Fonctions et Réactions Organiques I
(CH-233)

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Thursday, GRB330
10h15-12h00
Q/A session: 12h15-13h00

Outline

Kinetics and Thermodynamics

Reactivities of Carbonyl group

Introduction to Organometallics

Enolate Chemistry

Introduction to Rearrangement Reaction

Kinetics and Thermodynamics

Will be discussed:

1. Definition of kinetics and thermodynamics, K and k

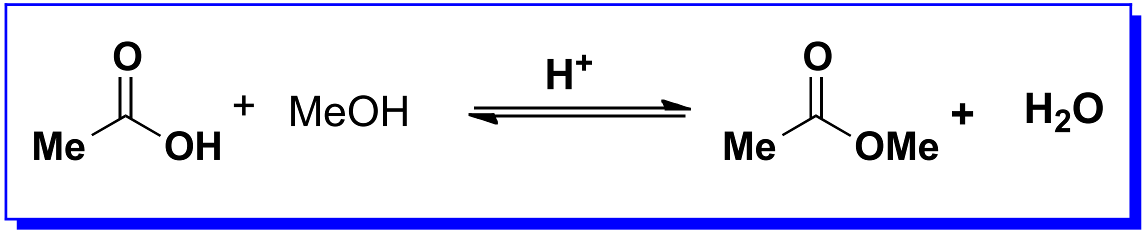
2. Kinetics
    - 2.1 Rate law, rate constant k, activation energy, Arrhenius equation
    - 2.2 Factors influence the reaction rate
    - 2.3 Collision theory
    - 2.4 Transition State theory
    - 2.5 The Hammond-Leffler Postulate
    - 2.6 The Curtin-Hammett Principle (eg. Dynamic kinetic resolution)

3. Thermodynamics
    - 3.1 Equilibrium constant, Gibbs free energy,
    - 3.2 Entropy and Enthalpy
    - 3.3 Kinetics vs Thermodynamic control (eg enolate formation)
    - 3.4 How to drive the equilibrium towards product (eg ester formation and ester hydrolysis
    - 3.5 Equilibrium constant and Temperature
    - 3.6 Irreversible reaction, production distribution and $\Delta G^{\ddagger}$

Kinetics

the word came from Greek "*kinesis*" means "*movement*"

Important parameter: Rate constant k (little k)



Kinetics study

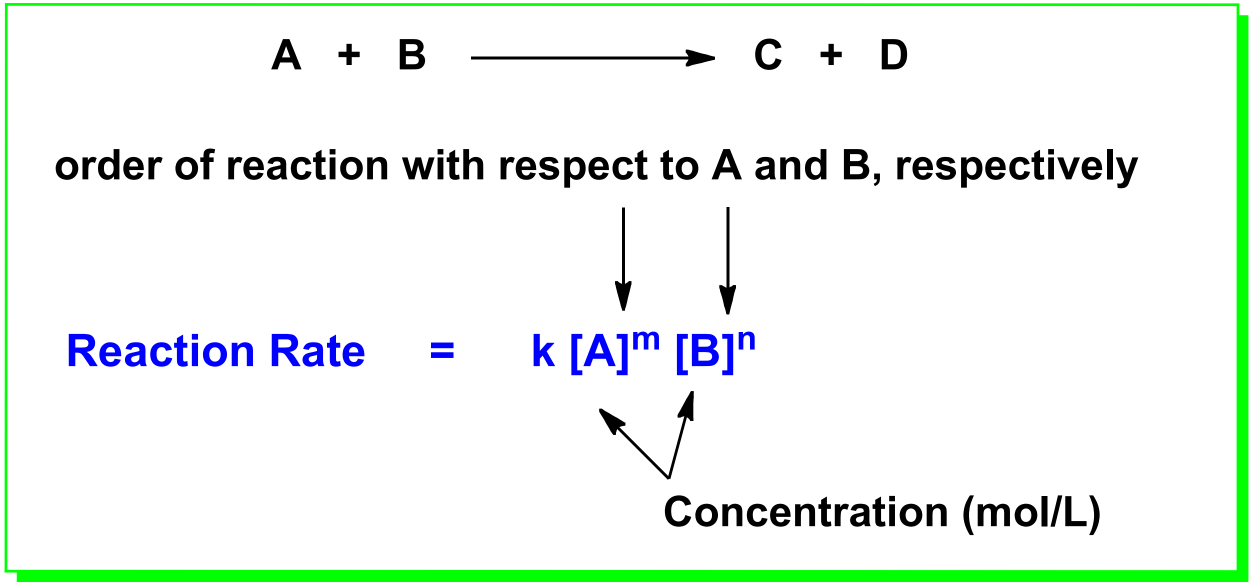
a) How fast the reaction goes
b) How the chemical bonds are re-organized (mechanism)
c) How the reaction was influenced by temperature, concentration, catalyst etc…
d) Important parameter: Rate constant k (little k)

Fundamentally: to know what happens to molecules during a chemical reaction

It tells how fast the reaction will go but doesn't tell you anything about the final composition of the reaction mixture.

