Fundamentals of Chemistry, Module III: Organic Chemistry

Semester-1, CCF-2022 (NEP)

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

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata
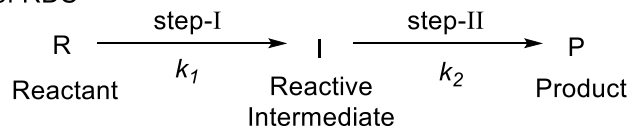
email: chiralkaushik@gmail.com

Energetics of organic reactions:

Kinetics of multistep reaction: The concept of RDS

Consider the following two-step reaction:

$$R \xrightarrow[k_1]{\text{step-I}} I \xrightarrow[k_2]{\text{step-II}} P$$

Reactant   Reactive   Product
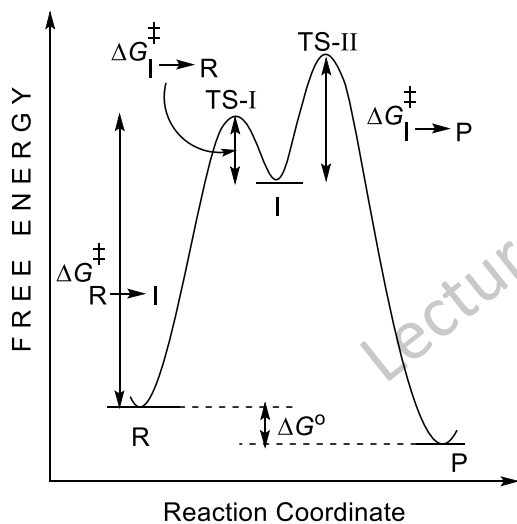Intermediate

As there are two steps, there are two energy barriers and two transition states. Let us assume that the TS for step-I (TS-I) is higher in energy than the TS for step-II (TS-II) and the energy barrier for first step is higher than that for the second step. If we also assume that overall this reaction is exergonic we have the following diagram:

$$\Delta G^{\ddagger}_{R \to I} > \Delta G^{\ddagger}_{I \to P}$$

All other things being equal, the rate of step-II is much faster than the rate of step-I. As a consequence, as soon as a molecule of intermediate is formed from R in step-I, it almost immediately reacts in step-II to give product P. The rate at which the product is formed from R is thus determined only by step-I, which is thus described as the *rate-determining step (RDS)*. Rate of reaction = $k_1[R]$

A rate-determining (rate-controlling or rate-limiting) step in a reaction occurring by a composite reaction sequence is an elementary reaction the rate constant for which exerts a strong effect — stronger than that of any other rate constant — on the overall rate. The RDS is the step of the reaction whose rate determines the observed rate of product formation. It is commonly the step with the *highest energy TS*. When there is only one step to a reaction, obviously it is rate-determining. However, in multistep reactions, the observed reaction rate is related to the *overall barrier height between the reactant and the highest energy TS*, and often concentrations of the co-reactants.
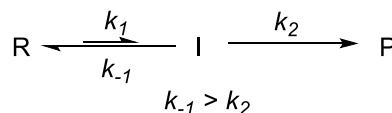
Note how an I is at a minima, while a TS is at a maxima

Reaction Coordinate

$$\Delta G^{\ddagger}_{R \to I} > \Delta G^{\ddagger}_{I \to P} \implies k_1 < k_2$$

but TS-II is of higher energy than TS-I

$$\Delta G^{\ddagger}_{I \to P} > \Delta G^{\ddagger}_{I \to R} \implies k_2 < k_{-1}$$

Once the intermediate is formed, it has two choices. It can go over to P or it can go back to R. According to the energy profile, going back to R is easier. Thus. step-I is reversible, and the eqm. b/w R and I favours the R:

$$R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_2} P$$

$$k_{-1} > k_2$$

This implies that, [R] >> [I]

and even though $k_1 < k_2$ $\boxed{k_1[R] > k_2[I]}$

Reaction Coordinate

$k_1[R] > k_2[I]$ Thus step-II is slower than step-I, and the second step is the RDS.

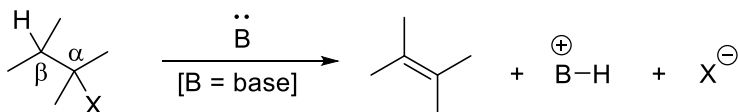rate of step-I   rate of step-II

The overall free energy of activation is defined as the difference between the highest energy TS (TS-II here) and the reactant (R). Mathematically, this can be expressed by the equation:

$$\Delta G^{\ddagger}_{R \to P} = \left(\Delta G^{\ddagger}_{R \to I} + \Delta G^{\ddagger}_{I \to P} - \Delta G^{\ddagger}_{I \to R} \right)$$

Energetics of organic reactions:

Kinetics of multipstep reaction: Three types of elimination reactions:

General scheme:

Two bonds are breaking: a) The Cβ-H bond, and b) the Cα-X bond

Two bonds are forming: a) The Cβ-Cα π-bond, and b) the B-H bond

Depending upon the timing of the breaking of the bonds we have three possibilities:

A] The Cβ-H and the Cα-X bond breaks simultaneously,
implying that the transformation takes place in one step, concerted way:
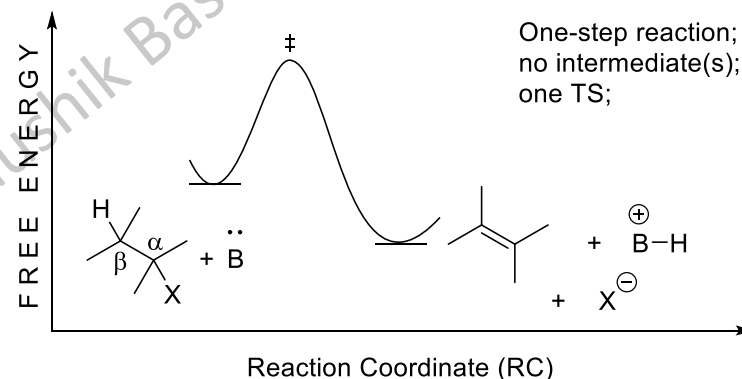

One-step reaction;
no intermediate(s);
one TS;
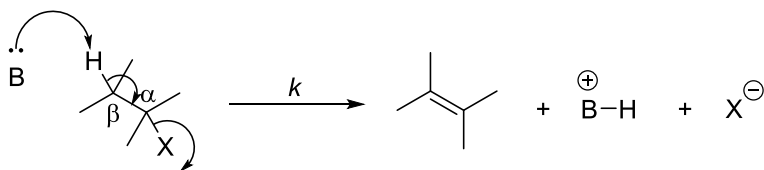
There is only one step. Therefore that is the RDS.
There are two molecules involved in the RDS: the RX and the base (B).
Therefore this is called the elimination, bimolecular (E2)

Rate of reaction = k [R-X] [B]

Reaction Coordinate (RC)

B] The Cα-X bond breaks first, forms a carbocation intermediate. Then Cβ-H bond breaks.
The transformation takes place in two steps, involves a reactive intermediate:

Two-step reaction;
one intermediate -
the carbocation;
two TSs;
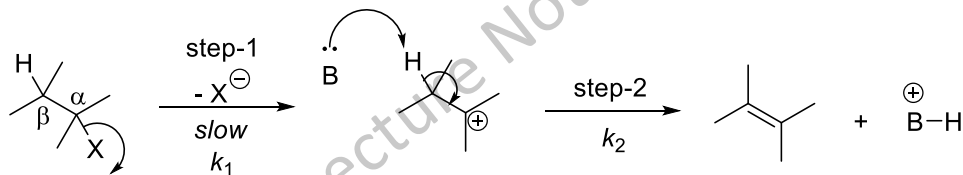
There are two steps. Step-1, i.e. carbocation formation is the RDS.
There is only one molecule involved in the RDS: the RX.
Therefore this is called the elimination, unimolecular (E1)
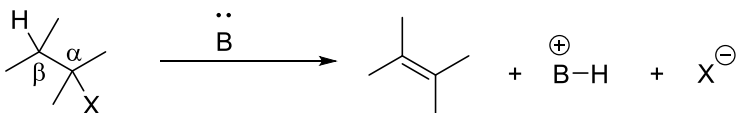
Rate of reaction = k_1 [R-X]

Note that the concentration of base does not affect
the rate, it is absent in the rate law. Base enters the
mechanism *after* the RDS is over.
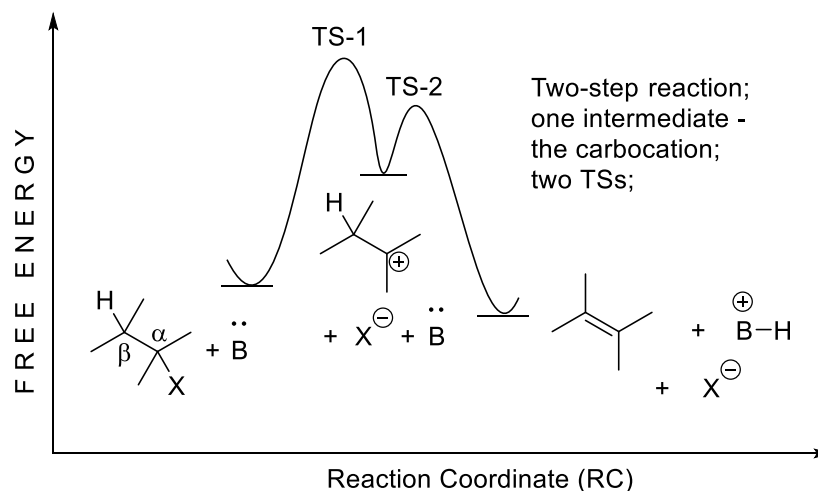
Reaction Coordinate (RC)

Energetics of organic reactions:

Kinetics of multipstep reaction: Three types of elimination reactions:

General scheme:

Two bonds are breaking: a) The $C\beta$-H bond, and b) the $C\alpha$-X bond

Two bonds are forming: a) The $C\beta$-$C\alpha$ π-bond, and b) the B-H bond

Depending upon the timing of the breaking of the bonds we have three possibilities:

C] The $C\beta$-H bond breaks first, forms a carbanion intermediate. Then $C\alpha$-X bond breaks. The transformation takes place in two steps, involves a reactive intermediate:

conjugate base of RX
(cB)
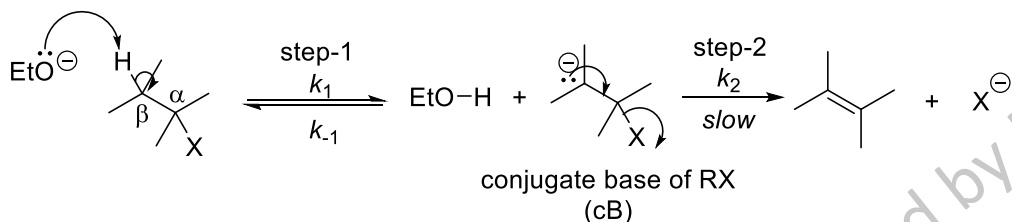
There are two steps. Step-2, i.e. ejection of X^- from the cB is the RDS.
There is only one molecule involved in the RDS: the cB.
Therefore this is called the elimination, unimolecular, via conjugate base (E1cB)
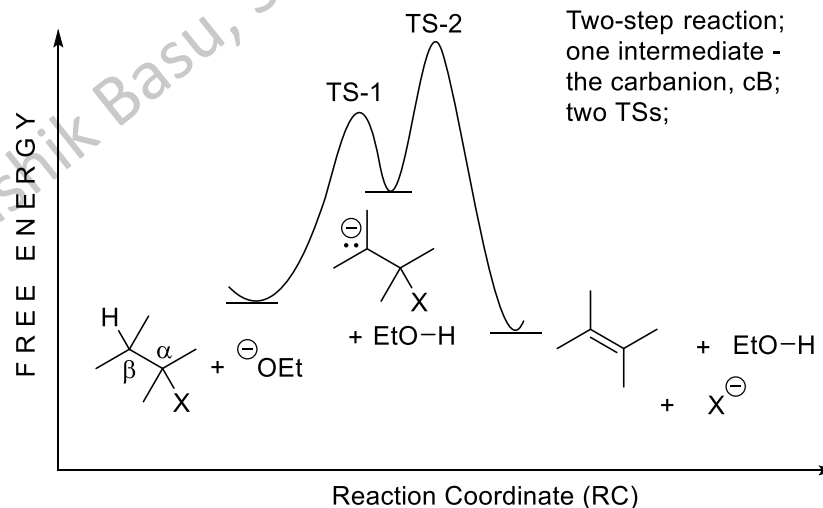
Rate of reaction = k [R-X] [B]

Derivation:

For step-1, $K_{eq.} = \dfrac{[cB][EtOH]}{[RX][EtO^-]}$

as EtOH is the solvent, its concentration does not change appreciably,
So [EtOH] is a constant.

Therefore,

$K = \dfrac{K_{eq.}}{[EtOH]} = \dfrac{[cB]}{[RX][EtO^-]}$

$[cB] = K[RX][EtO^-]$

Two-step reaction;
one intermediate -
the carbanion, cB;
two TSs;

Rate of reaction = k_2 [cB]

$= k_2 K$ [RX] [EtO$^-$]   (putting the value for [cB])

$= k$ [RX] [EtO$^-$]   where, $k = k_2 K$

It is seen that in the rate law, the concentration terms for those species appear which are involved in the mechanism *upto and including the RDS*.

If any species is invoved *after* the RDS, its concentration *does not* appear in the rate law.

Energetics of organic reactions:

Kinetics of multipstep reaction: The Hammond's postulate (aka Hammond-Leffler postulate) and its applications:

TS has only a fleeting existence and characterizing it experimentally is very difficult. Yet, if we want to improve the rate of a reaction, we *must* look to improve the rate of the RDS which will require at least some knowledge about the chemical structure at the TS. If we do not know what factors might stabilize the TS or what factors might destabilize it, we cannot predict how to reduce the free energy of activation so that we may improve the rate. Hammond's postulate gives a *qualitative* idea about the structure of the TS and the factors which might influence its stability. This is why this idea is extremely useful and valuable.

According to G. S. Hammond "if two states, for example a transition state and an unstable intermediate occur consecutively in a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures."

What does it mean?

The structure associated with the TS most *resembles* the adjacent reactant, intermediate, or product that it is closest in energy to, as long as the energy difference between the TS and the structure is not too large. When we say "resemble" we mean to say the structure that is at the TS will have strong similarity with the structure of the reactant, or the product, as the case may be and similar response to reaction variables such as temperature and solvent to that enity (reactant or product) which is closer to the TS in energy.
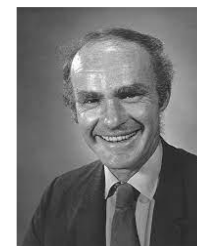
G. S. Hammond
(1921-2005)
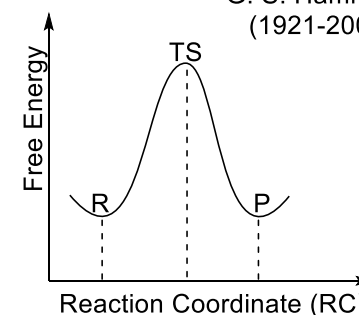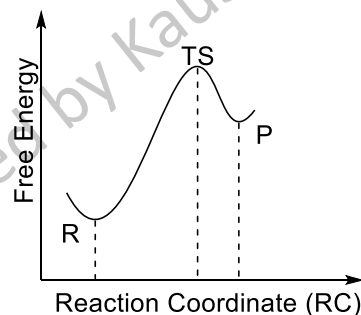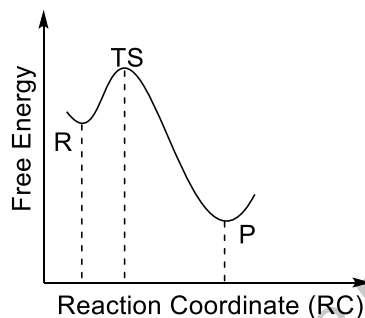
nature of the reaction step:	Exothermic/Exergonic	Endothermic/Endergonic	Thermoneutral
TS is closer to...	Reactant (R)	Product (P)	mostly equally distant from R and P
TS resembles...	Reactant (R)	Product (P)	does not resemble particularly either R nor P
TS known as...	early TS (reactant-like)	late TS (product-like)	neither early nor late TS

This means that the factors which stabilize the reactant in an exothermic step will also stabilize the TS, but of course the extent of TS stabilization will be different than the stabilization of the reactants, as the TS is not absolutely like the reactant but has a strong similarity. Following the same logic, for endothermic steps, we can say that the TS is energetically closer to the product here and thus the factors which stabilize the product in an endothermic step will also stabilize the TS. For thermoneutral or nearly thermoneutral steps, the TS will be halfway between R and P with its structure a close approximation of a 1:1 mixture of the structures of reactants and products.

Energetics of organic reactions:

Kinetics of multipstep reaction: The Hammond's postulate and its applications:

Trying to undestand Hammond's postulate with a bimolecular substitution reaction:
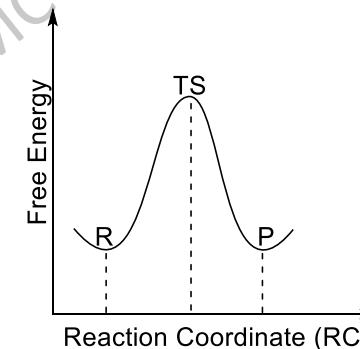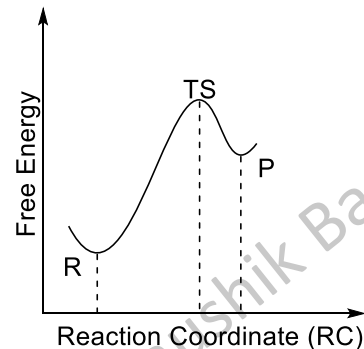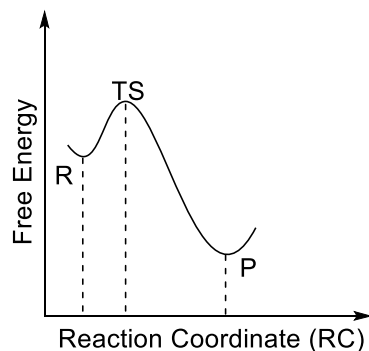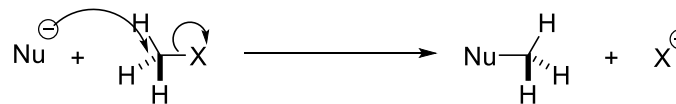

nature of the reaction step:	Exothermic/Exergonic	Endothermic/Endergonic	Thermoneutral
TS is closer to...	Reactant (R)	Product (P)	mostly equally distant from R and P
TS resembles...	Reactant (R)	Product (P)	does not resemble particularly either R nor P
TS known as...	early TS (reactant-like)	late TS (product-like)	neither early nor late TS
TS looks like:			
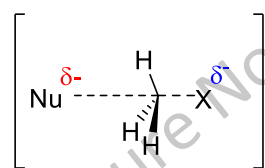
C-X bond is almost intact, C-Nu bond has formed very little

Nu has a greater partial negative charge than X does
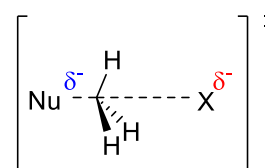
C-X bond is almost broken, C-Nu bond has almost formed

X has a greater partial negative charge than Nu does
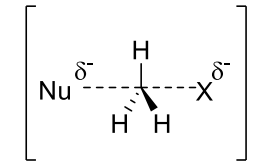
both C-X bond has broken and C-Nu bond has formed to an appreciable extent

the negative charge is more or less equally shared by X and Nu

Energetics of organic reactions:

Kinetics of multistep reaction: The Hammond's postulate and its applications:

Explaining the *regioselectivity* of HBr addition across the C=C

A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over all other possible directions. Reactions are termed completely (100%) regioselective if the discrimination is complete, or partially (x%), if the product of reaction at one site predominates over the product of reaction at other sites.
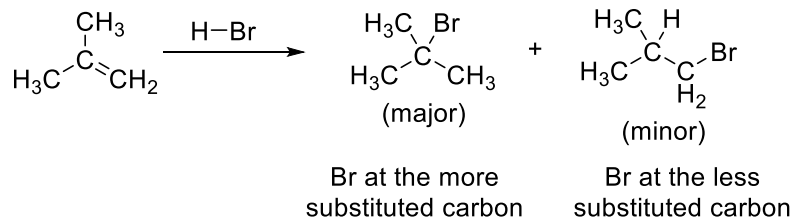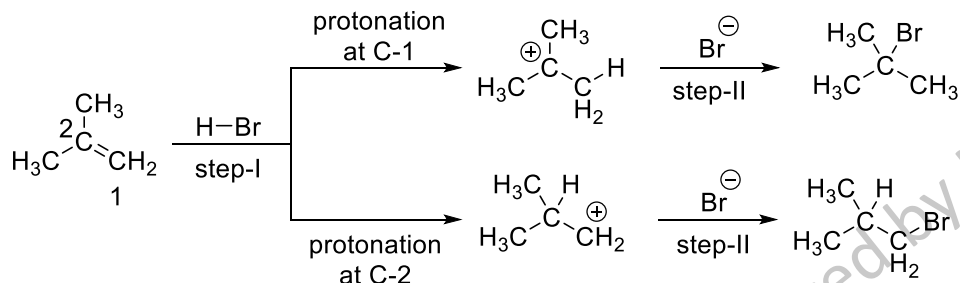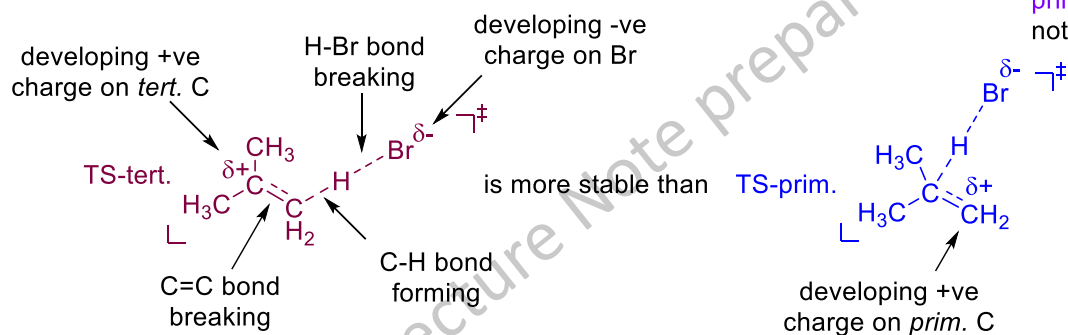
Br at the more substituted carbon (major)

