Organic Chemistry 1B
Semester-2, CBCS
Course: CEMA CC-2-3-TH

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Recommended texts:

Intermolecular and intramolecular reactions:

Consider the following two reactions where an anhydride (-O-CO-O-) linkage is formed:

**Reaction-1**

\[
\begin{align*}
\text{MeCO}_2\text{H} + \text{MeCO}_2\text{H} & \xrightarrow{\text{heat}} \text{MeCO}_2\text{O} \text{Me} + \text{H}_2\text{O} \\
\text{acetic acid} + \text{acetic acid} & \rightarrow \text{acetic anhydride} + \text{water}
\end{align*}
\]

**Reaction-2**

\[
\begin{align*}
\text{HOOC} - \text{C}_2\text{H}_4\text{OH} & \xrightarrow{\text{heat}} \text{C}_2\text{H}_4\text{O}_3\text{C}_2\text{H}_4 + \text{H}_2\text{O} \\
\text{phthalic acid} & \rightarrow \text{phthalic anhydride} + \text{water}
\end{align*}
\]

The first one is an intermolecular reaction whereas the second one is intramolecular. The Latin terms "inter" means "between" while "intra" means "within".

According to IUPAC:

Intramolecular: Descriptive of any process that involves a transfer (of atoms, groups, electrons, etc.) or interactions between different parts of the same molecular entity.

Intermolecular: Descriptive of any process that involves a transfer (of atoms, groups, electrons, etc.) or interactions between two or more molecular entities.

The first reaction does not proceed at all while the second one proceeds easily.

It is generally observed that for formation of small (3,4-membered) and medium-sized (5-7 membered) rings, the intramolecular reaction is both thermodynamically and kinetically favoured over the corresponding intermolecular variant.

**Reason behind thermodynamic preference:**

\[
\Delta G^0 = \Delta H^0 - T\Delta S^0
\]

In the given intermolecular reaction, two molecules are formed for every two consumed, so the amount of 'disorder' in the system does not change appreciably.

\[
\Delta S^0_{\text{inter}} \approx 0
\]

However, in the given intramolecular reaction, two molecules are formed at the cost of a single molecule, so the amount of such 'disorder' is increased.

\[
\Delta S^0_{\text{intra}} > 0
\]

As the number of molecules increases, entropy increases.

Let us assume that the \(\Delta H^0\) is almost same for both the intra and intermolecular reactions.

Because the same type of bonds are being broken and formed in each of *intra* and *intermolecular* reactions. For example, in the intermolecular reaction:

\[
\begin{align*}
\text{MeCO}_2\text{H} + \text{HO-CO-Me} & \xrightarrow{\text{intermolecular reaction}} \text{MeCO}_2\text{O} \text{Me} + \text{H}_2\text{O} \\
\text{O-H bond breaks} + \text{C-O bond breaks} & \rightarrow \text{C-O bond forms} + \text{O-H bond forms}
\end{align*}
\]

The same types of bonds are broken and formed in the intramolecular variant as well. So it can be assumed that the enthalpy change for both reactions would be closely similar. This is, however, an approximation.
Intermolecular and intramolecular reactions:

Thermodynamic analysis can thus be summarised as:

**Reaction-1**

\[
\text{MeCOOH} + \text{MeCOH} \xrightarrow{\text{heat}} \text{MeCOO} \text{Me} + \text{H}_2\text{O}
\]

\text{acetic acid} \quad \text{acetic anhydride}

**Reaction-2**

\[
\text{C6H4} \text{OH} + \text{C6H4OH} \xrightarrow{\text{heat}} \text{C6H4O} \text{C6H4O} + \text{H}_2\text{O}
\]

\text{phthalic acid} \quad \text{phthalic anhydride}

\[\Delta H^0\]
\[\Delta S^0\]
\[\Delta G^0\]

assumed to be close to zero

assumed to be the same for two reactions - common factor in comparing the \(\Delta G^0\) for the two reactions.

\[+ve\]

Recall, \(\Delta G^0 = \Delta H^0 - T\Delta S^0\)

From the analysis done, we can say: \(\Delta G^0\)\text{inter} > \(\Delta G^0\)\text{intra}

Thus, \((K_{eq})\text{inter} < (K_{eq})\text{intra}\)

Similarly,

\[
\text{C6H4O} \text{C6H4O} \xrightarrow{\text{H}^+} \text{C6H4O} + \text{H}_2\text{O}
\]

or

\[
\text{C6H4OH} \xrightarrow{\text{H}^+} \text{C6H4O} + \text{H}_2\text{O}
\]

is thermodynamically more favourable than

\[
\text{MeCOH} + \text{MeOH} \xrightarrow{\text{H}^+} \text{MeCO} \text{O} \text{Me} + \text{H}_2\text{O}
\]

is thermodynamically more favourable than

This favour for intramolecular reactions in case of 3-7 membered rings is due to the more favourable entropy change in case of the intramolecular variation. So it is an entropy-driven preference.
Intermolecular and intramolecular reactions:

Reason behind kinetic preference:

\[
\text{HO-CH-OH} + H^+ \rightarrow \text{O} + \text{H}_2\text{O} \quad \text{is much faster than}
\]

\[
\text{Me-CH-OH} + \text{Me-CH-OH} \rightarrow \text{Me-CH-CH-CH-Me} + \text{H}_2\text{O}
\]

i.e. the intramolecular reaction is kinetically more favourable than the intermolecular reaction.

