M. U. en Química, Universitat de València

44606 - Advanced Organic Chemistry

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Unit 1

Methods to Study Reaction Mechanisms in Organic Chemistry

Reference textbook: F. A. Carroll, Perspectives on Structure and Mechanism in Organic Chemistry, 2nd Ed., 2010, Wiley.

Thermodynamics and Kinetics in Organic Reactions

THERMODYNAMICS ⇨ Energy changes between reagents and products. Chemical balance. Spontaneity of the reaction.

KINETICS ⇨ Rate at which chemical processes occur: **Reaction Mechanisms**

Thermodynamics

Any organic reaction has associated enthalpy ΔH, entropy ΔS and Gibbs free energy ΔG changes. These variations <u>do not depend on the path followed </u>by the reaction. ΔG, ΔH and ΔS are **state functions**.

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

$\begin{cases} \Delta H = \text{entalpy change (kcal/mol)} \\ \Delta S = \text{entropy change (cal} \cdot \text{K}^{-1}\text{mol}^{-1} \text{ o eu.)} \\ \quad T = \text{temperature (K)} \end{cases}$

For a process in which P and T = constant

$\Delta G < 0 \rightarrow$ spontaneous process

$\Delta G > 0 \rightarrow$ non-spontaneous process

$\Delta G = 0 \rightarrow$ reversible process (in equilibrium)

2

Thermodynamics and kinetics in organic reactions

ΔH = heat of reaction at constant pressure $\begin{cases} \Delta H < 0 \text{ EXOTHERMIC reaction} \\ \Delta H > 0 \text{ ENDOTHERMIC reaction} \end{cases}$

Change in Enthalpy: The enthalpy changes (ΔH) for a given reaction can be estimated from the **bond energies**:

$-\Delta H = \Sigma$ energy of the bonds formed $- \Sigma$ energy of the broken bonds

Calculations of this type are only <u>approximate</u> since the bond energy values that are tabulated generally consider that the energy of a particular bond is independent of the rest of the structure, which is a very imprecise approximation.

Bond energy values (kcal/ mol)

A. Some Common Bond Energies[a]					
H—H	103	C—H	98	C=C	145
C—C	81	N—H	92	C≡C	198
O—O	34	O—H	109	N≡N	225
Cl—Cl	57	Cl—H	102	C=O	173
Br—Br	45	Br—H	87	C—O	79
I—I	36	I—H	71	C—N	66

B. Some Specific Bond-Dissociation Energies[b]					
H_3C—H	104	H_3C—CH_3	88	H_3C—F	108
CH_3CH_2—H	98	H_5C_2—CH_3	85	H_3C—Cl	84
H_2C=CH—H	104	$(CH_3)_2CH$—CH_3	83	H_3C—Br	70
H_2C=CHCH$_2$—H	85	$PhCH_2$—CH_3	70	H_3C—I	56
$PhCH_2$—H	85	H_5C_2—C_2H_5	87	H_3C—OH	91
H_2N—H	103	$(CH_3)_2CH$—$CH(CH_3)_2$	78		
CH_3NH—H	92				
CH_3O—H	102	H_2C=CH_2	163^c		
		HC≡CH	230^c		

Example: butene hydrogenation enthalpy calculation

$$H_3CCH=CHCH_3 \ + \ H_2 \ \rightleftharpoons \ CH_3CH_2CH_2CH_3$$

links formed	broken links
H–H 103	2 C–H 196
C=C 145	C–C 81
248	277

$-\Delta H = 277 - 248 = 29$ $\Delta H = -29$ kcal/mol

Thermodynamics and kinetics in organic reactions

There are also extensive compilations of **standard enthalpy of formation** and **standard free energy of formation** values of compounds from their constituent elements, ΔH^0_f and ΔG^0_f. The superscript ^{0} indicates that they refer to the substance in its standard conditions, at 25 ºC and 1 bar (0,987 atm). These data allow to calculate the values of ΔH^0 and ΔG^0 for a given reaction:

$$\Delta H^0 = \Sigma\ \nu_p \Delta H^0_{f\ (products)} - \Sigma\ \nu_r \Delta H^0_{f\ (reagents)}$$

$$\Delta G^0 = \Sigma\ \nu_p \Delta G^0_{f\ (products)} - \Sigma\ \nu_r \Delta G^0_{f\ (reagents)}$$

An additional problem in the use of the tabulated data is that in general the reactions occur in solution and the presence of the <u>solvent</u> influences the values of ΔG, ΔH and ΔS.

Change in Entropy

Entropy: tendency of the particles of a system to distribute the total energy among the maximum number of available energy levels (states)
Entropy can be considered as "a measure of the disorder of a system".
• In general, liquids have lower entropy than gases and solids are those that have a lower entropy. Thus, a reaction in which all the reactants are liquid and a gas is generated as a product will be favored from the entropic point of view.
• The reactions in which there is an increase in the number of molecules are favored by entropy.
• An open-chain molecule has a higher entropy than the corresponding cyclic molecule. Therefore the opening of a ring is favored entropically while the closure is unfavorable.

Thermodynamics and kinetics in organic reactions

ΔG is related to the value of the thermodynamic equilibrium constant, K through the equation:

$$\Delta G^0 = -RT\ \ln K$$

$\left\{ \begin{array}{l} R = \text{cte. molar gases} = 1{,}986\ \text{cal·grado}^{-1}\text{mol}^{-1} \\ T = \text{absolute temp. (K)} \\ \Delta G^0 = \text{kcal·mol} \end{array} \right.$

$$A \underset{}{\overset{K}{\rightleftharpoons}} B \qquad K = \frac{[B]_{eq}}{[A]_{eq}}$$
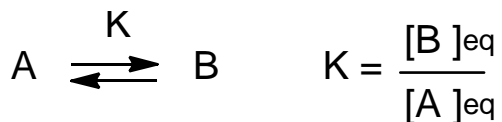
A	99.0	90.9	50	25	9.1	0.99	0.1
B	0.99	9.1	50	75	90.9	99.0	99.9
K	0.01	0.1	1	3	10	100	1000
ΔG⁰	+2.73	+1.36	0	-0.65	-1.36	-2.73	-4.09

(kcal/mol, 25 ºC)

Thermodynamic data do not consider time, therefore, if there is no relatively low energy reaction way, reagents that give rise to thermodynamically favorable reactions can coexist for very long periods of time without reacting. In other words, we must take into account the *kinetic factors* .

Thermodynamics and kinetics in organic reactions

Kinetics: Potential energy diagrams. Activation energy (E_a) and transition state (TS)

The reactions involve an energy barrier that must be exceeded in order for the reactants to become products. This energy barrier is called activation energy (E_a or $\Delta G^{\ddagger}$)

Every situation of the atoms throughout a chemical reaction possesses a certain energy associated with it. Since the reaction involves an approximation of the reactants and a breaking of bonds, these intermediate structures generally possess higher energies than those of the isolated reagents. As the reaction progresses, the potential energy of the system continues to increase until it reaches a maximum energy structure.

Activation energy : Difference between the energy of the reagents and the structure of maximum energy.

Transition state : Maximum energy structure.

Reaction coordinate : Measurement of the development of the transformation of the reactants to the products

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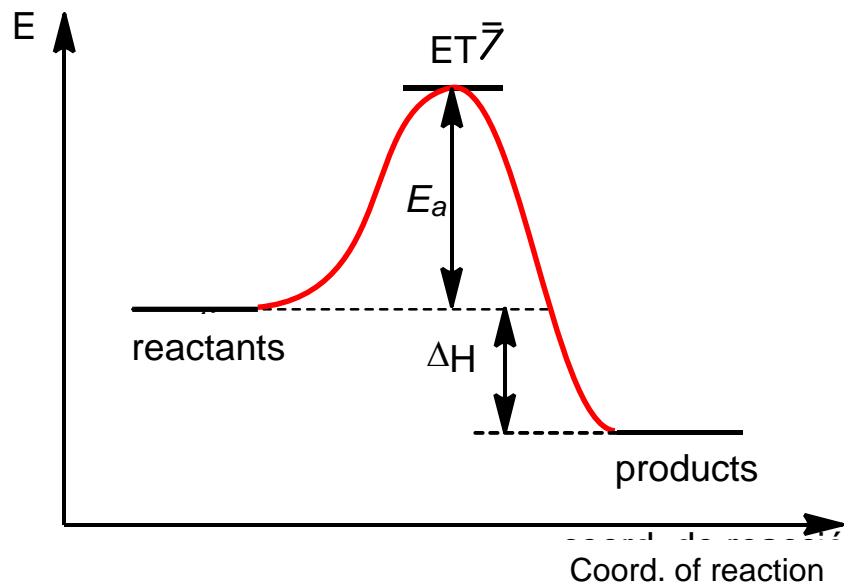
Tools to Determine Reaction Mechanisms

What is a reaction mechanism?

Detailed description at a molecular level, step by step, of how a chemical transformation occurs.

Namely:

- What links are broken, what new links are formed, and in what order.
- Information on the position of all nuclei and valence electrons of all participating species (reactants, products and solvent molecules).
- Information about the total energy of the system at each moment.

Tools to determine reaction mechanisms

How to determine the mechanism of a chemical reaction?

- Identification of reaction products.

- Determination of intermediates.

- Crossover experiments.

- Isotopic labeling.

- Stereochemical studies.

- Solvent effects.

- Computational studies.

- Kinetic studies

Rate equations

Kinetic Isotope Effects

It is important to note that the methods used to determine the reaction mechanisms are never conclusive. A mechanism is considered established, provided it explains all the experimental results. However, it can be refuted if new experimental facts appear that contradict it.

Identification of reaction products

The identification of the product or reaction products is a basic requirement in any investigation about the mechanism of a chemical reaction. It seems a trivial statement but it is not ...
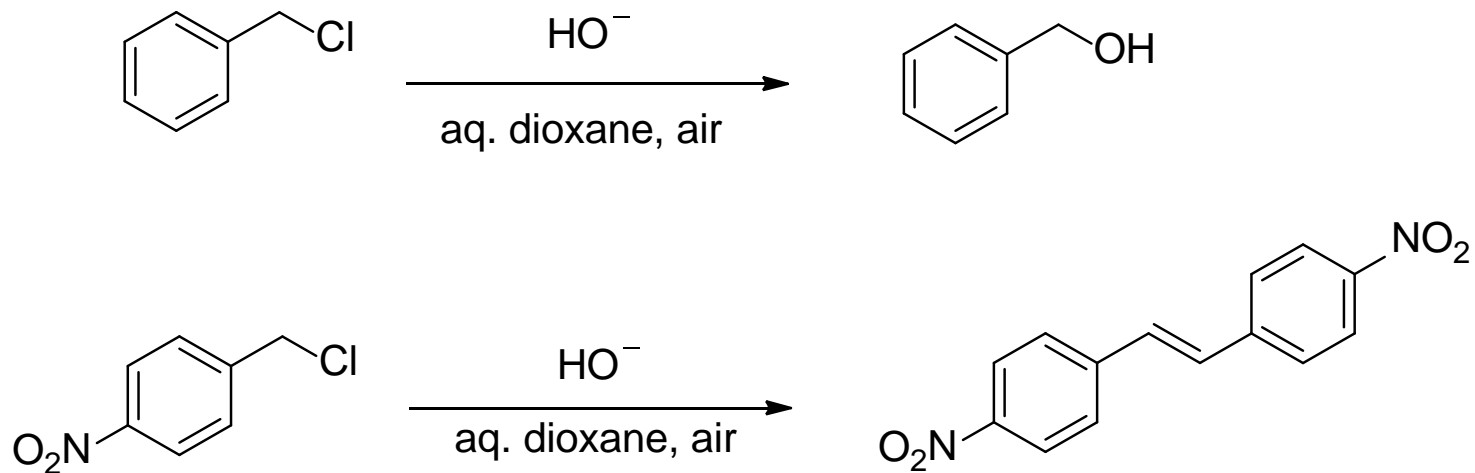
Ref: *J. Chem. Soc., Perkin Trans. 2*, **1974**, 31-35

Determination of reaction intermediates

Reagents and products constitute only the extremes of the mechanism of a reaction. For a complete description it is necessary to know what happens between them. An important aspect is to know the <u>number of stages of the reaction</u>.

If the reaction takes place in a single step (reactants - transition state - products) it is called **elementary reaction** . If it involves several steps, it is a **stepwise reaction**. An elementary reaction involves a **concerted process**, where bonds are formed and broken simultaneously. A stepwise reaction implies the appearance of one or more minima in the curve of the energy diagram. The chemical species that occupy these minimums are the **reaction intermediates**.
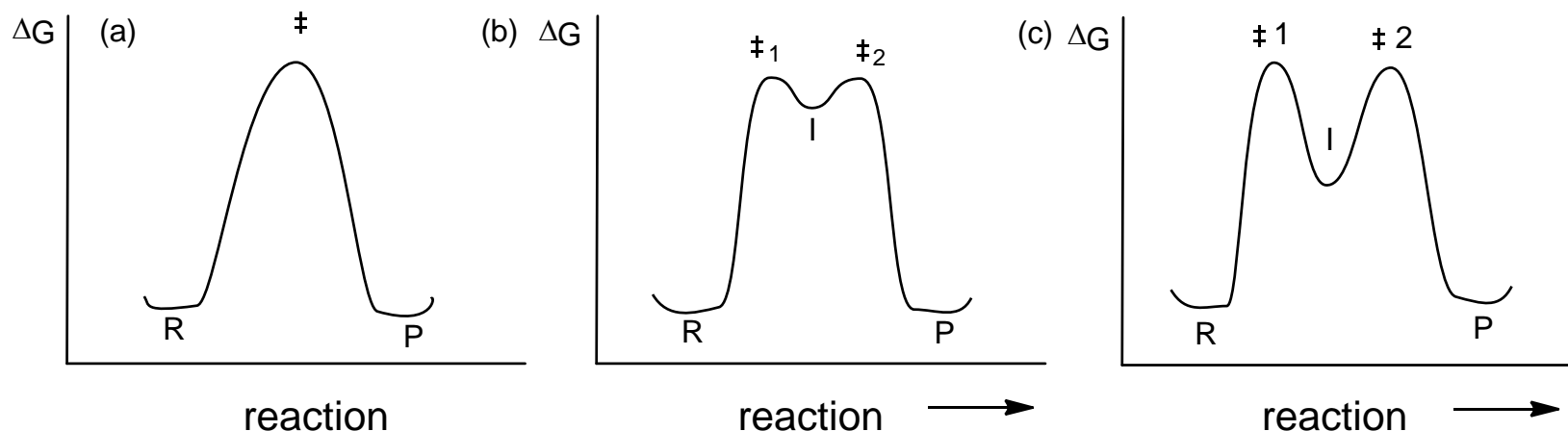
Diagrams of : (a) an elementary reaction; (b) stepwise reaction with an unstable intermediate and (c) stepwise reaction with a more stable intermediate (easier to detect and even to isolate)

Determination of reaction intermediates

The existence of reaction intermediates can be demonstrated in three different ways:

- ISOLATION AND IDENTIFICATION

- SPECTROSCOPIC DETECTION

- TRAPPING OF THE REACTIVE INTERMEDIATES

ISOLATION OF STABLE INTERMEDIATES

The most convincing evidence that a species acts as an intermediate of a reaction is its isolation and identification. This can take place when the intermediate is sufficiently stable (situation c of the previous graph)

CAUTION: Do not confuse an intermediate with a byproduct of the reaction.

If a substance isolated from a reaction mixture is subjected to the same reaction conditions as the reactants and leads to the same products, at a rate equal to or greater than that of the overall process, this substance will be very likely an intermediate of this reaction.

ISOLATION OF STABLE INTERMEDIATES

Example : conversion of 2,3-diacetoxybutanor to 2,3-dibromobutane (Winstein, Lucas, JACS 1939)

The isolation of intermediates is not always possible, so that the fact of not isolating a certain product of the reaction mixture does not rule out that it can be also an intermediate.
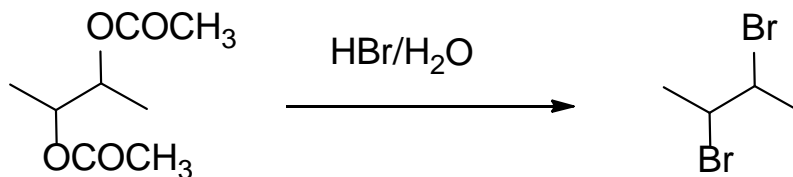
Products ... of the reaction mixture (incomplete reaction) are isolated:

a possible intermediate but that is not isolated:
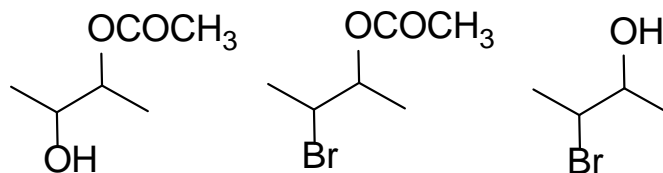
when treated separately with HBr / H_2O under the reaction conditions they lead to the dibromide. They are authentic intermediates
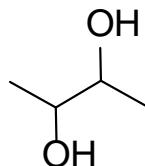
When treated separately with HBr/H_2O it does not lead to dibromide. It is not an intermediate of the reaction

ISOLATION OF STABLE INTERMEDIATES

Electrophilic aromatic substitution: The participation of Wheland intermediate (σ) has been demonstrated using strongly electrophilic reagents with slightly basic anions, and at very low temperatures.

Solid, stable to
a I<-50°C

Solid orange
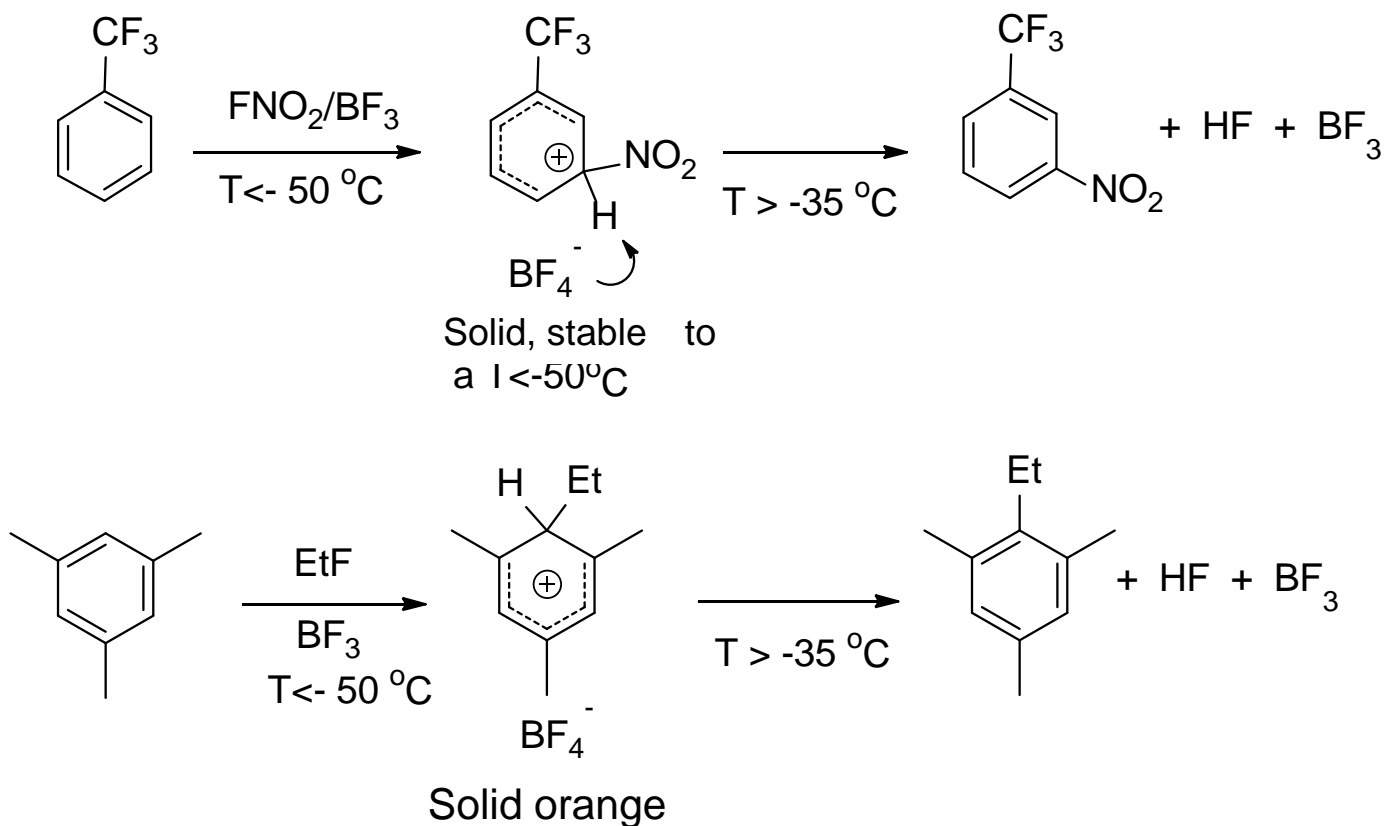
ISOLATION OF STABLE INTERMEDIATES

Nucleophilic aromatic substitution : The proposed mechanism involves the participation of an anionic intermediate (Mesenheimer complex)
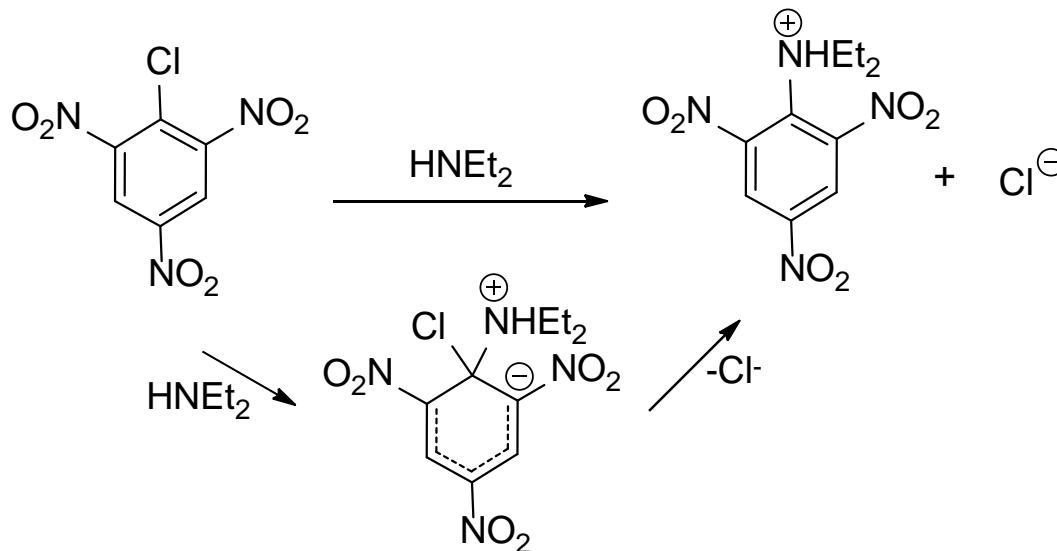
In some cases it has been possible to isolate from the reaction mixture similar species to the Mesenheimer complex.
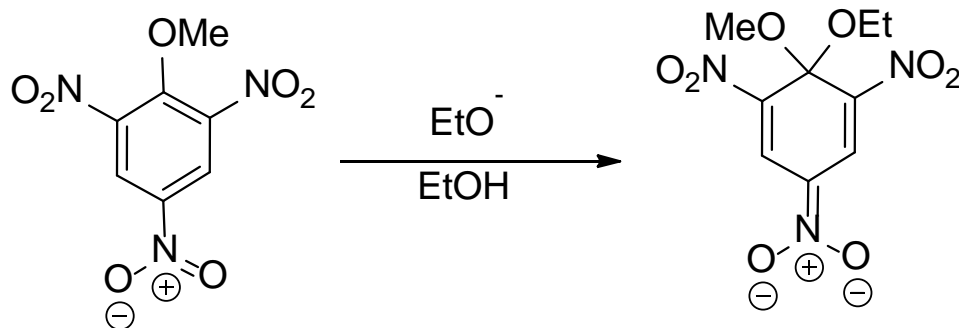
It has been isolated in the form of salt

DETECTION OF INTERMEDIATES BY SPECTROSCOPIC TECHNIQUES

If the intermediate is not stable enough to be isolated, but is in sufficient concentration in the reaction mixture, it can sometimes be detected by different methods, mainly spectroscopic: UV, IR, NMR, EPR (electron paramagnetic resonance), laser flash spectroscopy, etc.

An example of IR detection is in the photochemical isomerization of the following compound, for which a ketene intermediate is proposed (ketenes absorb at 2100-2130 cm^{-1}). By monitoring the reaction mixture by IR, the appearance of a band at 2118 cm^{-1} is observed, which grows until reaching a maximum intensity and then decreases until it disappears.

ketene
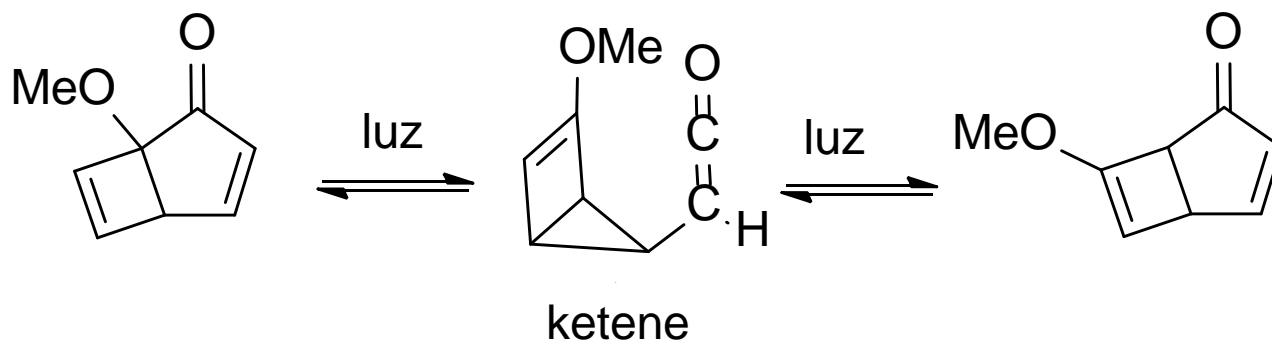
DETECTION OF INTERMEDIATES BY SPECTROSCOPIC TECHNIQUES

Another example: transformation of *o*- aminobenzoate into biphenylene, for which the participation of a benzyne intermediate is postulated as an intermediate. The benzyne participation is demonstrated by MS (*m/z* 76). A band at *m/z* 76 is observed in the mass spectrum of the mixture, which decreases with time, giving rise to another at *m/z* 152.


m/z 76

benzyne

m/z 152
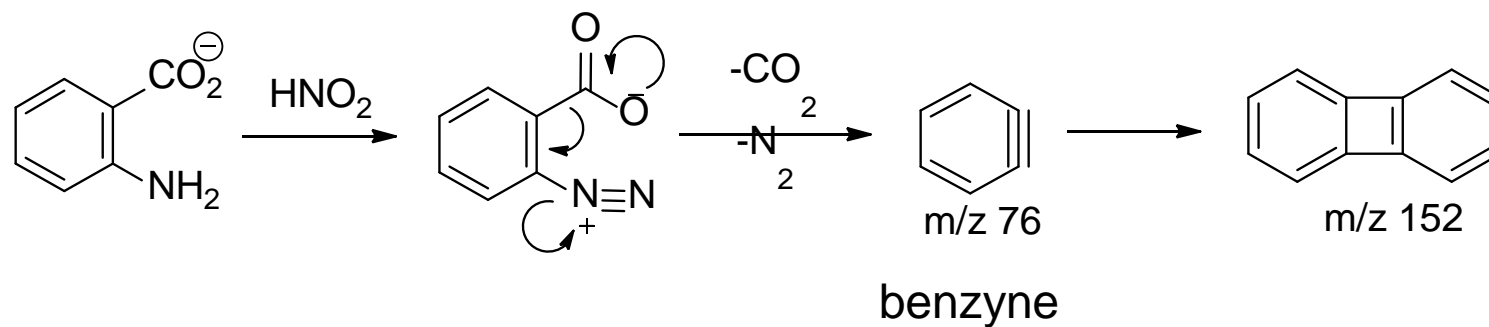
TRAPPING OF REACTIVE INTERMEDIATES

The **trapping** consists of reacting the proposed intermediate with a reagent that is added to the reaction mixture (in most cases) and identifying the product obtained.