Br at the less substituted carbon (minor)

Mechanism:

protonation at C-1

protonation at C-2

step-I

step-II

The tertiary bromide is formed from the tertiary carbocation while the primary bromide arises from the primary carbocation. As the protonation (i.e. the formation of the carbocation, step-I) is the RDS, the major product is dictated by how fast each of these carbocations are formed. The one that is formed faster, leads to the major product.
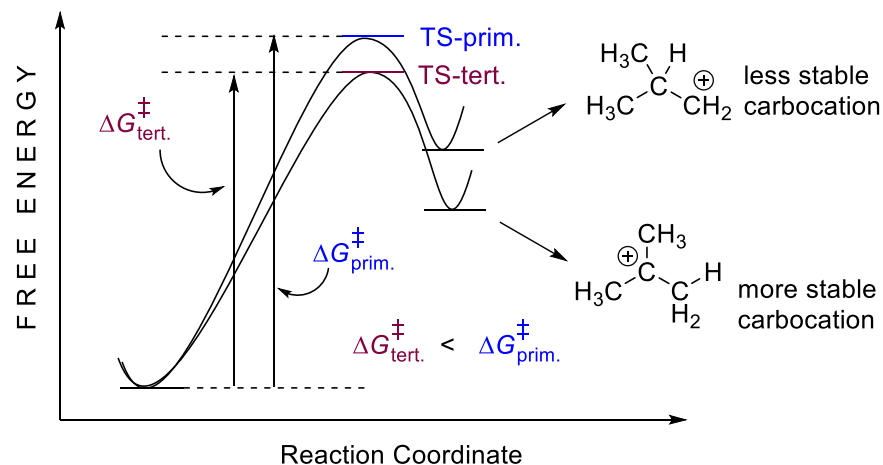
There are two possibilities of protonation, each goes via different TS. Each protonation step is endergonic in nature, thus each TS resembles the corresponding carbocation, and not the alkene.

As the tertiary carbocation is more stable than the primary one (why?), the TS leading to the tertiary carbocation is also more stable than the TS leading to the primary carbocation. Thus we have the following situation (energy profile does not include step-II):

developing +ve charge on *tert.* C

H-Br bond breaking

developing -ve charge on Br

TS-tert.

C=C bond breaking

C-H bond forming

is more stable than

TS-prim.

developing +ve charge on *prim.* C

As $\Delta G^{\ddagger}_{tert.} < \Delta G^{\ddagger}_{prim.}$ the tertiary cation forms at a much faster rate than the primary one, leading eventually to the major product where the Br is attached to the more substituted carbon.

$\Delta\Delta G^{\ddagger}$ decides how much more the tertiary carbocation will form w.r.t. the primary carbocation, larger this difference is, larger is the discrimination between two products' percentage.

FREE ENERGY

Reaction Coordinate

TS-prim.

TS-tert.

$\Delta G^{\ddagger}_{tert.}$

$\Delta G^{\ddagger}_{prim.}$

less stable carbocation

more stable carbocation

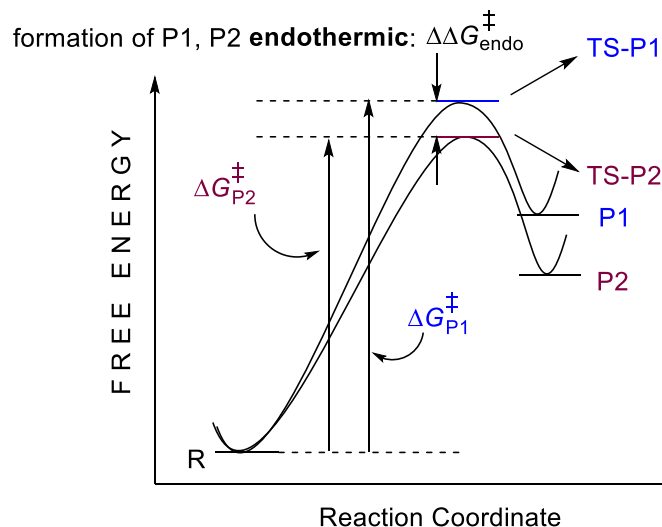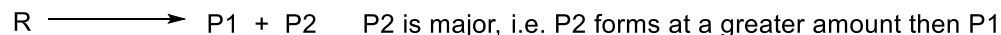$\Delta G^{\ddagger}_{tert.} < \Delta G^{\ddagger}_{prim.}$

This is what is the rationale behind the famous *Markownikoff's rule*.
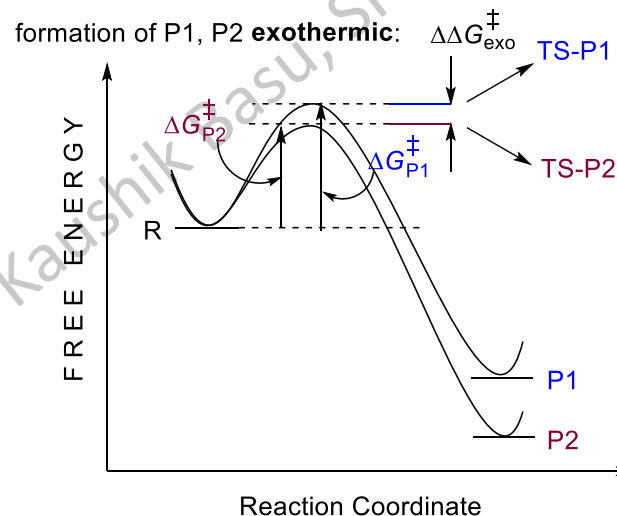
Energetics of organic reactions:

Kinetics of multipstep reaction: The Hammond's postulate and its applications:

Formation of multiple products: how does product stability influence the TS energy?

From the last slide, we've seen that if the reaction's outcome is dictated by kinetics, i.e. the rate at which the alternative TSs are accessed, then the difference of the two free energy of activations dictate how much dominant the major product would be over the minor product. Let us apply this concept for exo- and enothermic reactions. We have two situations:

$$R \longrightarrow P1 + P2 \quad \text{P2 is major, i.e. P2 forms at a greater amount then P1}$$

formation of P1, P2 **endothermic**: $\Delta\Delta G^{\ddagger}_{endo}$

formation of P1, P2 **exothermic**: $\Delta\Delta G^{\ddagger}_{exo}$

$$\Delta\Delta G^{\ddagger}_{endo} > \Delta\Delta G^{\ddagger}_{exo}$$

Note: in both cases, the thermodynamic stability difference b/w P1 and P2 is the same. It is the TSs energy difference that is changing.

The TSs are late in nature and they are mostly like P1 and P2 respectively.

Relative stability of the two products has profound influence on the relative energy of the two TSs.

Energy difference b/w the TS_{P1} and TS_{P2} is high (close to the energy difference b/w P1 and P2).

The reaction is *more selective*, i.e. the major product forms to a much greater extent. Thus kinetic discrimination is higher.

R is *less reactive*, has higher energy barriers to cross.

The TSs are early in nature and both of them are mostly like R.

Relative stability of the two products has very little influence on the relative energy of the two TSs.

Energy difference b/w the TS_{P1} and TS_{P2} is low (much lower than the energy difference b/w P1 and P2).

The reaction is *less selective*, i.e. the major product forms only to slightly greater extent. Thus kinetic discrimination is lower

R is *more reactive*, has lower barriers to cross.

In general, the *more reactive* a species is, the *less selective* it is and vice versa. This is the essenece of the *reactivity-selectivity principle* (*RSP*).

Energetics of organic reactions:

Theromodynamic and kinetic control of reactions:

Reaction can give two products: Which one would be the major?   R $\longrightarrow$ P1 + P2

Consider the following energy profile diagram:

Reaction Coordinate
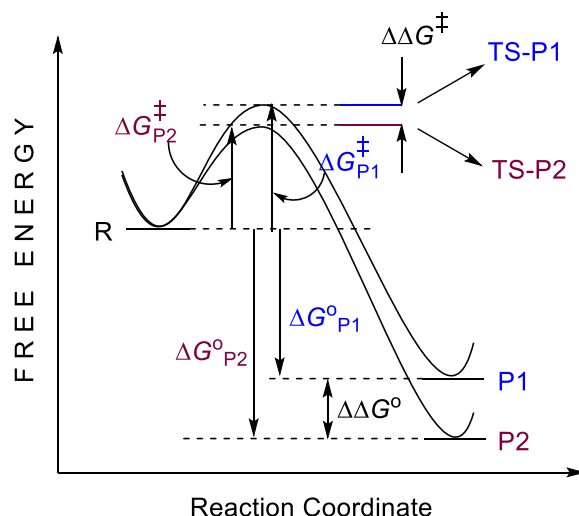
The product that is formed faster than the other is the KCP and it is the major product in an irreversible, kinetically-controlled reaction.

The product that is more stable of the two is the TCP and it is the major product in an reversible, thermodynamically-controlled reaction.
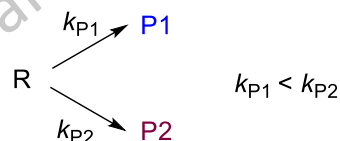
Which one would be the major product - that issue is settled by the fact that whether the reaction is reversible under the given condition or not.

reaction is *irreversible*

Product composition guided by the *energy difference b/w TSs*

$$\Delta\Delta G^{\ddagger}$$

P2 dominates the product mixture, the TS-P2 is lower in energy than TS-P1, so the former is accessed at a faster rate

R $\overset{k_{P1}}{\underset{k_{P2}}{\Big\langle}}$ P1, P2 $k_{P1} < k_{P2}$

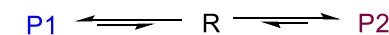This is called *kinetic control*.
P2 is the kinetically-controlled product (KCP)

reaction is *reversible*

Product composition guided by the *energy difference b/w the products*

$$\Delta\Delta G^{o}$$

There is eqm. b/w P1 and P2 via R:

P1 $\rightleftharpoons$ R $\rightleftharpoons$ P2

i.e.   P1 $\rightleftharpoons$ P2

P2 dominates the product mixture, it is more stable than P1, and dominates the eqm.

