Fundamentals of Chemistry, Module III: Organic Chemistry

Semester-1, CCF-2022 (NEP)

Course: CHEM-H-CC-2-2-TH

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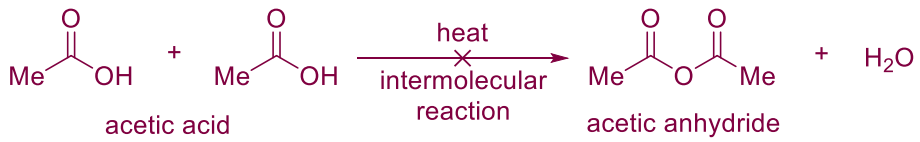
Recommended texts:

1. Study Guide to Organic Chemistry, Volume 1, Second Ed., by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 978-8192669564,
2. The Organic Chemistry Lifesaver 2, Mandal & Basu, Techno World, ISBN 978-8119777884.
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 978-0198728719

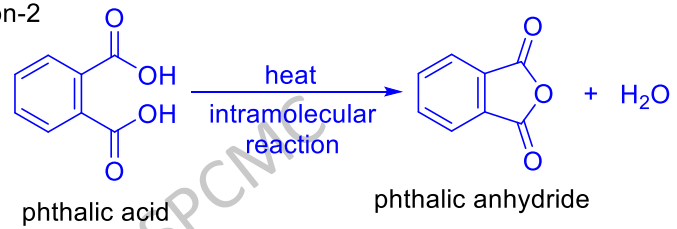
Intermolecular and intramolecular reactions:

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

Reaction-1



Reaction-2



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.

Page

Reason behind thermodynamic preference:

$$\Delta G^o = \Delta H^o - T\Delta S^o$$

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.

$$\Delta S^o_{inter} \sim 0$$

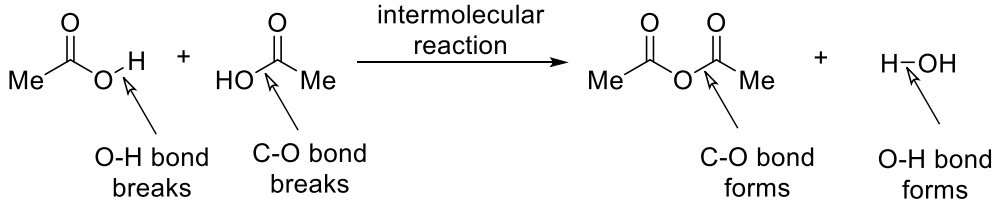
However, in the given intramolecular reaction, two molecules are formed at the cost of a single molecule, so the amount of such 'disorder' is increased.

$$\Delta S^o_{intra} > 0$$

As the number of molecules increases, entropy increases.

Let us assume that the ΔH^o 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:



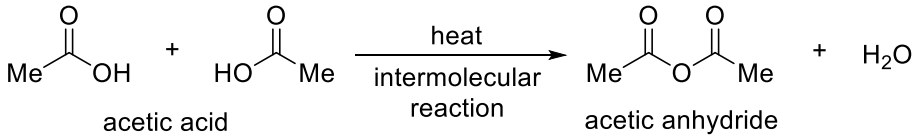
The same types of bonds are broken (O-H and C-O bonds) and formed (C-O and H-O bonds) in the intramoleular variant as well.

So it can be assumed that the enthalpy change for both reactions would be closely similar. This is, however, *a gross approximation*.

Intermolecular and intramolecular reactions:

Thermodynamic analysis can thus be summarised as:

Reaction-1

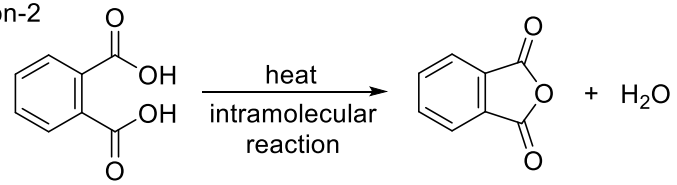


acetic acid — acetic anhydride

ΔH^o: *assumed* to be the same for two reactions - common factor in comparing the ΔG^o for the two reactions.

