how the statistical factor as well as the alkene stability both favour the pyrolysis of the tertiary alcohol ester:

\[
\begin{align*}
\text{nine such primary hydrogens} & \quad \text{Me} \quad \text{O} \quad \text{O} \quad \text{H} \\
\text{TS features partly-formed C=C of a disubstituted alkene} & \quad \text{Me} \quad \text{O} \quad \text{H} \\
\text{+} & \quad \text{Me} \quad \text{CO}_2 \quad \text{H} \\
\end{align*}
\]
Elimination reactions:

Pyrolytic syn-elimination (Ei):

B) Pyrolysis of xanthates:

One of the most-studied pyrolytic eliminations is the **pyrolysis of xanthates, known as the Chugaev reaction** (Tschugaeff reaction).

Xanthate esters are made by reacting alcohols with a base such as NaOH, KOH or NaH, followed by reaction of the alkoxide with carbon disulfide and then capturing the metal xanthate by $S_{N2}$ reaction with an alkyl halide, usually methyl iodide.

**Preparation of xanthates:**

When the starting alcohol possess at least one $\beta$-hydrogen, pyrolytic elimination becomes possible. The xanthate ester is purified as much as possible and is then heated, usually by distillation at atmospheric pressure and at temperatures in the region of 150-250°C, to induce decomposition to an alkene along with carbon oxysulfide and a mercaptan (thiol). The stereochemistry of the elimination is syn and it proceeds through a six-membered cyclic TS, like that we have seen for pyrolysis of acetates:

**Chugaev reaction:**

Overall, this is a **transformation of an alcohol into an olefin**.

The **temperature** at which the xanthates get pyrolysed is **significantly less** than that required for acetates.

This is because - i) **xanthate pyrolysis is entropically more favourable**, generating three product molecules, olefin, thiol and carbon oxysulfide from one reactant molecule, the xanthate ester while for acetate pyrolysis we get two product molecules, the olefin and the acetic acid from one reactant molecule, the acetate ester, and ii) a strong C=O bond forms at the expense of a relatively weak C=S bond here.

The lower reaction temperature is synthetically useful as this avoids side reactions such as decomposition and isomerisation of the product alkenes, the problems that are regularly seen in acetate pyrolysis.
Elimination reactions:

Pyrolytic syn-elimination (Ei):

B) Pyrolysis of xanthates:

The syn-stereochemistry was proved by the stereospecific pyrolysis of the diastereoisomeric S-methyl xanthates of 3-phenyl-2-butanol:

The syn-stereochemistry was also demonstrated in cyclic systems:
Elimination reactions:

Pyrolytic syn-elimination (E1):

B) Pyrolysis of xanthates:

For acyclic system there is a modest preference for 1,2-disubstituted product to be obtained with E-stereochemistry but the regioselectivity is often rather weak because of the two opposing factors - product stability (rather TS stability leading to olefins) and statistical factors.

For this reason, simple xanthate esters derived from acyclic secondary alcohols often give mixture of products.

\[ \text{O} \quad \text{S} \quad \text{S} \quad \text{Me} \]
\[ \text{O} \quad \text{S} \quad \text{S} \quad \text{Me} \]
\[ \beta' \quad \beta' \quad \beta' \quad \beta' \]
\[ \beta'-\text{H} : \beta-\text{H} = 1 : 1 \]
\[ \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \]
\[ (28\%) + (13\%) \]
\[ (29\%) + (13\%) \]
\[ \text{E}-\text{isomers are the minor products as the corresponding TSs are destabilized by the close proximity of two alkyl groups.} \]
\[ \beta'-\text{H} : \beta-\text{H} = 3 : 1 \]

Chugaev reaction's substrate scope is limited. The reaction is nonetheless useful because it provides a means of dehydration of alcohol without the possible complications of carbocation rearrangement (recall in this regard the acid-catalysed E1 reactions of alcohols).