This is called *thermodynamic control*.
P2 is the thermodynamically-controlled product (TCP)

In this case, P2 is both the KCP and the TCP.
It is the major product under both conditions.

IUPAC definition of kinetic control: The term characterizes conditions (including reaction times) that lead to reaction products in a proportion governed by the relative rates of the parallel (forward) reactions in which the products are formed, rather than by the respective overall equilibrium constants.
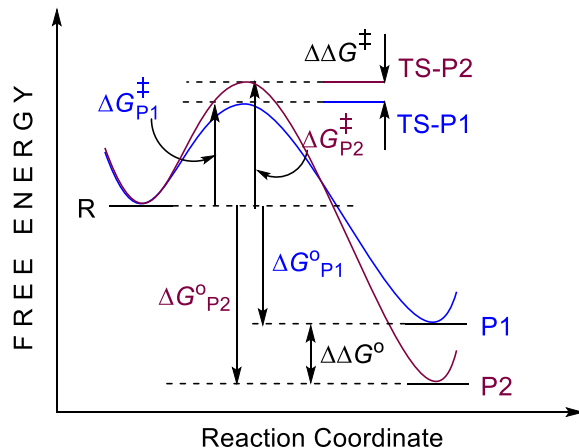
IUPAC definition of thermodynamic control: The term characterizes conditions that lead to reaction products in a proportion governed by the equilibrium constant for their interconversion and/or for the interconversion of reaction intermediates formed in or after the rate-limiting step. (Some prefer to describe this phenomenon as 'equilibrium control'.)

Energetics of organic reactions:

Thermodynamic and kinetic control of reactions:

Reaction can give two products: Which one would be the major?   R $\longrightarrow$ P1 + P2

Consider the following energy profile diagram:

Which one would be the major product - that issue is settled by the fact that whether the reaction is reversible or not.

Reaction Coordinate

The product that is formed faster than the other is the KCP and it is the major product in an irreversible, kinteically-controlled reaction.

The product that is more stable of the two is the TCP and it is the major product in an reversible, thrmodynamically-controlled reaction.
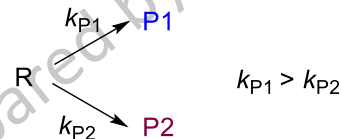
reaction is *irreversible*

Product composition guided by the *energy difference b/w TSs*

$$\Delta\Delta G^{\ddagger}$$

P1 dominates the product mixture, the TS-P1 is lower in energy than TS-P2, so the former is accessed at a faster rate

R with $k_{P1} \to$ P1 and $k_{P2} \to$ P2, $k_{P1} > k_{P2}$

This is called *kinetic control*.
P1 is the kinetically-controlled product (KCP)

When the reactions are irreversible, KCP is the major product, i.e. P1 is the major product.
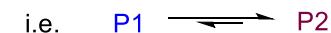
When are reactions irreversible?
If -

a) the reaction temp. is delibarately kept low, and

b) the reaction is done very rapidly so that the backward reaction does not get a chance to happen

reaction is *reversible*

Product composition guided by the *energy difference b/w the products*

$$\Delta\Delta G^{o}$$

There is eqm. b/w P1 and P2 via R:

P1 $\rightleftharpoons$ R $\rightleftharpoons$ P2

i.e.   P1 $\rightleftharpoons$ P2

P2 dominates the product mixture, it is more stable than P1, and dominates the eqm.

This is called *thermodynamic control*.
P2 is the thermodynamically-controlled product (TCP)

When the reactions are reversible, TCP is the major product, i.e. P2 is the major product.

When are reactions reversible?
The reactions have a chance to become reversible if -

a) we increase the temp. so that both the forward and the backward reactions get faser and eqm. is reached, and

b) if we allow a very long time for the reaction to go on, since every reaction can become reversible if proper amount of time is given to attain the eqm.

In this case, the TCP and KCP are different, and it depends on the reaction condition which one would be the major product. These cases are relatively less frequent than those where the same product is the KCP as well as the TCP. Let us explore this sitution with a few examples.

Energetics of organic reactions:

Thermodynamic and kinetic control of reactions:

1,2- and 1,4-addition of hydrogen bromide to a conjugated diene:

We have the following observation where the *product ratio changes with temperature*:

What is going on?

Recall, rate of reaction (for both forward as well as backward) increases with rise in temp. So at a higher temp. the reactions become reversible and eqm. is achieved. The product that dominates in this condition is thus the TCP, i.e. in this case the 1,4-addition product.
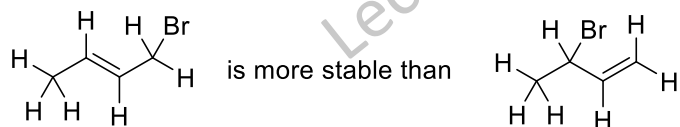
TCP:

1,4-addition product
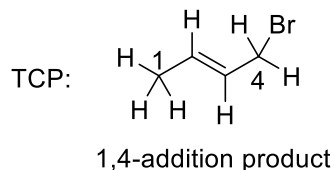
At low temp. the reactions are essentially irreversible and the reaction is then under kinetic control. The product that dominates in this condition is the KCP, i.e. in this case the 1,2-addition product.
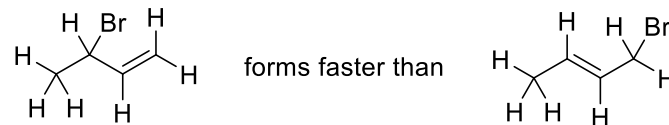
KCP:

1,2-addition product
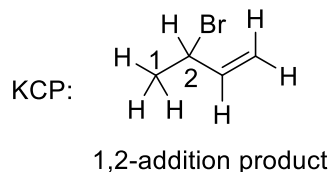
We can thus say:

a) 1,4-addition product is the TCP, which means

is more stable than

b) 1,2-addition product is the KCP, which means

forms faster than

c) Once the reaction is done at low temp. and a the product mixture is obtained in a certain ratio in favour of the 1,2-addition product (KCP), increasing the temp. changes the ratio in favour of the 1,4-addition product (TCP) - the 1,2-addtion product converts to 1,4-addition product at higher temp.

1,2-addition product   1,4-addition product

$-80\,^{o}C$ 80%   20%

1,3-butadiene   HBr $40\,^{o}C$

20%   80%

$40\,^{o}C$
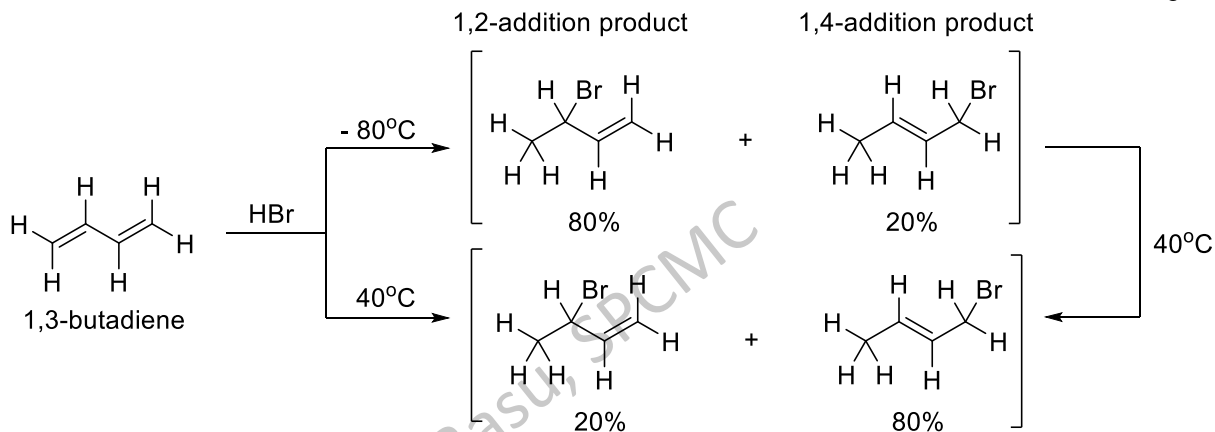
Numbering scheme in the addition product:

1,3-butadiene   1,2-addition product   1,4-addition product
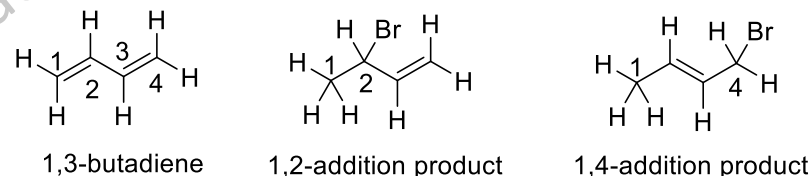
numbering scheme *does not* follow IUPAC convention

Energetics of organic reactions:

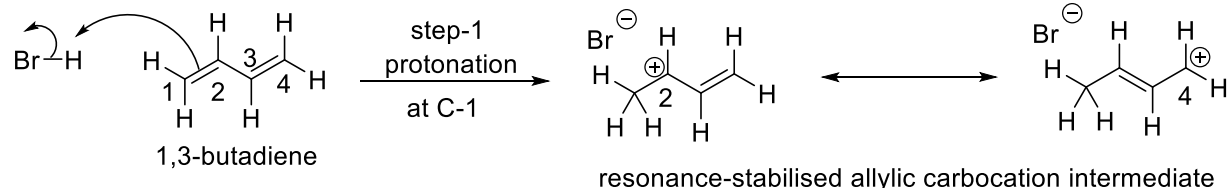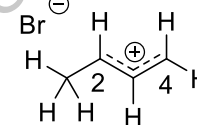Theromodynamic and kinetic control of reactions: 1,2- and 1,4-addition of hydrogen bromide to a conjugated diene:

Mechanism of HBr addition:

the positive charge is delocalised over three carbon atoms - it manifests on C-2 and on C-4, both these carbons are electrophilic and can combine with a nucleophilic species


1,3-butadiene

resonance-stabilised allylic carbocation intermediate

resonance hybrid of allylic carbocation intermediate

Step-1 is the RDS. It is regioselective. protonation occurs at C1 and not at C2.

Why regioselective?