ΔS^o: *assumed* to be close to zero

Reaction-2



phthalic acid — phthalic anhydride

ΔH^o: +ve

Recall, $\Delta G^o = \Delta H^o - T\Delta S^o$

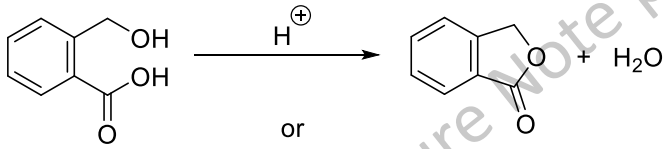
From the analysis done, we can say: $\Delta S^o_{inter} < \Delta S^o_{intra}$

Meaning, $\Delta G^o_{inter} > \Delta G^o_{intra}$ (as ΔH^o does not play any role)

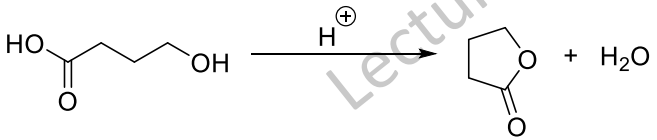
Thus, $(K_{eq.})_{inter} < (K_{eq.})_{intra}$

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.

Similarly,

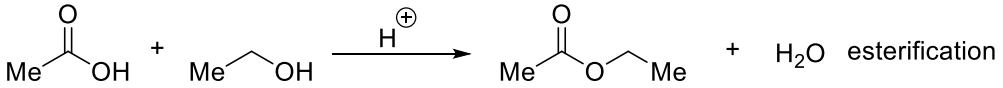


or

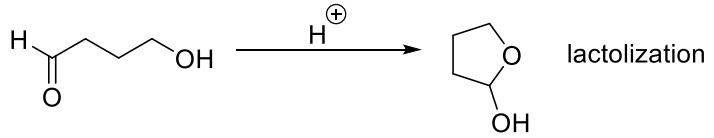


lactonization

is thermodynamically more favourable than



esterification



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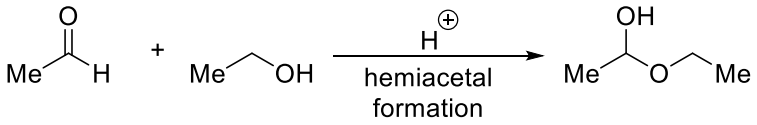
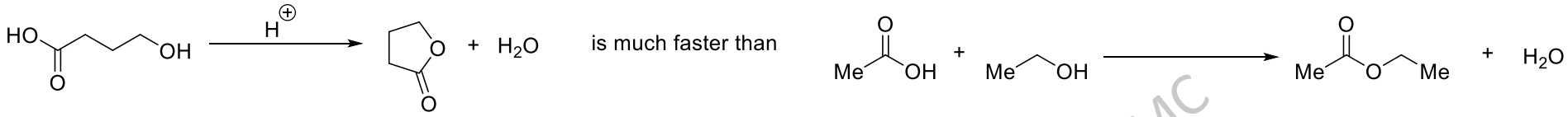


Intermolecular and intramolecular reactions:

Reason behind kinetic preference:



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

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

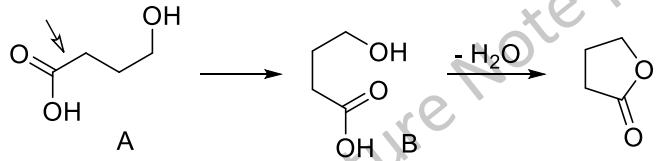
rate constant — concentration

As concentration increases, so does the rate.

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 rections.

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 moleculules 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.

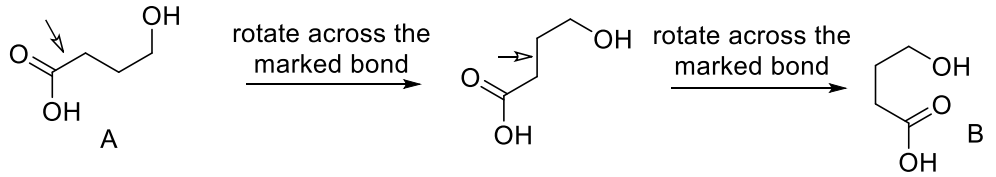
Consider this issue in another way - *in terms of entropy*:



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 relatively small.