The added reagent should not affect the course of the reaction in any other way than by capturing the reactive intermediate. The disappearance rate of the starting reagent must be exactly the same.

Benzynes: They are very reactive intermediates that are postulated in some nucleophilic aromatic substitution reactions.

Mixture of para and meta
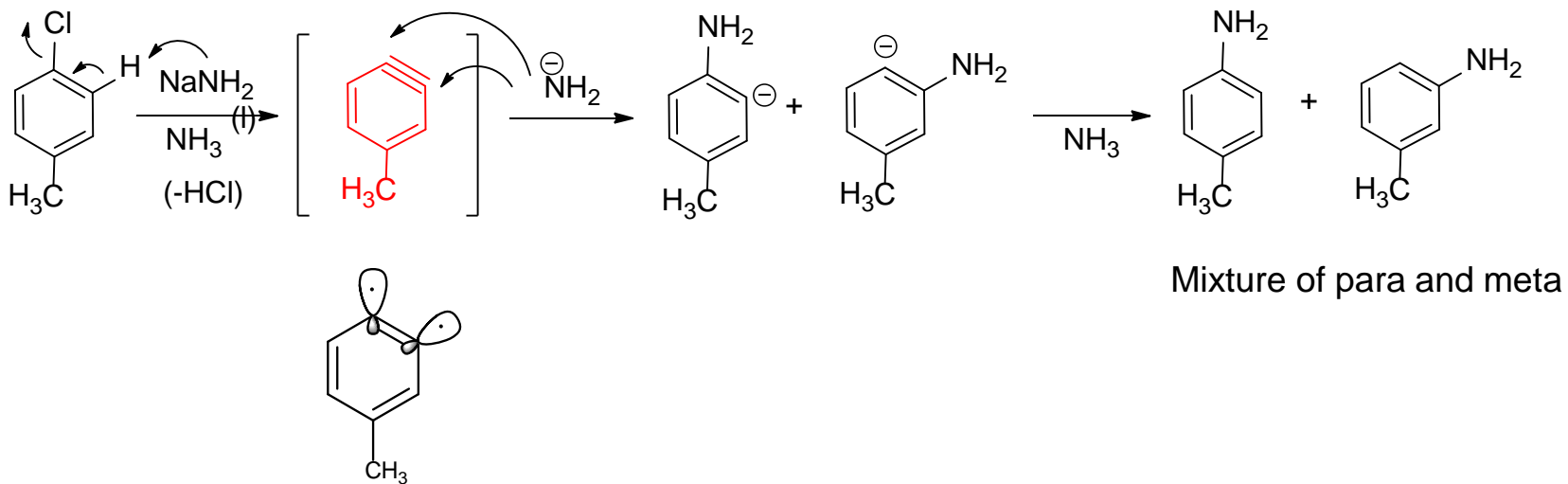
TRAPPING OF REACTIVE INTERMEDIATES

Benzyne is highly reactive and can be trapped with a multitude of dienes in Diels-Alder reactions, giving rise to easily identifiable products.


furano

1-naftol
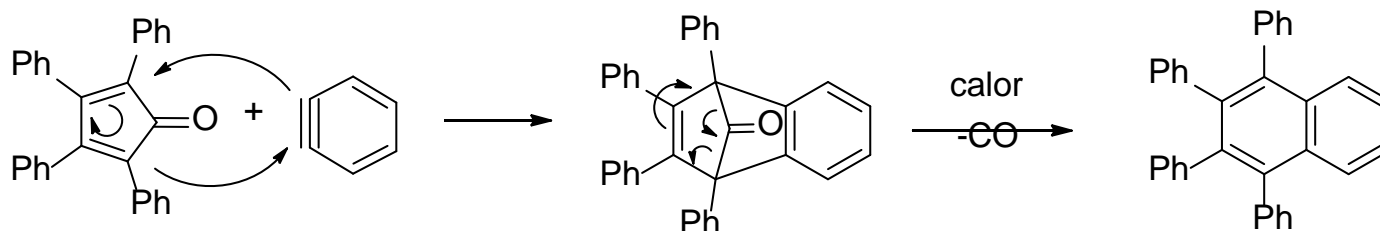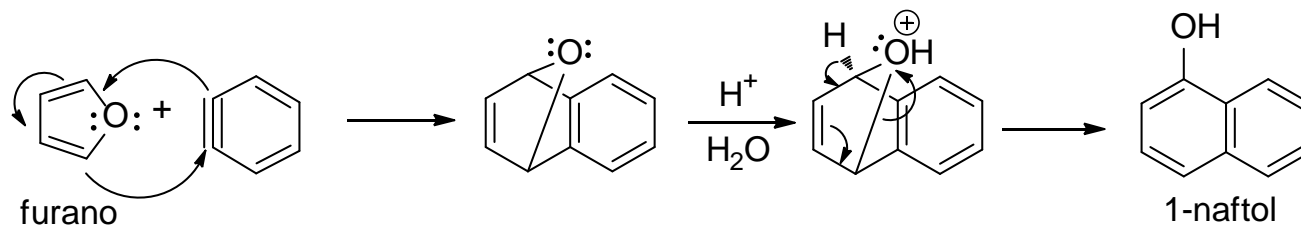
tetraphenylcyclopentadienone (tetracyclone); strongly colored

calor
-CO

Naphthalene derivative (colorless)

anthracene

triptycene
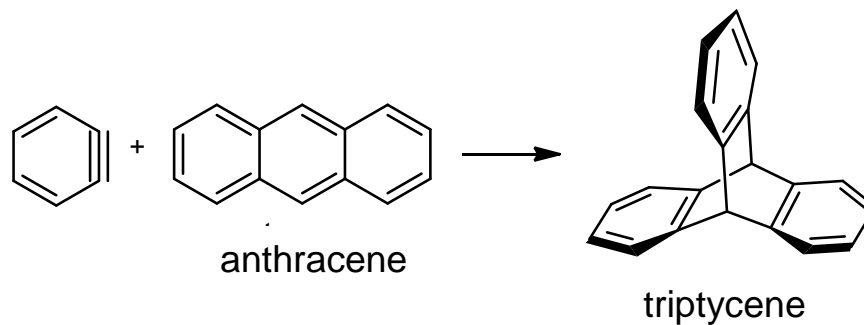
TRAPPING OF REACTIVE INTERMEDIATES

Cationic species (double bond bromination): One of the various mechanisms proposed for the bromination of butene with Br_2/CCl_4 involves the formation of a cationic (electrophilic) species. The fact that the addition of a nucleophile (methanol) to the reaction mixture leads to products that incorporate methanol in its structure demonstrates this hypothesis. Determining the specific nature of the cationic intermediate may require other experiments (eg, stereochemical studies).
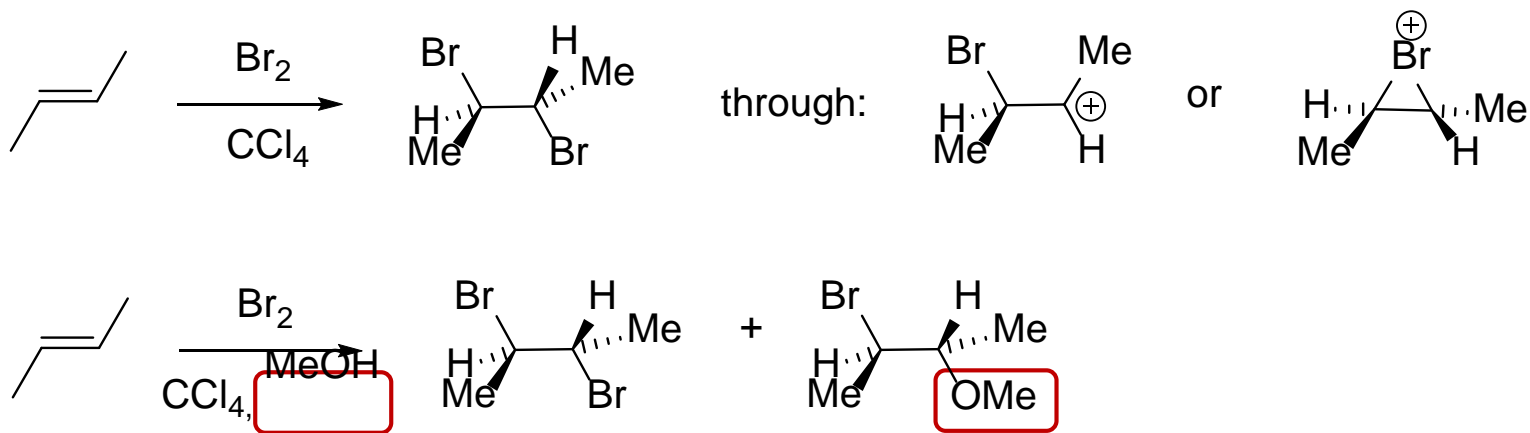
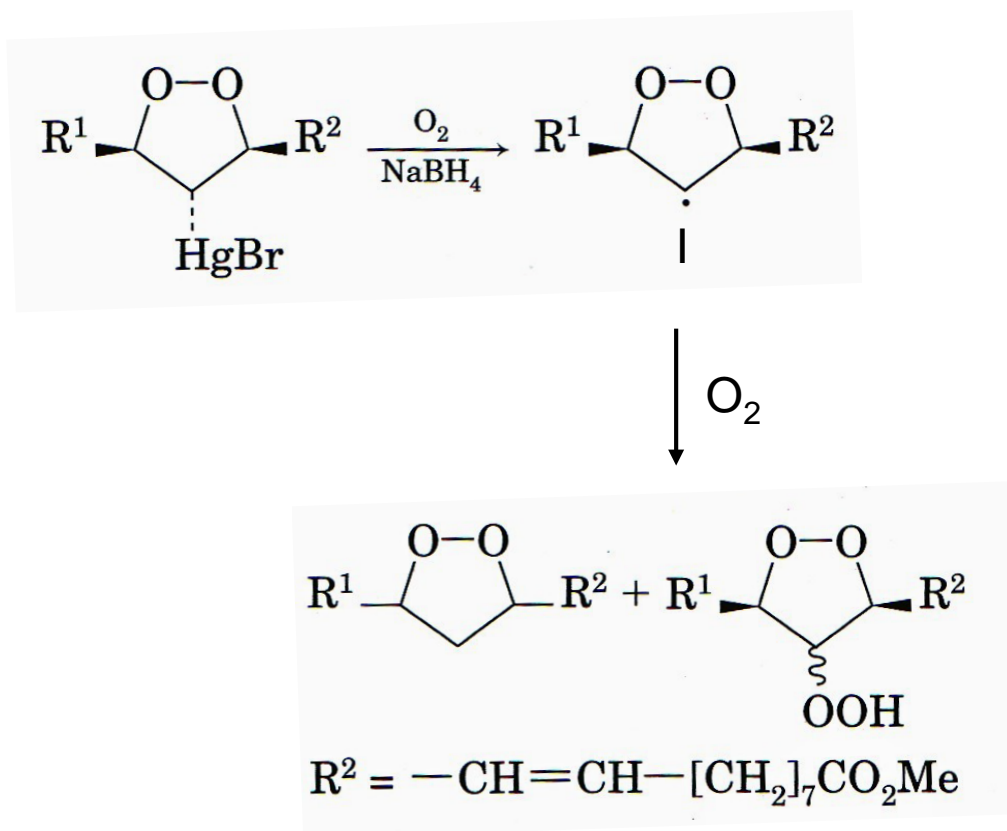# TRAPPING OF REACTIVE INTERMEDIATES

Radicals: Radical species can be captured with different reagents, e.g. <u>oxygen</u>, with which they give hydroperoxides. In some cases trapping experiments may be useful to <u>discard</u> a compound as an intermediate in a reaction. This approach involves demonstrating that the proposed intermediate should be trapped if it were found in the reaction mixture.

Example: A proposed mechanism for the transposition of allylic hydroperoxides involves intermediate **I** that could not be trapped by oxygen (even at high pressure).
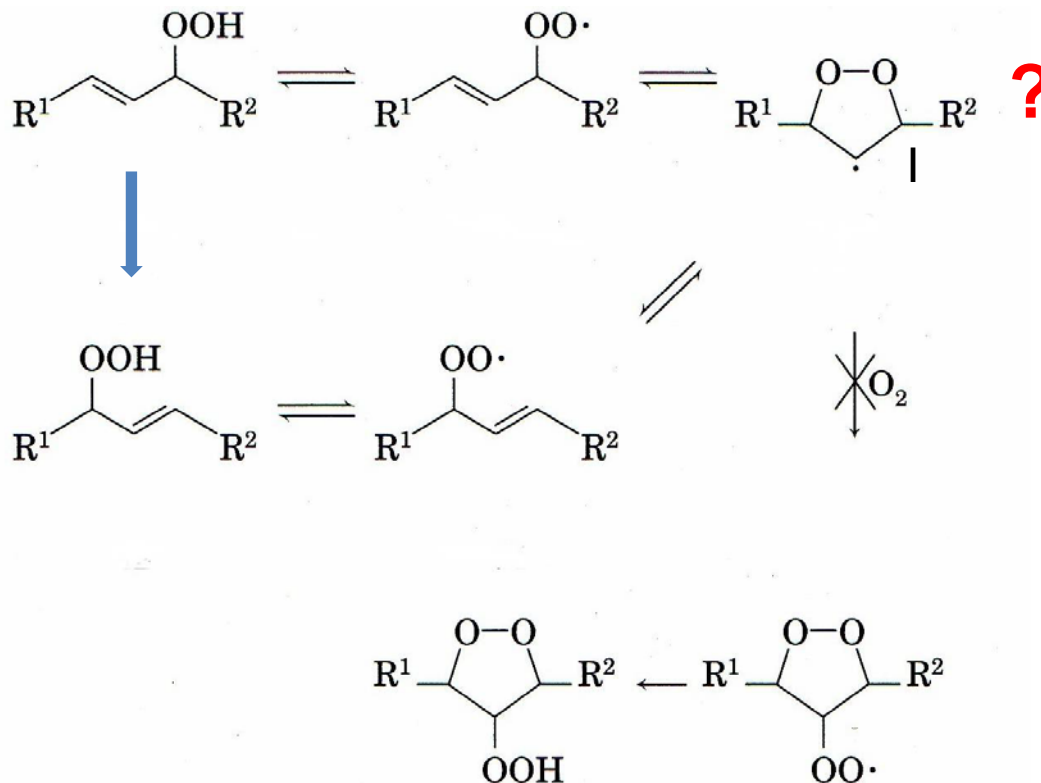
Porter i Zuraw (*J. Chem. Soc. Chem. Commun.* **1985**, 472) prepared intermediate **I** by an alternative route and demonstrated that this intermediate does react with oxygen <u>at ambient T and pressure</u> .This result therefore discards the above mechanism for the transposition of allylic hydroperoxides.

$R^2 = -CH{=}CH-[CH_2]_7CO_2Me$

TRAPPING OF REACTIVE INTERMEDIATES

Carbanions (Internal trap) The nature of a reaction intermediate can also clarified by changing the substrate structure, providing a new reaction pathway for the intermediate.

For example, in the interconversion of the mandelate enantiomers by the mandelate racemase enzyme, the participation of a carbanion intermediate followed by protonation is postulated.
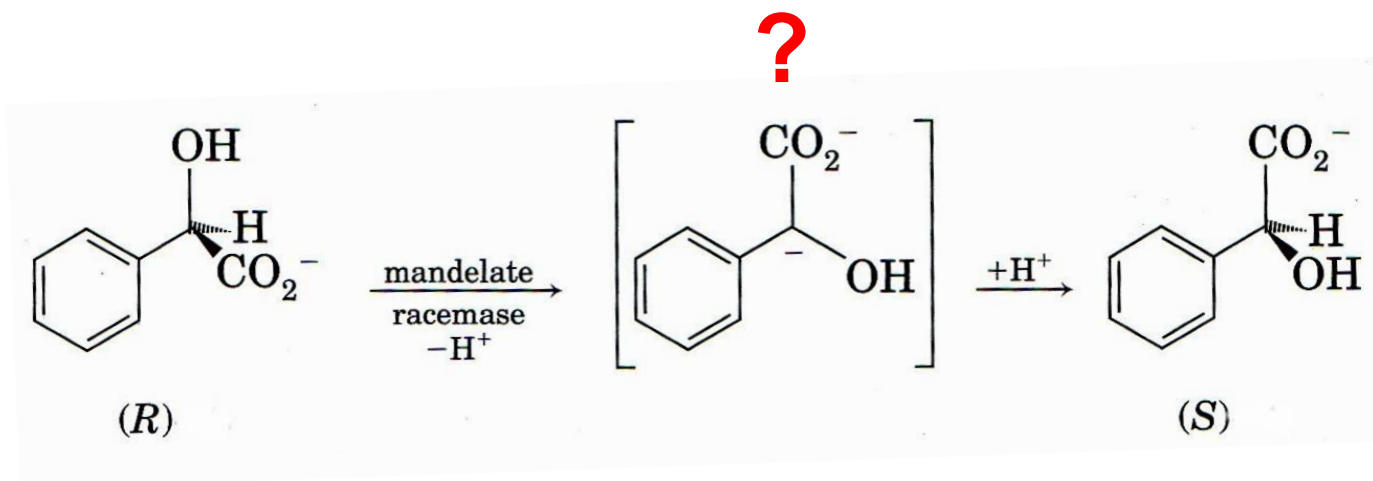
The existence of a carbanionic intermediate could be demonstrated by adequately modifying the structure of the mandelate ion.

TRAPPING OF REACTIVE INTERMEDIATES

Thus, the treatment of *p-* (bromomethyl) mandelate with the enzyme *mandelato racemase* forms *p* -methylbenzoylformate through the elimination of a bromide. This result suggests the formation of carbanion during the racemization of mandelate. In this case, the bromomethyl group acts as an internal carbanion trap.
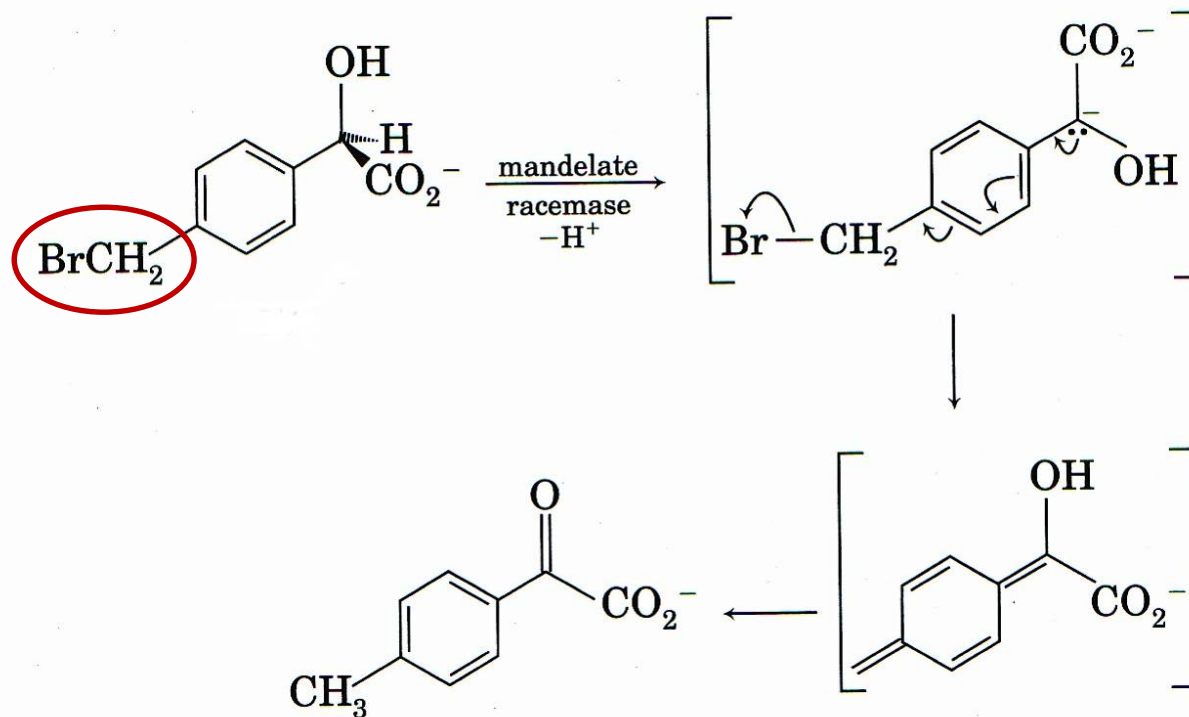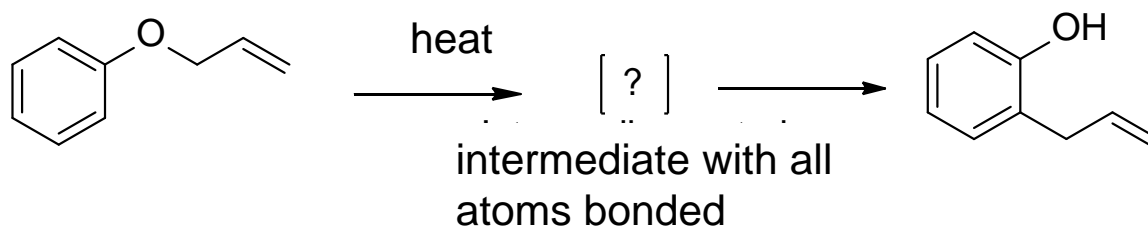
Crossover experiments

These experiments are particularly useful in the study of reactions implying molecular rearrangements. They consist of carrying out the reaction with a mixture of two reactants, one unlabeled and another "labeled" (eg with a methyl group) on both of the possible fragments that rearrange, and observe the corresponding products.
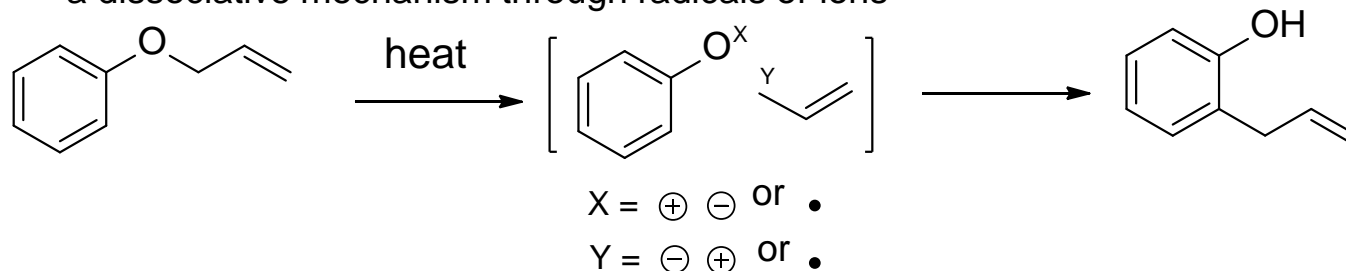If we consider for example the Claisen reaction, two mechanisms can be proposed:

The Claisen reaction:

a) a non-dissociative mechanism

intermediate with all
atoms bonded
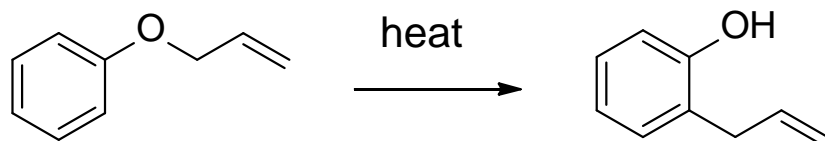
b) a dissociative mechanism through radicals or ions

X = $\oplus$ $\ominus$ or •
Y = $\ominus$ $\oplus$ or •

Crossover experiments

We prepare a mixture of reactants in which both the migrating group and the rest of the molecule are labeled (for example with a methyl group). First you have to check that the marking does not change the reaction. After the reaction, we analyze the products and look at whether a part of the labeled reactant has been incorporated into a part of the unlabeled reactant. The appearance of <u>recombination products</u> (E and F) would indicate that a <u>dissociative mechanism</u> exists (this is not the case of the Claisen reaction).
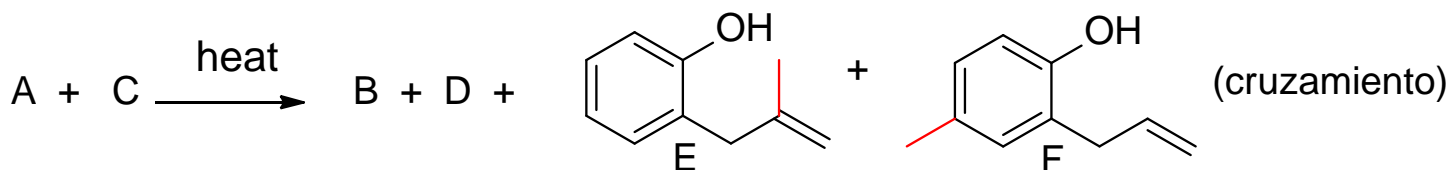
a) Reactions of the reactants marked separately
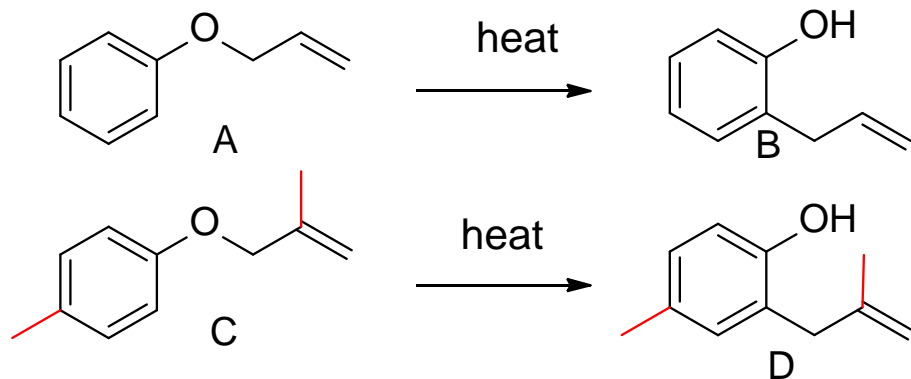
b) Possible results of crossover experiments
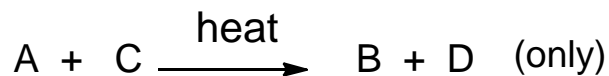
A + C $\xrightarrow{\text{heat}}$ B + D (only)   There is no crossover

A + C $\xrightarrow{\text{heat}}$ B + D +   +   (cruzamiento)

Crossover experiments

Attention:

The results of the previous experiences have to be carefully considered :

If crossover products are observed we can conclude that there is fragmentation of the reactants and recombination of the fragments during the reaction.

If the crossover products are not observed, the results are not conclusive. It could happen that dissociation occurs but the two fragments remain nearby (e.g. in a solvent cage) so that the recombination was faster than the diffusion of the fragments from the solvent cage, which would not produce the cross products.

➡ Only the POSITIVE results are conclusive!

Isotopic labeling

Substituents (usually Me groups) are used as labels in crossover experiments. This in some cases can alter the reactivity of the molecule. The use of isotopes as labels causes minor alterations and may be more advantageous.

