Organic Chemistry-2

Semester-2, CBCS

Course: CEMA-CC-2-3-TH

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Recommended texts:

Elimination reactions:

E2 reaction:

Stereochemical outcome of E2 reaction: Stereospecificity:

The stereoelectronic requirement of anti-orientation of the groups being eliminated sometimes dictate that stereoisomeric starting materials afford stereoisomeric products, an outcome known as stereospecificity.

A reaction is termed stereospecific if the starting materials differing only in their configuration are converted into stereoisomeric products. This is best understood with an example.

Consider an organohalide that can exist in two different diastereoisomeric forms, stilbene dibromide:

- **meso-isomer** and **active isomer** (one of the enantiomeric pair)

When these isomers are separately treated with NaOEt, we get the dehydrobromination reactions via E2 mechanism. The products are also diastereoisomeric to each other:

- **meso-isomer**
  - When treated with NaOEt, it gives an **(E)-alkene**
  - Note how the two phenyls are on the same side yet the configuration is not \( Z \), but \( E \)

- **active isomer**
  - When treated with NaOEt, it gives a **(Z)-alkene**
  - Note how the two phenyls are on the opposite side yet the configuration is not \( E \), but \( Z \)

CIP priority of \( Br > Ph \)

These reactions are stereospecific, as the choice of the starting material dictates which stereoisomer of the product would form.

- If we are to synthesise the \( E \)-alkene, we need to take the meso-dibromide as the substrate.
- But if we want the \( Z \)-alkene, we must take one of the active dibromide isomers.
- In addition, a most striking feature of this reaction is the unusually slow rate at which the meso-isomer reacts whereas the active-isomer reacts much faster.

We need to explain these issues.
Elimination reactions:

E2 reaction:

Stereochemical outcome of E2 reaction: Stereospecificity:

\[
\begin{align*}
\text{meso-isomer} & \xrightarrow{\text{NaOEt}} \text{alkene} \\
\text{active isomer} & \xrightarrow{\text{NaOEt}} \text{alkene}
\end{align*}
\]

Remember that in each case, be it the meso or the active isomer, the hydrogen and the bromine on adjacent carbons must be placed anti to each other. Once that is done, we have to see how that arrangement in a particular steroisomer of the reactant influences the stereochemistry of the product.

Let us consider the relevant conformers then for both the meso- and the active dibromides:

Formation of E-alkene:

For the meso-isomer, placing any one of H and the Br on its adjacent carbon anti to each other implies that the alkene that is formed have the E-configuration. There is no other choice. You are welcome to choose the other H,Br pair for this stereoisomer and try the E2, placing those groups anti - you will still end up with the same E-alkene. The mechanism imposes this restriction here. You cannot form a Z-alkene from this molecule unless you do the reaction from the syn-periplanar conformation. And that is impossible because the anti-form being available any dehydrobromination will proceed only from there.

Formation of Z-alkene:

With the active isomer, OTOH, the anti-periplanar arrangement of any one of H and the Br on its adjacent carbon leads to the Z-alkene. Again, your hands are tied, and there is no other choice, it doesn't matter which hydrogen you start with. If you are to form an E-alkene from this molecule, you have to do the reaction from a syn-periplanar conformation, and that, as you know by now, is not going to happen.

Notice how these stereospecific reactions automatically qualify as stereoselective reactions as well, because one steroisomer of the product is preferentially formed. However, not all stereoselective reactions are stereospecific in nature, as we will see later.
Elimination reactions:

E2 reaction:

Stereochemical outcome of E2 reaction: Stereospecificity:

\[
\text{meso-isomer} \quad \text{NaOEt} \quad \text{meso-isomer} \quad \text{(E)-alkene} \quad \text{is slower than} \quad \text{active isomer} \quad \text{NaOEt} \quad \text{(Z)-alkene}
\]

In order to explain the difference in rates between the two diastereoisomeric dibromides, we have to inspect two things:

i) for any strain that is present in the particular conformer from which the E2 takes place and

ii) then judge whether the corresponding TS suffers from the same destabilization or not.

Formation of E-alkene:

The meso isomer reacts at a slower rate compared to the active isomer because the former has the following problems -

- i) the concentration of the reactive conformer (where H and Br are anti) is very low because of the destabilising gauche interactions between the two phenyl rings and the dipolar repulsion between two C-Br dipoles, and

- ii) the TS is destabilised due to the close proximity of the two phenyl rings which come even closer to each other as the reaction proceeds (notice how the gauche phenyls eventually become eclipsed in the product alkene).

Formation of Z-alkene:

Study Guide to Organic Chemistry
- Saha et al. Volume 2 (ISBN 9788192669588)
Elimination reactions:

E2 reaction:

Stereochemical outcome of E2 reaction: Stereospecificity:

The dehydrobromination reaction of meso-isomer of stilbene dibromide is so slow that given any other option, this molecule will exercise that.

A case in point is the treatment of the active and the meso-isomers of this dibromide with pyridine.

While the active isomer still undergoes dehydrobromination and affords the (Z)-1-bromo-1,2-diphenylethene, the meso-isomer, instead of HBr elimination, opts for debromination (loses Br₂, another E2 reaction) and produces E-stilbene!

How does that happen?

This result suggests that to the meso-isomer - i) the reactive conformer for the debromination, where the two bromines need to be placed anti, is much more accessible than the reactive conformer for dehydrobromination, and ii) the TS for the debromination reaction must be more easily accessed than the TS for the dehydrobromination, i.e., the debromination TS is more stable than the dehydrobromiation TS.