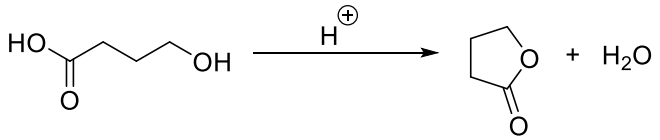


Only two rotations sufficient to bring the two ends close to each other - loss of rotational entropy in accessing the conformation suitable for cyclization is not very high,

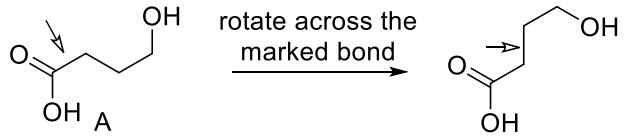
What about the intermolecular version?!

Intermolecular and intramolecular reactions:

Reason behind kinetic preference:



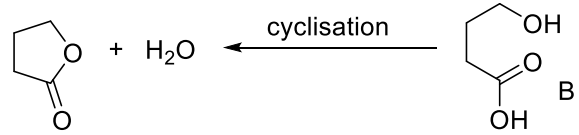
is much faster than



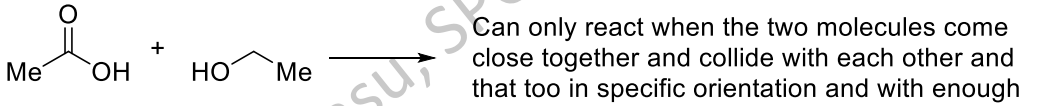
acyclic reactant has higher conformational flexibility

rotate across the marked bond

rotate across the marked bond

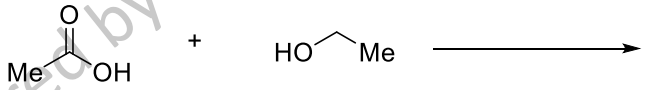


cyclic product has lower conformational flexibility



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.



translational degree of freedom 3

translational degree of freedom 3

TS where both molecules are together

translational degree of freedom 3

(3 translational degrees of freedom are lost)

Conformational entropy decreases

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 froming 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.

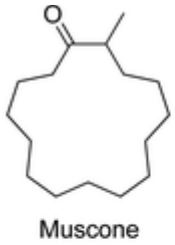
In case of the intermolecular reaction cited above, two separate molecules need to combine to form a single TS structure. This means that a significant penalty of translational entropy has to be paid, leading to a more negative $\Delta S^{\ddagger}$ for intermolecular reaction. But for the intramolecular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

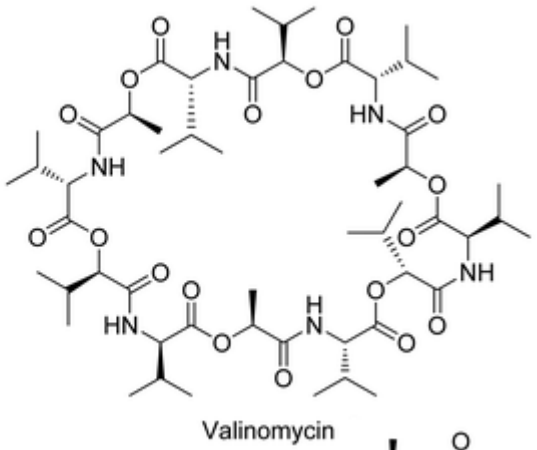
Intermolecular and intramolecular reactions:

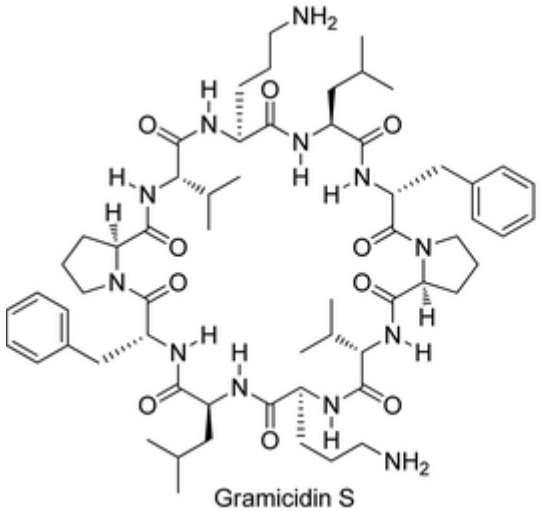
Not all intramolecular reactions are favourable.