Commonly used isotope labels:

^{1}H substituted by **D** (**^{2}H**). Deuterium shows no signal in NMR while the proton does.

^{12}C replaced by **^{13}C**. ^{13}C has a magnetic moment and is active by NMR. In the NMR spectrum the labeled product shows more intense signals (in the marked position) than the unlabeled product.

^{16}O replaced by **^{18}O** and **^{17}O** . The ^{17}O is active by NMR.

In addition to NMR, the labeled compounds can be differentiated by IR spectroscopy and mass spectrometry.
Tritium (**^{3}H**) and **^{14}C** are radioactive and are not very useful except when there is fragmentation.

Isotopic labeling

^1H substituted by D (^2H). Deuterium does not signal in the NMR spectrum while the proton does.


Diastereotopic (2 signals)
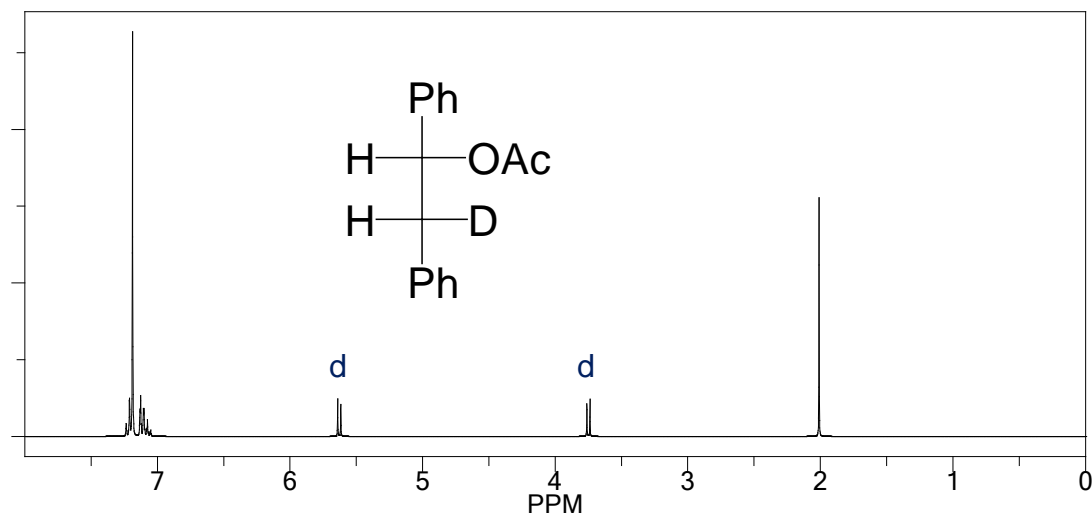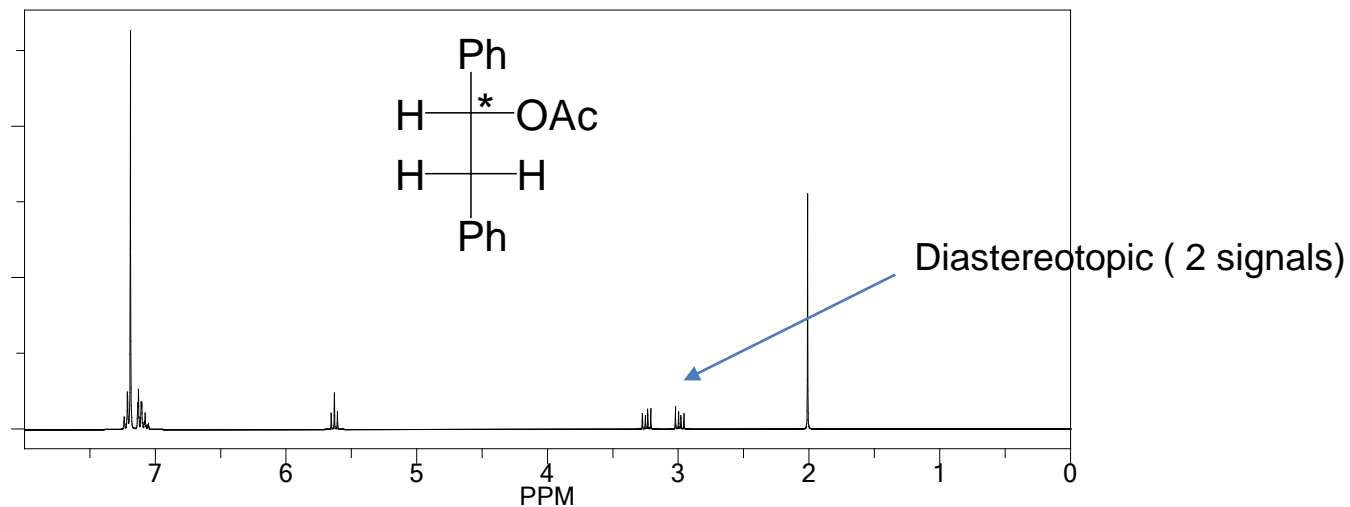
Isotopic labeling

^{12}C replaced by ^{13}C. ^{13}C has a nuclear spin of 1/2 and is NMR active. In the NMR spectrum, the labeled product shows more intense signals (corresponding to the marked position) than the unlabeled product.
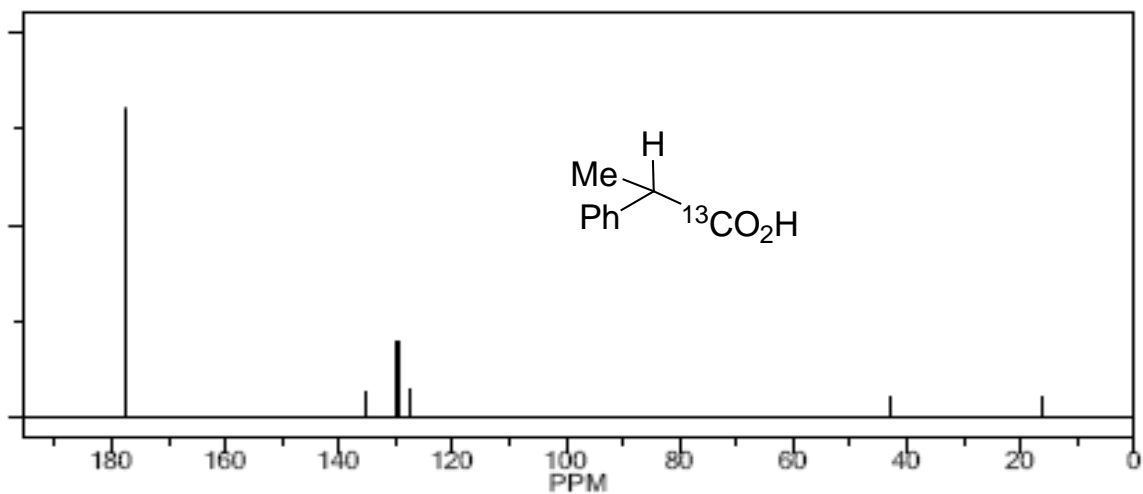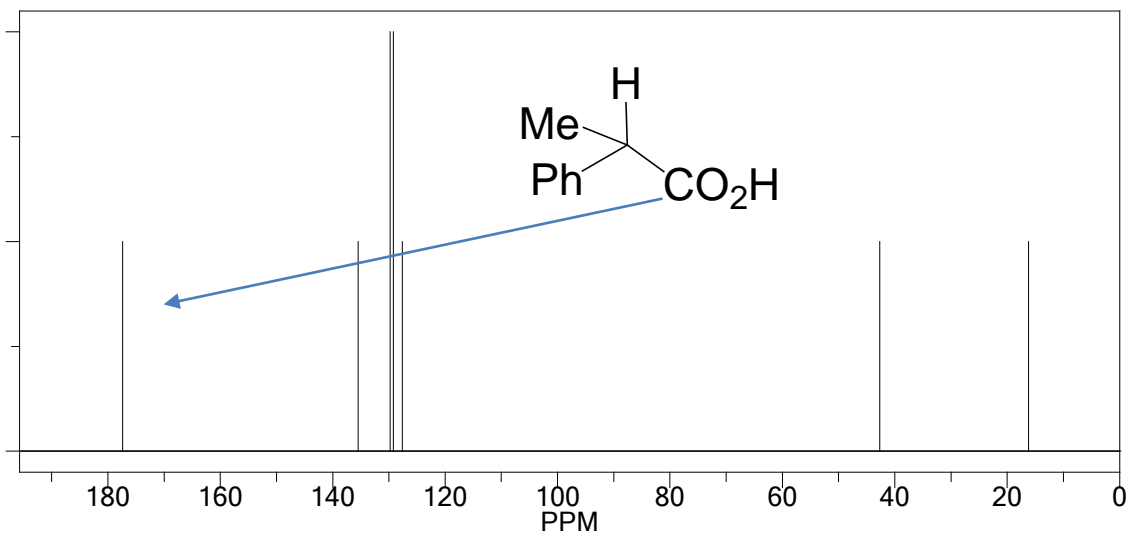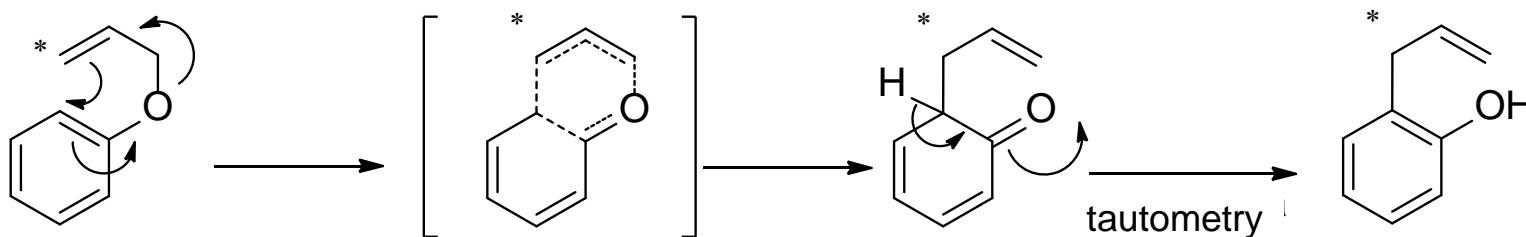
Isotopic labeling

Example of application: Thermal and photochemical Claisen's reactions

Thermal Claisen's reaction : The isotopic distribution in the product is explained by a <u>concerted</u> mechanism for transposition, followed by tautomerism.


calor

$* = {}^{13}C$

Only 1 product is observed

Not observed

Concerted mechanism

H

tautometry
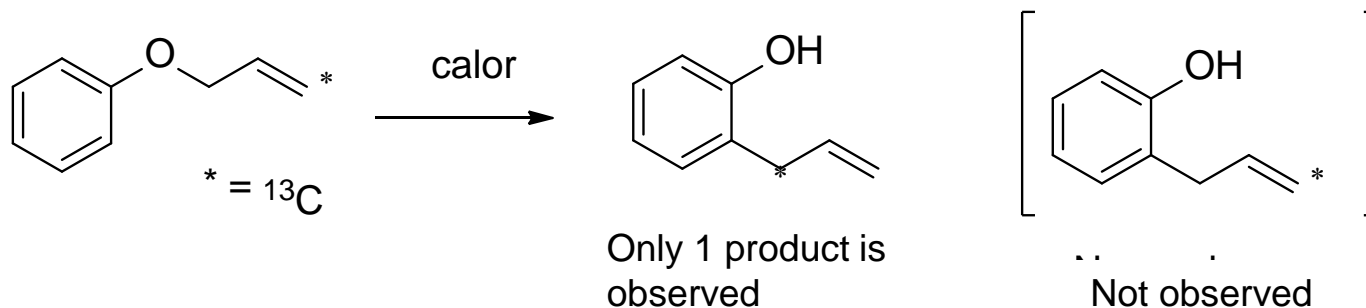
Isotopic labeling

Claisen's photochemical reaction :

The isotopic distribution in the product is explained by a <u>dissociative</u> mechanism. Other experiments show that the intermediates are of the radical type. The dissociation of the CO bond gives an allylic radical with two equivalent resonant forms, one of them is the labeled carbon with the radical. The recombination of the fragments occurs at both ends of the allylic radical giving two products marked differently.

* = ^{13}C

1 : 1

Radical mechanism

Keto-enol tautometry

1 : 1
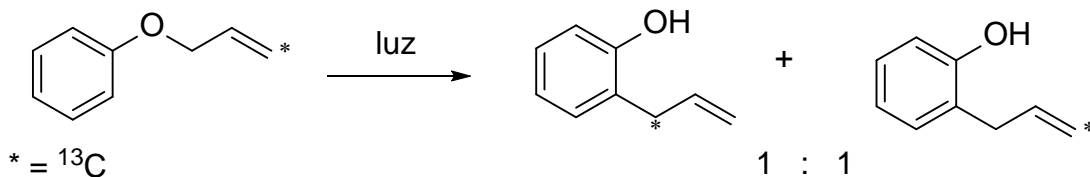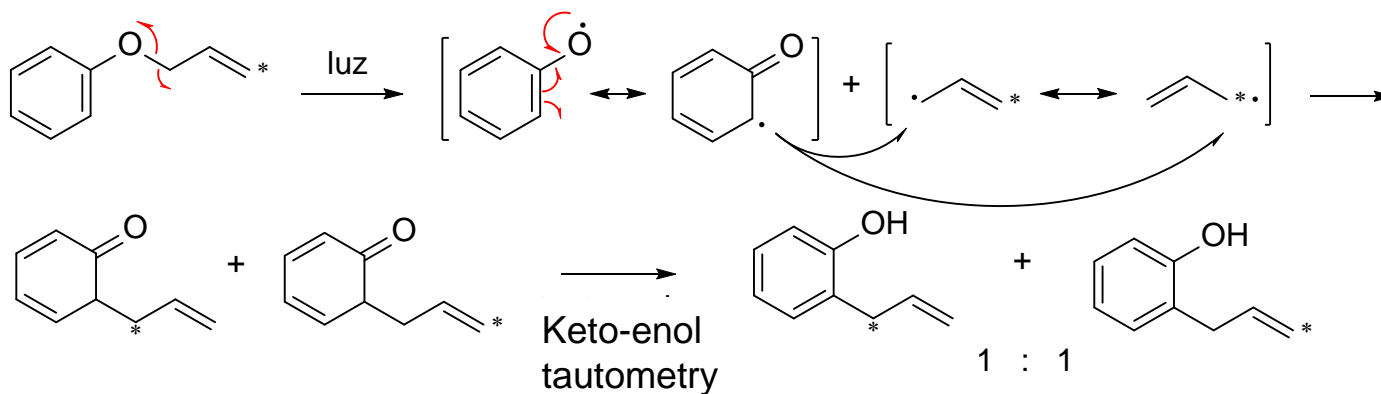
Another example: Thermal isomerization of benzocyclobutene to styrene .

Two mechanisms have been proposed:
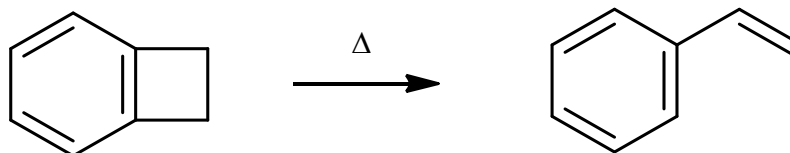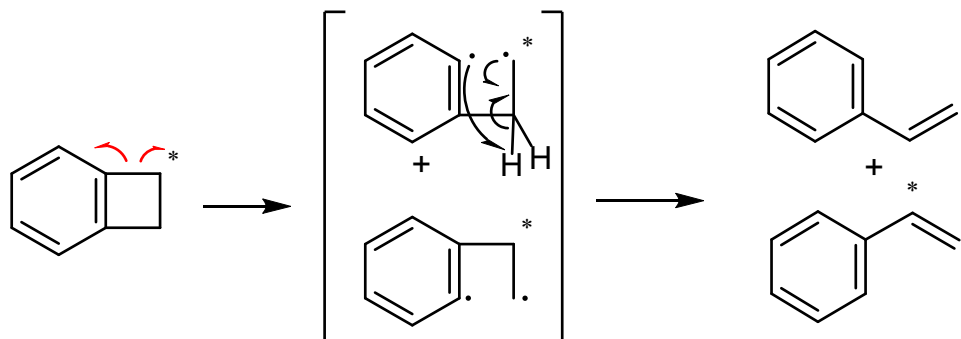
a) Homolysis to a diradical, followed by 1,3 hydrogen transfer. This mechanism would produce styrene with the isotopic label evenly distributed between the two atoms of the double bond.

Isotopic labeling

b) Mechanism through electrocyclic valence isomerizations, hydrogen migrations and interconversions of phenylcarbene-1,2,4,6-tetraene. This mechanism would produce styrene with the brand distributed evenly between carbon β and C-2 of styrene.
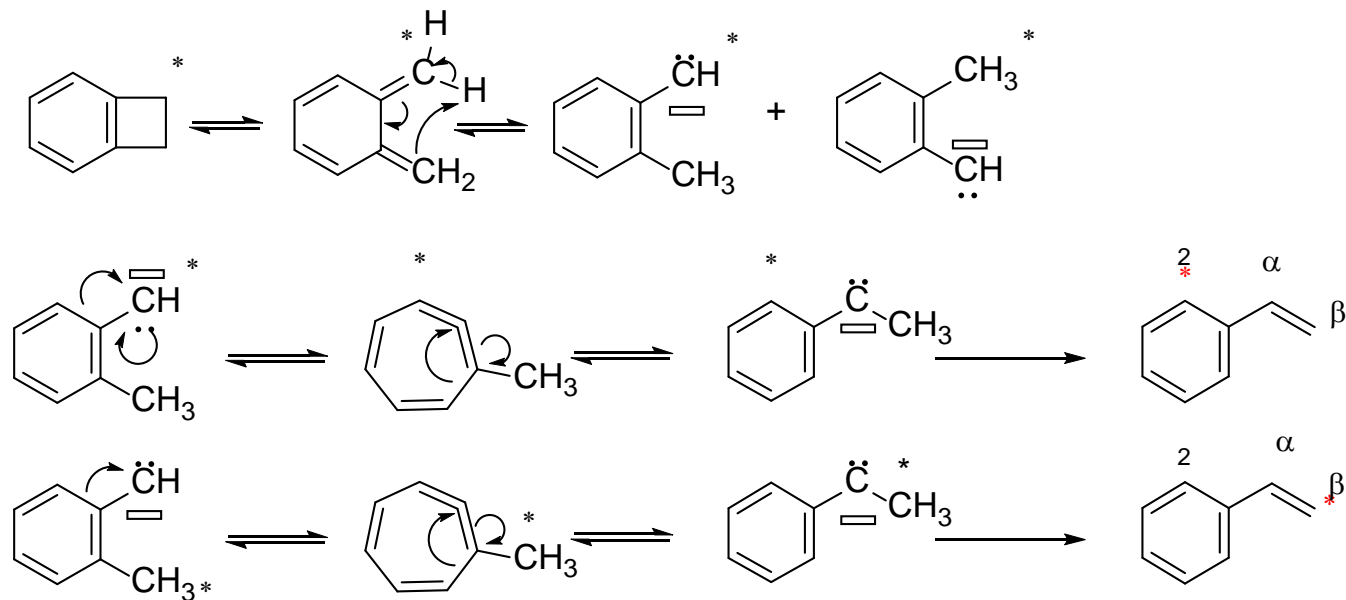
An analysis of the mixture gave the following distribution: β (48%), α (14%), C-2 (30%). This result suggests that the two mechanisms *a* and *b* work and that the reaction takes place in 75% by mechanism *b* and in 25% by mechanism *a* .

Stereochemical studies

The study of the stereochemistry of the reaction can give valuable information about its mechanism. A classic example is <u>nucleophilic substitution reactions</u> with enantiomerically pure chiral halides. Obtaining an enantiomerically pure product with inversion in the configuration is characteristic of a S_N2 mechanism. Obtaining a racemate is characteristic of an S_N1 mechanism. The chirality of the reactant is lost due to the formation of a planar carbocation intermediate.

34
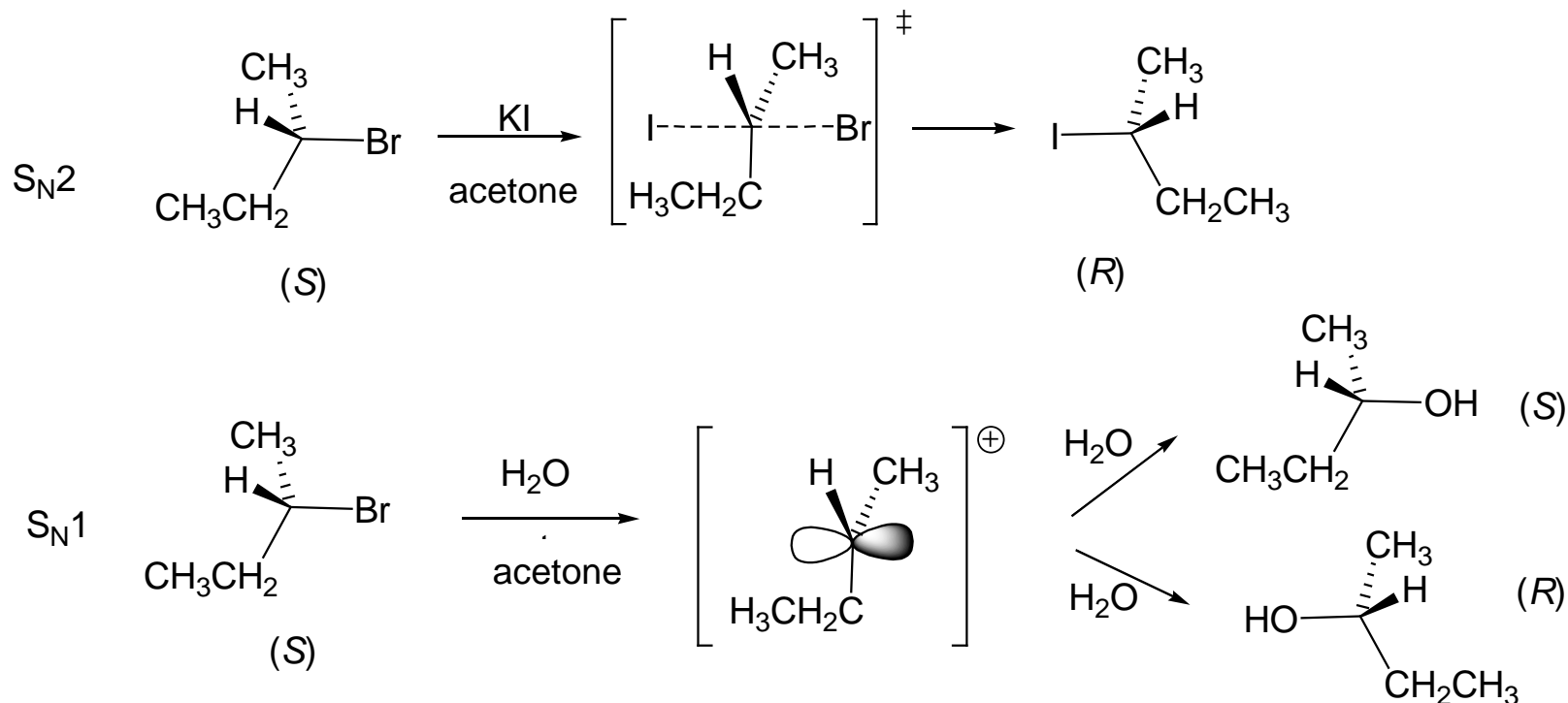
Solvent effects

Most chemical reactions take place in solution.
The solvent **interacts** with all the chemical species presented in the reaction mixture (solvation). Solvation can stabilize both reactants and transition states (TS), decreasing their energy. This can modify the energies of activation and therefore the rate and course of the reaction.

Characteristics of solvents and solvation:
Polar solvents have a great capacity to solvate charged species or with high dipole moments through electrostatic type interactions. These solvents usually have high dielectric constant (ϵ) and high dipole moments μ .
Protic solvents can also solvate chemical species by forming hydrogen bonds.
Finally, some solvents act as Lewis acids or bases to form charge transfer complexes with solutes.

Solvent effects

Classes of solvents

Protic: The solvent has OH or NH functions; They have high dipole moment due to C-O and C-N links.
Examples: Water, alcohols, amines, carboxylic acids.

Polar aprotic : They present a high dipole moment and, normally, giving properties (Lewis bases), but without mobile protons.
Examples: HMPA, DMSO, acetonitrile, nitromethane, N,N-disubstituted amides, ketones.

Non-polar aprotic : Under dipolar moment and without mobile protons. Some may present basic character (ethers and esters).
Examples: hydrocarbons (hexane, benzene, toluene), halocarbons (carbon tetrachloride, chloroform, dichloromethane, 1,2-dichloroethane), ethers (ether, THF, dimethoxyethane).

Solvent effects

Effect of the solvent on the reaction rate

The solvent can solvate and stabilize both the **reactants** and the **transition states** (**TS**). This can affect the activation energies and therefore the reaction rate.
Example: Hydrolysis of *tert* -butyl chloride (S_N1)

Poor solvation of the reactant

TS with greater solvation
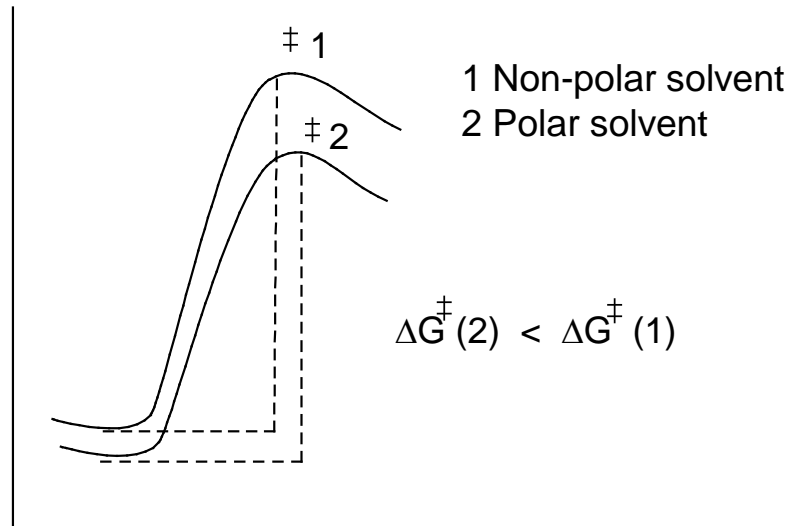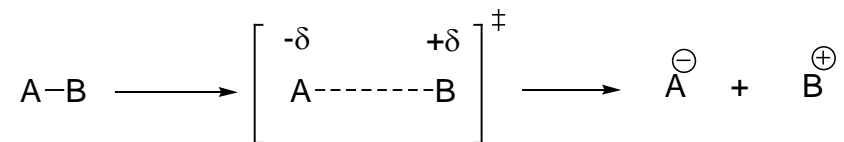
Separated solvated ions
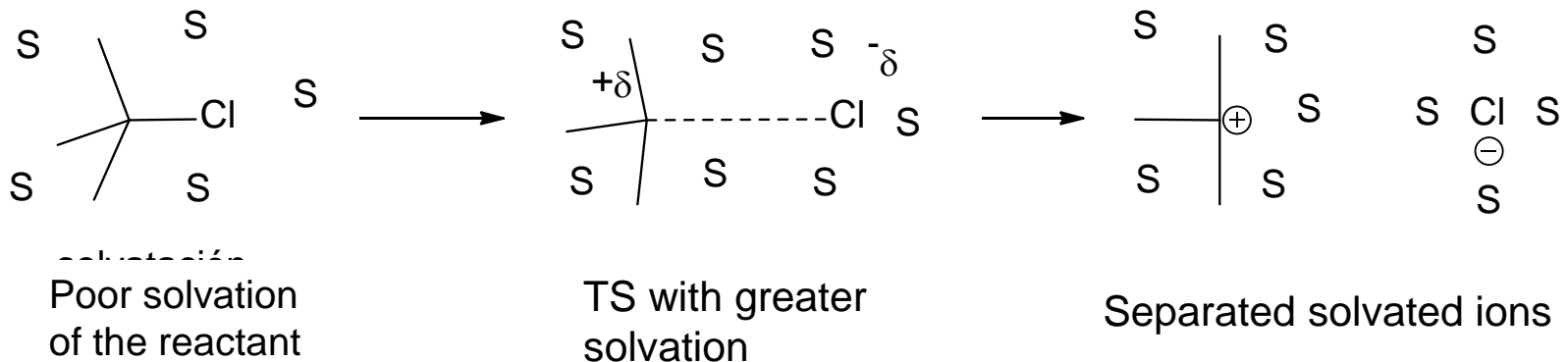
The solvation of the chemical species varies as the system evolves. The stabilization of TS depends on its structure and on the characteristics of the solvent.
Polar and protic solvents favor the separation of charges in the TS.
Apolar and aprotic solvents do not favor the separation of charges in the TS.