Step-1 is endothermic, involves formation of carbocation intermediate. From Hammond's postulate, the TS for carbocation formation should be a late-TS and it should mimic the resultant carbocation more than it does the starting diene. So, for protonations at alternative sites, we have the following situations:

developing *p* orbital here

1,3-butadiene

resonance-stabilised allylic carbocation intermediate
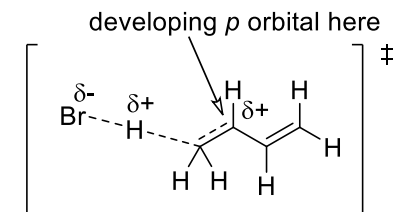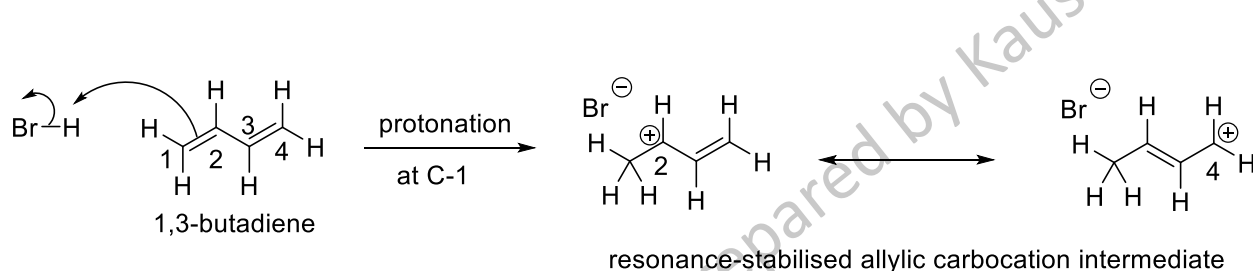
$\delta+$ charge on secondary carbon, in addition, there is conjugation of the developing vacant p orbital with the adjacent C=C (allylic-type conjugation) - more stable TS

primary carbocation, no allylic stabilisation
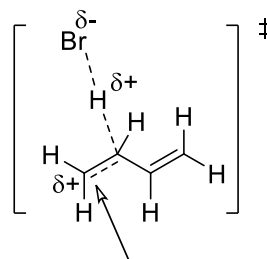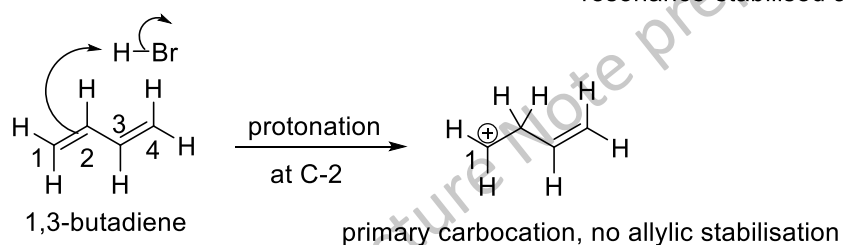
$\delta+$ charge on primary carbon, and there is no conjugation of the developing vacant p orbital with the remote C=C (no allylic-type conjugation) - less stable TS

developing *p* orbital here

Therefore, the protonation proceeds selectively at C1 and not at C2 as the free energy of activation associated with the formation of the allylic carbocation is less compared to that associated with formation of the primary carbocation. The allylic carbocation forms faster as well as it is more stable. This is why it is selectively formed and further leads to formation of 1,2- and the 1,4-addition products.
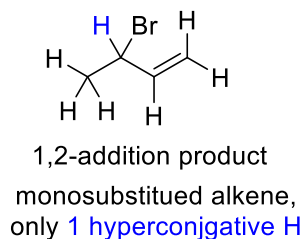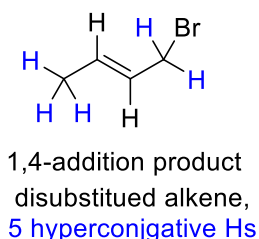
Energetics of organic reactions:

Theromodynamic and kinetic control of reactions: 1,2- and 1,4-addition of hydrogen bromide to a conjugated diene:

Mechanism of HBr addition (contd.):

Once the resonance-stabilised allylic carbocation is formed, it is immidiately quenched by the nucleophilic bromide; the allylic carbocation is electrophilic at two sites, C2 and C4, attack of bromide at C2 provides the 1,2-addition product while attack at C4 gives the 1,4-addition product.

Now we need to answer the following questions:

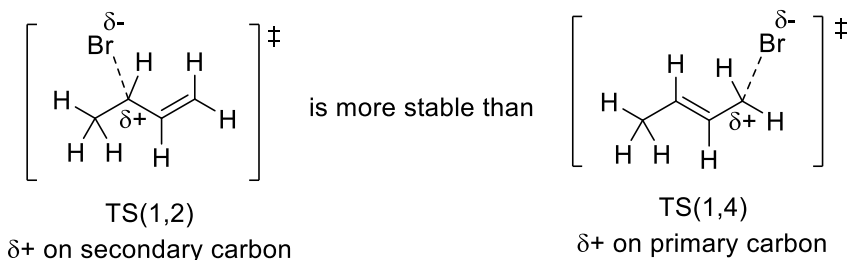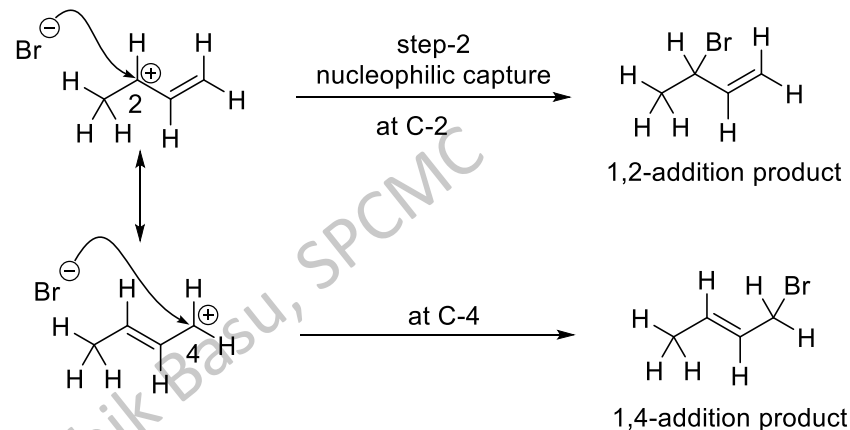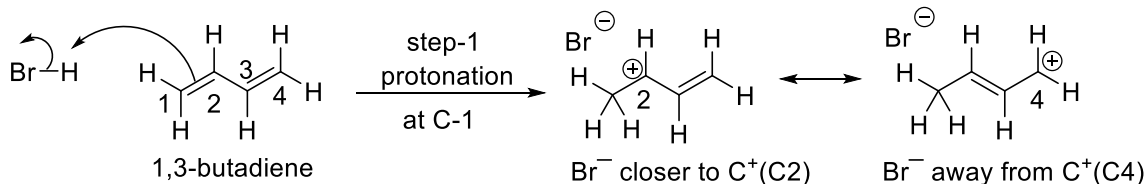a) Why is the 1,4-addition product more stable than the 1,2-addition product?

1,4-addition product
disubstitued alkene,
5 hyperconjgative Hs

1,2-addition product
monosubstitued alkene,
only 1 hyperconjgative H

As more substituted alkenes are more stable than isomeric, less substitued alkenes, the 1,4-addition product is more stable than the 1,2-addition product

b) Why does the 1,2-addition product form faster than 1,4-addition product?

Any discrimination must arise in the step-2, as step-1 is common for both products. We must look at the two TSs for the respective step-2. Step-2 being exothermic (as the carbocation intermediate is being quenched here), the TSs mimic the carbocation more than the products.

Clearly, TS(1,2) is more stable than TS(1,4) as the partial positive charge is on the more substituted carbon in the former. As more substituted carbocations are more stable than less substitued ones, same is ture for incipient carbocations.

Secondly, as the carbocation generates by protonating the C1 with HBr, bromide remains in close proximity to C2 than it is for C4; this *proximity effect* favours 1,2-addition:

step-2
nucleophilic capture
at C-2

1,2-addition product

at C-4

1,4-addition product

TS(1,2)
$\delta+$ on secondary carbon

is more stable than

TS(1,4)
$\delta+$ on primary carbon

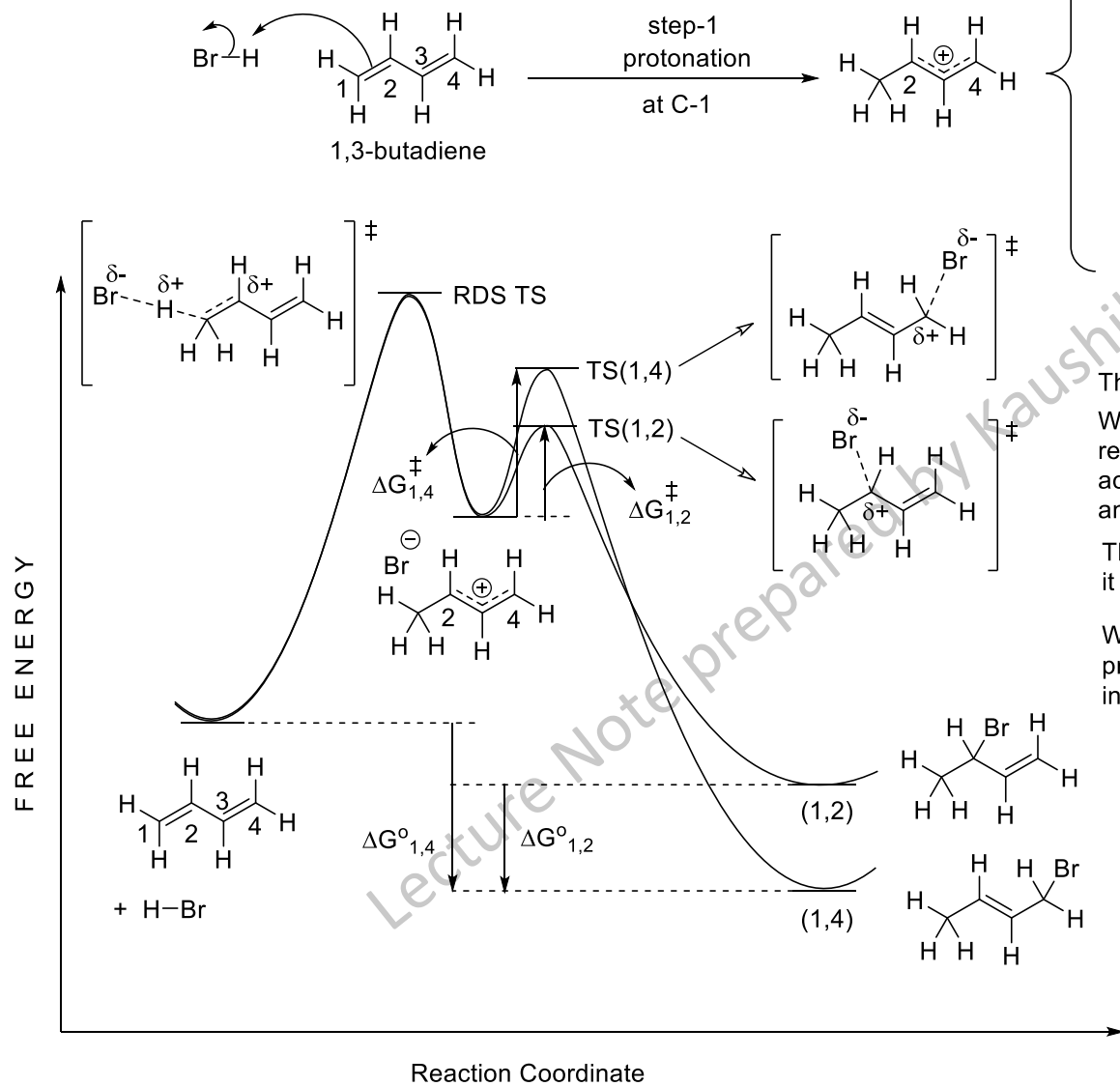TS(1,2) is thus accessed by the allylic carbocation intermediate at a rate faster than the same int. accesses TS(1,4), leading to faster formation of the 1,2-addition product

The bromide has to *travel a lot more* to reach C4, so attack at C2 is more favoured, leading to faster formation of 1,2-addition product.