Rate of Reaction: Rate Law

The speed at which reactant is transformed into product.
It is generally measured in terms of amount of reactant consumed over a period of time.



$$A + B \longrightarrow C + D$$

order of reaction with respect to A and B, respectively

$$\text{Reaction Rate} = k\,[A]^m\,[B]^n$$

Concentration (mol/L)

Note:

*** In this reaction rate expression, the order (m and n) is irrelevant to the stoichiometry of the reaction, *i.e.* irrelevant to the final equation of the reaction.**

*** Need to know the mechanism of the reaction. e.g. Rate law of S_N2 vs S_N1**

Rate Law: Where Is the Temperature Effect

$$\text{Reaction Rate} = k\,[A]^m\,[B]^n$$

In the above rate law, it seems that the reaction rate depended only on The concentration of the reactants.

Reaction rate is concentration-dependent, but how about other factors such as temperature, catalyst et al…which we know that also change the rate of reactions. Where do these parameters fit into the equations?

→ **they are integrated in the rate constant k.**

→ **The Arrhenius equation**

Arrhenius Equation

Frequency factor

$$k\,(T) = Ae^{-\frac{E_a}{RT}}$$

Activation energy (J·mo^{l-1})

Temperature (Kelvin)

rate constant
at temperature T

The gas constant = 8.314462 J·mol^{-1}·k^{-1}

Frequency factor is also called: pre-exponential factor, near constant with temperature.

Note: Both E_a and $\Delta G^{\ddagger}$ have been used as symbols for activation energy

By measuring the rate constant at different temperatures, we can work out the activation energy of the given reaction.

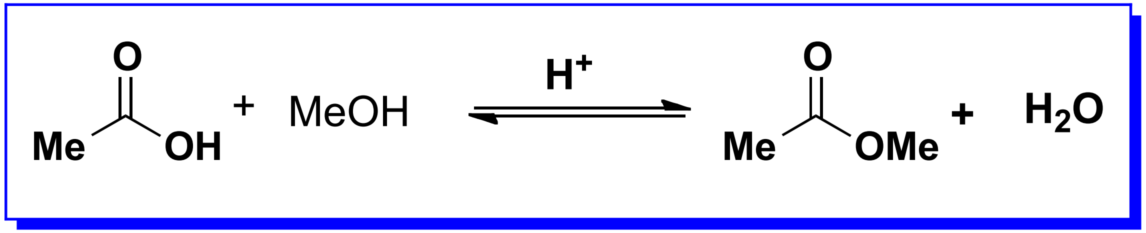
$$\frac{k_1}{k_2} = \frac{Ae^{-\frac{E_a}{RT_1}}}{Ae^{-\frac{E_a}{RT_2}}} \Longrightarrow \ln\frac{k_1}{K_2} = -\frac{E_a}{RT_1} + \frac{E_a}{RT_2} = \frac{E_a}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

Thermodynamics

* **Thermodynamics study the heat flow during physical and chemical changes.**

* **About how stable the product they are in one state *vs* another**
(Note: it is not about things moving and changing!!!)

***Important parameter: Equilibrium constant K (Capital K)**



Thermodynamics study:

a) **Energy gained or released**
b) **Relative stability of products vs starting materials**
c) **Important parameter: Equilibrium constant K (Capital K)**

$$A + \text{heat} \longrightarrow B$$ ***endothermic reaction***

$$A \longrightarrow B + \text{heat}$$ ***exothermic reaction***

Thermodynamic data have no direct correlation with reaction rate.

Equilibrium Constant and Rate Constant

Chemical equilibrium is a dynamic state. The forward and backward reactions continue just as they do when a system is away from equilibrium. However, when equilibrium has been reached, these forward and backward rates are *equal*. As a result, there is no change in the concentration of any of the species, even though the reactions are still going on. For the following reaction :

$$A + B \rightleftharpoons C + D$$

***Assuming*[a] that the rate of the forward reaction is: $k_f[A][B]$ and that of the reverse reaction is $k_r[C][D]$.**

At equilibirum, these two rates are equal, so: $k_f[A]_{eq}[B]_{eq} = k_r[C]_{eq}[D]_{eq}$.