Solvent effects

Hughes-Ingold's Rules
They indicate how the reaction rate varies with the solvent as a function of the change in the distribution of the charge when passing from the reagent to the transition state. We have several possibilities.

1. Charge separation: The rate increases with increasing polarity of the solvent.

$$A{-}B \longrightarrow \left[\begin{array}{cc} {}^{-\delta} & {}^{+\delta} \\ A\text{-------}B \end{array} \right]^{\ddagger} \longrightarrow \overset{\ominus}{A} \;+\; \overset{\oplus}{B}$$

‡1

‡2

1 Non-polar solvent
2 Polar solvent

$\Delta G^{\ddagger}(2) \;<\; \Delta G^{\ddagger}(1)$

Example: S_N1 reaction

$$R{-}\overset{\displaystyle R}{\underset{\displaystyle R}{C}}{-}X \xrightarrow{H_2O} \overset{\displaystyle R}{\underset{\displaystyle R}{\overset{\oplus}{C}}}{-}R \;\; X^{\ominus} \xrightarrow{H_2O} R{-}\overset{\displaystyle R}{\underset{\displaystyle R}{C}}{-}OH$$
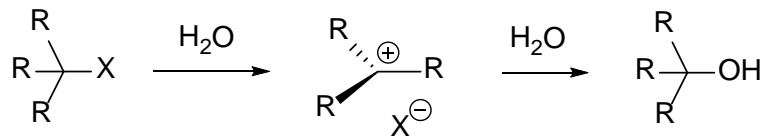
Solvent effects

Hughes-Ingold's Rules
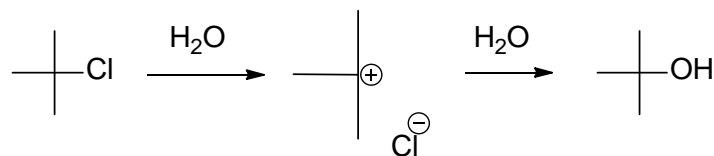
Example: Effect of the polarity of the solvent on the reaction rate of solvolysis of tert-butyl chloride
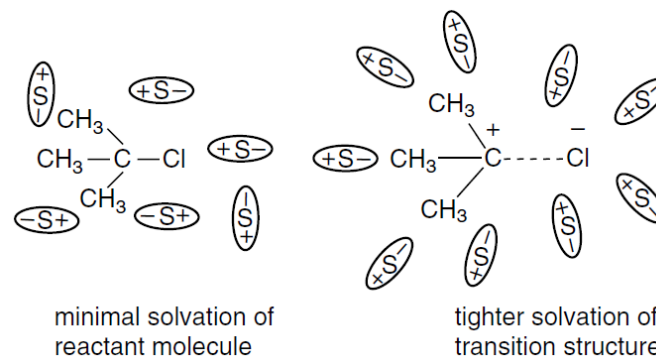

$$\log \frac{k_{solvent}}{k_{80\%\ ethanol}} = Y$$

minimal solvation of reactant molecule

tighter solvation of transition structure

Table 3.34. Y Values for Some Solvent Systems.[a]

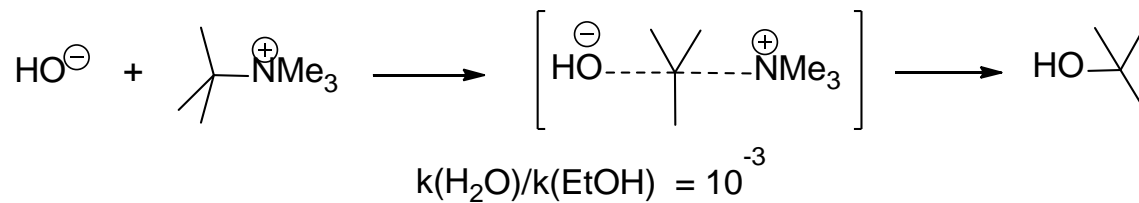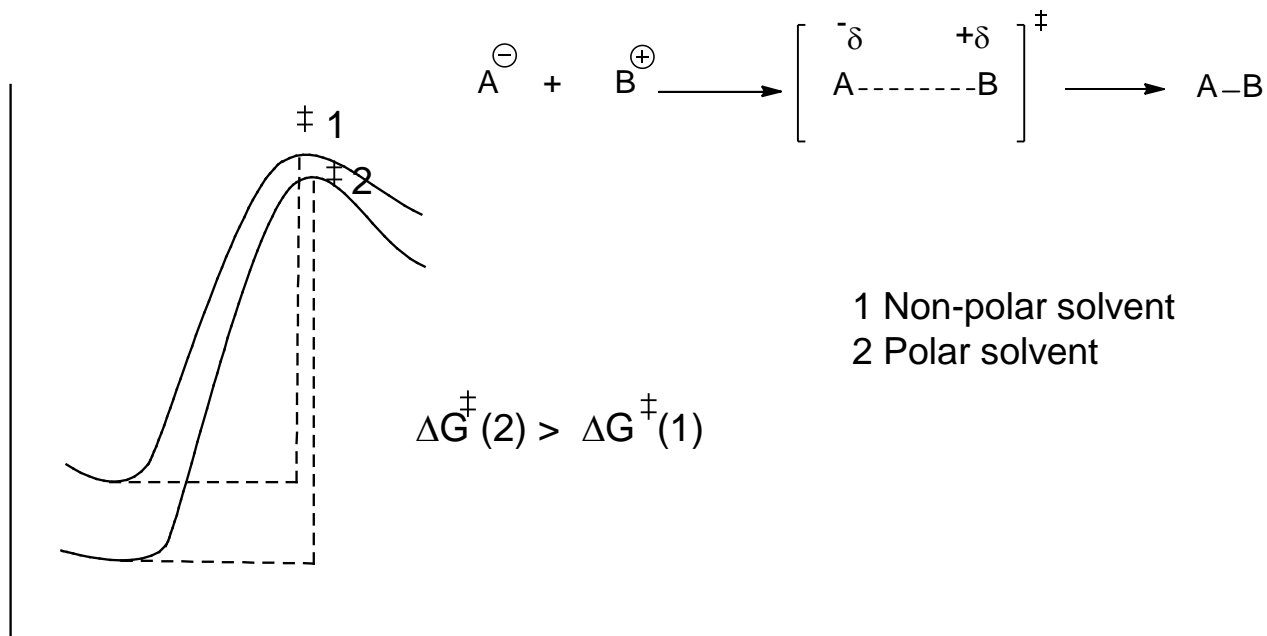| Ethanol-water	Y	Methanol-water	Y	Other solvents	Y
100:0	−2.03	100:0	−1.09	Acetic acid	−1.64
80:20	0.00	80:20	0.38	Formic acid	2.05
50:50	1.65	50:50	1.97	t-Butyl alcohol	−3.2
20:80	3.05	10:90	3.28	90:10 acetone:water	−1.85
0:100	3.49			90:10 dioxane:water	−2.03

a. From A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2770 (1956).

The rate can reach up to 10^6 times

Solvent effects

Hughes-Ingold's Rules

2. Charge neutralization: Reactions favored by aprotic and apolar solvents.

$$A^{\ominus} + B^{\oplus} \longrightarrow \left[\begin{array}{c} {}^{-}\delta \quad\quad +\delta \\ A\text{-------}B \end{array} \right]^{\ddagger} \longrightarrow A-B$$

‡ 1
‡ 2

1 Non-polar solvent
2 Polar solvent

$\Delta G^{\ddagger}(2) > \Delta G^{\ddagger}(1)$

$$HO^{\ominus} + \bigg\rangle\!\!-\!\overset{\oplus}{N}Me_3 \longrightarrow \left[HO^{\ominus}\text{----}\bigg\rangle\!\!\!\bigg\langle\text{----}\overset{\oplus}{N}Me_3 \right] \longrightarrow HO\!-\!\bigg\rangle\!\!\!\bigg\langle$$

$k(H_2O)/k(EtOH) = 10^{-3}$

Solvent effects

Hughes-Ingold's Rules

3. Charge dispersion: Slightly favored by aprotic and apolar solvents.

$$A^{\ominus} + B \longrightarrow \left[\overset{\delta-}{A} \text{------} \overset{\delta-}{B} \right]^{\ddagger} \longrightarrow \begin{cases} C + D^{\ominus} \\ [A-B]^{\ominus} \end{cases}$$

$$A + B^{\oplus} \longrightarrow \left[\overset{\delta+}{A} \text{------} \overset{\delta+}{B} \right]^{\ddagger} \longrightarrow \begin{cases} C + D^{\oplus} \\ [A-B]^{\oplus} \end{cases}$$

$\Delta G^{\ddagger}(2) > \Delta G^{\ddagger}(1)$

1 Non-polar solvent
2 Polar solvent

$$HO^{\ominus} + \overset{}{\underset{}{\diagup}}-Br \longrightarrow \left[HO \text{---} \overset{-\delta}{\diagup} \text{---} \overset{-\delta}{Br} \right] \longrightarrow HO-\diagup + Br^{\ominus}$$

$k(H_2O)/k(EtOH) = 0.2$
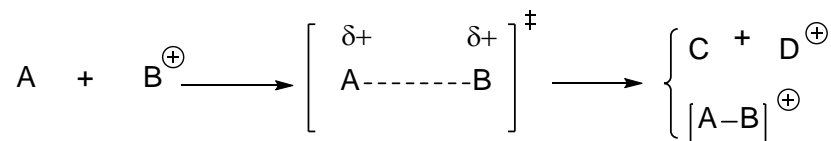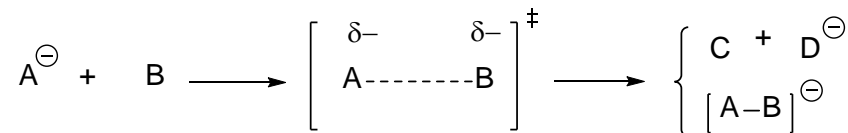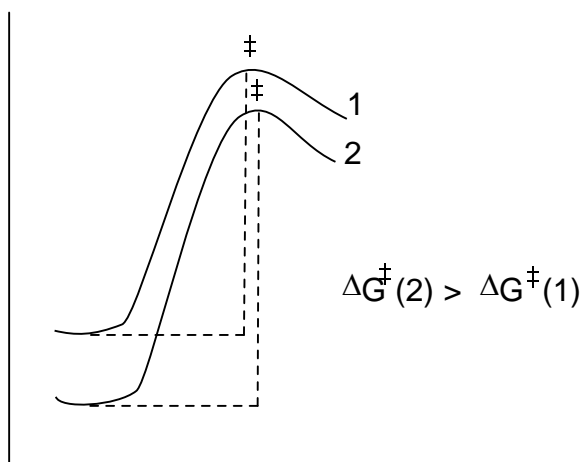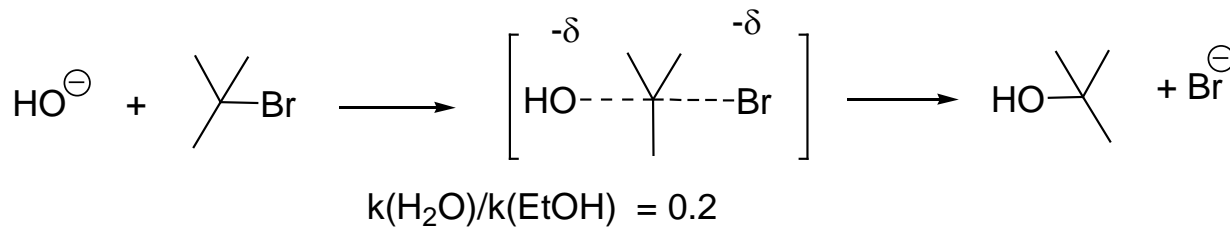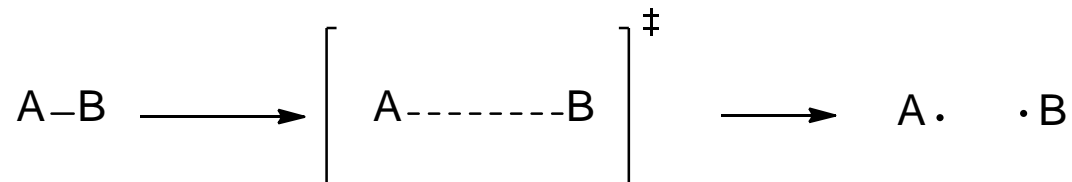
Solvent effects

Hughes-Ingold's Rules

4. Dissociation with charge dispersion: Slightly favored by polar solvents.

$$A{-}B^{\ominus} \longrightarrow \left[\begin{array}{c} {}^{-\delta} \quad\quad {}^{-\delta} \\ A{-}{-}{-}{-}{-}{-}{-}B \end{array} \right]^{\ddagger} \longrightarrow A^{\ominus} \;+\; B$$

$$A{-}B^{\oplus} \longrightarrow \left[\begin{array}{c} {}^{+\delta} \quad\quad {}^{+\delta} \\ A{-}{-}{-}{-}{-}{-}{-}B \end{array} \right]^{\ddagger} \longrightarrow A \;+\; B^{\oplus}$$
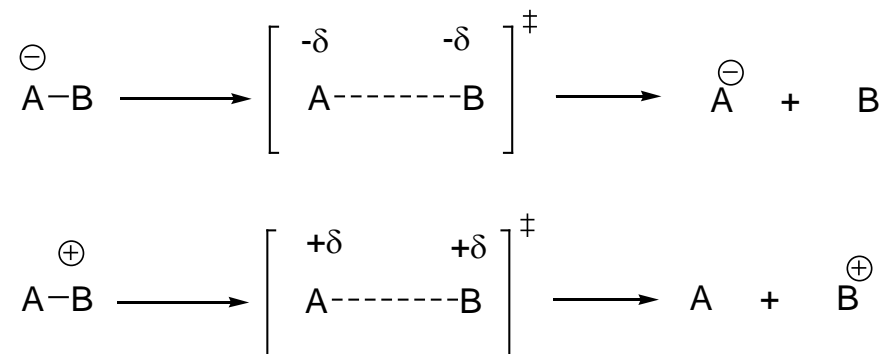
5. Non-ionic reaction (radical or pericyclic): No effect of the polarity of the solvent.

$$A{-}B \longrightarrow \left[A{-}{-}{-}{-}{-}{-}{-}B \right]^{\ddagger} \longrightarrow A\cdot \quad \cdot B$$
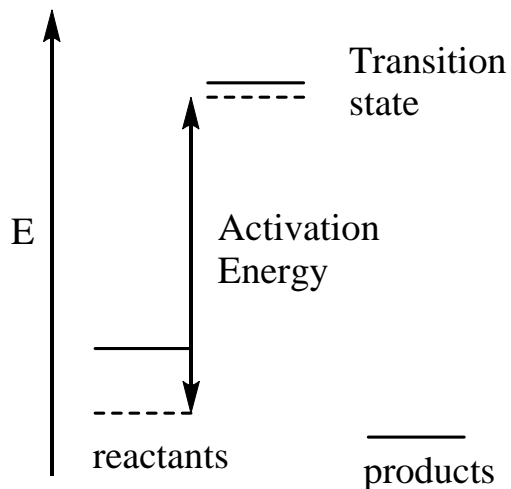
Radical reactions are not affected by the polarity of the solvent since no charged species are generated during its course.
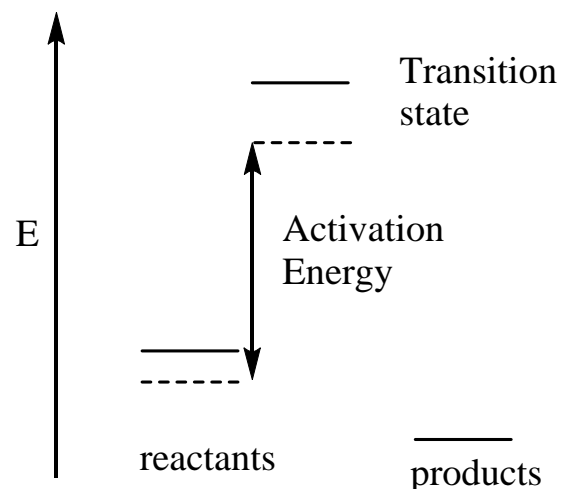
Solvent effects

In summary:

Reactants more polar than
the transition state

Transition state more polar
than the reactants

= with less polar solvent

- - - - - = with more polar solvent

v decreases with increasing
polarity of the solvent

v increases with increasing
polarity of the solvent

Note: In very fast reactions (controlled by the diffusion of the species)
the **viscosity** of the solvent plays an important role. The higher the viscosity (for the
same polarity), the lower the reaction rate.

Solvent effects

Solvent polarity: solvatochromic scales

Solvent polarity   ⟶   Difficult to define and quantify

The use of quantifiable macroscopic parameters of the solvent (such as its dielectric constant or the dipole moment of its molecules) is not sufficient to accurately describe the solvation of a solute by the solvent.
Several parameters and <u>empirical</u> scales have arisen, to measure the polarity of a solvent, as well as the different types of interactions of the solvent with the solute, both specific (as H-bonding) and non-specific (polarity effects)

Many of these scales are obtained from the displacements of absorption wavelengths of certain compounds (solvatochromism) depending on the polarity of the
solvent: **Solvatochromic Polarity Scales** .

Negative solvatochromism / Positive solvatochromism — Excited state (S_1) — Fundamental state (S_0)
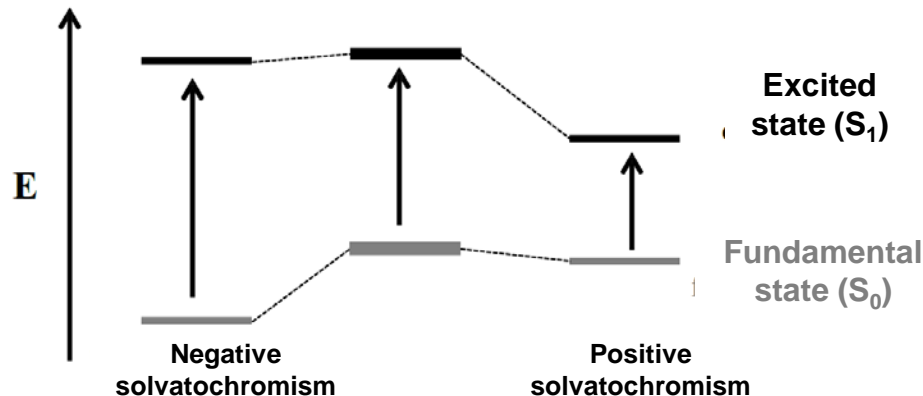
Solvent effects

Examples of polarity solvatochromic scales:

Scales α and β describe the donor or acceptor H-bonding ability (respectively) of a donor solvent (HBD) or acceptor (HBA); the scale $E_T(30)$ of polarity of the solvent of Reichardt or the scale π^* of dipolarity/ polarizability of Kamlet.
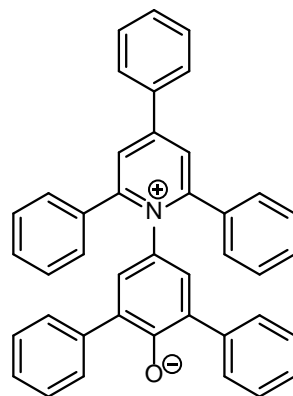
30

TABLE 6.1 Selected Solvent Parameters

| Solvent	ε^a	$\mu(D)^a$	Z^b	$E_T(30)^c$	π^*	β	α^d
Formamide	111.0	3.37	83.3	56.6	0.97	0.48^e	0.71
Water	78.4	1.8	94.6	63.1	1.09	0.47^e	1.17
Formic acid	58.5	1.82		54.3	0.65^e	0.38^e	1.23^g
Dimethyl sulfoxide	46.5	4.06	71.1	45.1	1.00	0.76	0.00
N,N-Dimethylformamide	36.7	3.24	68.5	43.8	1.00^e	0.76^e	0.00
Nitromethane	35.9	3.56		46.3	0.85	0.06^e	0.22
Acetonitrile	35.9	3.53	71.3	45.6	0.75	0.40^e	0.19
Methanol	32.7	2.87	83.6	55.4	0.60	0.66^e	0.93
Hexamethylphosphoramide	29.3	4.31	62.8^f	40.9	0.87^e	1.05^e	0.00
Ethanol	24.5	1.66	79.6	51.9	0.54	0.75^e	0.83
1-Propanol	20.4	3.09	78.3	50.7	0.52	0.90^e	0.84^e
1-Butanol	17.5	1.75	77.7	50.2	0.47	0.84^e	0.84^e
Acetone	20.6	2.69	65.7	42.2	0.71	0.43^e	0.08
2-Propanol	19.9	1.66	76.3	48.4	0.48	0.84^e	0.76
Pyridine	12.9	2.37	64.0	40.5	0.87	0.64	0.00
t-Butyl alcohol	12.5	1.66	71.3	43.3	0.41	0.93^e	0.42^e
Methylene chloride	8.9	1.14	64.2	40.7	0.82	0.10^e	0.13^e
Tetrahydrofuran	7.58	1.75		37.4	0.58	0.55	0.00
1,2-Dimethoxyethane	7.20	1.71	62.1^f	38.2	0.53	0.41	0.00
Acetic acid	6.17	1.68	79.2	51.7	0.64	0.45^e	1.12
Ethyl acetate	6.02	1.82		38.1	0.55	0.45	0.00
Chloroform	4.80	1.15	63.2^g	39.1	0.58	0.10^e	0.20^e
Diethyl ether	4.2	1.15		34.5	0.27	0.47	0.00
Benzene	2.27	0	54.0^f	34.3	0.59	0.10	0.00
Carbon tetrachloride	2.23	0		32.4	0.28	0.10^e	0.00
n-Hexane	1.89	0.085		31.0	-0.04^e	0.00	0.00

F. A. Carroll (2010) "Perspectives on structure and mechanism in Organic Chemistry"

Computational studies

By using theoretical methods, virtual experiments (*in silico*) can be designed to evaluate possible reaction paths.

It is normally assumed that the reagents are in the gas phase. However, new computational methods are capable of simulating solvent molecules.

Example: Reaction of hydrogen transfer between acridane and α-methylstyrene
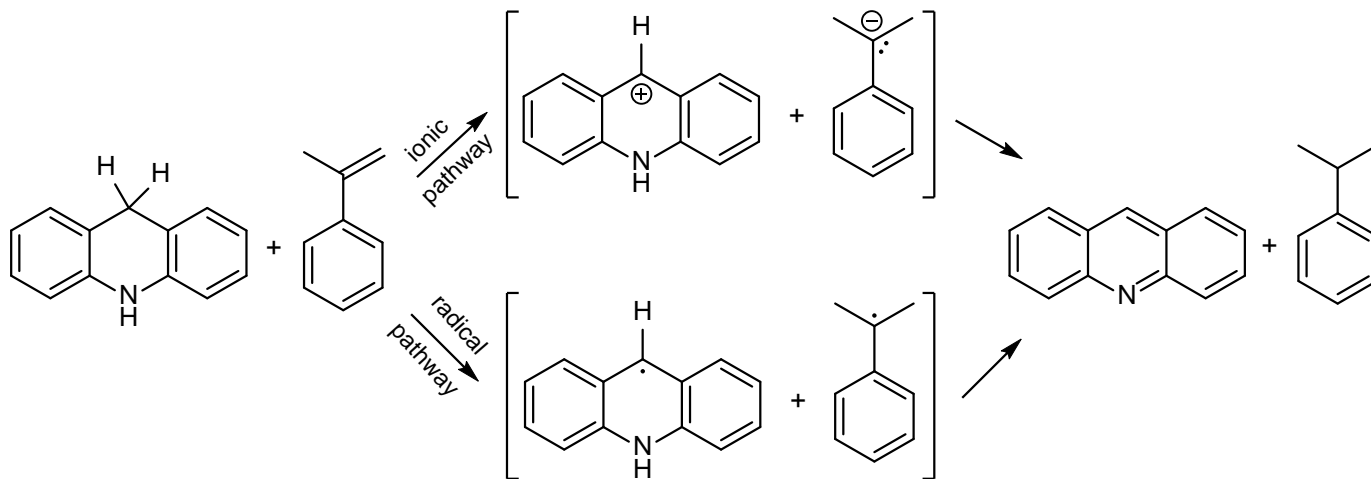
Chan, B.; Radom, L. *J. Phys. Chem. A* **2007**, *111,* 6456

Computational studies using density functional theory (DFT) showed that in the gas phase, the calculated energy barrier was lower for the radical mechanism than for the ionic pathway in all the studied cases. On the other hand, the calculations in solution were more complex, indicating that the pathway depended to a great extent on the solvent.

KINETIC STUDIES IN THE DETERMINATION OF REACTION MECHANISMS: RATE EQUATIONS

The rate equation is an important data in the determination of mechanisms. However, it is not enough to prove a mechanism, since the same kinetic equation can be compatible with more than one mechanism.
Kinetic studies support a mechanism but do not confirm it. Rather, kinetics can only rule out proposed mechanisms that do not predict the observed experimental kinetic results

The procedure involves:

-Postulation of various mechanisms

-Formulation of the theoretical rate equations according to the proposed mechanisms.

-Experimental determination of the rate equation.

-Comparison:

> Coincidence: Possible mechanism
> Discordance: discarded mechanism

Kinetic studies imply **mechanistic proposals prior** to the experiments. When experimental kinetic data do not agree with a mechanism, it is automatically discarded.

KINETIC STUDIES: RATE EQUATIONS

The rate equation is a mathematical expression that indicates the variation of the concentration of a reactant or a product as a function of time

$$n_A A + n_B B + n_C C \rightarrow n_P P$$
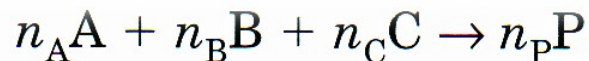
$$v = \frac{1}{n_P}\frac{d[P]}{dt} = -\frac{1}{n_A}\frac{d[A]}{dt} = -\frac{1}{n_B}\frac{d[B]}{dt} = -\frac{1}{n_C}\frac{d[C]}{dt} = k_r[A]^a[B]^b[C]^c$$

k is the rate constant,

a, b and c are the orders of the reaction with respect to A, B and C, respectively

a + b + c is the overall order of the reaction (usually whole numbers, although they can also be fractional or zero)

Experimentally, the rate equation is determined by measuring the variation in the concentration of one of the reactants with time.