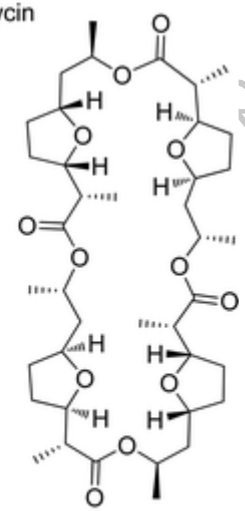
Synthesising large ring compounds (macrocycles) is a particularly difficult challnge for an organic chemist.

A few important macrocyclic structures:





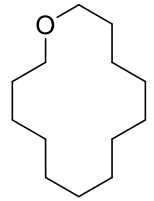




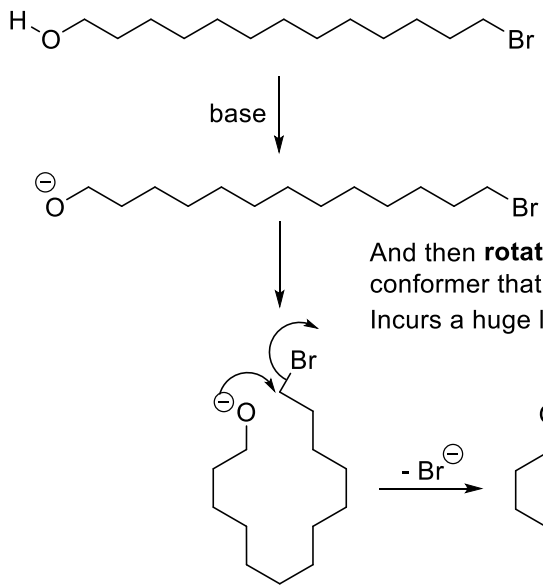
Why is that difficult?

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 rectant 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:



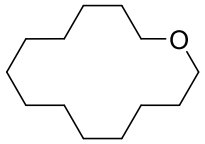
And then **rotate a lot of bonds** to access the conformer that can cyclise to our target ether. Incurs a huge loss of conformational entropy.

Intermolecular and intramolecular reactions:

Not all intramolecular reactions are favourable.

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

To make this cyclic ether:



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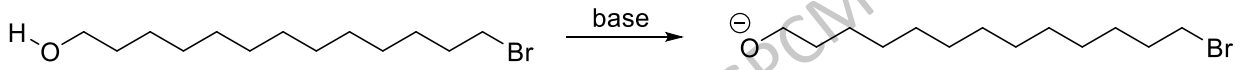

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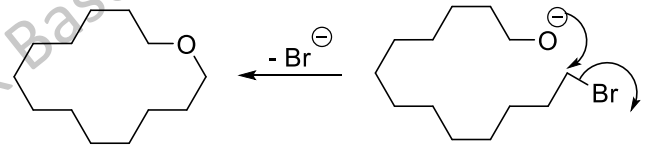
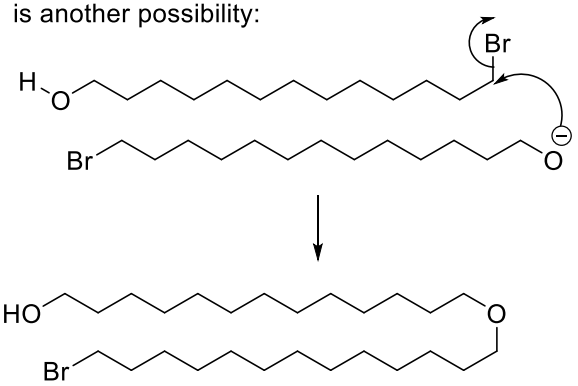


This involves a huge loss of conformational entropy, and so the reaction will be very slow.

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



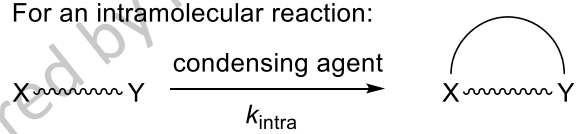
This time there is also loss of entropy - two molecules collide to become one - translational entropy is lost, but, in this case, the magnitude of that is *smaller* compared to the loss of conformational entropy and the dimerization (and subsequent intermolecular reactions, eventually to polymerization)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

$\Delta S^{\ddagger}_{intra}$ is more negative than $\Delta S^{\ddagger}_{inter}$

⇩

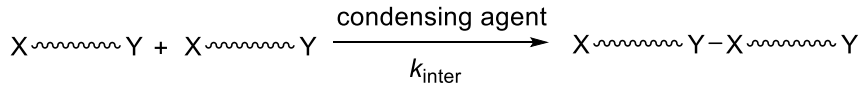
Intermolecular reaction (dimerization) is favoured over intramolecular reaction.