Rearranging gives: $k_f / k_r = [C]_{eq}[D]_{eq} / [A]_{eq}[B]_{eq}$

Since $K_{eq} = [C]_{eq}[D]_{eq} / [A]_{eq}[B]_{eq}$

We conclude: $K_{eq} = k_f / k_r$

The equilibrium constant is therefore the ratio of the rate constants of the forward and backward reactions.

[a] Note that we can not write a rate law according to the balanced reaction equation.

K vs k: A Short Summary

* The equilibrium constant (capital K) depends on the overall reaction equation;
K tells you the ratio of products to reactants at equilibrium
K doesn’t include solids or pure liquids because they’re essentially-constant concentrations are already absorbed into the equilibrium constant.
K is independant of reaction mechanism.

- *Both reactants and products appear in the equation*

* Le Chatelier principle: for exothermic reactions, heat is a product; for endothermic reactions, heat is a reactant.

$\mathrm{A} + \text{heat} \longrightarrow \mathrm{B}$ *endothermic reaction*

$\mathrm{A} \longrightarrow \mathrm{B} + \text{heat}$ *exothermic reaction*

* The rate constant (k) has no dependence on the overall reaction equation but instead depends on the reaction *mechanism,* the elementary steps.

* k tells you the rate of an elementary step in the reaction mechanism.

* You can't know the rate law until you know the reaction mechanism and have identified the slowest step (Rate-limiting step).

** Only reactants appear in the rate law*.

Reaction Rate: How to Increase it?

Increasing the T (but not linear, Arrhenius equation)

At higher T, molecules moving faster and collide with higher energy, hence faster reaction (Collision theory). *Most commonly the rate goes up with temperature, but this is not always the case. For example the reaction rate for the reaction* $2NO + O2 \rightarrow 2NO_2$ *decreases with increasing temperature*.

Increasing concentration (Collision theory)

The greater of the concentration, the greater the chance for collision, the greater the chance for proper orientation, the greater the chance for effective collisions, and the higher the rate (for reaction involving gas, increase the pressure, increase the effective concentration).

The rate of an intramolecular reaction is independent of concentration.

Using catalyst

Lowing activation energy (E_a), eg Enzyme, acid, base…

Increasing surface area (for heterogeneous reaction)

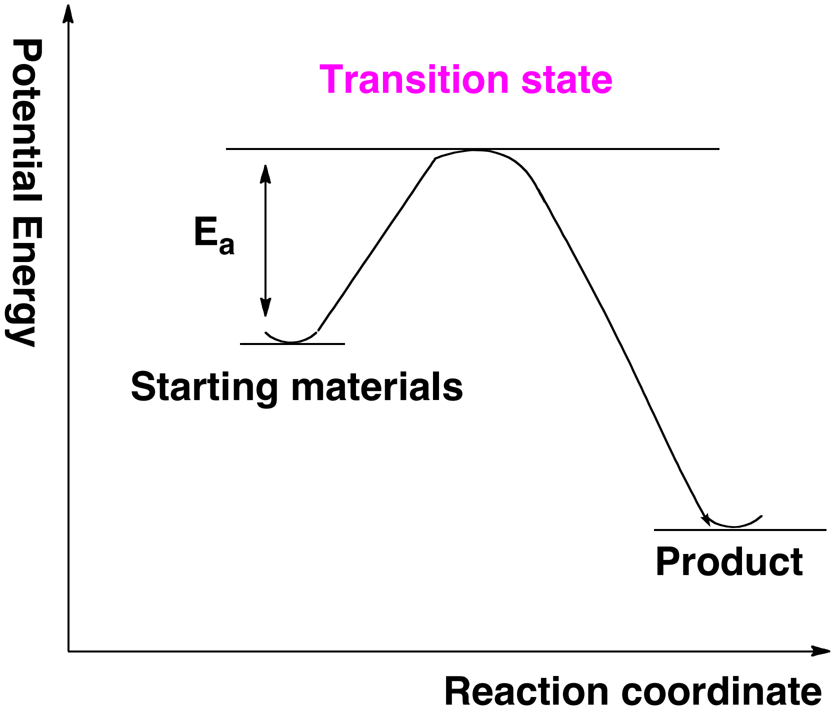
(e.g. using Nanoparticle catalyst)

Reaction Coordinate, Transition State and Activation Energy

The minimum energy pathway from reactants to products is called the *reaction coordinate*

The **transition state** exists at the potential energy maxima, and the difference in energy between this maxima and the reactants is called the *activation energy* (*E*a)

Activation energy is the miminum energy required in order for a reaction to occur.