KINETIC STUDIES: RATE EQUATIONS

In reactions that only have <u>one single step</u> (elementary reactions) the overall order of the reaction coincides with the **molecularity** (number of molecules involved). For reactions with more than one elementary step, this does not usually happen.

	molecularity	equation	order
$A \xrightarrow{k_1} P$	1	$v = -d[A]/dt = k_1 [A]$	1
$A + B \xrightarrow{k_2} P$	2	$v = -d[A]/dt = -d[B]/dt = k_2 [A][B]$	2
$2A \xrightarrow{k_2} P$	2	$v = d[P]/dt = -d[A]/2dt = k_2 [A]_2$	2

Integrated rate equations:

They are more useful than the differential rate equations since they allow comparing the experimental concentration values with those predicted by the rate equation, and calculate the velocity constants.

For example, for a first-order reaction

$$A \xrightarrow{k_1} P \qquad \frac{-d[A]}{dt} = k_1[A] \qquad \frac{d[A]}{[A]} = -k_1 dt$$
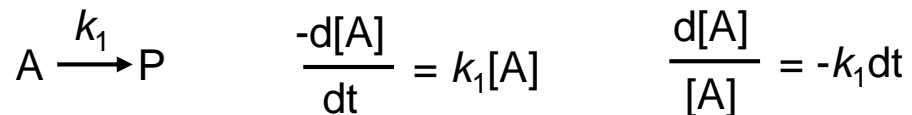
KINETIC STUDIES: RATE EQUATIONS

$$\int_{[A]_0}^{[A]} \frac{d[A]}{[A]} = -k_1 \int_0^t dt$$

$$\ln[A] - \ln[A]_0 = -k_1 t$$

$$\ln[A] = \ln[A]_0 - k_1 t$$
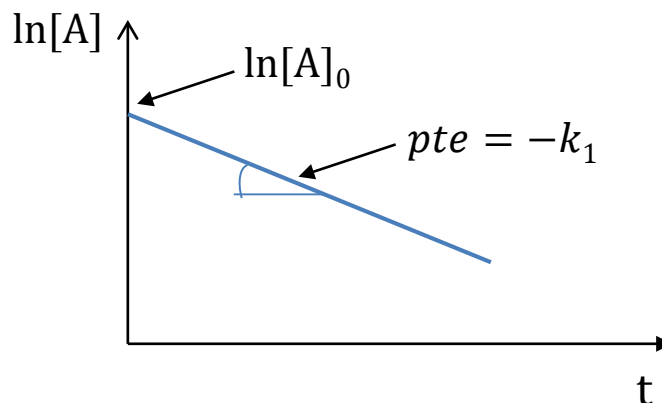
$$[A]_0 = [A] + [P]$$

$$[A] = [A]_0 - \boxed{[P]}$$

If we measure the appearance of product

The integrated form of the first and second order equations is as follows:

Order 1 $\ln [A] = \ln [A]_o - k_1 t$

Order 2   a) $2\,A \longrightarrow P$ $1/[A] = 1/[A]_0 + 2k_2 t$

         b) $A + B \longrightarrow P$ $\ln([A]/[B]) = \ln([A]_0/[B]_0) + ([A]_o - [B]_o)\, k_2 t$

     This equation can be simplified in two cases:

     If $[A]_0 = [B]_0$ then $[A] = [B]$ and $1/[A] = 1/[A]_0 + k_2 t$

     If $[B] \approx$ constant, during the reaction (e.g. solvation conditions), then

         $v = -d[A]/dt = k_2[B]_0[A] = k_{obs}[A]$ (pseudo-first order kinetics)

KINETIC STUDIES: RATE EQUATIONS

Rate equation in a stepwise reaction:

Consider the following consecutive reaction, with two elementary steps:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

The rate of product formation will be:

$$v = d[C]/dt = k_2[B]$$

However, the concentration of B varies with time according to:

$$d[B]/dt = k_1[A] - k_2[B]$$

You can find **exact solutions** for these rate equations. The corresponding integrated equations indicate the variation of the concentrations of A, B and C as a function of time.
The following figures show the graphs of the integrated velocity equations corresponding to different values of k_1 and k_2.

Variation of the concentrations of A, B and C as a function of time

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

for $k_2/k_1 = 0.33$

for $k_2/k_1 = 3.3$
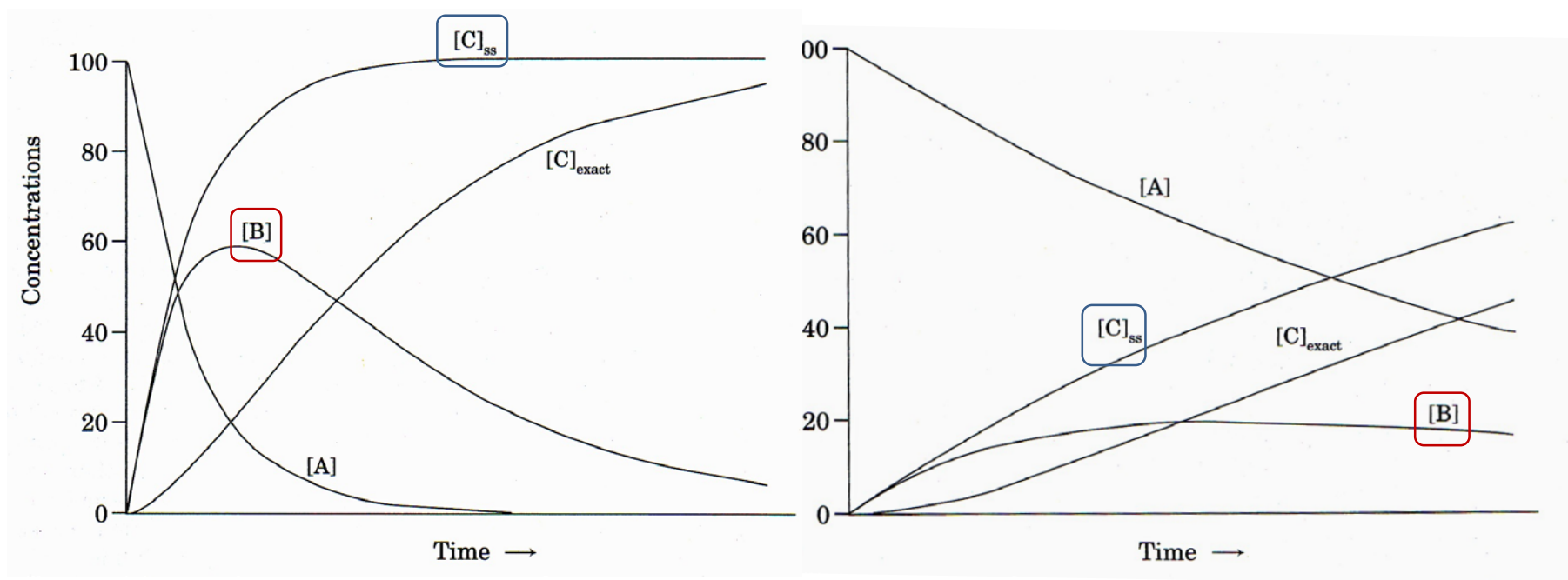
[B] = Concentration of intermediate species B
$[C]_{exact}$ = Exact concentration of C
$[C]_{ss}$ = Concentration of C obtained by applying the steady state approximation.

KINETIC STUDIES: RATE EQUATIONS

Variation of the concentrations of A, B and C as a function of time,

for $k_2/k_1 = 33$

$[C]_{SS}$= Concentration of C obtained by applying the steady state approximation.
$[C]_{exact}$= Exact concentration of C
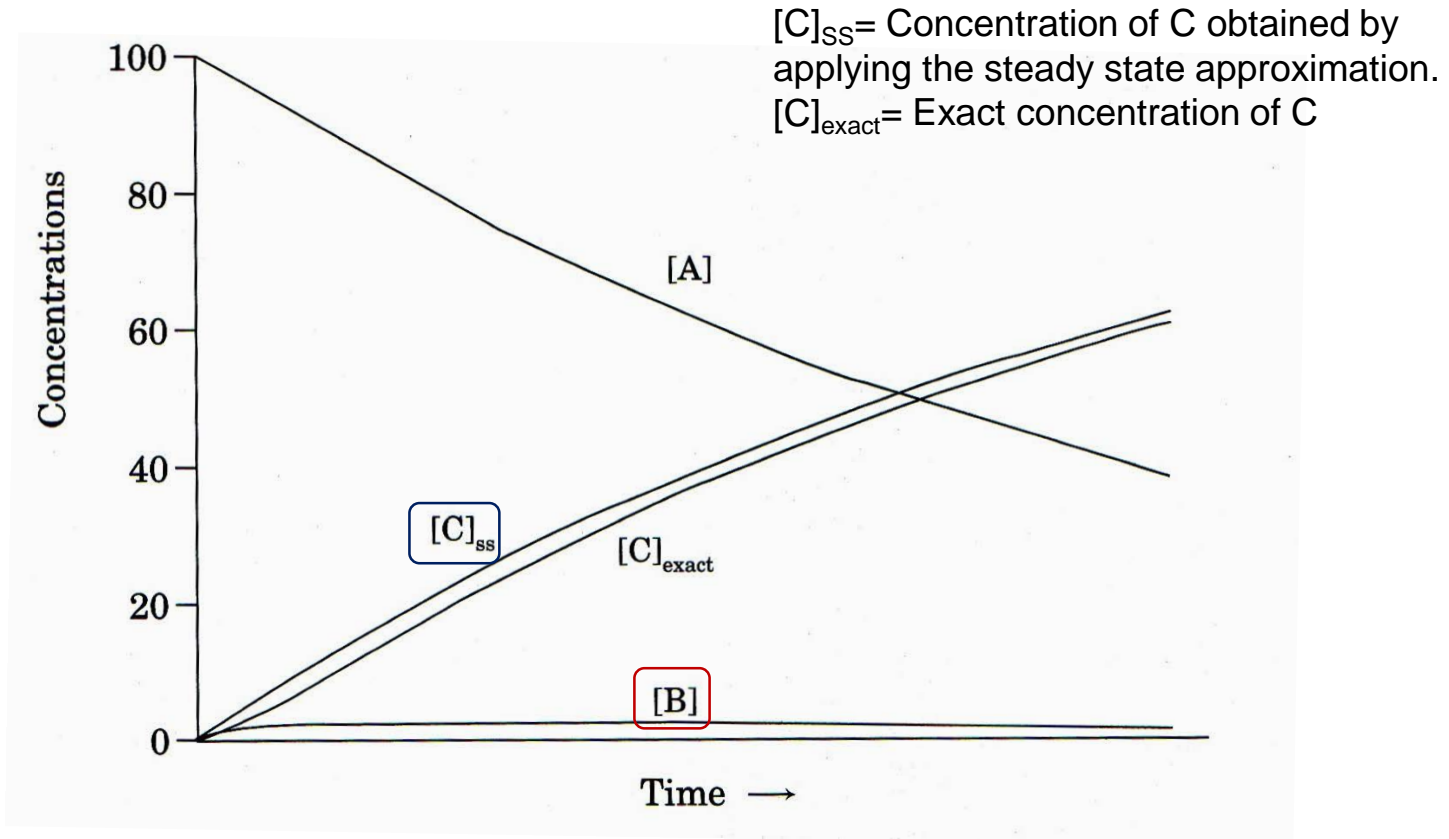
When $k_2/k_1 \uparrow\uparrow$ ($k_2 >> k_1$) the [B] remains low and constant $\implies$ $[C]_{SS} \approx [C]_{exact}$

KINETIC STUDIES: RATE EQUATIONS

Steady-state approximation:

If $k_2 >> k_1$, once the reaction is in progress, [B] stays very low and does not vary with time (**steady state**). Once the SS is reached, the amount of B that is formed in the first stage is immediately consumed in the second stage.

In that situation:

$$d[\text{B}]/dt = k_1[\text{A}] - k_2[\text{B}] \approx 0$$

$$k_2[\text{B}] \approx k_1[\text{A}].$$

$$r = d[\text{C}]/dt = k_2[\text{B}] \approx k_1[\text{A}]$$

The overall rate of the reaction will be equal to or very close to that of the <u>slowest step</u> of the reaction sequence (the rate-determining step).

Therefore, the <u>kinetic data</u> provide information on the <u>rate-determining step</u> of the reaction or previous steps, but not of those who follow it. If a reactant appears specifically in the experimental rate equation, it will be involved in the rate-determining step of the reaction or in any of the preceding ones.

The validity of the SS hypothesis depends on the relative magnitudes of k_1 and k_2. The greater k_2/k_1 the difference between $[\text{C}]_{ex}$ and $[\text{C}]_{ss}$ is smaller.

KINETIC STUDIES: RATE EQUATIONS

Consider a more complicated reaction, including a bimolecular step.

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\longrightarrow} D$$
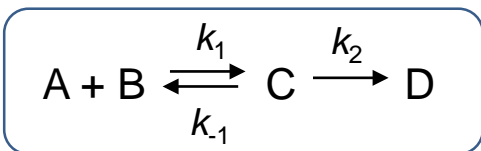
$$v = d[D]/dt = k_2[C]$$

The concentration of C varies with time. The equation can not be solved exactly, but it can be approximated using numerical integration methods.

But we can also apply the steady-state approximation to [C]:

$$d[C]/dt = k_1[A][B] - k_2[C] - k_{-1}[C] = 0$$

$$k_1[A][B] = (k_{-1} + k_2)[C] \qquad [C] = \frac{k_1}{k_{-1} + k_2} [A][B]$$

$$v = k_2[C] = \frac{k_2 k_1}{k_{-1} + k_2} [A][B]$$

The relationship between k_{-1} and k_2 (k_{-1}/k_2) is called *the partition factor*, and is a measure of the propensity of intermediate C to advance to products or revert to reactants.

KINETIC STUDIES: RATE EQUATIONS

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\longrightarrow} D \qquad\qquad d[D]/dt = \{k_2 k_1 / (k_2 + k_{-1})\}[A][B]$$

We now have two possible behaviors, depending on the ratio k_{-1}/k_2

a) If $k_{-1} \gg k_2$, then $(k_2 + k_{-1}) \approx k_{-1}$ and the equation remains as :

$$v \approx \frac{k_2 k_1}{k_{-1}} [A][B] = k_2 \frac{k_1}{k_{-1}} [A][B] \qquad\qquad \frac{k_1}{k_{-1}} = K_1 = \text{pre-equilibrium constant}$$

K_1 is the equilibrium constant for a rapid pre-equilibrium between reactants and intermediate, in which the chemical species involved in the slow stage of the reaction are formed.

b) If $k_2 \gg k_{-1}$ then $(k_2 + k_{-1}) \approx k_2$ and the equation remains as :

$$v \approx \frac{k_2 k_1}{k_2} [A][B] = k_1 [A][B]$$

The kinetics behaves as if the reaction had only the first stage.
The determining stage of the reaction rate is the formation of C.

Nitration of benzene: The application of kinetic studies involves the comparison of the experimental equation with the predictions made on different mechanistic schemes. For the nitration of benzene we can propose three mechanisms:

Mechanism 1

The rate-determining step is the addition of the electrophile to the benzene ring. The reaction is of 2nd order with respect to nitric acid, 1st order with respect to benzene and - 1st with respect to nitrate

Limiting stage

$$2\,HONO_2 \underset{k_{-1}}{\overset{\overset{k_1}{fast}}{\rightleftharpoons}} H_2\overset{+}{O}NO_2 + NO_3^-$$

$$\bigcirc + H_2\overset{+}{O}NO_2 \xrightarrow[k_2]{slow} \overset{H\quad NO_2}{\bigcirc^{+}} + H_2O$$

$$\overset{H\quad NO_2}{\bigcirc^{+}} \xrightarrow{fast} \overset{NO_2}{\bigcirc} + H^+$$

$$rate = k_2[H_2\overset{+}{O}NO_2][benzene] = \frac{k_2 k_1}{k_{-1}} \frac{[HONO_2]^2}{[NO_3^-]}[benzene]$$

$$= k_{obs} \frac{[HONO_2]^2}{[NO_3^-]}[benzene]$$
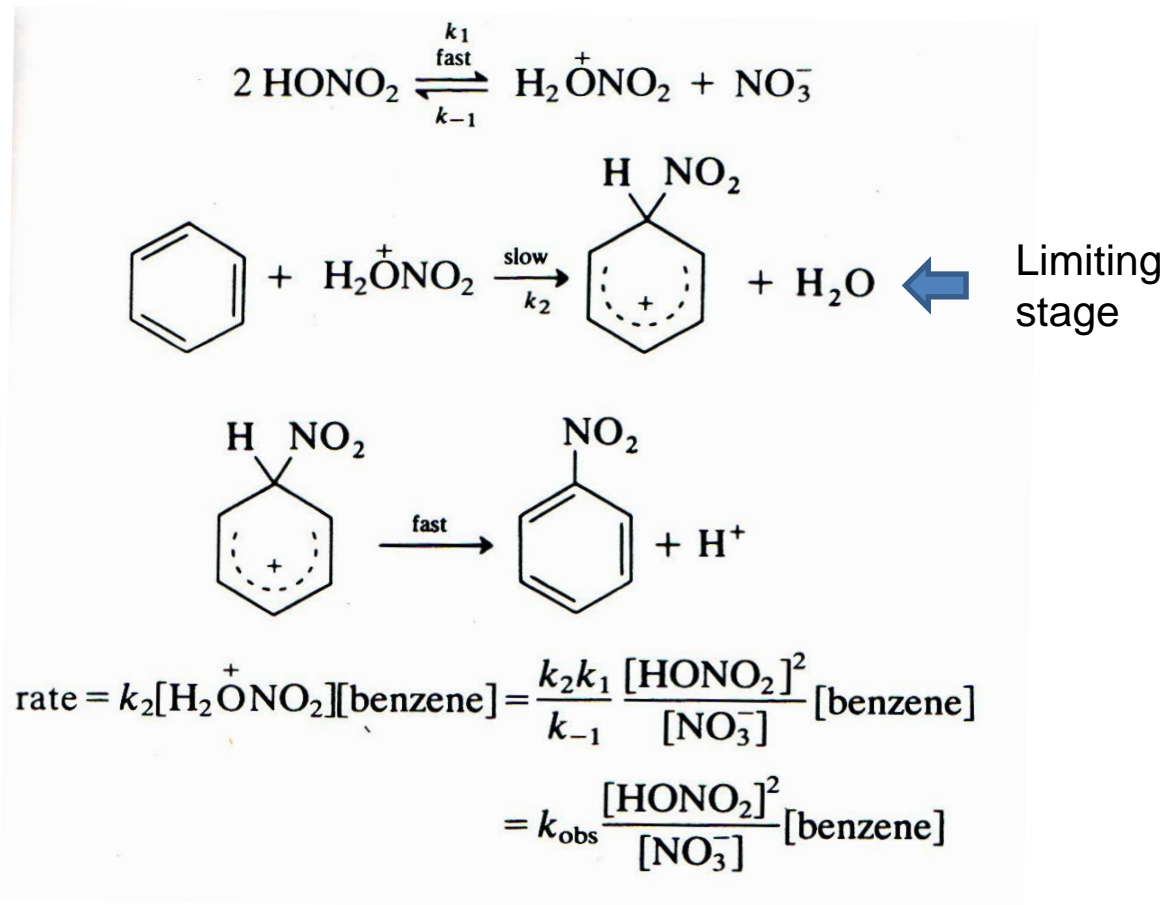
KINETIC STUDIES: RATE EQUATIONS

Mechanism 2

The rate-determining step is the dissociation of nitric acid to form the electrophile (nitronium ion). The reaction would be of 2nd order with respect to nitric acid and of order - 1st with respect to the nitrate ion

$$2\ HONO_2 \underset{k_{-1}}{\overset{\overset{fast}{k_1}}{\rightleftharpoons}} H_2\overset{+}{O}NO_2 + NO_3^-$$

$$H_2\overset{+}{O}NO_2 \underset{k_2}{\overset{slow}{\longrightarrow}} H_2O + NO_2^+$$

$$NO_2^+ + \overset{fast}{\rightleftharpoons} $$
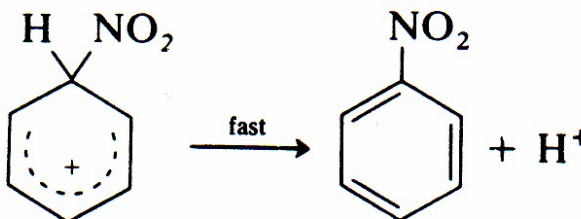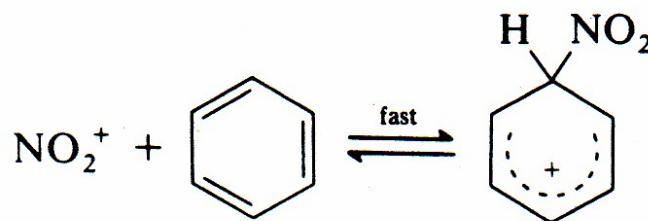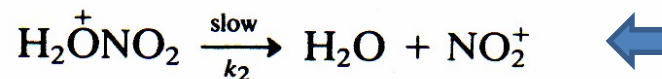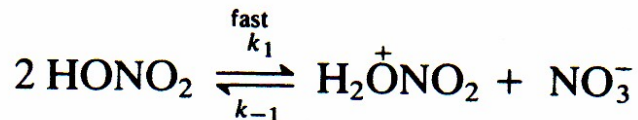
$$rate = \frac{k_1 k_2}{k_{-1}} \frac{[HONO_2]^2}{[NO_3^-]} = k_{obs}\frac{[HONO_2]^2}{[NO_3^-]}$$

KINETIC STUDIES: RATE EQUATIONS

Mechanism 3

The rate-determining step is the loss of a proton to recover the aromaticity. The reaction would be of order 1st with respect to benzene, 2nd with respect to nitric acid and - 1st with respect to nitrate.

$$2\ HONO_2 \underset{k_{-1}}{\overset{\overset{\text{fast}}{k_1}}{\rightleftharpoons}} NO_2^+ + NO_3^- + H_2O$$
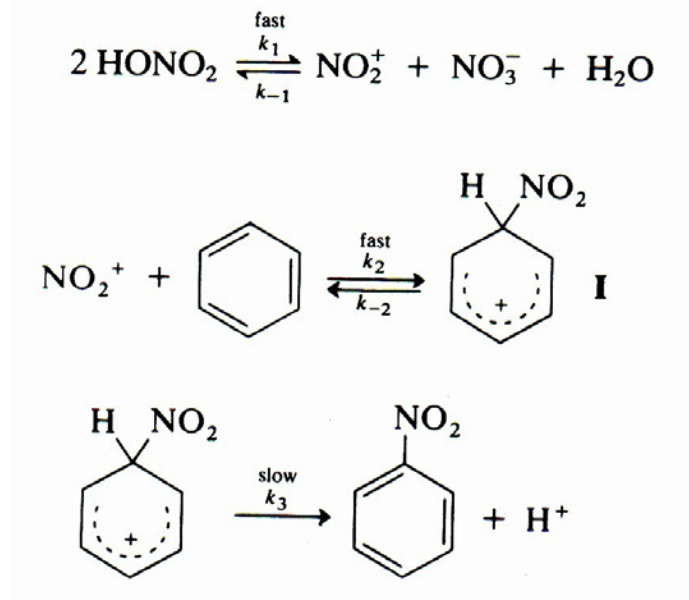
The third reaction is rate determining

$$\text{rate} = k_3[\mathbf{I}]$$

[I] is able to express in termes of the rapid equilibrium through which it forms

$$k_{-2}[\mathbf{I}] = k_2[NO_2^+][\text{benzene}]$$

$$[NO_2^+] = \frac{k_1[HNO_3]^2}{k_{-1}[NO_3^-][H_2O]}$$

$$\text{rate} = k_3 \frac{k_2[\text{benzene}]k_1[HNO_3]^2}{k_{-2}k_{-1}[NO_3^-][H_2O]}$$

$$\text{rate} = \frac{k_{obs}[HNO_3]^2[\text{benzene}]}{[NO_3^-][H_2O]}$$

$$= k_{obs} \frac{[HNO_3]^2[\text{benzene}]}{[NO_3^-]} \qquad \text{if } [H_2O] \gg [\text{benzene}]$$

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KINETIC STUDIES: RATE EQUATIONS

Nitration of benzene:

The 2<u>nd</u> <u>mechanism</u> is zero order with respect to benzene. This mechanism is the one that has been established as valid for the nitration of benzene thanks to kinetic studies.

Mechanisms 1 and 3 give very similar kinetic equations, differing only in the inclusion of water. However, if the concentration of water is very high (because it is used as a solvent) it would remain constant throughout the reaction and would be included in the rate constant. Under these conditions, kinetic studies would not allow to differentiate between mechanisms 1 and 3.

KINETIC THEORIES: ARRHENIUS EQUATION AND TRANSITION–STATE THEORY

The meaning of the rate constant (k) and its dependence on temperature can be discussed based on two major kinetic theories. This provides important information about the transition state and reaction mechanisms.

ARRHENIUS EQUATION AND THEORY OF COLLISIONS

The **Arrhenius equation** relates the rate constant (k) to the temperature and the activation energy (Ea)

$$k = A\,e^{-E_a/RT}$$

A = pre-exponential factor
E_a = activation energy

Graphic representation

Taking logarithms,

$$\ln k = \ln A - E_a/RT$$

(actually lnA is obtained from the equation taking values of T and lnk at some intermediate point of the graph)
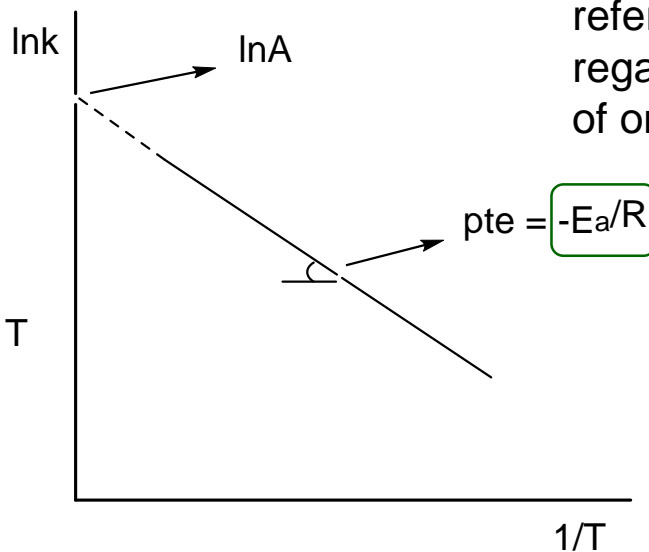
Attention! This value of E_a refers to the overall reaction, regardless of whether it consists of one or several steps

lnk

lnA

pte = -Ea/R

1/T

KINETIC THEORIES: ARRHENIUS EQUATION AND TRANSITION–STATE THEORY

Collision Theory

It has its origin in the kinetic theory of gases. It is based on the following premises:

- The higher the concentration of reactants, the greater the number of collisions. At higher temperature the molecular movement increases and therefore the number of collisions
- The reaction rate is lower than the number of collisions between molecules.
- Only collisions with a certain approximation geometry lead to the products.
- Only collisions that exceed a certain energy (E_a) allow the passage to products.
The speed constant (for an *elementary stage*) is given by:

$$k = P \cdot Z \cdot e^{-Ea/RT} = Ae^{-Ea/RT} \qquad \text{(Arrhenius equation)}$$

Z = number of collisions per unit of time
P is a probabilistic factor that indicates collisions with proper orientation
exp(-E_a /RT) indicates the ratio of collisions that exceeds the E_a according to statistical mechanics

TRANSITION STATE THEORY (EYRING EQUATION)

$$\text{reactants} \xrightarrow{\ k\ } \text{products} \qquad v = k\,[\text{react}]$$

- In the transition from the reactants to the products, the system passes through a chemical species that occupies a maximum of energy (transition state or activated complex)

$$\text{reactants} \; \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \; \text{TS}^{\neq} \; \xrightarrow{\ k_2\ } \text{products}$$
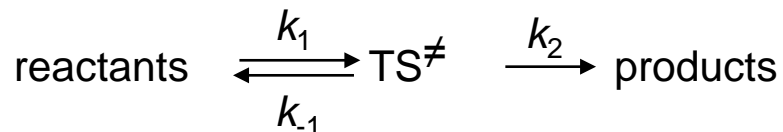
- The rate of the reaction is given by the rate of passage of the system through the transition state (TS)

$$v = k_2\,[\text{ET}^{\neq}]$$

Statistical mechanics predicts that the rate at which the activated complex decomposes to give the products or the reactants is the same:

$$k_2 = k_{-1} = \boxed{\nu^{\neq} = \frac{k_B T}{h}}$$

$\nu^{\neq}$ = Decomposition frequency of the $\text{TS}^{\neq}$ or universal rate constant for the $\text{TS}^{\neq}$

where k_B = Boltzmann's constant and h = Planck's constant

$\nu^{\neq} \sim 6 \times 10^{12}\ \text{s}^{-1}$ to T amb

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KINETIC THEORIES: ARRHENIUS EQUATION AND TRANSITION–STATE THEORY

One of the main premises of the Transition-State Theory is that the activated complex is in quasi-equilibrium with the reactants.