For an intramolecular reaction:



Rate of intramolecular reaction = k_{intra} x [X~~Y] x [condensing agent]

For an intermolecular reaction:



Rate of intermolecular reaction = k_{inter} x $[X\sim\sim Y]^2$ x [condensing agent]

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

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:

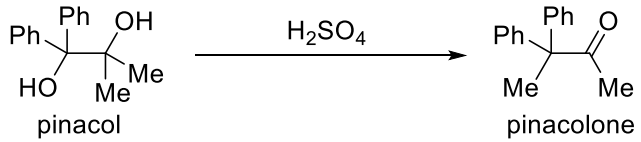
Method to distinguish between inter- and intramoleular reaction:

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.

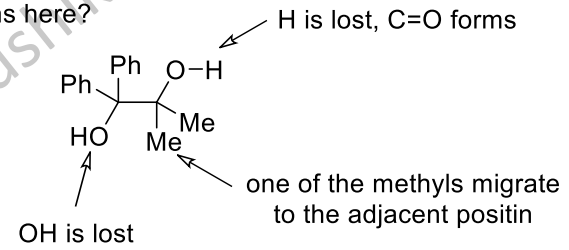
Consider the pinacol-pinacolone rearrangement:



pinacol pinacolone

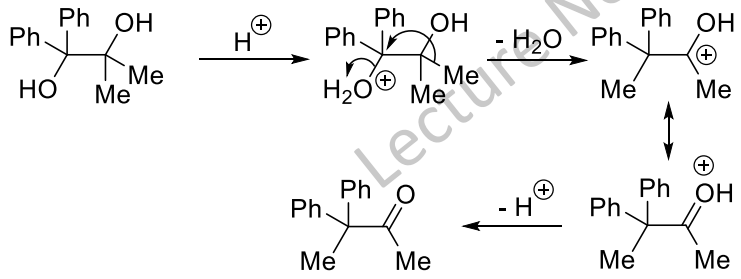
This is a *rearrangement accompanied by dehydration*

What happens here?



Two mechanisms are proposed:

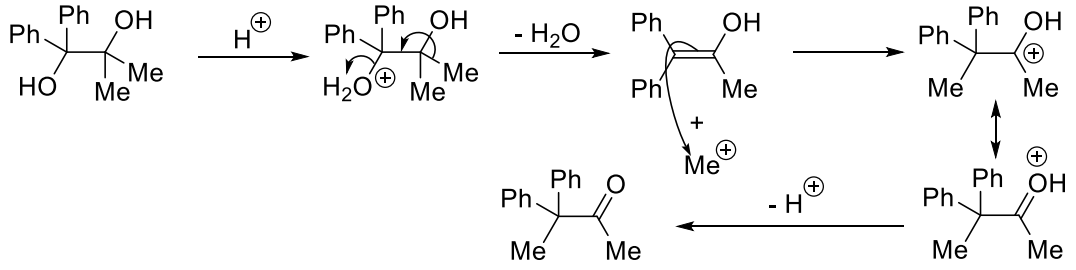
Mechanism-1 (*intramolecular*)



methyl never completely detatched from the rest of the mocecule in the course of the reaction

Mechanism-2 (*intermolecular*)

methyl completely detatched from the rest of the mocecule in the course of the reaction



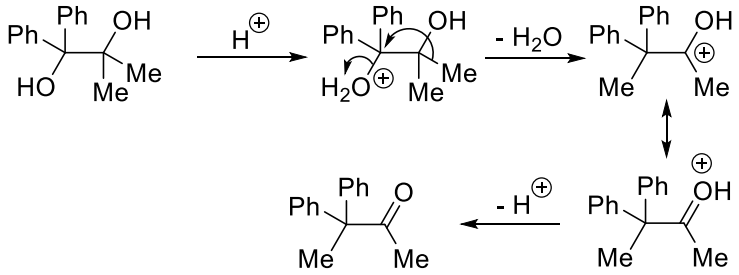
So which one is actually operating?