1,3-butadiene

step-1
protonation
at C-1

Br⁻ closer to C⁺(C2)

Br⁻ away from C⁺(C4)

Energetics of organic reactions:

Thermodynamic and kinetic control of reactions:

Overall energy profile diagram of 1,2- and 1,4-addition of hydrogen bromide to a conjugated diene:

1,3-butadiene

step-1 protonation at C-1

step-2 nucleophilic capture at C-2

1,2-addition product

at C-4

1,4-addition product

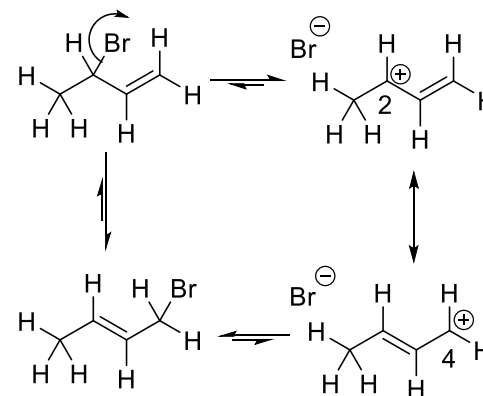$$\Delta G^{\ddagger}_{1,4} > \Delta G^{\ddagger}_{1,2}$$

The 1,2-addition product forms faster than the 1,4-addition product.

When the reactions are carried out at low temperatures, the reverse reactions do not take place to any appreciable extent. Note the large activation barriers for the backward reaction (conversion of the 1,2- and the 1,4-product to the allylic cation).

The 1,2-addition product (KCP) dominates the product mixture as it is formed faster than the 1,4-addition product.

When temp. is raised, the backward reactions start happening. The 1,2 product **still forms faster**, but at this temp. it can also get converted into the 1,4-product in the following way:

RDS TS

TS(1,4)

TS(1,2)

$\Delta G^{\ddagger}_{1,4}$

$\Delta G^{\ddagger}_{1,2}$

$\Delta G^{o}_{1,4}$

$\Delta G^{o}_{1,2}$

(1,2)

(1,4)

+ H−Br

FREE ENERGY

Reaction Coordinate

So, essentially now there is an eqm. b/w the 1,2- and 1,4-product. As the latter is more stable, it accumulates and dominates the product mixture under this condition. TCP is the major product.
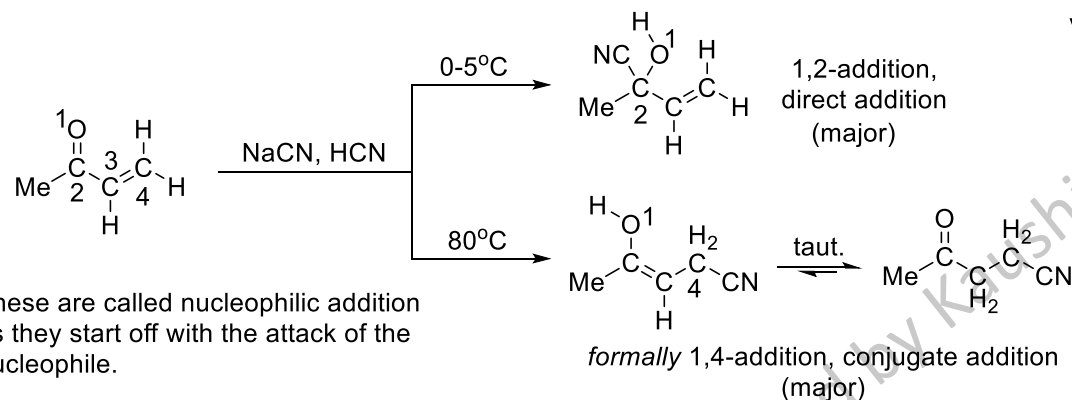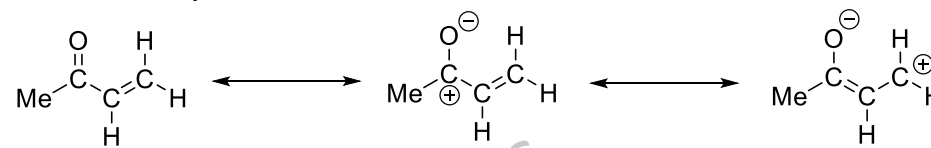
Energetics of organic reactions:

Theromodynamic and kinetic control of reactions: Nucleophilic addition to α,β-unsaturated carbonyls

There are two electrophilic sites on an α,β-unsaturated carbonyl compound like methyl vinyl ketone (MVK), the carbonyl carbon and the β-carbon:

Both these positions can be attacked by a nucleophile.

Addition of HCN into MVK affords two products. The major product is determined by the reaction condition:
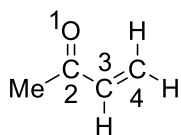

0-5°C — 1,2-addition, direct addition (major)

NaCN, HCN

80°C — *formally* 1,4-addition, conjugate addition (major)

via

These are called nucleophilic addition as they start off with the attack of the nucleophile.

taut.

keto-form more stable than enol-form
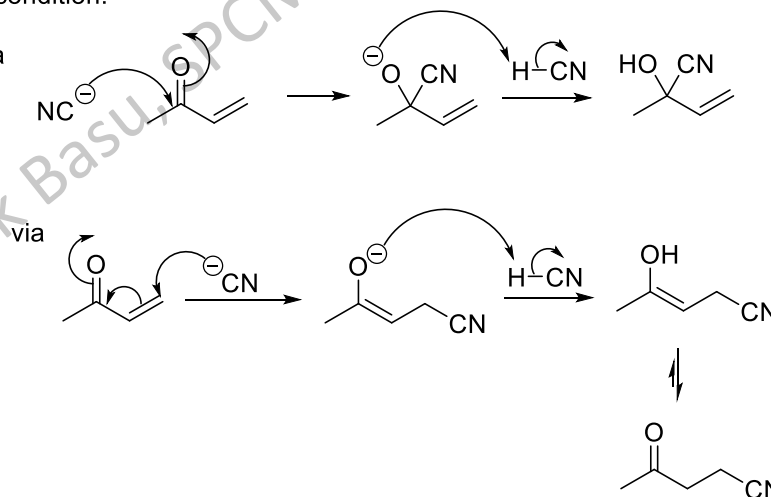
Clearly, the direct addition product is the KCP and the conjugate addition product is the TCP.

Explanation:

C2 is more electrophilic than C4, as EW -I effect of =O is greater at C2.
-R effect of =O makes both positions e-deficient, but -I falls off with distance; so C4 experiences less -I than C2.
The nucleophilic cyanide ion feels greater Coulombic attraction towards the more electrophilic C2 carbon than for C4.
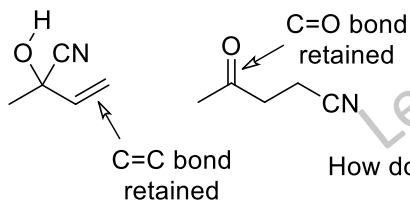Attack at C2 is faster, associated with lower free energy of activation.
The direct addition product is the KCP, and is the major product when reactions are irreversible.

C=C bond retained

C=O bond retained

C=O is a stronger bond than C=C. Thus the conjugate addition product is thermodynamically more stable than the direct addition product. It is the TCP and dominates when reactions are reversible and eqm. is achieved.
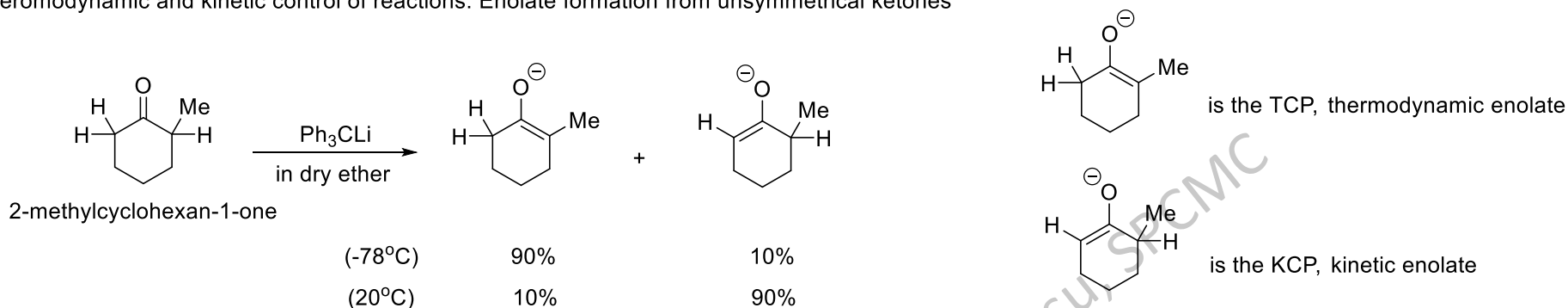
How does the direct addition product convert to the conjugate addition product under equilibrating conditions:
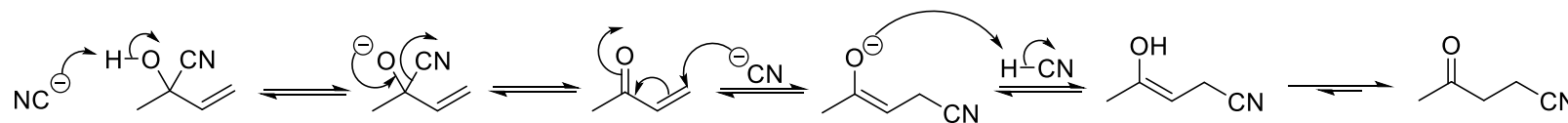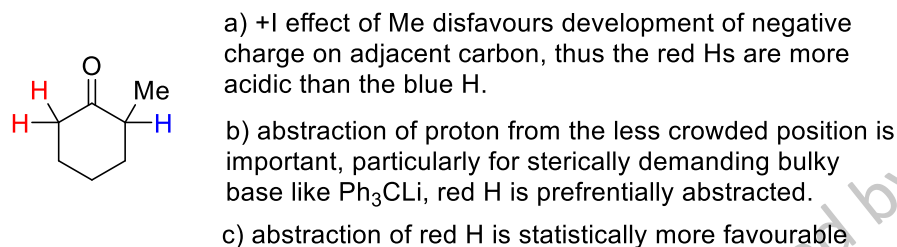
collapse of cyanohydrine to liberate enone - then conjugate addition and proton tansfers