Recall, rate of reaction \( r = k [R] \)

As concentration increases, so does the rate.

rate constant \quad concentration

For the intramolecular reaction described above, the two reacting parts (COOH and OH) belong to the same molecule and they are only few bonds apart. So we can say that those parts are almost always close enough to each other. So the probability of those two coming together and reacting is very high. In other words, the effective concentration of the reacting groups is very high for the intramolecular reactions.

For the intermolecular reaction described above, the two reacting parts (COOH and OH) belong to the two different molecules (acetic acid and ethanol) and they can only react if the two molecules come close and collide, in the right orientation and with right amount of energy. Clearly, the probability of this happening is less than that seen for the intramolecular variation. Thus, the effective concentration of the reacting species is much less for the intermolecular version, and it is expected to be slower.

Consider this issue in another way - in terms of entropy:

for cyclisation to happen we need to access conformation B

to access B from A we need to rotate the intervening C-C bonds so that the COOH and OH come close to each other.

this means that conformational flexibility of the molecule is decreasing when we are trying to access the particular conformation B - this is one type of entropy loss - conformational entropy (i.e. entropy due to free internal rotation).

But, crucially, we do not need to rotate too many bonds to access conformation B, so the loss of conformational entropy is small.

Only two rotations sufficient to bring the two ends close to each other - loss of rotational entropy not very high,

What about the intermolecular version?!


**Intemolecular and intramolecular reactions:**

Reason behind kinetic preference:

\[
\begin{align*}
&\text{HO-} |\text{C-} |\text{HO} \quad \overset{H^+}{\rightarrow} \quad \text{O} \quad + \quad \text{H}_2\text{O} \\
\text{HO-} |\text{C-} |\text{OH} \quad \text{rotate across the red bond} \quad \rightarrow \quad \text{O} \quad + \quad \text{OH} \\
\text{acyclic reactant has higher conformational flexibility} \quad \text{rotate across the red bond} \quad \rightarrow \quad \text{O} \quad + \quad \text{OH} \\
\text{cyclic product has lower conformational flexibility} \quad \text{cyclisation} \quad \rightarrow \quad \text{OH} \\
\text{Conformational entropy decreases}
\end{align*}
\]

- is much faster than
- Can only react when the two molecules come close together and collide with each other and that too in specific orientation and with enough energy.

Therefore, to react, both molecules must sacrifice this individual freedom to move around and come close enough to collide. This is also a loss of entropy as microscopic disorder diminishes. Two molecules, freely moving around independent of each other, must enter into a specific arrangement - this results in the loss of translational entropy.

For the given reactions, the loss of translational entropy for intermolecular reactions is much more than the loss of conformational entropy for the intramolecular reaction. This is because the ring that is forming has a smaller size (5-membered) and we can access the reactive conformation B by rotating a very small number of bonds.

\[
\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger
\]

- Higher the free energy of activation, slower is the reaction rate.

\[
\Delta S^\ddagger = S_{TS} - S_{Reactant}
\]

- If the entropy of activation is negative, i.e. the TS is more organized than the reactant ($S_{TS} < S_{Reactant}$), it contributes to make the free energy of activation more positive, which decreases the rate.

In case of the intermolecular reaction cited above, two separate molecules need to combine to form a single TS structure. This means that a significant penalty of translational entropy has to be paid, leading to a more negative $\Delta S^\ddagger$ for intermolecular reaction. But for the intramolecular reaction $\Delta S^\ddagger$ is less negative, as a single molecule forms a single TS structure where only rotational freedom is lost.
Intermolecular and intramolecular reactions:

Not all intramolecular reactions are favourable.

Synthesising large ring compounds (macrocycles) is a particularly difficult challenge for an organic chemist.

A few important macrocyclic structures:

Why is that difficult?

For cyclising to form a large ring, we need to take a large acyclic reactant and rotate many of its intervening C-C bonds to access the reactive conformation where the two reacting groups are close in space. As the acyclic reactant is large to begin with, it has a large conformational entropy, most of which is lost on cyclisation. Thus the entropy penalty in this case is much higher than in forming small ring compounds.

Suppose we want to make this cyclic ether:

We can take the following acyclic bromoalcohol and treat it with a suitable base:

And then rotate a lot of bonds to access the conformer that can cyclise to our target ether.
**Intermolecular and intramolecular reactions:**

Not all intramolecular reactions are favourable. Synthesising large ring compounds (macrocycles) is a particularly difficult challenge for an organic chemist.