Intermolecular and intramolecular reactions:

Crossover experiment:

Two mechanisms are proposed for pinacol-pinacolone rearrangement:

Mechanism-1 (*intramolecular*)



methyl never completely detatched from the rest of the mocecule in the course of the reaction

Mechanism-2 (*intermolecular*)

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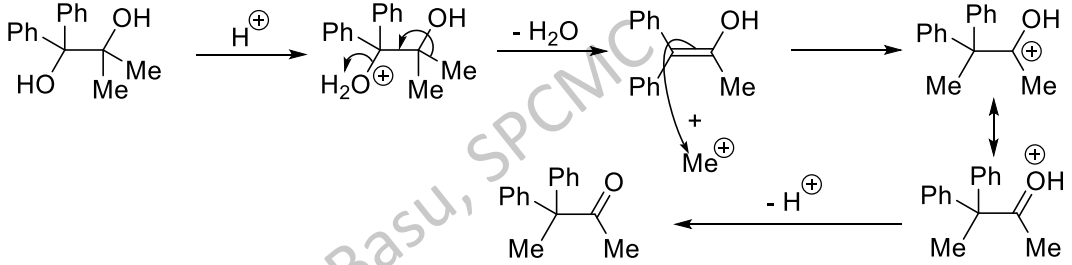
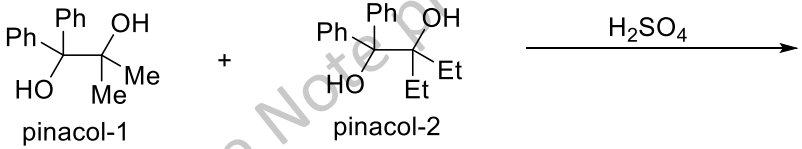


So which one is actually operating?

To settle this issue, we do a crossover experiment.

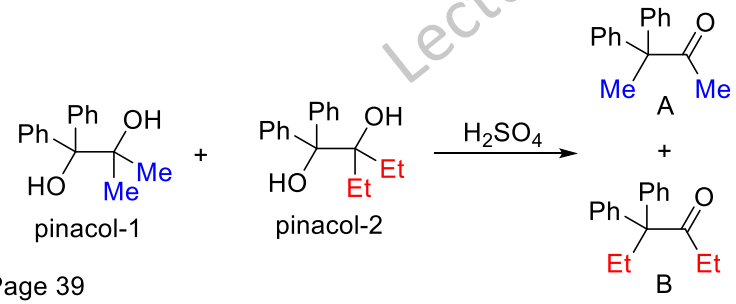
Take two pinacols of closely similar structure and see what products they individually form:

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



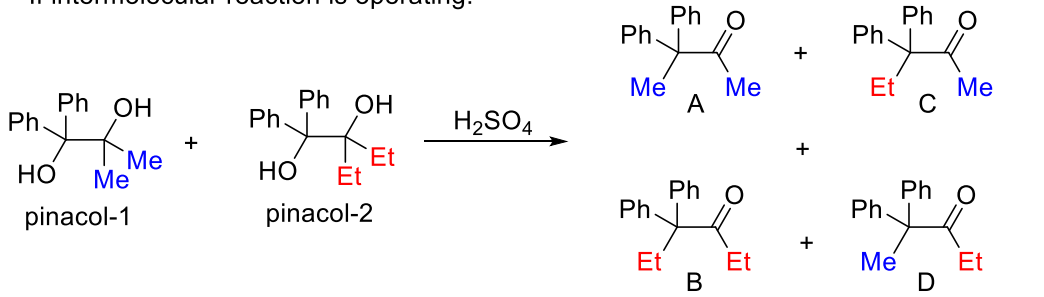
We need to see how many and what products are formed from this mixture.