So, you can define an equilibrium constant for this process as

$$\text{reactants} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{TS}^{\neq} \xrightarrow{k_2} \text{products} \qquad K^{\neq} = \frac{k_1}{k_{-1}} = \frac{[\text{TS}^{\neq}]}{[\text{react}]}$$
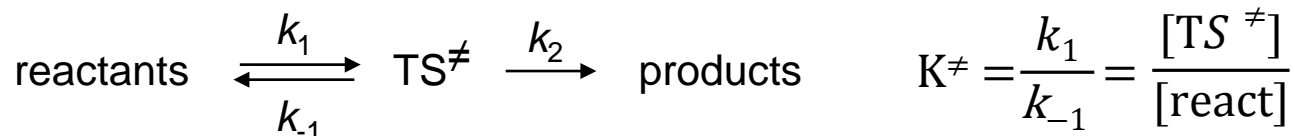
from where:

$$v = k_2 [\text{TS}^{\neq}] = \frac{k_B T}{h} K^{\neq} [\text{react}]$$

To consider the fact that not all vibration in the TS has to lead to the products, a variable parameter is introduced, the transmission coefficient (κ) that takes values between 0.5 and 1 (normally = 1)

$$v = \frac{\kappa k_B T}{h} K^{\neq} [\text{react}] = k [\text{react}] \quad \Longrightarrow \quad k = \frac{\kappa k_B T}{h} K^{\neq}$$

The equilibrium constant for the $\text{TS}^{\neq}$ can be expressed as a function of $\Delta G^{\neq}$

$$K^{\neq} = e^{-\Delta G^{\neq}/RT} \quad \Longrightarrow \quad \boxed{k = \frac{\kappa k_B T}{h} e^{-\Delta G^{\neq}/RT}} \quad \textbf{Eyring equation}$$

Eyring equation:
$$k = \frac{\kappa k_B T}{h}\, e^{-\Delta G^{\neq}/RT}$$

and considering that $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$ $\Rightarrow$
$$k = \frac{\kappa k_B T}{h}\, e^{-\Delta H^{\neq}/RT}\, e^{\Delta S^{\neq}/R}$$

and expressed in logarithmic form :

$$\ln k = \ln \frac{\kappa k_B T}{h} - \frac{\Delta H^{\neq}}{RT} + \frac{\Delta S^{\neq}}{R}$$

κ = transmission coefficient (~ 1)
k_B = Boltzmann constant (= $1.38\cdot10^{-16}$ erg K^{-1})
T = temperature (K)
h = Planck constant(= $6.626\cdot10^{-27}$ erg·s)
R = gas constant(= 1.987 cal K^{-1} mol^{-1})

If we divide the Eyring equation by T and take logarithms:

$$\ln \frac{k}{T} = \underbrace{\ln \frac{\kappa k_B}{h} + \frac{\Delta S^{\neq}}{R}}_{\text{cte.}} - \frac{\Delta H^{\neq}}{R}\frac{1}{T}$$

Graphic representation of the Eyring equation ("Eyring plot")

$\ln (k/T)$

const

$$\text{pend} = -\frac{\Delta H^{\neq}}{R}$$

1/T

$$\boxed{\Delta S^{\neq}} = R \ln \frac{kh}{T\kappa k_B} + \frac{\Delta H^{\neq}}{T}$$

65
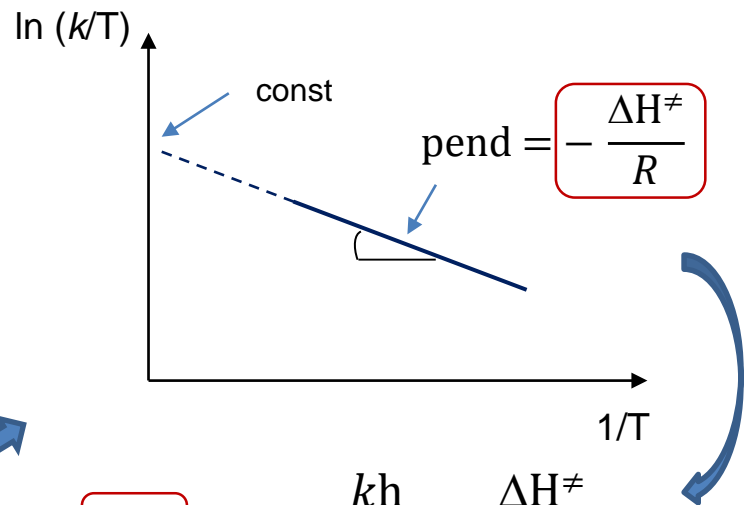
KINETIC THEORIES: ARRHENIUS EQUATION AND TRANSITION–STATE THEORY

From the representation of the Eyring equation: $\boxed{\Delta H^{\neq} \text{ (cal mol}^{-1})}$

And from the equation, substituting the calculated value of $\Delta H^{\neq}$ and using the values of k and T of one of the experiments: $\boxed{\Delta S^{\neq} \text{ (cal K}^{-1} \text{ mol}^{-1} \text{ or eu)}}$

Note: This treatment assumes that both $\Delta H^{\neq}$ and $\Delta S^{\neq}$ <u>do not vary with the T</u> in the range of temperatures studied.

Relation between the Arrhenius equation and Eyring equation

Arrheniuns's equation: $\quad k = A\, e^{-Ea/\mathrm{RT}}$

Eyring equation:

$$\ln k = \ln A - \frac{E_a}{\mathrm{RT}}$$

$$\ln k = \ln \frac{\kappa k_B T}{h} - \frac{\Delta H^{\neq}}{RT} + \frac{\Delta S^{\neq}}{R}$$

Both equations are not strictly comparable since the Arrhenius equation derives from empirical data of the macroscopic rate constant of the global reaction, whereas that of Eyring analyzes the microscopic rate constant of a single elementary step of the reaction.

However, we can make comparisons for <u>unimolecular or bimolecular single-step reactions</u>.

KINETIC THEORIES: ARRHENIUS EQUATION AND TRANSITION–STATE THEORY

We have two possible situations:

a) Reactions in solution at **p = constant**

Under these conditions it is considered that $\Delta H^{\neq}$ is independent of T. We can derive both expressions with respect to 1/T

Arrhenius eq. $\Rightarrow$ $\dfrac{d(\ln k)}{d(\frac{1}{T})} = \dfrac{-Ea}{R}$

$E_a = \Delta H^{\neq} + RT$

$\Delta H^{\neq} = E_a - RT$

Eyring eq. $\Rightarrow$ $\dfrac{d(\ln k)}{d(\frac{1}{T})} = -T - \dfrac{\Delta H^{\neq}}{R}$

(T = average tem.p of the studied range)

And now we can compare the pre-exponential factor of Arrhenius eq. (A) with $\Delta S^{\neq}$

$$k = A\, e^{-Ea/RT} = \frac{A}{e}\, e^{-\Delta H^{\neq}/RT}$$

From where $A = e\,\kappa\,\dfrac{k_B T}{h}\, e^{\Delta S^{\neq}/R}$ and $\Delta S^{\neq} = R\,(\ln A - 24.76 - \ln T)$

KINETIC THEORIES: ARRHENIUS EQUATION AND TRANSITION–STATE THEORY

b) Gas phase reactions

Now $\Delta H^{\neq}$ is not independent of T

Under these conditions

$$\Delta H^{\neq} = E_a + (\Delta n^{\neq} - 1)RT$$

being $\Delta n^{\neq}$ the change of the number of molecules when going from reactants to TS$^{\neq}$

For a unimolecular reaction: $\Delta n^{\neq} = 0$
For a bimolecular reaction: $\Delta n^{\neq} = -1$

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ reflect the structure of the TS‡:

In the TS the bonds are partially formed and broken, this is reflected in a higher energy content of the TS with respect to the reactants: $\Delta H^{\ddagger} > 0$

$\Delta S^{\ddagger}$ is a measure of the change in the order of the system when going from reactants to TS‡.

Transition state is highly ordered $\longrightarrow$ $\Delta S^{\neq} < 0$

Disordered transition state $\longrightarrow$ $\Delta S^{\neq} > 0$

Examples:

Cyclopentadiene dimerization
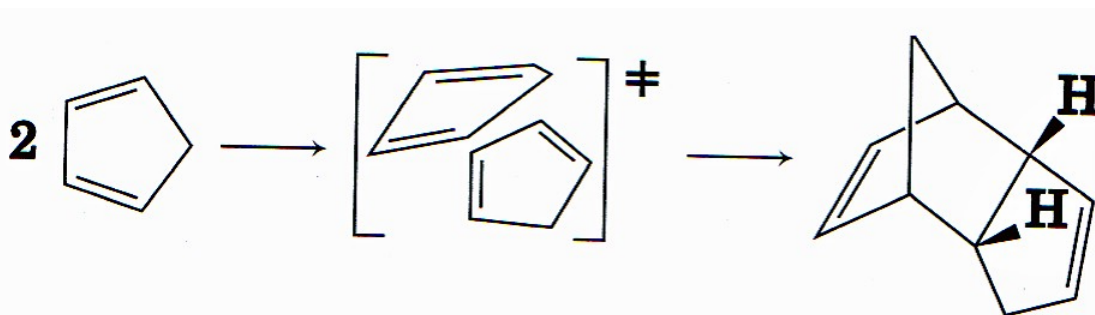
$\Delta H^{\ddagger}$ = 15,5 Kcal/mol. This relatively low value is characteristic of concerted reactions in which the bonds are broken and formed simultaneously.

$\Delta S^{\ddagger}$ = -26 eu. The large negative value indicates the loss of degrees of rotational and translational freedom as we go from two independent molecules to an TS formed by a single chemical species.

Decomposition of 1,1'-isobutane

$$Bu-N=N-Bu \rightarrow 2Bu\cdot + N_2$$
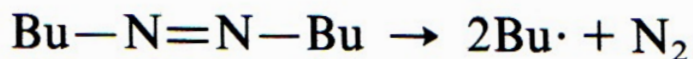
$\Delta H^{\ddagger} = 52$ Kcal/mol. This relatively high value is due to the breaking of links without formation of new

$\Delta S^{\ddagger} = +19$ eu. The positive value is due to the separation of fragments when passing from reactants to TS, increasing the number of degrees of freedom

Fragmentation of tert- *butyl* hydroperoxide

$$(CH_3)_3CO-OC(CH_3)_3 \xrightarrow{\Delta} \left[(CH_3)_3CO\cdots OC(CH_3)_3\right]^{\ddagger} \longrightarrow 2\,(CH_3)_3CO\cdot$$
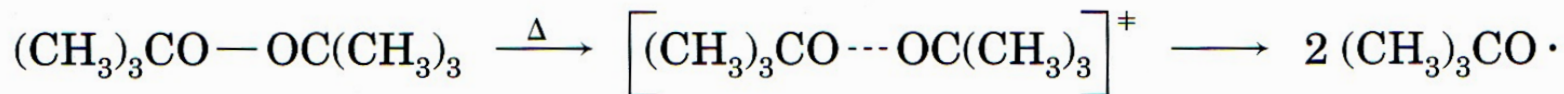
$\Delta S^{\ddagger} = +13.8$ eu.

PRINCIPLE OF MICRO-REVERSIBILITY

This principle states that in a reversible reaction the path through which the reaction occurs in one direction is the same as that in the reverse reaction.
As a consequence of this principle you can obtain information about the transition state both from the reactants and from the products

KINETIC CONTROL AND THERMODYNAMIC CONTROL

When a mixture of reactants can evolve to give two or more products, the composition of the reaction mixture varies according to the conditions and the reaction time.

Thermodynamic control: If the reaction is carried out at a sufficiently high temperature and the mixture is maintained for a sufficiently long time to allow an **equilibrium to** be established between the different products that are formed, the concentration of each one in the reaction mixture depends on its free energy value G, with the most thermodynamically stable product predominating.

Kinetic control: If the reaction is carried out in conditions that **do not** allow to establish an equilibrium between products, the composition of the mixture is given by the **rate** at which each product is formed. The product that forms faster predominates.

KINETIC CONTROL AND THERMODYNAMIC CONTROL

Example: The Friedel-Crafts alkylation reaction of chlorobenzene with isopropyl chloride

(kinetic product)   (thermodynamic product)
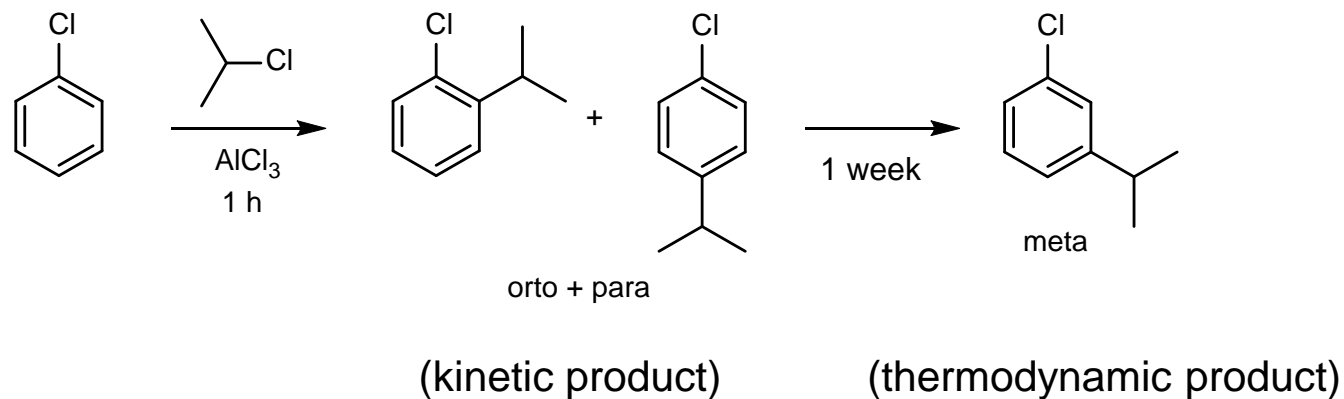
If the reaction is stopped after 1 h, a mixture of *ortho* and *para* is mainly obtained. But if it is left for 1 week, *meta* product predominates.

Under thermodynamic control conditions of all species are in equilibrium and the most stable product predominates (thermodynamic)
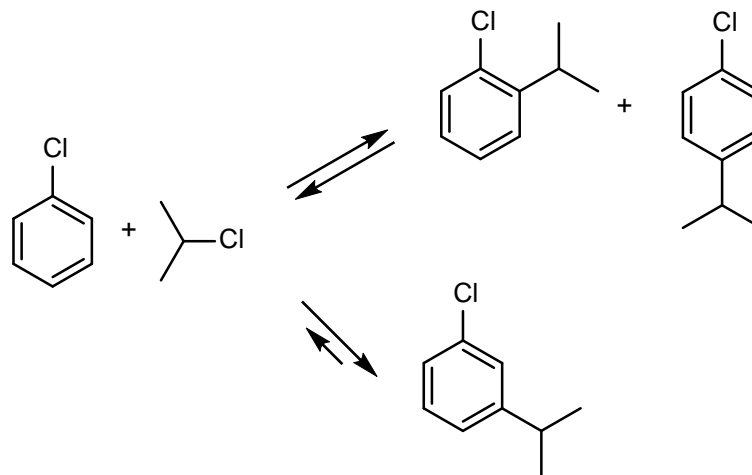
KINETIC CONTROL AND CURTIN-HAMMETT PRINCIPLE

Kinetic control

It can be shown that under kinetic control the distribution of the products ([C]/[D]) is determined by the difference of the activation free energies ($\Delta\Delta G^{\neq}$) that lead to such products

Assume "irreversible" reactions:

$$B \xleftarrow{k_B} A \xrightarrow{k_C} C$$

$$\frac{[C]}{[B]} = \frac{v_C}{v_B} = \frac{k_c[A]}{k_B[A]} = \frac{k_c}{k_B}$$
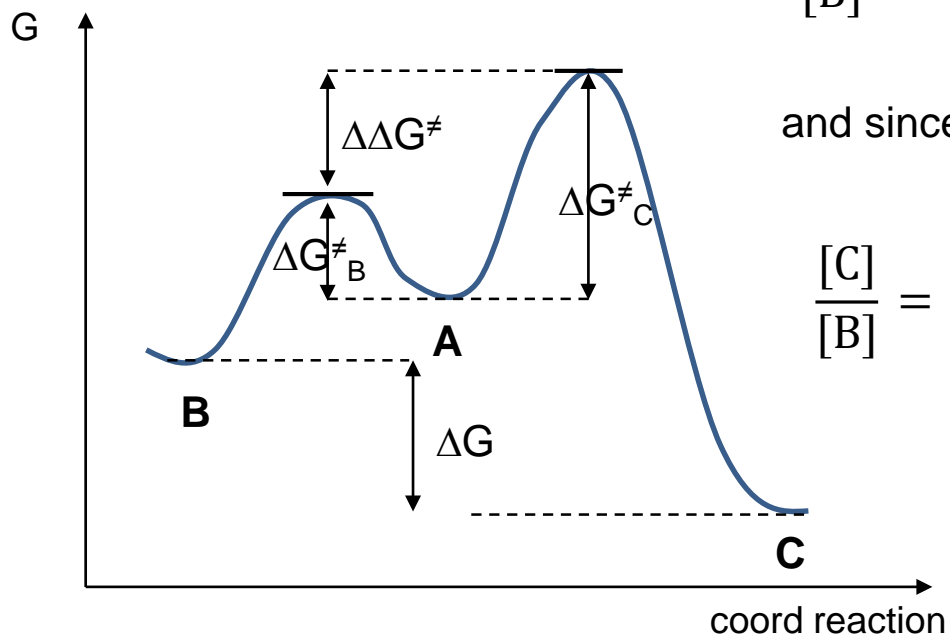
and since $k = \dfrac{\kappa k_B T}{h}\, e^{-\Delta G^{\neq}/RT}$

$$\frac{[C]}{[B]} = \frac{e^{-\Delta G^{\neq}_C/RT}}{e^{-\Delta G^{\neq}_B/RT}} = \boxed{e^{-\Delta\Delta G^{\neq}/RT}}$$

KINETIC CONTROL AND CURTIN-HAMMETT PRINCIPLE

$$B \xleftarrow{\quad k_B \quad} A \xrightarrow{\quad k_C \quad} C$$

Table 6.2 Product ratios and differences in activation free energy for competitive, irreversible reactions.

[C]/[B]	$\Delta\Delta G^{\ddagger}$ (25°, kcal/mol)
1	0.0
2	0.41
5	0.96
10	1.36
100	2.73
1,000	4.09
10,000	5.45

Because the term $\Delta\Delta G^{\neq}$ is in the exponent, small changes in the difference of energies of activation entail important changes in the distribution of the products

KINETIC CONTROL AND CURTIN-HAMMETT PRINCIPLE

Curtin-Hammet principle

An interesting situation related to the composition of the mixture of products under **kinetic control** occurs when the reactant has two or more reactive conformations leading to different products. It is often <u>mistakenly</u> thought that the proportion between the products is identical to the proportion of the conformers from which they are derived. This is only the case when the interconversion between the conformers is much slower than the subsequent reaction (which rarely happens).

anti

k_3
$-(HCl)$

trans-stilbe

$k_1 \parallel k_2$

gauche

k_4
$-(HCl)$

cis-stilbe
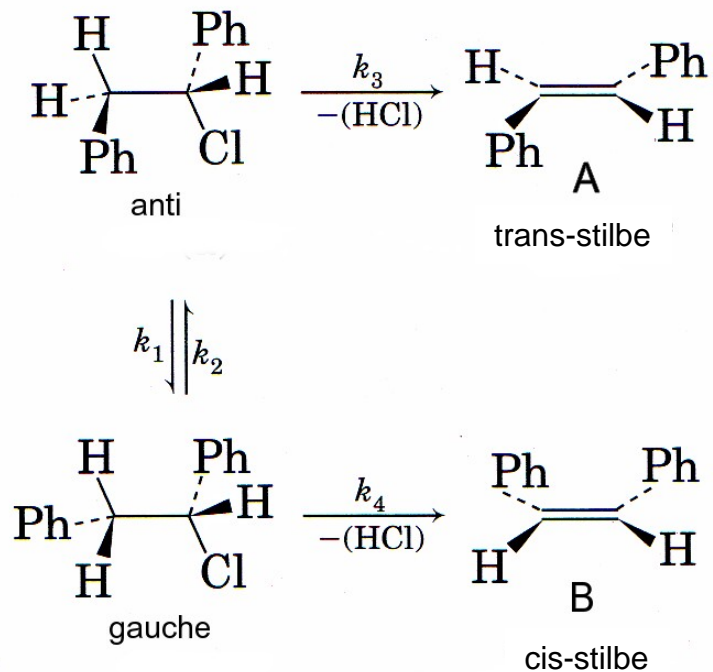
KINETIC CONTROL AND CURTIN-HAMMETT PRINCIPLE

The distribution ratio of the cis/trans products is only determined by the difference between their activation-free energies $(\Delta\Delta G^{\neq})$
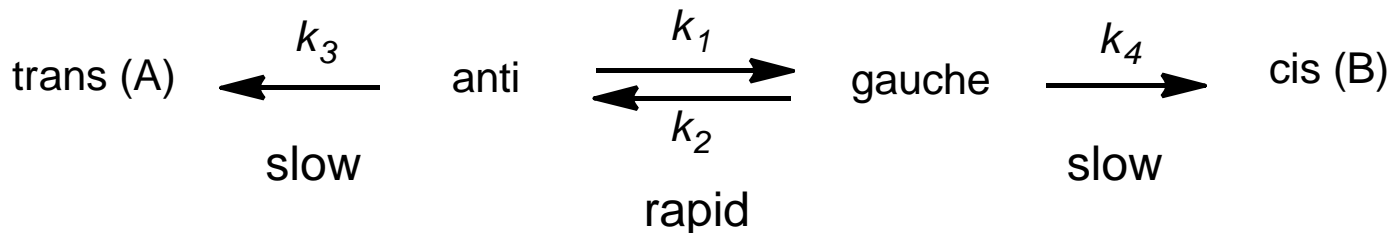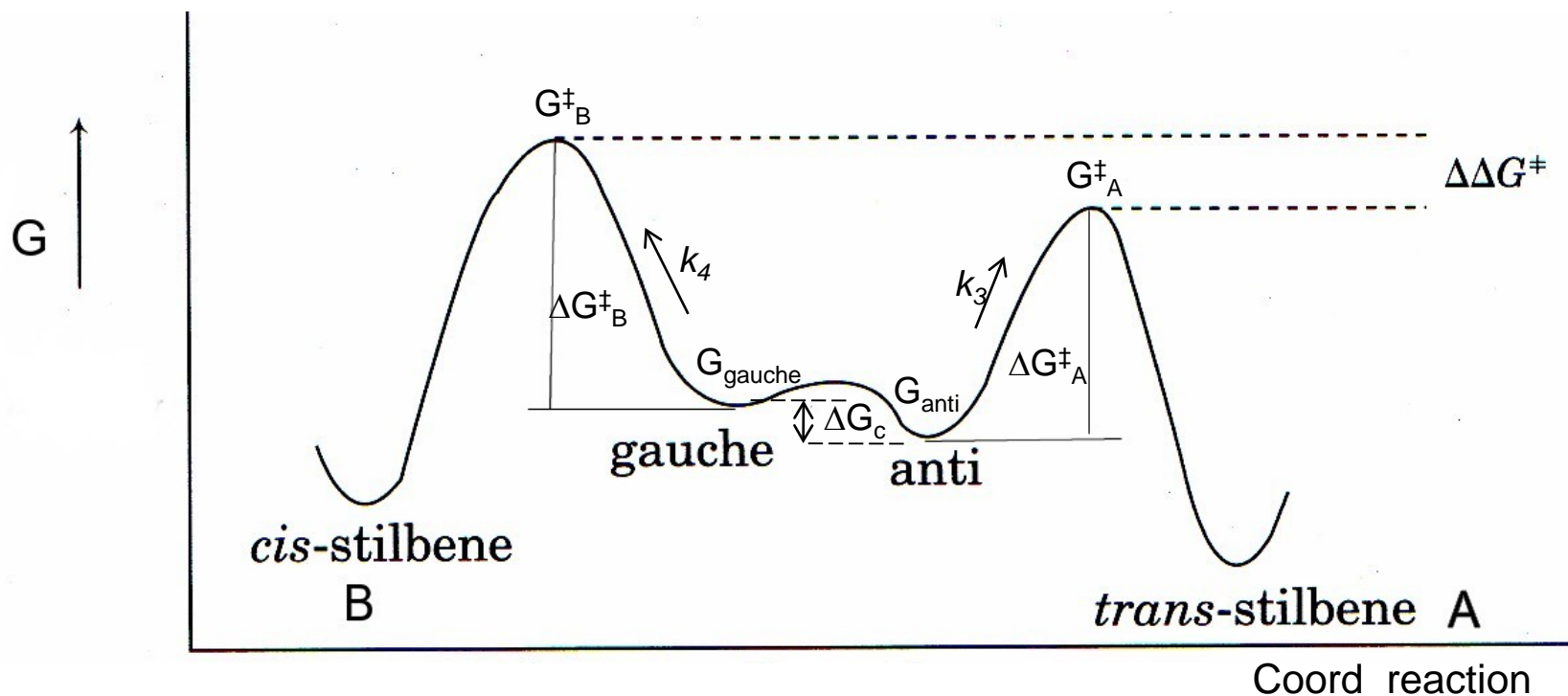
KINETIC CONTROL AND CURTIN-HAMMETT PRINCIPLE

Curtin-Hammett principle (Demonstration)

There is a conformational equilibrium K_c =[gauche]/[anti] = k_1/k_2

Formation rate of A, $v_A = k_3$[anti]

Formation rate of B, $v_B = k_4$[gauche]= k_4 Kc [anti]

The product ratio (kinetic control) [A]/[B] = $v_A/v_B = k_3/K_c k_4$

Putting k in function of the equation of Eyring and K_c in function of ΔG_c

[A]/[B] = exp (- $\Delta G^{\ddagger}_A$/RT) / [exp (-ΔG_c/RT) x exp (-$\Delta G^{\ddagger}_B$/RT)] =

 = exp [(-$\Delta G^{\ddagger}_A$ + ΔG_c + $\Delta G^{\ddagger}_B$)/RT] = exp [(-$G^{\ddagger}_A$+G_{anti}+G_{gauche}-G_{anti} + $G^{\ddagger}_B$ − G_{gauche})/RT]

 = exp [($G^{\ddagger}_B$-$G^{\ddagger}_A$)/RT] = exp[$\Delta\Delta G^{\neq}$/RT]

That is, the product ratio <u>does not depend on ΔG_c (conformational equilibrium)</u> but on the energy difference between the transition states that lead to products A and B.