Let's check whether these assumptions are correct:

Dehydrobromination:

![Dehydrobromination diagram]

The meso-isomer opts for the debromination because both the reactive conformer and the TS related to that reaction is more accessible than the corresponding conformer and TS related to the dehydrobromination.

The debromination is a viable alternative with pyridine (and also with zinc, or iodide), but not with ethoxide, which, when used, results in a slow dehydrobromination only.

Debromination:

![Debromination diagram]

as O is a hard base / nucleophile & Br is soft, O prefers to attack the β-H and not the β-Br.
Elimination reactions:

E2 reaction: Stereochemical outcome of E2 reaction: Stereospecificity:

The active isomer, even when treated with pyridine, loses HBr and not Br₂. Let us try to understand why the dehydrobromination is a much better option than debromination for this substrate.

Dehydrobromination:

\[
\text{active isomer} \rightarrow \text{conformer-b (stabilised, more populated)} \rightarrow (Z)-1\text{-bromo-1,2-diphenylethene}
\]

The active isomer opts for the dehydrobromination because both the reactive conformer and the TS related to that reaction is more accessible than the corresponding conformer and TS related to the debromination.

Debromination:

\[
\text{active isomer} \rightarrow \text{conformer-a (destabilised, less populated)} \rightarrow \text{Z-stilbene}
\]

when B = ethoxide or pyridine

Summary of the results of these E2 reactions:

<table>
<thead>
<tr>
<th>reactant (stilbene dibromide)</th>
<th>products formed with NaOEt</th>
<th>products formed with pyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>meso-isomer</td>
<td>(via HBr elimination)</td>
<td>(via Br₂ elimination)</td>
</tr>
<tr>
<td>E-isomer</td>
<td></td>
<td>E-stilbene</td>
</tr>
<tr>
<td>active isomer</td>
<td>(via HBr elimination)</td>
<td>Z-isomer</td>
</tr>
</tbody>
</table>

Note:

When B is pyridine, it can effect both dehydrobromination and debromination.

It depends on the starting isomer. When B is NaOEt, for both isomers, dehydrobromination is the outcome.
Elimination reactions:

E2 reaction: Stereochemical outcome of E2 reaction: Stereospecificity:

Before ending this section, let us revisit the concept relating to stereoselective and stereospecific reactions.

*We have stated that stereospecific reactions are always steroselective in nature, but the reverse is not always true.*

The first part of this statement is easy to understand. Let us rationalize that.

For a stereospecific reaction, one particular stereoisomer of the reactant affords one particular stereoisomer of the product while a different stereoisomer of the reactant gives a different stereoisomer of the product. Hence, to determine whether a reaction is stereospecific, we have to examine the product ratio from the different stereoisomers of the reactant. *Because the other stereoisomer(s) of the product is either not formed at all (100% stereospecific, as we have seen the dehydrobromination of the meso and the active isomers of stilbene dibromide) or formed as a minor product (we have not seen many example of this), a stereospecific reaction always results in preferential formation of one of the stereoisomers of the product and hence, by definition, it is stereoselective.*

The second part, i.e. not all stereoselective reactions are stereospecific are best understood by particular examples.

Consider the following E2 reaction of 2-bromopentane:

\[
\text{Br} \quad \xrightarrow{\text{NaOEt}} \quad (E)-\text{pent-2-ene (51%)} + (Z)-\text{pent-2-ene (18%)} + \text{pent-1-ene (31%)}
\]

Just by looking at the product composition, we can tell the following:

a) the reaction is regioselective, 69% of the product mixture is the more substituted alkene, the Zaitsev product,

b) the reaction is stereoselective, more accurately, diastereoselective, because the *E*-alkene is formed in preference to the *Z*-alkene.

Is it stereospecific?

For that we need to check the two stereoisomers (in this case enantiomers) of the starting organohalide separately and see the product ratio produced by each. In this case, it turns out that the same product mixture is obtained, irrespective of the configuration of the starting material 2-bromopentane:

\[
\begin{align*}
\text{(R)-2-bromopentane} & \quad \xrightarrow{\text{NaOEt}} \quad (E)-\text{pent-2-ene (51%)} + \text{pent-1-ene (31%)} \\
\text{(S)-2-bromopentane} & \quad \xrightarrow{\text{NaOEt}} \quad (Z)-\text{pent-2-ene (18%)}
\end{align*}
\]

Why is that? Because the TSs for the formation of each of the three products from the two enantiomers are themselves enantiomeric to each other and therefore those products are formed at exactly the same rate from either the R- or the S-isomer.
Elimination reactions:

E2 reaction: Stereochemical outcome of E2 reaction: Stereospecificity:

In the base-induced dehydrobromination of 2-bromopentane, the same product mixture is obtained, irrespective of the configuration of the starting material:

\[
\text{(R)-2-bromopentane} \quad \xrightarrow{\text{NaOEt}} \quad \text{(E)-pent-2-ene (51\%)} \quad + \quad \text{pent-1-ene (31\%)} \quad + \quad \text{(Z)-pent-2-ene (18\%)}
\]

Why is that?

Because the TSs for the formation of each of the three products from the two enantiomers are themselves enantiomeric to each other and therefore those products are formed at exactly the same rate from either the R- or the S-isomer.

We will demonstrate this with the two TSs for the formation of the major product, E-2-pentene from both the R- and S-organohalide.

This result means that these two E2 reactions are not stereospecific, because no matter which stereoisomer of the starting material is taken, we get the same product composition and that, by the definition of stereospecific reaction, does not qualify. This set thus represents an example of reactions that are stereoselective, but not stereospecific.