If intramolecular reaction is operating:



If intermolecular reaction is operating:

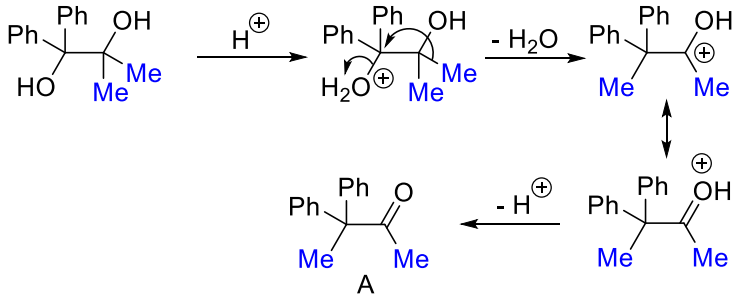
normal products crossover products



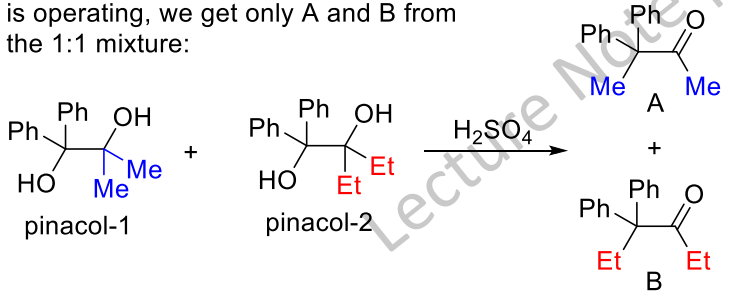
Intermolecular and intramolecular reactions:

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

Mechanism-1 (*intramolecular*)

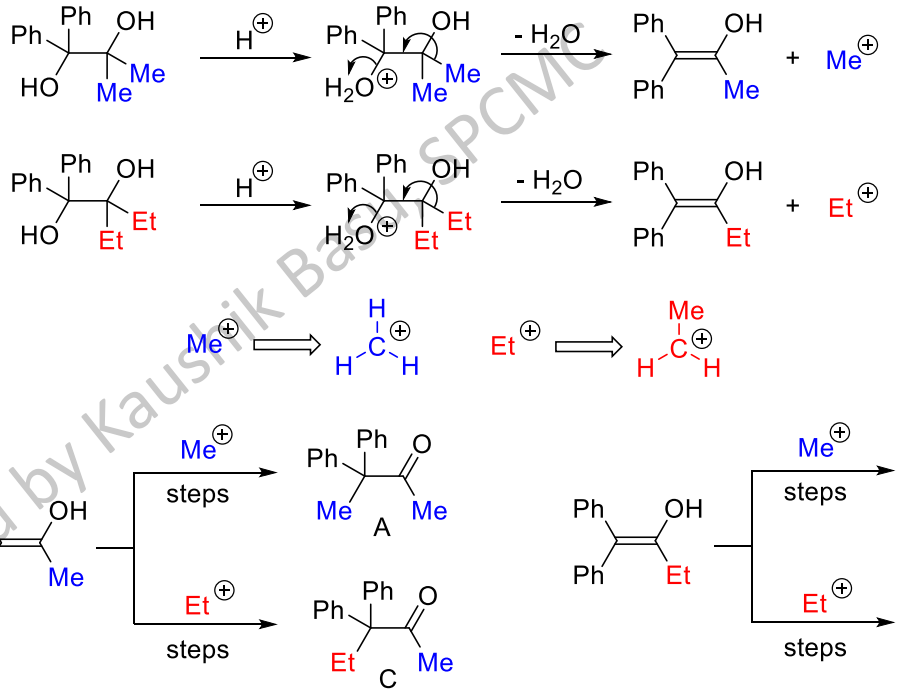


Therefore, if intramolecular reaction is operating, we get only A and B from the 1:1 mixture:

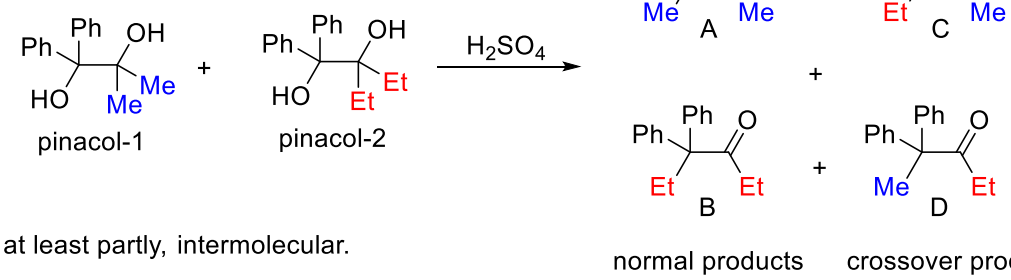


In reality, *no crossover product is found*, so we can reasonably conclude that the pinacol-pinacolone rearrnagement is intramolecular in nature.

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:



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