Energetics of organic reactions:

Theromodynamic and kinetic control of reactions: Enolate formation from unsymmetrical ketones

2-methylcyclohexan-1-one

(-78°C)	90%	10%
(20°C)	10%	90%

is the TCP, thermodynamic enolate

is the KCP, kinetic enolate

Explanation for KCP:

a) +I effect of Me disfavours development of negative charge on adjacent carbon, thus the red Hs are more acidic than the blue H.

b) abstraction of proton from the less crowded position is important, particularly for sterically demanding bulky base like Ph$_3$CLi, red H is prefrentially abstracted.

c) abstraction of red H is statistically more favourable

For these reasons, the red H from the less substituted α-carbon is abstracted at a faster rate, leading to the kinetic enolate.
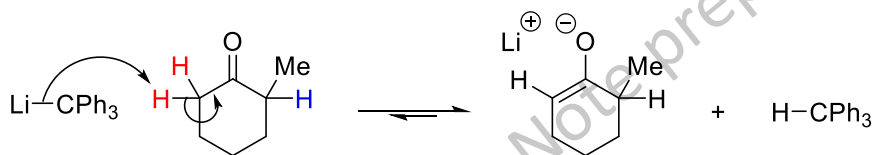

kinetic enolate can be the major product by:
i) using bulky, very strong base, b) doing the reaction at a lower temp.,
iii) making sure that the ketone compound does not remain in excess
iv) using non-protic solvent that cannot act as proton source

thermodynamic enolate can be the major product by:
i) using small-sized, relatively weak base, b) doing the reaction at a higher temp., iii) making sure that the ketone compound remain in little excess, iv) using protic solvent that promotes prototonation of the initially formed kinetic enolate and thus encouraging equilibration with the thermodynamic enolate

Explanation for TCP:

is thermodynamically more stable than
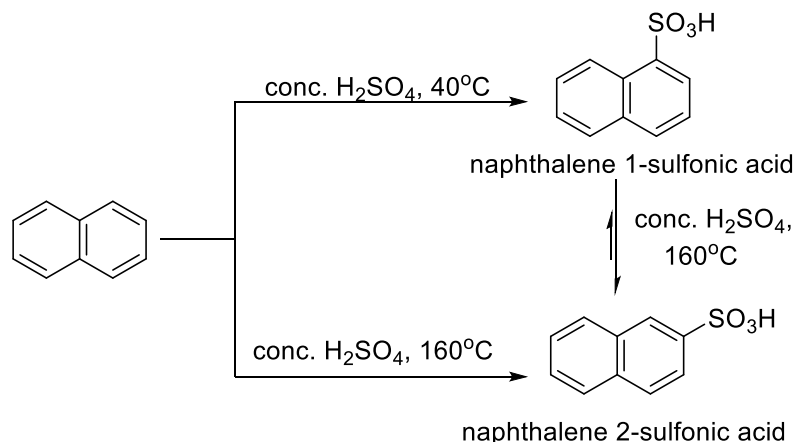
more substituted C=C   less substituted C=C
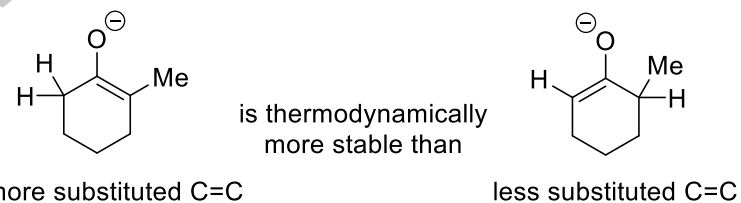
When temp. is raised the kineic enolate converts into the thermodynamic enolate through a proton exchange equilibrium set up between the kinetic enolate and as-yet-unreacted ketone. So, presence of slight excess of ketone during enolate formation is necessary here. We are using non-protic solvent ether here, so the only proton source available is the unenolised ketone.

unenolised   kinetic enolate   thermodynamic   unenolised
ketone   enolate   ketone (regen,)
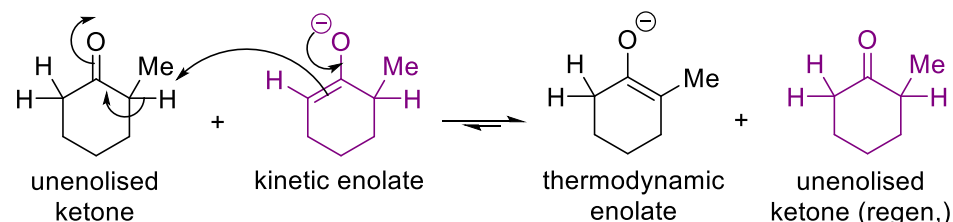
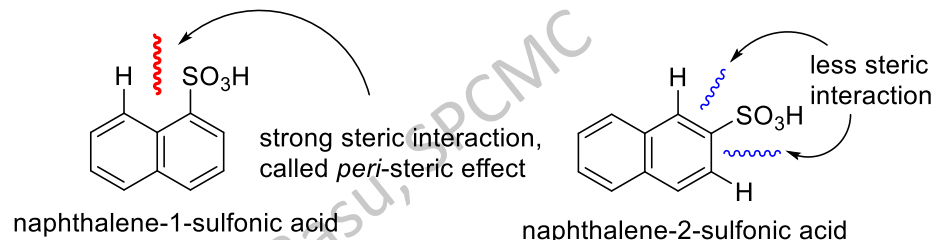Point to note that the base used here is very strong, so it will quantitaively deprotonate the ketone. That's why adding the base to the ketone promotes equilibration as there is some excess ketone present in the reaction medium when the base is being added. If a weaker base such as hydroxide is used, it cannot deprotonate the ketone fully, and there is always unenolised ketone present, and the order of addition matters little.

Energetics of organic reactions:

Theromodynamic and kinetic control of reactions: Sulfonation of naphthalene

naphthalene 1-sulfonic acid

conc. H_2SO_4, 40°C

conc. H_2SO_4, 160°C

conc. H_2SO_4, 160°C

naphthalene 2-sulfonic acid

Naphthalene 1-sulfonic acid is the KCP, forms faster.
Naphthalene 2-sulfonic acid is the TCP, is more stable of the two.

strong steric interaction, called *peri*-steric effect

naphthalene-1-sulfonic acid

less steric interaction
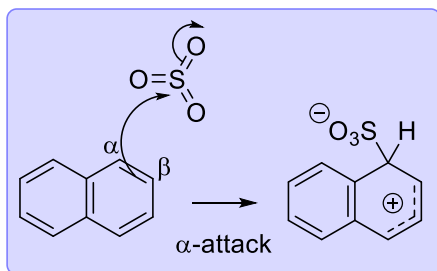
naphthalene-2-sulfonic acid

This is why the 2-sulfonic acid isomer is more stable than the 1-sulfonic acid isomer and the former is the TCP.

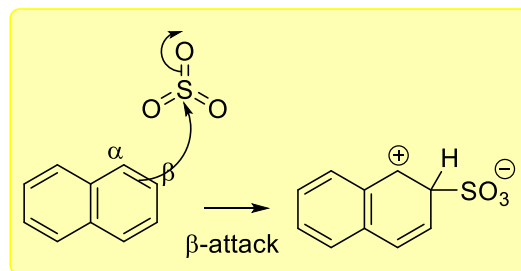Why does the 1-sulfonic acid isomer form faster?

This is an electrophilic substitution on naphthalene. Reaction proceeds by an electrophilic attack on a particular position to afford a carbocationic intermediate (σ-complex). The σ-complex loses proton in the second step and aromaticity is regained.

Because formation of σ-complex is the RDS and it is endothermic, the TS for its formation mimics the cationic σ-complex closely. The more stable σ-complex means the corresponding TS is more stable as well w.r.t. the TS that corresponds to the less stable σ-complex. So that TS will be accessed at a faster rate.

By counting the number of canonical forms we can conclude that the σ-complex for α-attack more stable than σ-complex for β-attack. This means that the attack at the α-position is kinetically favoured.

α-attack

β-attack

other canonicals, where aromaticity in adjacent ring is interrupted, are ignored

proton transfer

proton transfer
to regain aromaticity

α-attack

is faster than

β-attack

This implies that 1-sulfonic acid isomer will form faster than the 2-isomer, i.e. it is the KCP.
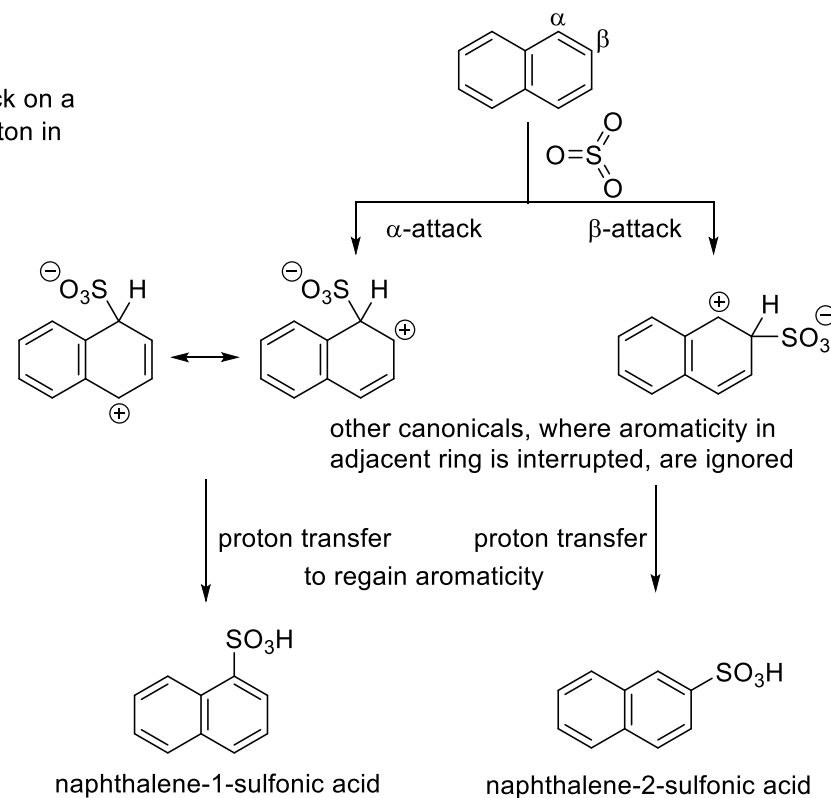
naphthalene-1-sulfonic acid

naphthalene-2-sulfonic acid

Energetics of organic reactions:

Theromodynamic and kinetic control of reactions: Sulfonation of naphthalene

How does the 1-sulfonic acid isomer convert to the 2-isomer?