Reaction coordinate without intermediate

The reaction coordinate is used to describe the progress of the reaction. This axis is not necessarily time, it could be a structural parameter or group of parameters, e.g., fraction of bond dissociation.

Transition State

Transition state: The state corresponding to the highest energy along the reaction coordinate. It is often marked with double dagger ‡ symbole

Transition state cannot be directly observed and cannot be isolated.

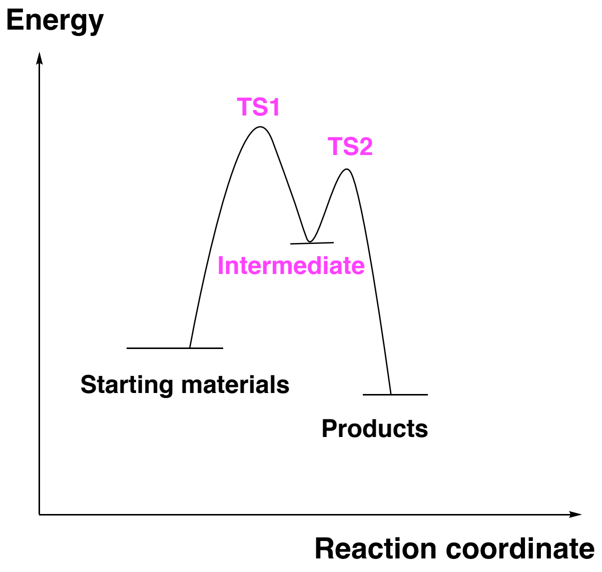
They have a fleeting existence (order of ~ 10^{-13} s).
However, techniques like Femtochemical IR spectroscopy has been developed allowing chemists to have a close look of its structure.

The transition state is an unstable transitory combination of reactant molecules that occurs at a potential energy maximum. It can either go on to form products or fall apart to return to the unchanged reactants. The energy difference between the reactants and the potential energy maximum is referred to as the *activation energy (ΔE_a or $\Delta G^‡$).*

Energy is needed to convert reactant to the transition state, so the state is a high-energy substance. The potential energy of the system increases at this point because:

a) The approaching reactant molecules must overcome the mutual repulsive forces between the outer shell electrons of their constituent atoms.
b) Atoms must be separated from each other as bonds are broken.
Remember: Breaking bond need energy, forming bond release energy.

Transition State and Intermediate



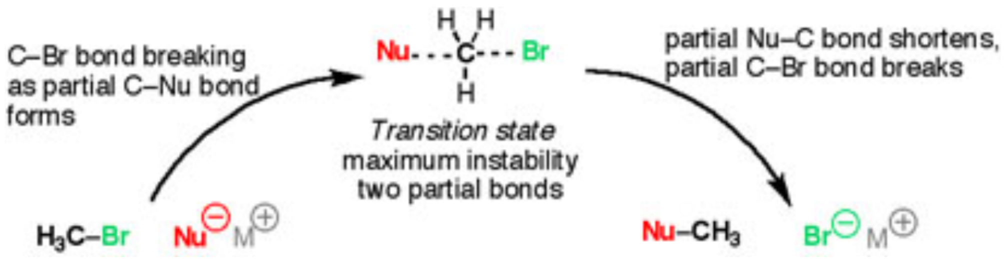
Important: distinguish the transition state from the intermediate

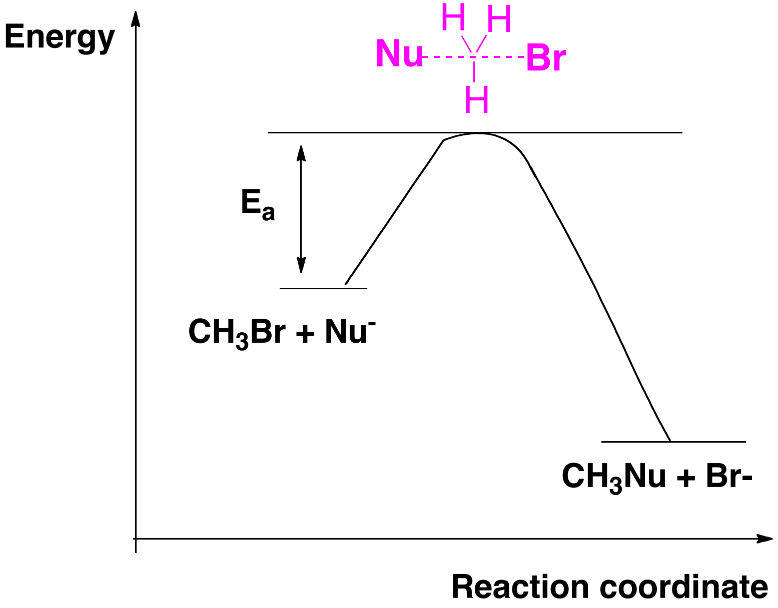
Transition state exists at a potential energy maximum