A case in point is the synthesis of 3,3-dimethyl-1-butene (t-butyl ethylene). It is synthesised from pinacolyl alcohol via xanthate pyrolysis. When acid-catalysed E1 elimination is attempted on this substrate, carbocation rearrangement leads to the formation of 2,3-dimethylbut-2-ene as the major product. The synthetic utility of this reaction is also enhanced by the fact that there is no possibility of formation of regioisomeric olefin mixture.

\[ \text{O} \quad \text{NaBH}_4 \]
\[ \text{pinacolone} \]
\[ \text{O} \quad \text{OH} \]
\[ \text{pinacolyl alcohol} \]
\[ \text{1. KOH, CS}_2 \quad 2. \text{Mel} \]
\[ \text{O} \quad \text{SMes} \]
\[ \text{200°C} \]
\[ \text{H}_2\text{SO}_4, \text{H}_2\text{O}, \text{heat} \]
\[ \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \]
\[ \text{1,2] Me shift} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \]
\[ \text{2,3-dimethylbut-2-ene} \]

The other advantage of this selective method of alcohol dehydration is avoiding the acid medium altogether, which may cause damage to other acid-sensitive parts of certain substrates.
Elimination reactions:

Pyrolytic syn-elimination (E1):

C) Pyrolysis of N-oxides: Cope elimination:

Another well-known concerted syn-elimination is the Cope elimination, which involves thermal fragmentation of a suitable tertiary amine oxide into an alkene and a hydroxylamine derivative. The tertiary amine oxide must contain at least one β-hydrogen and it can be easily made by oxidizing the corresponding tertiary amine.

Unlike the acetate of xanthate pyrolysis, this syn-elimination involves a five-membered cyclic TS. The anionic oxygen atom is the base here.

$$\begin{align*}
\text{H} & \quad \text{Me} \\
\text{N} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

 tertiary amine with at least one β-H

$$\begin{align*}
\text{H} & \quad \text{Me} \\
\text{N} & \quad \text{Me} \\
\text{H} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

tertiary amine oxide

$$\begin{align*}
\text{H} & \quad \text{Me} \\
\text{N} & \quad \text{Me} \\
\text{H} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

five-membered cyclic TS

The syn-stereochemistry of the reaction was demonstrated by the stereospecific Cope elimination of the diastereoisomeric 2-amino-3-phenylbutane oxides.

$$\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Me}
\end{align*}$$

threo isomer

$$\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{Me}
\end{align*}$$

Φ-H eclipsed

$$\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

Ph-Φ eclipsed

Interestingly, the threo isomer reacts at a lower temperature than the erythro.

This is rationalised by the fact that for the erythro isomer, the TS is more destabilized due to the presence of the phenyl-methyl eclipsing interaction while the TS for the threo isomer avoids that successfully.

$$\begin{align*}
\text{Me} & \quad \text{β} \\
\text{H} & \quad \text{H} \\
\text{Ph} & \quad \text{N} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

erythro isomer

$$\begin{align*}
\text{Me} & \quad \text{H} \\
\text{Ph} & \quad \text{Me}
\end{align*}$$

(90%)

$$\begin{align*}
\text{Me} & \quad \text{β} \\
\text{H} & \quad \text{H} \\
\text{Ph} & \quad \text{N} \\
\text{Me} & \quad \text{Me}
\end{align*}$$

erythro isomer

$$\begin{align*}
\text{Me} & \quad \text{H} \\
\text{Ph} & \quad \text{Me}
\end{align*}$$

(7%)
Elimination reactions:

Pyrolytic syn-elimination (E1):

C] Pyrolysis of N-oxides: Cope elimination:

However, in absence of such a large difference between the acidities of protons on different β-carbons, the regioselectivity of Cope elimination is in general almost solely guided by the number of such β-protons available for abstraction from each alkyl group:

Two such secondary hydrogens

three such primary hydrogens

Product ratio approximately 2:3

Two such secondary hydrogens

One tertiary hydrogen

Product ratio approximately 2:1

This regioselectivity is in stark contrast to E2 elimination of quaternary ammonium salts where there is an overwhelming preference for the Hofmann product:

Product ratio approximately 1:49
Elimination reactions:

Pyrolytic syn-elimination (Ei):

C] Pyrolysis of N-oxides: Cope elimination:

The reaction is **stereoselective** and favours the formation of the $E$-alkene by minimising the eclipsing interactions in the TS:

\[
\begin{array}{c}
\text{Me} \quad \text{Et} \\
\text{O} \quad \text{N} \\
\text{O} \quad \text{Me}
\end{array}
\]

**TS leading to the $Z$-alkene**

\[
\begin{array}{c}
\text{Me} \quad \text{Et} \\
\text{O} \quad \text{N} \\
\text{O} \quad \text{Me}
\end{array}
\]