C-S bond is weak

conc. H_2SO_4, 40°C → naphthalene 1-sulfonic acid

conc. H_2SO_4, 160°C

conc. H_2SO_4, 160°C → naphthalene 2-sulfonic acid
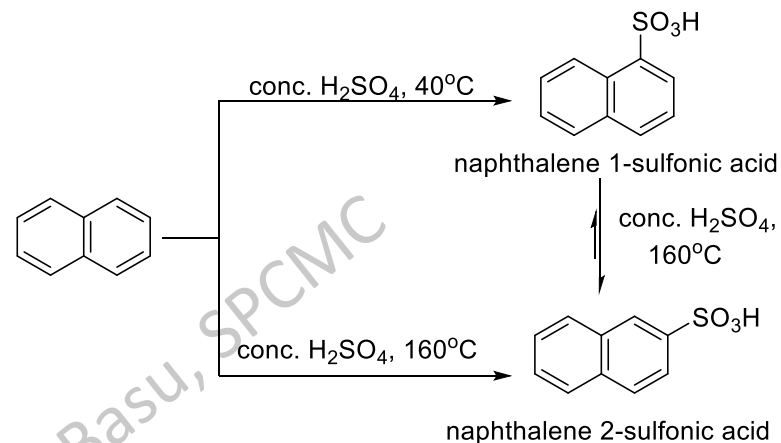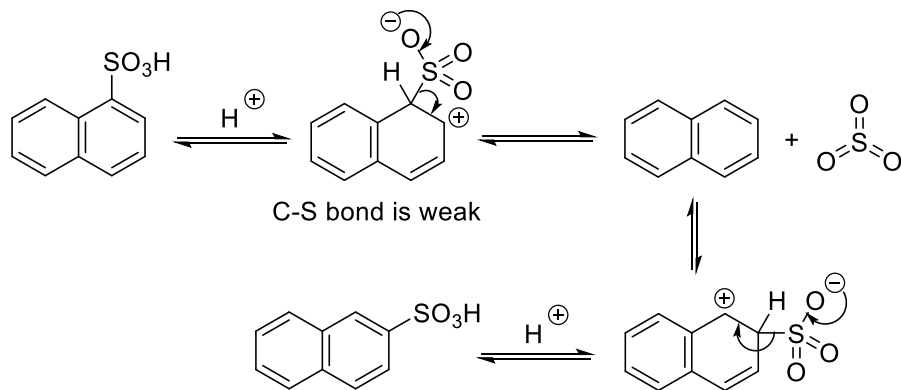
The reverse of sulfonation starts with protonation at the α-position bearing the SO$_3$H group. Then SO$_3$ is lost to regenerate naphthalene. This further attacks the β-position to eventually afford the 2-isomer.

Point to note: protonation at α-position is more favourable than at β-position, and, conversion of 1-isomer to 2-isomer is associated with relief of *peri*-steric strain.
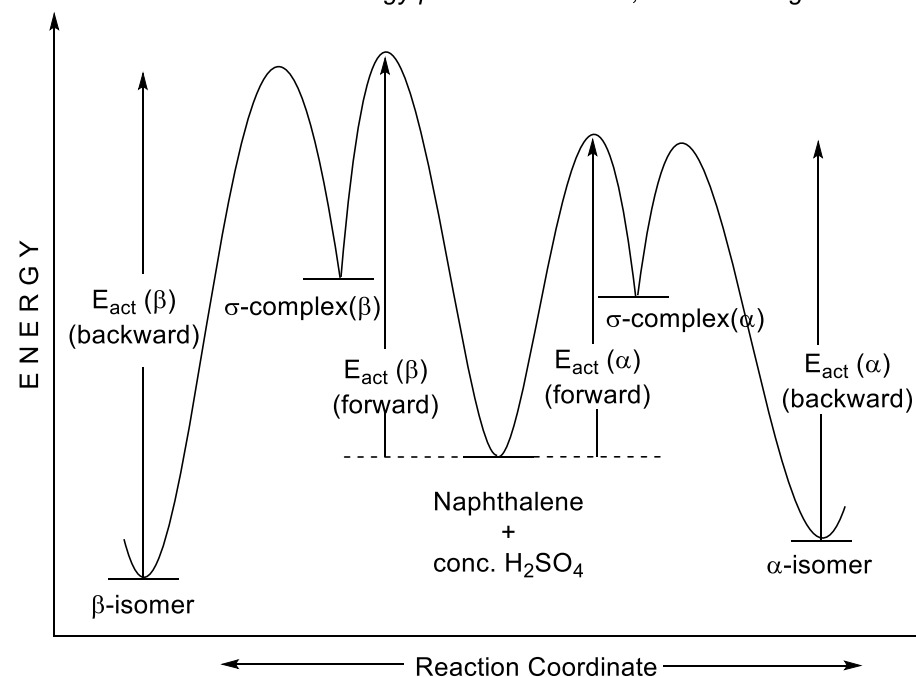
$E_{act}(\beta)$ > $E_{act}(\alpha)$
(forward)   (forward)

α-isomer will be formed at a faster rate - the KCP, predominant product at lower temp. when reactions are irreversible.

$E_{act}(\beta)$ >>> $E_{act}(\alpha)$
(backward)   (backward)

Thus at a higher temperature the α-isomer follows the reverse course more easily than the β-isomer. So at higher temperatures, with longer reaction time, β-isomer accumulates and becomes the major product, - the TCP.

Read this energy profile "inside out", not "left to right"

E N E R G Y

$E_{act}(\beta)$ (backward)

σ-complex(β)

$E_{act}(\beta)$ (forward)

$E_{act}(\alpha)$ (forward)

σ-complex(α)

$E_{act}(\alpha)$ (backward)

Naphthalene + conc. H_2SO_4

β-isomer

α-isomer

Reaction Coordinate

Energetics of organic reactions:

Theromodynamic and kinetic control of reactions: Semicarbazone formation

A striking demonstration of kinetic control vs. thermodynamic (equilibrium) control of products is provided by an experiment in which *equimolar* amounts of cyclohexanone, furfuraldehyde and semicarbazide hydrochloride are mixed in a solution of KOAc in 50% aqueous ethanol (solution pH is buffered at pH=5).

The product isolated after a reaction period of 20 seconds was cyclohexanone semicarbazone. However, when the reaction was allowed to proceed for 2.5 hours, the product was furfural semicarbazone.
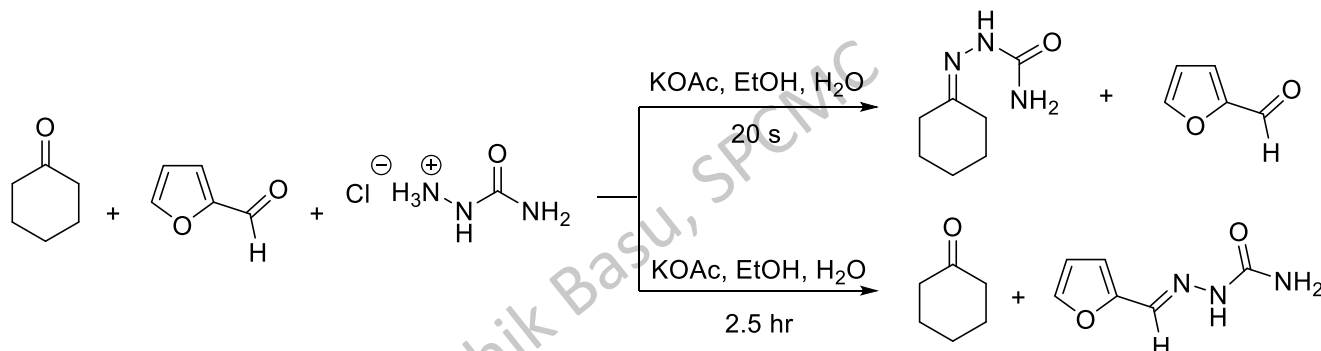
The semicarbazide reacts with cyclohexanone 60 times faster than it does with the aldehyde but the equilibrium constant for the aldehyde is about 300 times greater than that of the ketone.

KOAc, EtOH, H_2O
20 s

KOAc, EtOH, H_2O
2.5 hr

Clearly, the semicarbazone derivative from cyclohexanone is the KCP and is the exclusive product when the reaction is worked up rapidly, without giving any opportunity for eqm. to establish. The furfural semicarbazone is the TCP and is the exclusive product when the reaction is allowed to go on for a long time and then worked up. The long reaction time is conducive for establishment of eqm. and TCP dominates.
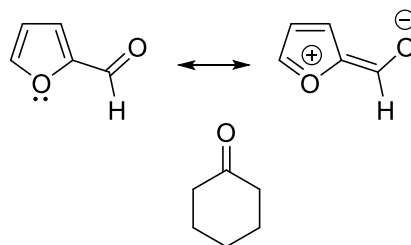
Why does the semicarbazone of cyclohexanone form faster than that of furfural?

The first step of semicarbazone formation involves nucleophilic attack of the semicarbazide *N* to the electrophilic carbonyl carbon of the substarte:
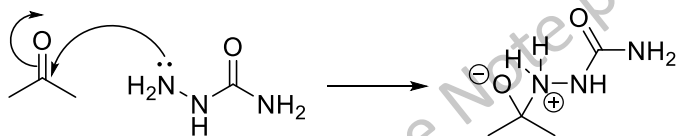
As the electrophilicity of the C=O increases, this reaction proceeds faster and overall rate of semicarbazone formation increases.

The electrophilicity of the carbonyl group of furfural is somewhat reduced due to the following conjugation with the ring oxygen:

The cyclohexanone carbonyl group has no such conjugation and is more electrophilic, reacts more readily with semicarbazone and forms the KCP.

Why is the semicarbazone of furfural more stable than that of cyclohexanone?

resonance-stabilised semicarbazone
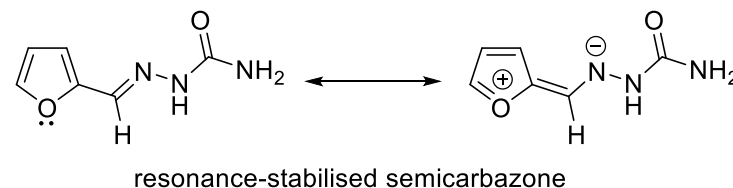
No such stabilisation is available for cyclohexanone semicarbazone.