An intermediate is a molecule like any other, existing in a potential energy minimum, and detectable by conventional means; it may be highly energetic compared to reactants and products, but it is not unstable in the sense that a transition state is.

Transition states involve kinetics, intermediate species involve thermodynamics

S_N2: Reaction Coordinate, Rate law

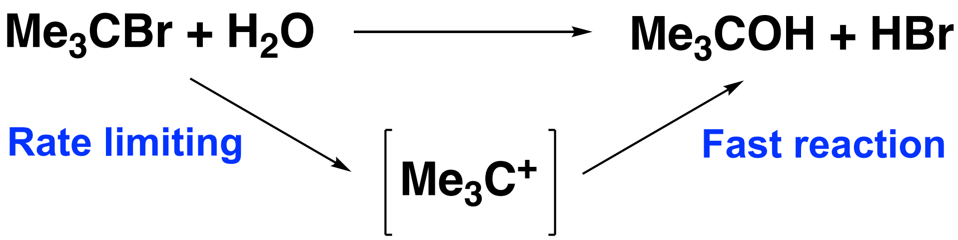




S_N2 mechanism, inversion of absolute configuration (Walden inversion)

Reaction rate = k $[CH_3Br]\ [Nu^-]$

S_N1: Reaction Coordinate, Rate law

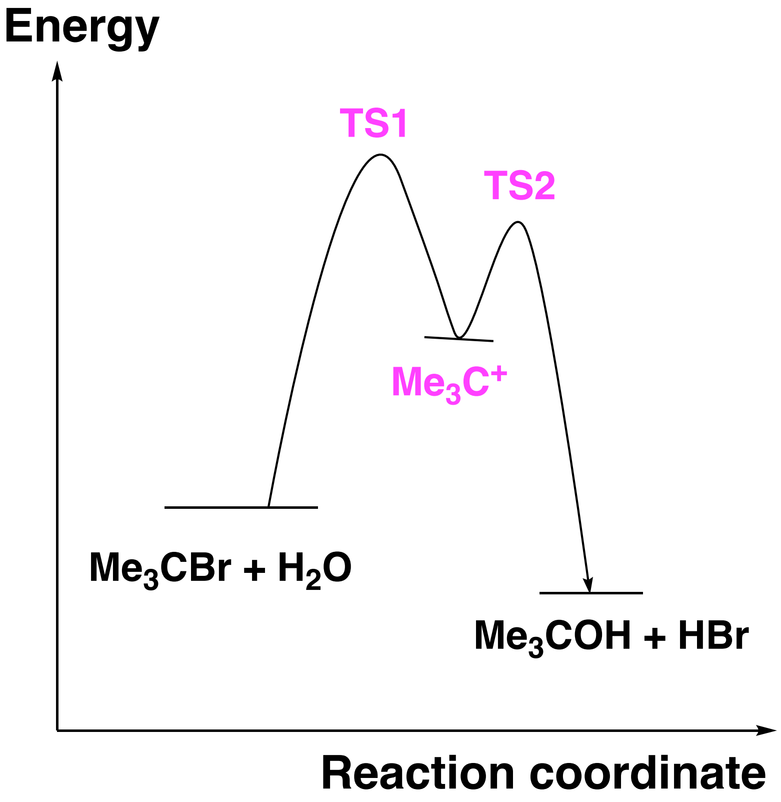


$Me_3CBr + H_2O \longrightarrow Me_3COH + HBr$

Rate limiting

$[Me_3C^+]$

Fast reaction



S_N1 mechanism

Reaction rate = k [MeC_3Br]

The Hammond Postulate (Hammond-Leffler)

Transition state cannot be isolated, so how to infer its structure:
Hammond postulate (Hammond-Leffler postulate) helps.