KINETIC CONTROL AND CURTIN-HAMMETT PRINCIPLE

Curtin-Hammet principle (Statement)

The ratio of products formed from conformational isomers is not determined by the conformer population, but by the relative energy of the TS leading to the final products.

A reaction can proceed through a minority conformation if it provides access to a lower energy of TS (Transition State).

The principle is applicable to any reaction in which there is a rate equilibrium between two molecular entities of different reactivity: keto–enol tautomerism, protonated forms...

NATURE OF THE TRANSITION STATE: THE HAMMOND POSTULATE

The transition states possess an extremely short half-life and it is not possible to make experimental measurements that give direct information about their structure.

Hammond (JACS 1955, 334) established a series of circumstances in which it is possible to relate the structure of an TS with that of other chemical species on which it is possible to obtain this information.

Hammond Postulate: If two consecutive states of a reaction, as for example, a transition state and an unstable intermediate, have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures

1st case : "early" TS

TS

R

P
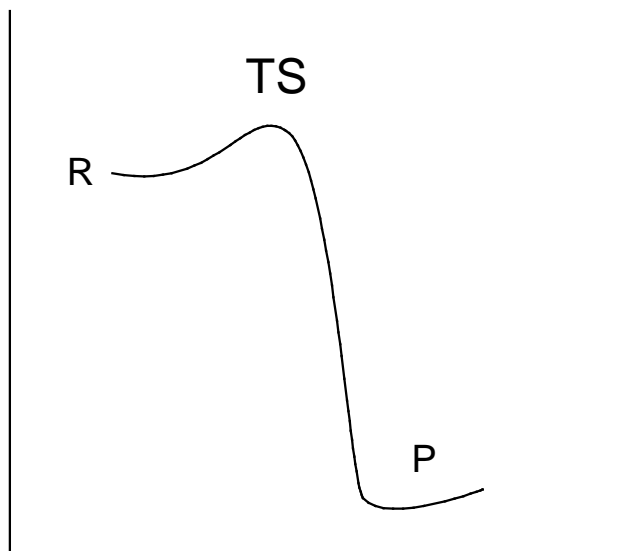
Exothermic elementary reaction

Low Ea

$E(ET) \approx E (R)$

The structure of the TS is
similar to that of the reactant

NATURE OF THE TRANSITION STATE : HAMMOND POSTULATE

2nd case: "late" TS
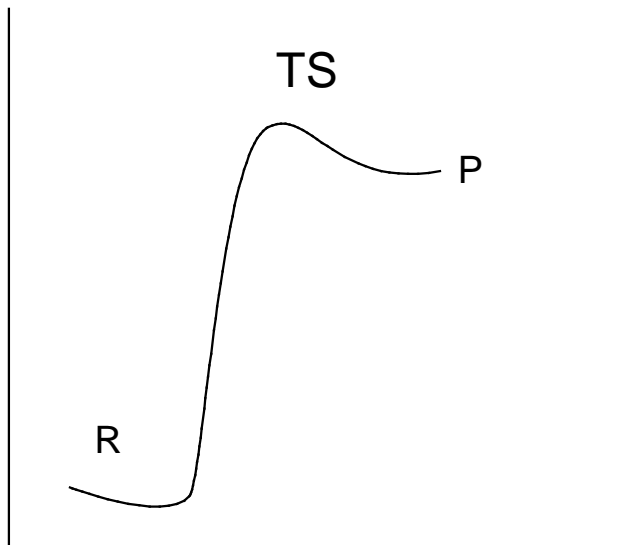
Endothermic elementary reaction

High Ea

$E(ET) \approx E(R)$

The structure of the TS is similar to that of the products

3rd case: central or symmetric TS
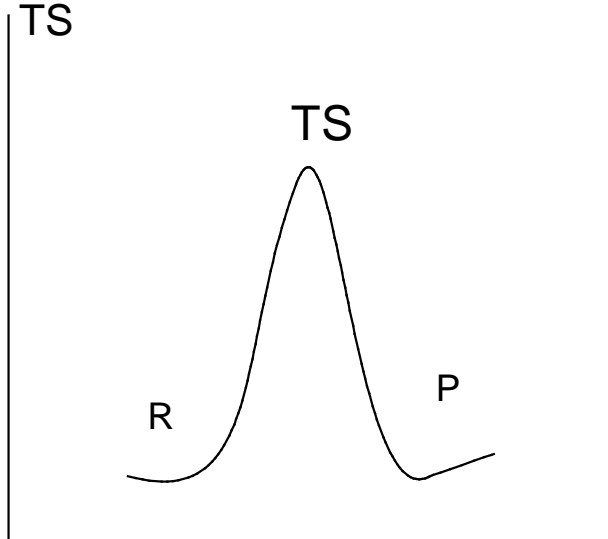
Thermoneutral elementary reaction

$E(R) << E(ET) >> E(P)$

Neither the reactant nor the product are good models for TS

NATURE OF THE TRANSITION STATE : HAMMOND POSTULATE

Example: Radical halogenation

Me$_2$C(H)Et →[Br$_2$ / light] Me$_2$C(Br)Et   90%   + others

Me$_2$C(H)Et →[Cl$_2$ / light] Me$_2$C(Cl)Et 40% + MeCH(Cl)... 25% + others

Initiation   X-X →[light] 2 X•   (1)

Propagation   X• + R-H ⟶ R• + HX   (2) ⇐

R• + X$_2$ ⟶ R-X + X•   (3)
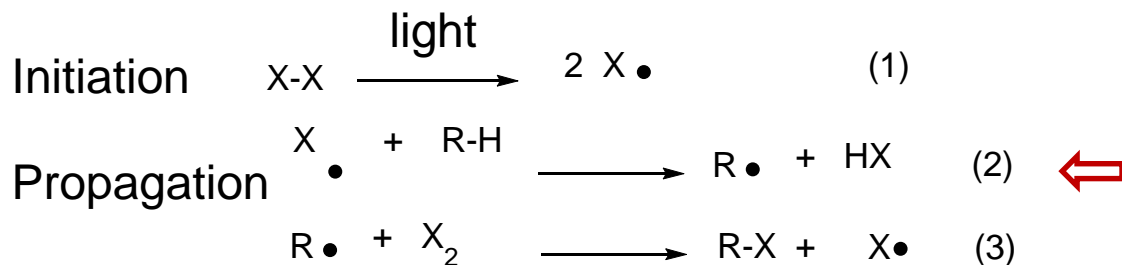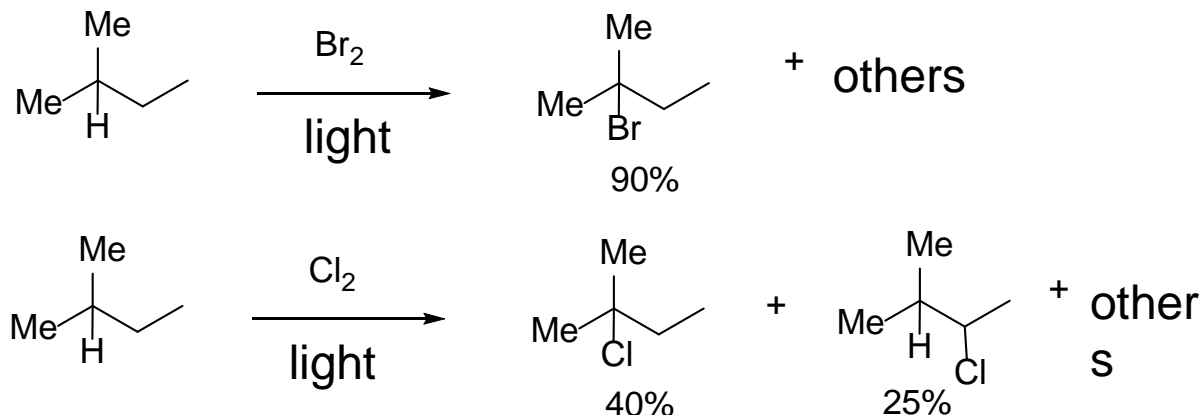
Step 2 is the rate-determining step and responsible for differentiation between primary, secondary and tertiary carbons

Bromination is selective 3> 2> 1

Chlorination is not selective

NATURE OF THE TRANSITION STATE : HAMMOND POSTULATE

Bromination

TS

R• + BrH

Br• + RH
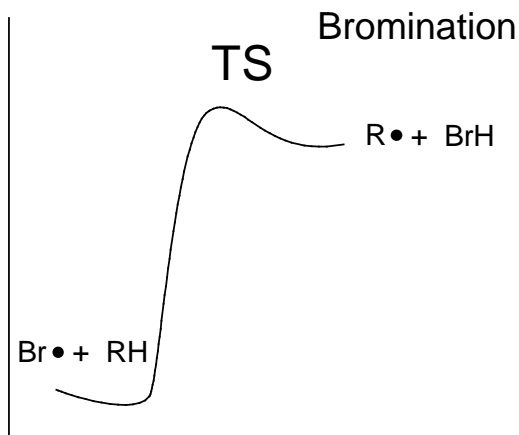
E (C-H)= 98 Kcal/mol, E (H-Br)= 87 Kcal/mol

Bromination: step (2) is endothermic with a late TS.

The energy and structure of the TS are similar to that of the radicals that are formed.

The variations in the energy of the TS are parallel to that of the radicals.

$\Delta G(TS3) < \Delta G(TS2) < \Delta G(TS1)$

Chlorination

TS

Cl• + RH

R• + ClH
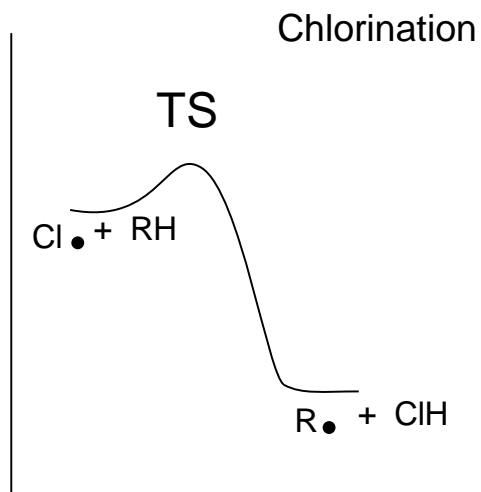
E (C-H)= 98 Kcal/mol, E (H-Cl)= 102 Kcal mol

Chlorination: step (2) is exothermic with an early TS.

The energy and structure of the TS are similar to the reactants' and vary little as a radical 3, 2 or 1 is formed.

Reaction is not selective

Selectivity in radical halogenation with fluorine and bromine

CH₃-CH(CH₃)(CH₃) + X₂ →(hν)→ X·CH₂-CH(CH₃)(CH₃) + CH₃-C(CH₃)(CH₃)-X + HX
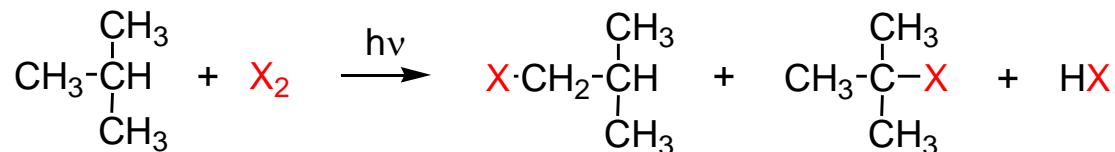
	Statistical	proportion	90	:	10	
	Observed	for **F₂**	86	:	14	Low selectivity
	Observed	for **Br₂**	<1	:	>99	Highly selective
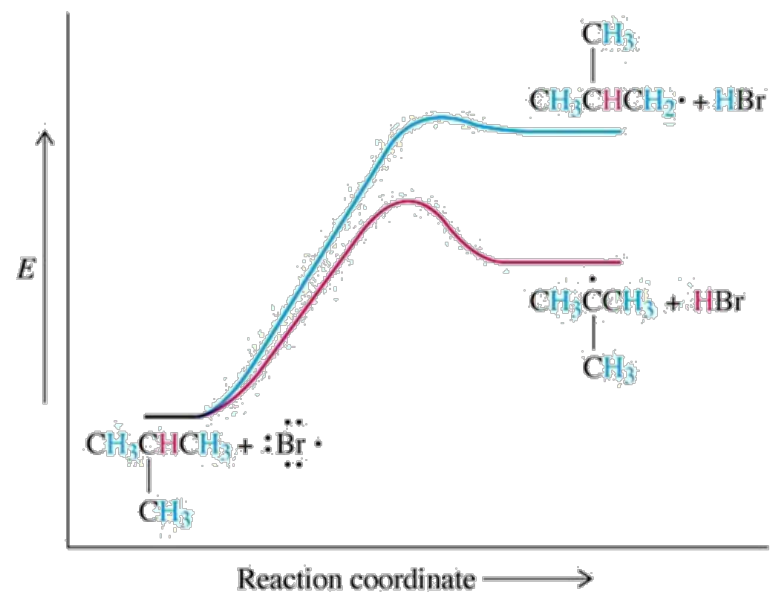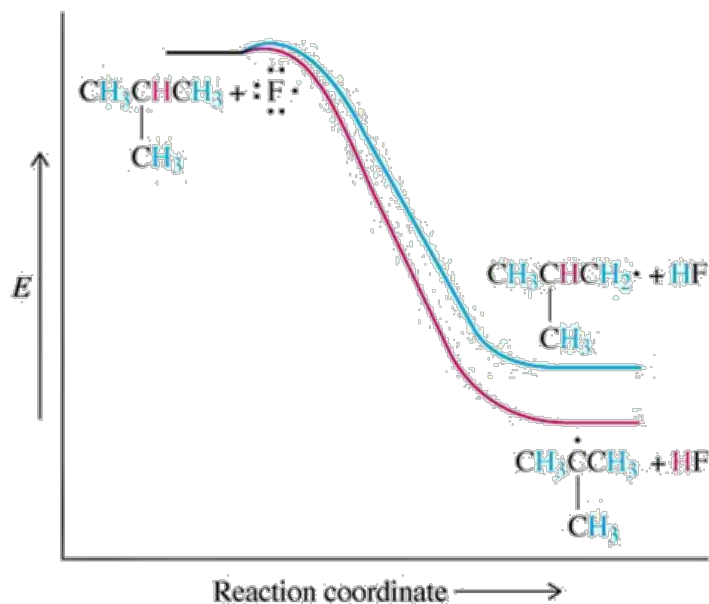
KINETIC ISOTOPE EFFECTS

Definition: It is the variation in the rate of a reaction that occurs when replacing an atom with one of its isotopes (normally heavier).

In general, the substitution by a heavier atom causes a decrease in the reaction rate.

The most applied is the replacement of hydrogen by deuterium:

Observed isotopic effect: k_H/k_D

       where k_H and k_D are the reaction rates with H and deuterium, correspondingly

k_H/k_T is greater as tritium is radioactive

Other different hydrogen atoms give low isotopic effects

Classification:

    - Primary kinetic isotope effect (PKIE)

    -Secondary kinetic isotope effect

        -Alpha, α , normal, ($k_H/k_D > 1$) or reverse ($k_H/k_D < 1$)

        -Beta, β (is always normal)

KINETIC ISOTOPE EFFECTS

Primary kinetic isotope effect (PKIE)

The H atom (or its heaviest isotope) is a part of the bond that breaks during the slow (rate-limiting) step of the reaction.

The value of PKIE is varied from 2 to 7

$$\boxed{k_H/k_D = 2\text{-}7}$$

D Bond, which
 | is broken
—C—
 |
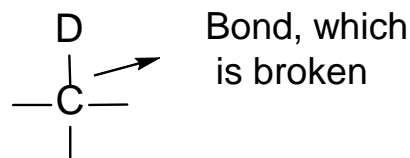
Information given by the PKIE:

1. A substantial k_H / k_D value (greater than 2) is strong evidence that the C-H (D) bond is broken during the slow step of the reaction (the rate-limiting step).

2. The value of the PKIE provides qualitative information on the position of the TS to reactants or products:

Low PKIE indicates an early or late TS

$$[C\text{----}H\text{----------}A]^{\neq}$$
$$[C\text{---------}H\text{----}A]^{\neq}$$
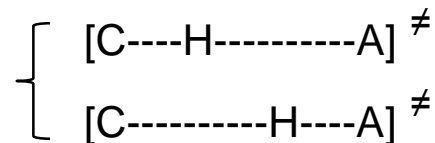
Near PKIE to the theoretical
maximum (6-7) indicates a central TS

$$[C\text{-------}H\text{-------}A]^{\neq}$$
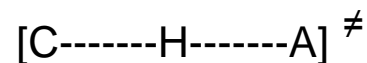
KINETIC ISOTOPE EFFECTS

Examples of primary kinetic isotope effect (PKIE)

k_H/k_D = 4.6 (77 ^{o}C)

k_H/k_D = 6.1 (25 ^{o}C)

k_H/k_D = 4.0 (190 ^{o}C)
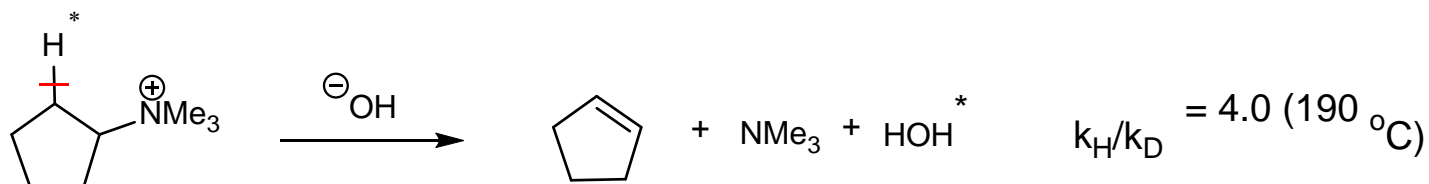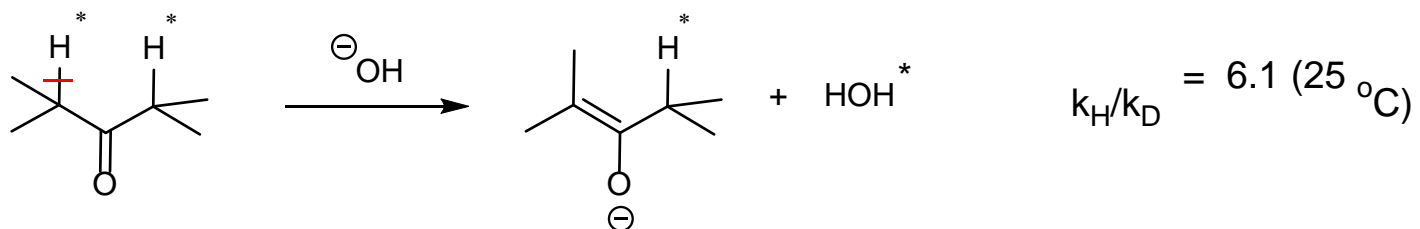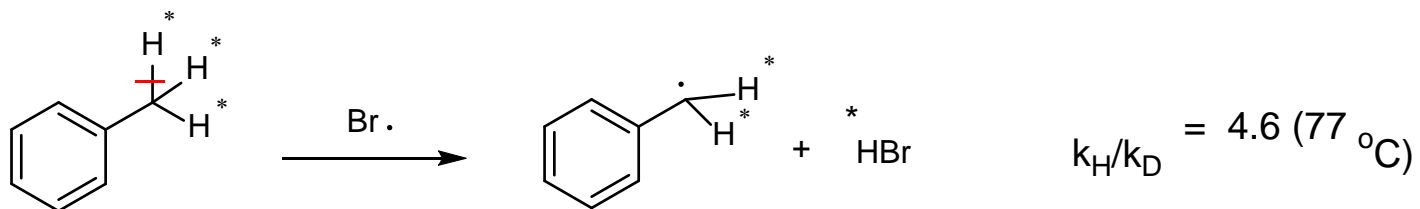
KINETIC ISOTOPE EFFECTS

Origin of primary kinetic isotope effect

Let's consider as a model the unimolecular thermal homolytic breaking of a C-H bond in methane

$$CH_4 \xrightarrow{\Delta} [H_3C\text{-------}H]^{\neq} \longrightarrow H_3C\cdot \ + \ \cdot H$$
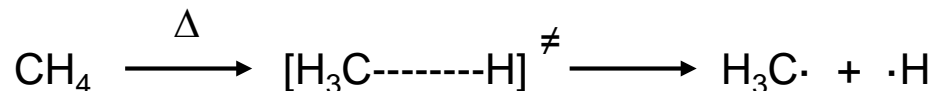
It is considered that the C-H bond is completely broken in the transition state, so the bond dissociation energy (D_0) coincides with the activation energy of the process (Ea)

Internuclear distance (C-H)
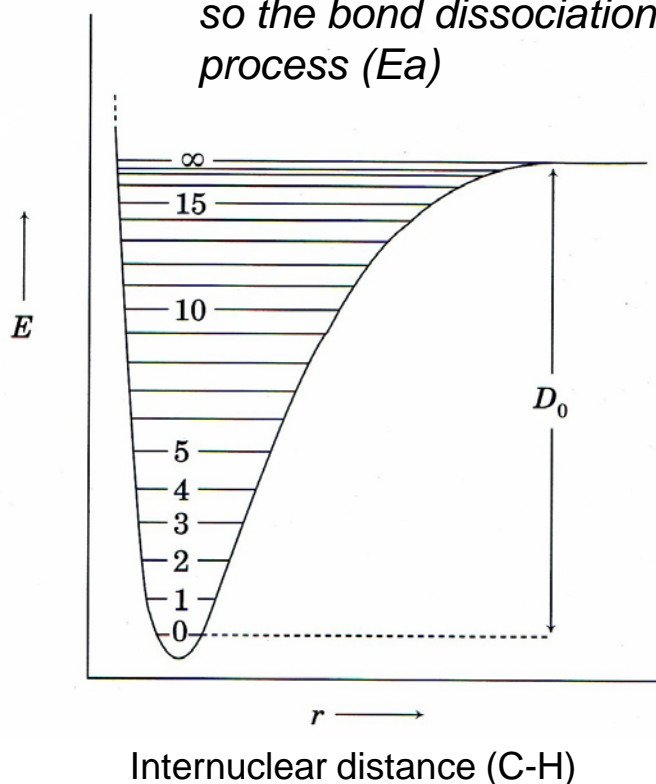
- The electronic E of the fundamental state varies with the internuclear distance ***r***
- Each electronic level has several vibrational levels, whose energy is given as:

$$E = h\nu \, (v + \tfrac{1}{2}) \qquad \nu = \frac{1}{2\pi} \sqrt{k/\mu} \qquad \mu = \frac{m_1 m_2}{m_1 + m_2}$$

- At T room 99% of the molecules are at the level $v = 0$, with $E_0 = \frac{1}{2}$ hn (zero point energy, ZPE)

The dissociation energy D_0 of the C-H bond is the difference between the value of E at infinity (where the vibration C-H becomes movement) and the energy at the zero point (E_0).

KINETIC ISOTOPE EFFECTS

Origin of PKIE. Unimolecular process (dissociation)

What happens if C-H is substituted by C-D?
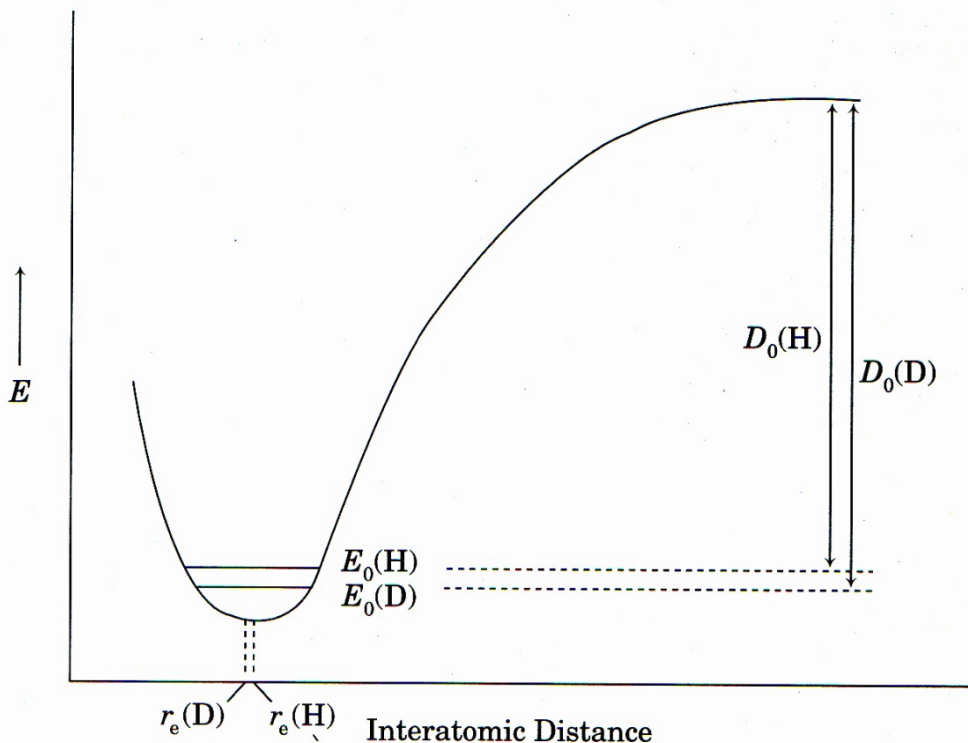
$$\nu = \frac{1}{2\pi} \sqrt{k/\mu} \qquad y \qquad \mu = \frac{m_1 \cdot m_2}{m_1 + m_2}$$

-The value of vibrational energy at the zero point (v = 0) depends on the reduced mass (m) of the atoms that forms the bond.

-The vibrational energy at the zero point for the C-H bond is greater than for C-D (D and H have different mass).

-The energy in the dissociation limit is the same in both cases (there is no bond and therefore there is no vibrational energy).

-The dissociation energy of the C-D bond is greater than that of the C-H bond.

-The length of the C-D bond is less than that of the C-H bond.

KINETIC ISOTOPE EFFECTS

Estimation of the primary kinetic isotope effect. Unimolecular process (dissociation).

An estimate of the difference in energies can be made at the zero point considering only the stretching vibrations of the C-H (D) bond (by IR).

$$E_0(H) = \tfrac{1}{2}\, h\nu_{C-H} = \tfrac{1}{2}\, hc\tilde{\nu}_{C-H}$$

$$E_0(D) = \tfrac{1}{2}\, h\nu_{C-D} = \tfrac{1}{2}\, hc\tilde{\nu}_{C-D}$$

$$D_0(D) - D_0(H) = E_0(H) - E_0(D) = \tfrac{1}{2}\, hc(\nu_{C-H} - \nu_{C-D}) = \tfrac{1}{2}\, hc\, (3000-2200) = 400\, hc$$

$$= 400\ cm^{-1} \times 6.625\ 10^{-34}\ J\cdot s \times 3\ 10^{10}\ cm\cdot s^{-1} = 7.95\ 10^{-21}\ J\ molec^{-1}$$

$$= 7.95\ 10^{-21}\ J\ molec^{-1} \times 6.023 \cdot 10^{23}\ molec\ mol^{-1} \times 0.24\ cal\ J^{-1} = 1.149\ cal\ mol^{-1}$$

The dissociation rate will be given by the Arrhenius equation

$$k_H = A_H\, \exp(-E_a(H)/RT)$$

$$k_D = A_D\, \exp(-E_a(D)/RT)$$

$$k_H/k_D = A_H/A_D\, \exp[(D_0(D)-D_0(H))/RT] = \exp[(E_0(H)-E_0(D)/RT] = \exp[1.149\ cal\ mol^{-1}/(1.98 cal\ mol^{-1}K^{-1} \times 300\ K)] = \exp(1.94) = 7$$

KINETIC ISOTOPE EFFECTS

Estimation of the primary kinetic isotope effect. Non-unimolecular process.