To make this cyclic ether:

We can take the following acyclic bromoalcohol and treat it with a suitable base:

And then rotate a lot of bonds to access the conformer that can cyclise to our target ether.

This involves a huge loss of conformational entropy and so the reaction will be very slow.

However, the alternative, intermolecular reaction (dimerization) is another possibility:

This time there is also loss of entropy - two molecules collide to become one - translational entropy is lost, but the magnitude of that is smaller compared to the loss of conformational entropy and the dimerization (and subsequent intermolecular reactions, eventually to polymerization) is kinetically favoured than the intramolecular cyclization.

\[ \Delta S_{\text{intra}}^+ \] is more negative than \[ \Delta S_{\text{inter}}^+ \]

Intermolecular reaction (dimerization) is more favoured over intramolecular reaction.

\[ \frac{\text{Rate of intermolecular reaction}}{\text{Rate of intramolecular reaction}} = \frac{k_{\text{intra}}}{k_{\text{inter}}} \times \frac{1}{[X \sim Y]} \]

We can clearly see from the equation derived that as the concentration of substrate X–Y is lowered, the ratio between the rates of intramolecular reaction and intermolecular reaction increases. Thus at a very low concentration of the substrate a situation may be achieved where the intermolecular reaction will be effectively suppressed and the intramolecular reaction will be more preferred.
Intermolecular and intramolecular reactions:

Method to distinguish between inter- and intramolecular reaction:

**Crossover experiment:**

The purpose of every crossover experiment is to determine whether reactions take place intra- or intermolecularly. In a crossover experiment two substrates differing from each other by a double substituent variation are reacted as a mixture. This substrate mixture is subjected to the same reaction conditions in the crossover experiment that the two individual substrates had been exposed to in separate experiments. This double substituent variation allows one to determine the origin of the reaction products from their structures, i.e., from which parts of which starting materials they were formed.

The product mixture is then analyzed. There are two possible outcomes. It can contain nothing other than the two products that were already obtained in the individual experiments. In this case, each substrate would have reacted only with itself. This is possible only for an intramolecular reaction. The product mixture of a crossover experiment could alternatively consist of four compounds. Two of them would not have formed from the individual experiments. They could have been produced only by “crossover reactions” between the two components of the mixture. A crossover reaction of this type can only be intermolecular.

Consider the pinacol-pinacolone rearrangement:

![Reaction diagram](image)

This is a rearrangement accompanied by dehydration.

What happens here?

- H is lost, C=O forms
- OH is lost
- One of the methyls migrate to the adjacent position

Two mechanisms are proposed:

**Mechanism-1 (intramolecular)**

![Reaction diagram](image)

**Mechanism-2 (intermolecular)**

![Reaction diagram](image)

So which one is actually operating?
Intermolecular and intramolecular reactions:

Crossover experiment:

Two mechanisms are proposed for pinacol-pinacolone rearrangement:

**Mechanism-1 (intramolecular)**

![Mechanism-1 diagram]

**Mechanism-2 (intermolecular)**

![Mechanism-2 diagram]

So which one is actually operating?

To settle this issue, we do a crossover experiment.

Take two pinacols of closely similar structure and see what products they individually form:

**Pinacol-1**

![Pinacol-1 reaction]

**Pinacol-2**

![Pinacol-2 reaction]

AND

**Pinacol-2**

![Pinacol-2 reaction]

Now we take a 1:1 mixture of the two pinacols and carry out the same experiment:

![Mixture reaction]

We need to see how many and what products are formed from this mixture.

If intramolecular reaction is operating:

![Intramolecular reaction products]

If intermolecular reaction is operating:

![Intermolecular reaction products]
Intermolecular and intramolecular reactions:

Crossover experiment: Using it to determine what actually operates for pinacol-pinacolone rearrangement

**Mechanism-1 (intramolecular)**

Therefore, if intramolecular reaction is operating, we get only A and B from the 1:1 mixture:

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{OH} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} & \quad \text{OH} & \quad \text{H}_2\text{O} & \quad \text{Me} \\
\text{Ph} & \quad \text{Ph} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Et} & \quad \text{OH} & \quad \text{Et} & \quad \text{Et} \\
\text{Ph} & \quad \text{Ph} & \quad \text{O} & \quad \text{Et} & \quad \text{Et} \\
\end{align*}
\]

**Mechanism-2 (intermolecular)**

Therefore, if intermolecular reaction is operating, we get not only A and B, but also C and D from the 1:1 mixture:

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{OH} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} & \quad \text{OH} & \quad \text{Et} \\
\text{Ph} & \quad \text{Ph} & \quad \text{O} & \quad \text{Et} \\
\end{align*}
\]

In reality, no crossover product is found, so we can reasonably conclude that the pinacol-pinacolone rearrangement is intramolecular in nature.

If there were any crossover product, we could conclude that the reaction is, at least partly, intermolecular.