**TS leading to the $E$-alkene**

\[
\begin{array}{c}
\text{Me} \quad \text{Et} \\
\text{O} \quad \text{N} \\
\text{O} \quad \text{Me}
\end{array}
\]

The temperature required for Cope elimination is much less than that for acetate or xanthate pyrolysis. Heating at only 100-150°C is sufficient and sometimes even lower temperatures can be used. The reason for this is threefold -

i) In Cope elimination the species that abstracts the proton from the $\beta$-position is an anionic oxygen atom which is a much stronger base than either the carbonyl oxygen (as in acetate) or thiocarbonyl sulfur (as in xanthate). As the base strength increases, the activation energy for intramolecular proton abstraction drops, reaction can be done at a much lower temperature,

\[
\begin{array}{c}
\text{O} \quad \text{R} \\
\text{O} \quad \text{S} \\
\text{O} \quad \text{N}
\end{array}
\]

acetate pyrolysis  xanthate pyrolysis  $N$-oxide pyrolysis

more basic centre

ii) the N-oxide is a 1,2-dipole where clear cut charge separation is present. On elimination, the charges disappear in the products. This **charge neutralisation** is another driving force that facilitates this reaction, and

\[
\begin{array}{c}
\text{O} \quad \text{R} \\
\text{O} \quad \text{S} \\
\text{O} \quad \text{N}
\end{array}
\]

acetate pyrolysis  xanthate pyrolysis  $N$-oxide pyrolysis

weaker bond

iii) the weak C-N+ bond breaks in the substrate.

For reasons already mentioned, the milder reaction condition makes this elimination reaction synthetically useful.
Elimination reactions:

Pyrolytic syn-elimination (E1):

C]Pyrolysis of N-oxides: Cope elimination:

The other interesting feature of Cope elimination is the extraordinarily sensitivity of the reaction rate to solvent effects.

i) A million-fold increase can be obtained going from protic to aprotic solvents.
ii) Within aprotic solvents, decreasing polarity significantly increases the reaction rate.

The relative rate retardation for Cope eliminations in protic solvents (i.e. those solvents that can act as hydrogen bond donors) is a result of the hydrogen bonding between the amine oxide and the solvent which reduces the basicity of the anionic oxygen atom.

When aprotic solvents are used, the anionic oxygen is free from H-bonds, and it becomes a far stronger base, leading to an increase in the rate.

The other way of looking at this solvent effect is to take into consideration the differential effect of solvents upon the reactant and the TS.

Notice how the amine oxide reactant (where charge is well separated) is much more polar than either the TS (where charges are partly neutralised) or the product alkene and hydroxylamine derivative (where charges are fully neutralised).

Therefore, when protic solvents are used, the reactant is much more effectively solvated than either the TS or the products. This leads to a relatively high activation energy, and a slow rate of reaction in protic solvents.

When the protic solvent is replaced by an aprotic solvent (the one that cannot act as an H-bond donor), the rate would increase dramatically. The reactant, the TS and the products, all of them will suffer from a lack of solvation because the solvent cannot offer any H-bonding opportunities now, but the extent of desolvation wouldn't be the same. Due to its more prominent polar nature, the reactant will suffer from the lack of solvation to a much greater extent than either the TS or the product.

As a result, on moving from a protic to an aprotic solvent, the reactant will be more destabilised than the TS will be. This implies that the activation energy would decrease and rate will become faster.

This is very much like the solvent polarity effect observed for an SN2 reaction between an uncharged electrophile R-X and a negatively charged nucleophile \( \text{Nu}^- \). Recall that the reactant is more polar than the TS there as well.
Elimination reactions:

Pyrolytic syn-elimination (Ei):

C) Pyrolysis of N-oxides: Cope elimination:

Seleno-Cope / selenoxide elimination: An important technique to prepare $\alpha,\beta$-unsaturated double bonds:

An extension of Cope elimination reaction is the selenoxide elimination which is a regioselective, mild method for the preparation of $\alpha,\beta$-unsaturated carbonyl compounds that can serve as useful synthetic precursors. The following scheme is instructive:

Concluding remarks: These syn-elimination reactions are pericyclic in nature, belonging to the group transfer reaction class. More precisely, the acetate and xanthate elimination reactions represent retro-ene reactions, while N-oxide and selenoxide eliminations are examples of 1,2-dipolar retro-ene.

Any further analysis of these classes of reactions are reserved for future.