C-----H------------------A

Early TS

$E_a(D) \approx E_a(H)$

Exothermic reaction

TS is similar to the reactants'

The C-H (D) bond is only slightly broken in the TS.

The differences in energy at the zero point for the C-H and C-D bonds are similar in the reactant and in the TS.

Small difference is expected between the energies of activation for the reactions with H or D and therefore the observed KIE is low
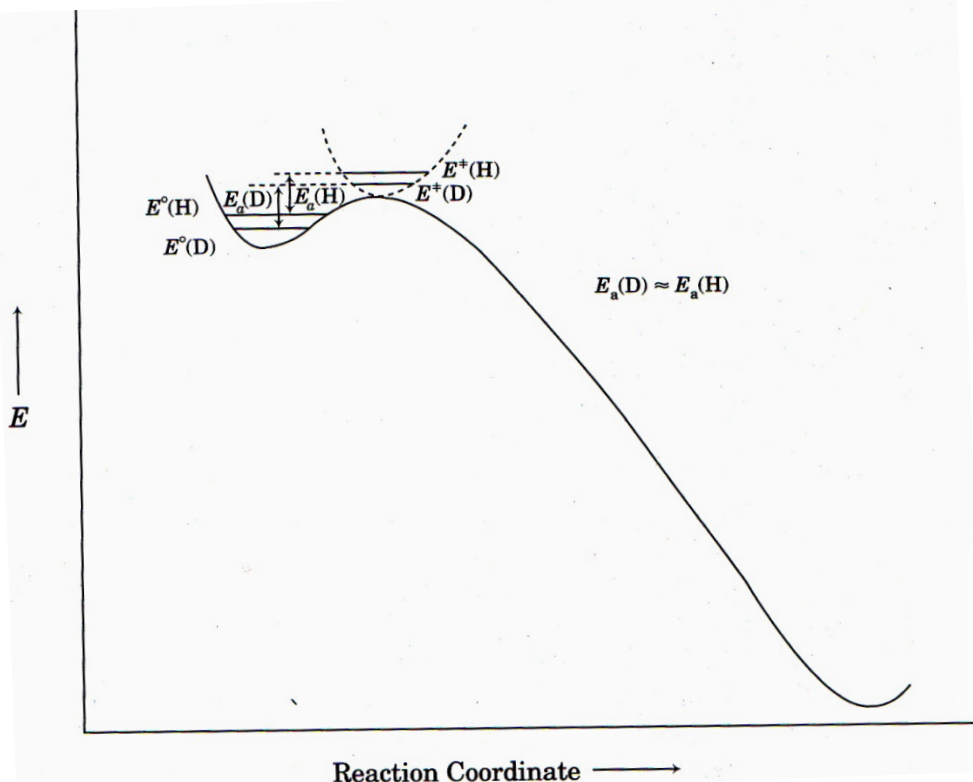
KINETIC ISOTOPE EFFECTS

The primary kinetic isotope effect. Non-unimolecular process.

$$C\text{-------------------}H\text{-----}A$$

Late TS
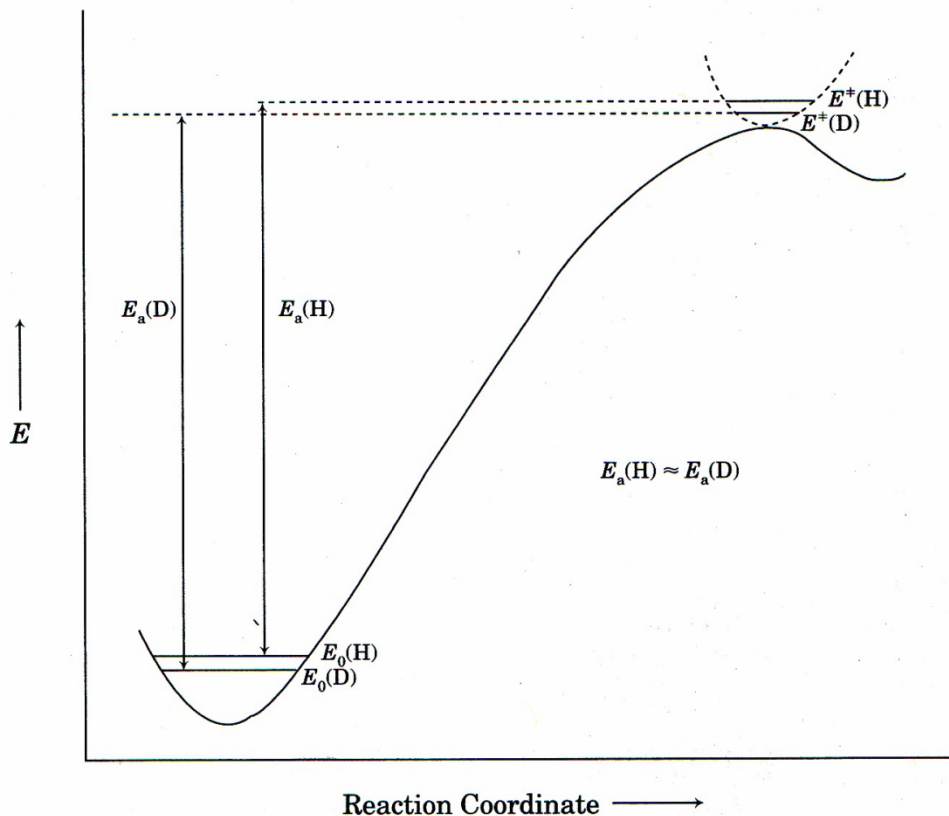
Endothermic reaction

TS is similar to the products'

The C-H (D) bond is practically formed in the TS.

The differences in energy at the zero point for the C-H and C-D bonds are similar in the reactant and in the TS.

The situation is similar to the case of a near TS, consequently a low KIE can be expected

$E_a(D)$ $E_a(H)$

E

$E_a(H) \approx E_a(D)$

$E^{\ddagger}(H)$
$E^{\ddagger}(D)$

$E_0(H)$
$E_0(D)$

Reaction Coordinate $\longrightarrow$

The primary kinetic isotope effect. Non-unimolecular process.

C - - - - - - - - - - H - - - - - - - - - - A

Central TS
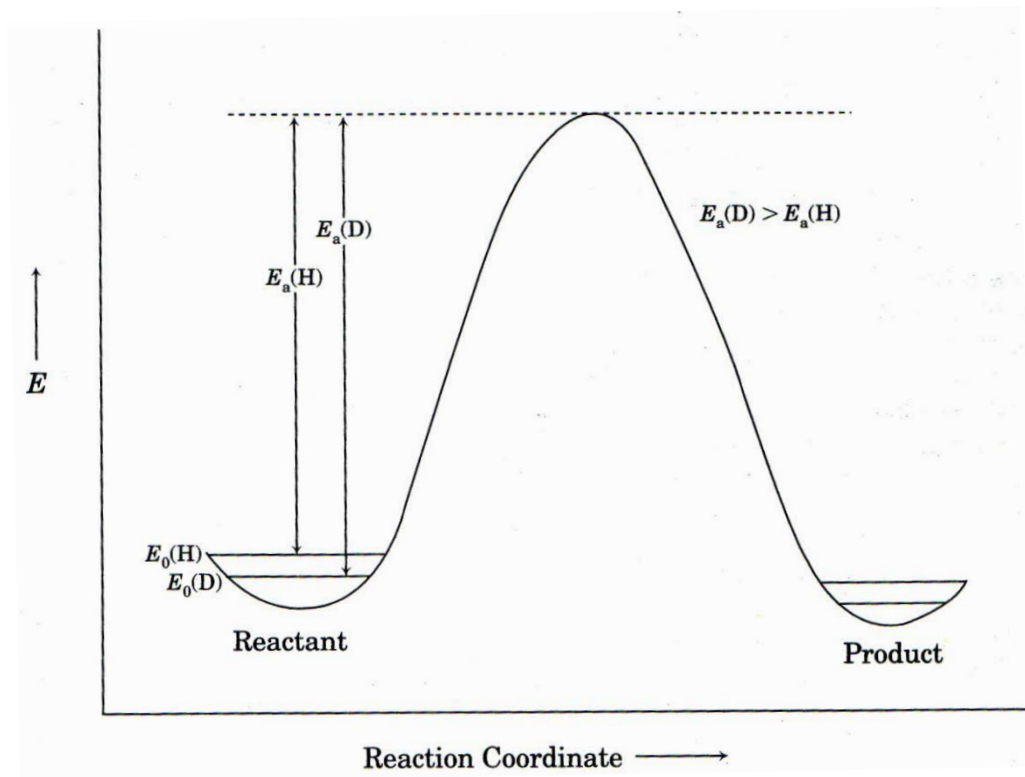
Thermoneutral reaction

In TS, the C-H or C-D bond is very weak and its energies are close to each other.

In this situation Ea (D)> Ea (H) and we expect a high KIE.

$E_a(D)$

$E_a(H)$

$E_a(D) > E_a(H)$

E

$E_0(H)$
$E_0(D)$

Reactant

Product

Reaction Coordinate

KINETIC ISOTOPE EFFECTS

The secondary kinetic isotope effect. (SKIE)

Substitution affects an atom near the bond that breaks during one of the rate determining stages, but is not part of it (kH / kD = 0.7-1.5)

α **SKIE k_H/k_D = 0.7-1.5**

X   Bond, which is broken

—|—D
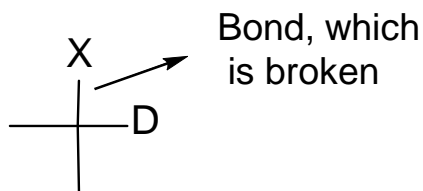
Normal: k_H/k_D = 1-1.5 change from sp^3 to sp^2 to sp

Inverse: k_H/k_D = 0.7-0.9 change from sp to sp^2 to sp^3

β **SKIE k_H/k_D = 1.0 - 1.3**

Bond, which is broken

X

D—|—|—
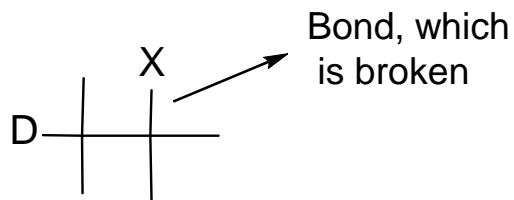
The most studied correspond to reactions S_N1

KINETIC ISOTOPE EFFECTS

The secondary kinetic isotope effect (SKIE). Examples

$k_H/k_D = 1.18$ Normal α SKIE

$k_H/k_D = 0.73$ Inverse α SKIE

$k_H/k_D = 1.15$ β SKIE
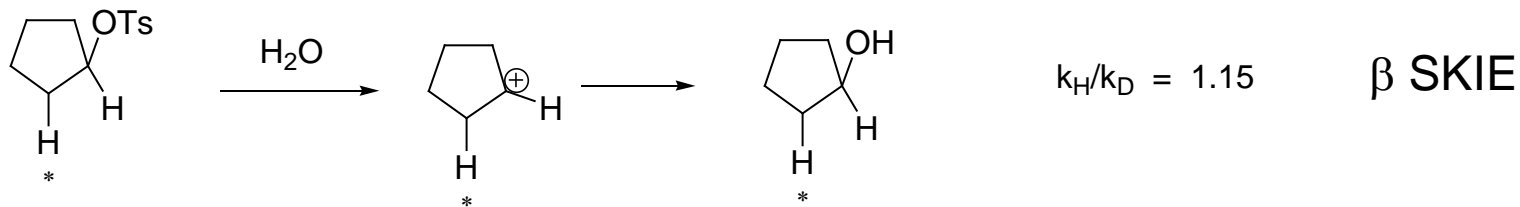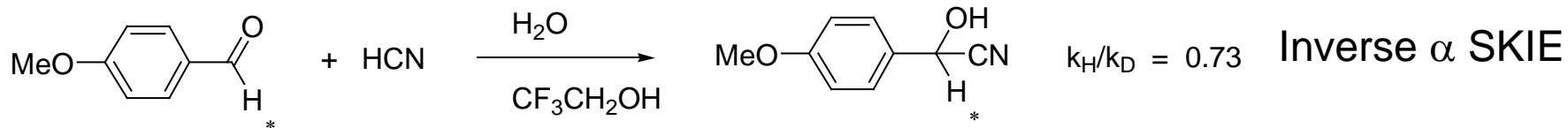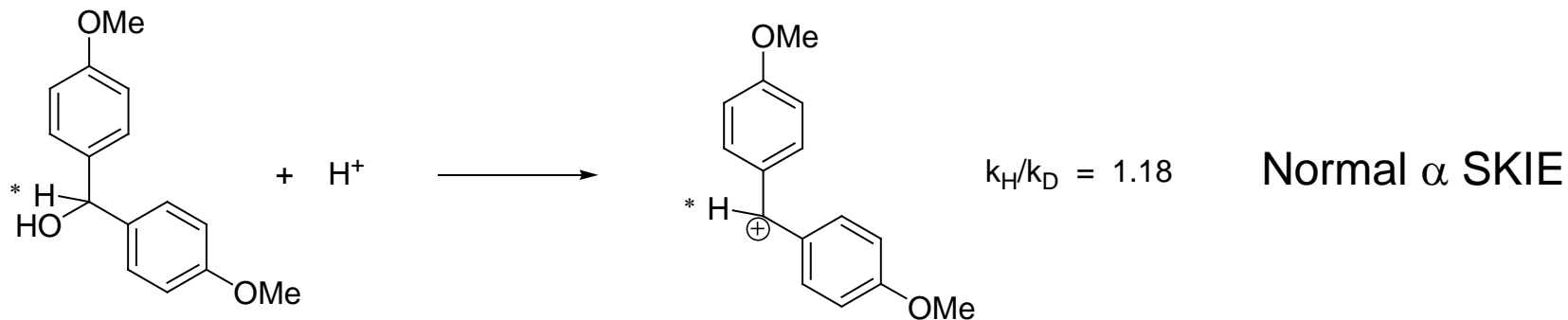
KINETIC ISOTOPE EFFECTS

Origin of the α-secondary kinetic isotope effect

Origin of α SKIE is in the changes in the frequency of vibration of the C-H or C-D bond in the transition state because of changing in the hybridization of the carbon bonded to H or D. Specifically in the out of the plane bending vibrations.

$$sp^3 \longrightarrow sp^2 \longrightarrow sp$$

$E_o(H)$
$E_o(D)$

$E_o(H)$
$E_o(D)$

α SKIE NORMAL
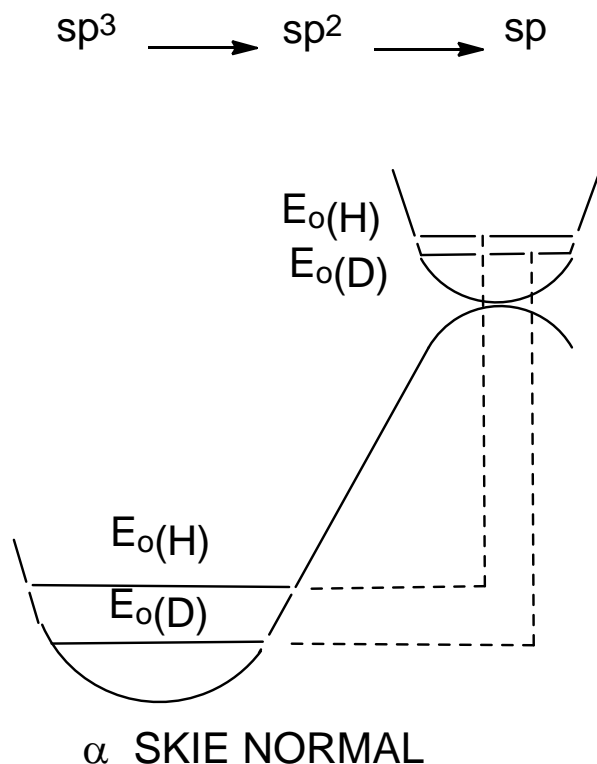
Normal: Transition from a sp^3 hybridization to sp^2 involves a decrease in the energy of the C-H and C-D bending vibrations in the TS relatively to the reactant, which is more pronounced for the C-H bond than C-D. Consequently $k_H > k_D$.

Inverse: The opposite situation takes place $k_H < k_D$.

Consider the following S_N1 reaction

starting material C_{sp3}-H	intermediate C_{sp2}-H
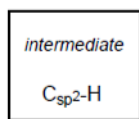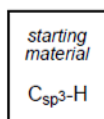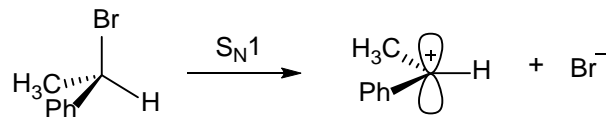
We don't know what transition-state frequency is; assume is between starting material and product.

$\nu_{stretch}$ =	2950 cm^{-1}	3050 cm^{-1}
$\nu_{in\text{-}plane\ wag}$ =	1350 cm^{-1}	1350 cm^{-1}
$\nu_{out\text{-}of\text{-}plane\ wag}$ =	1350 cm^{-1}	800 cm^{-1}

reaction coordinate

(C-Br bond breaking)   (C-O bond making)
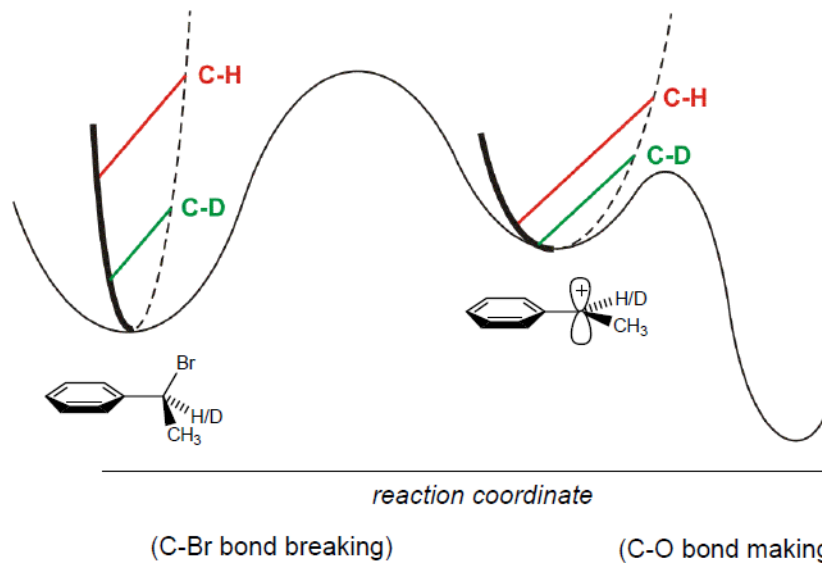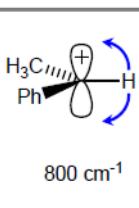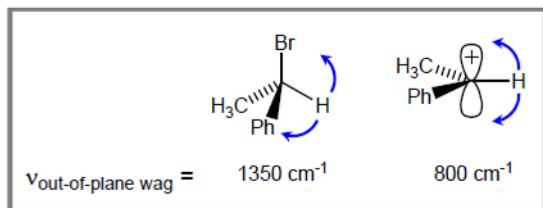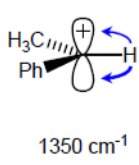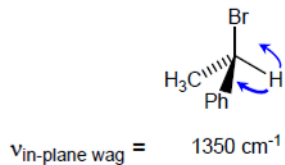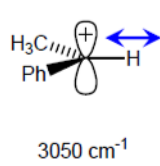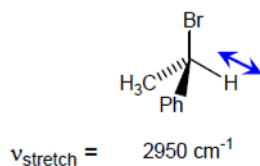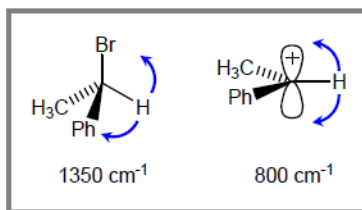
$\Delta G^{\ddagger}_H < \Delta G^{\ddagger}_D$

$k_H > k_D$

$$\frac{k_H}{k_D} > 1$$

(= 1.1 here)

> 1 because ν decreased in rate-determining step (relative to starting material)

$1350 \text{ cm}^{-1} < \nu_{wag} < 800 \text{ cm}^{-1}$

reaction coordinate

(C-Br bond breaking)   (C-O bond making)
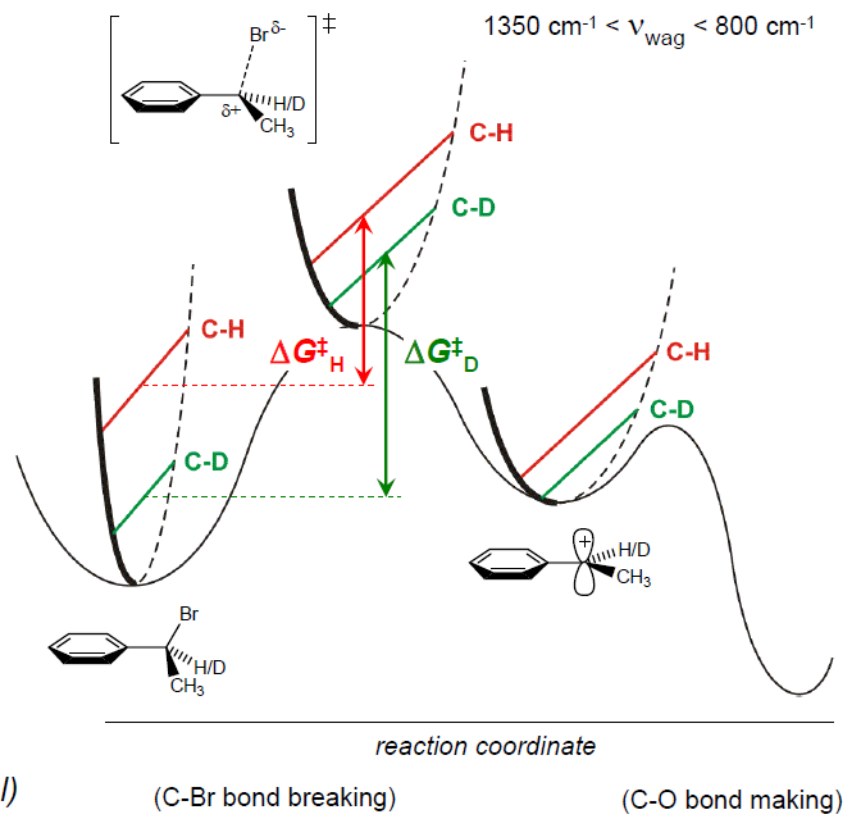
KINETIC ISOTOPE EFFECTS

$$\frac{k_H}{k_D} \text{ can also be } < 1:$$

$$\frac{k_H}{k_D} = 0.95$$
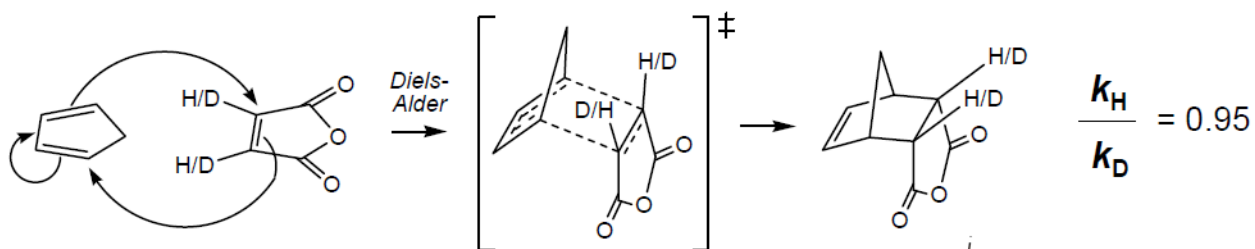
sp^2 → sp^3 hybridization at C-H/D shows opposite trend from previous example;

$$\Delta G^{\ddagger}_H > \Delta G^{\ddagger}_D$$
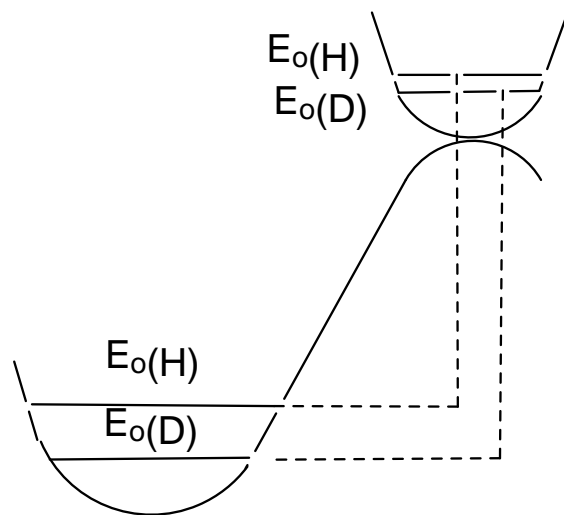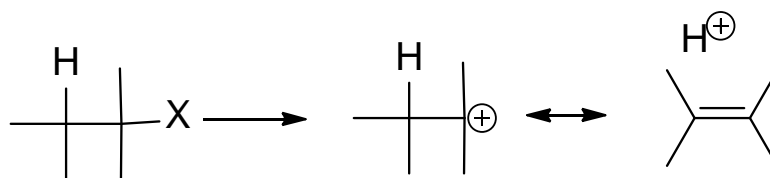
$$k_H < k_D$$

$$\frac{k_H}{k_D} < 1$$
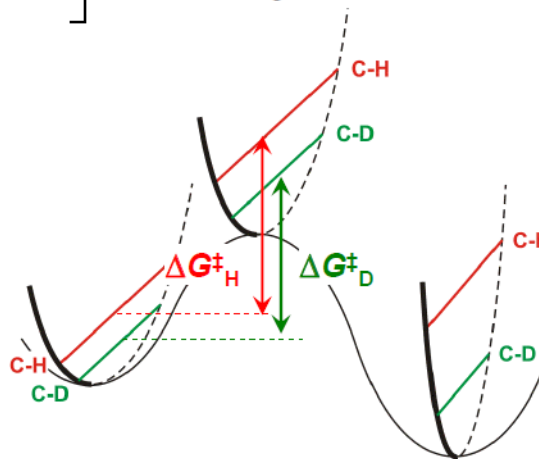
KINETIC ISOTOPE EFFECTS

Origin of the β- secondary kinetic isotope effect

β SKIE is studied in S_N1 reactions. The C-H bond (β) weakens in the transition state that leads to the intermediate carbocation. Consequently, the difference in energy at the zero point between C-H and C-D is lower in the TS than in the reactants and $k_H > k_D$
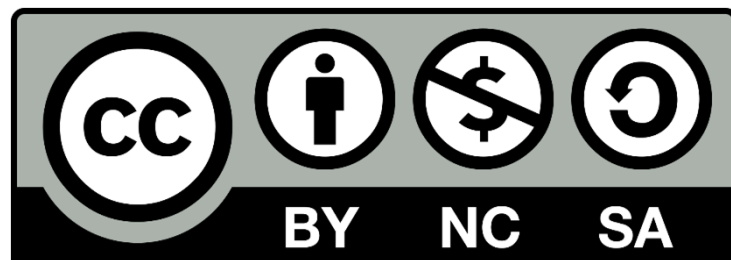

β SKIE

Este material docente ha sido elaborado en el marco de una convocatoria de ayudas para el desarrollo de proyectos de innovación educativa y mejora de la calidad docente (convocado por el Vicerectorat de Polítiques de Formació i Qualitat Educativa de la Universitat de València, en el curso 2017-2018). Código: UV-SFPIE_RMD17-725369

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