*** A reaction involving reactants of high energy will require relatively little change in geometry to reach the transition state compared to a reaction involving reactants of low energy.**

*** In highly exothermic reactions, the transition state should resemble the reactants (early transition state).**

*** In highly endothermic reactions, the transition state should resemble the products (late transition state).**

- **Probably more importantly: the transition states for reactions involving unstable intermediates (usually higher energy than reactants and products) can be closely approximated by the intermediates themselves. *But note: Transition states involve kinetics, intermediate species involve thermodynamics*.**

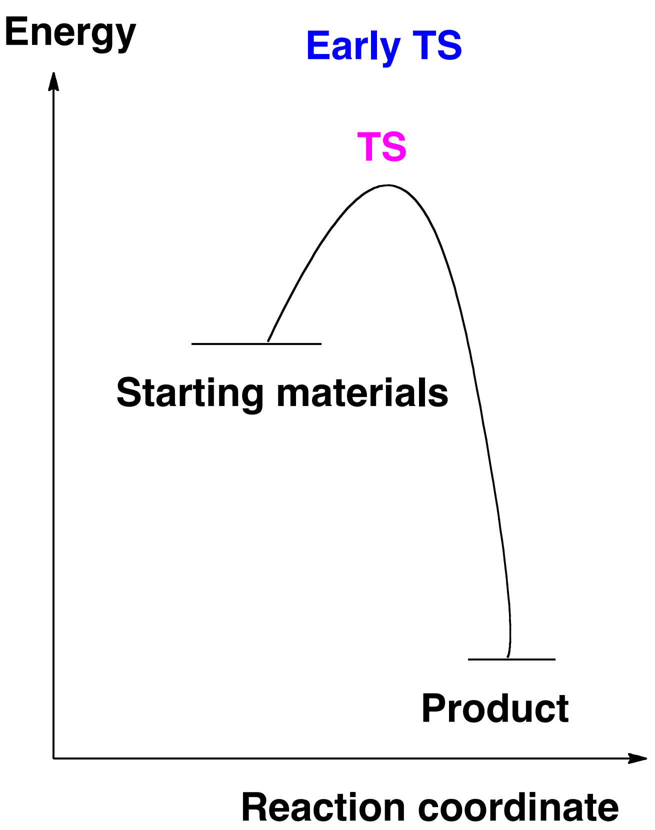
The Hammond Postulate (Hammond-Leffler)

Close in energy, close in structure

The transition state bears the greater resemblance to the
less stable species (reactant or reaction intermediate/product)

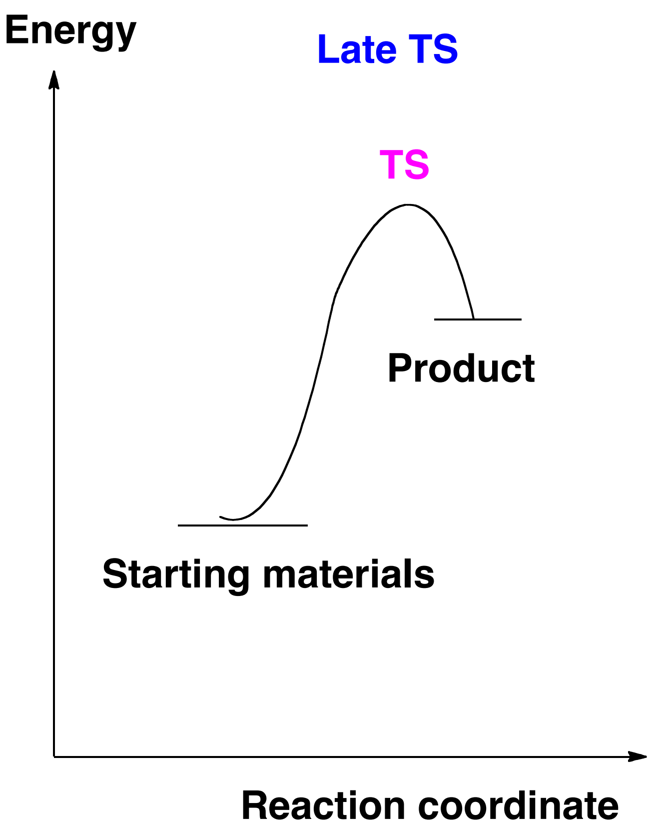
When the transition state is closer in energy to the
products rather than the starting materials, those factors
that stabilize the products will stabilize the transition state
to a greater degree

Transition States


Early TS

Exothermic reaction

The structure of TS resembles that of the starting materials

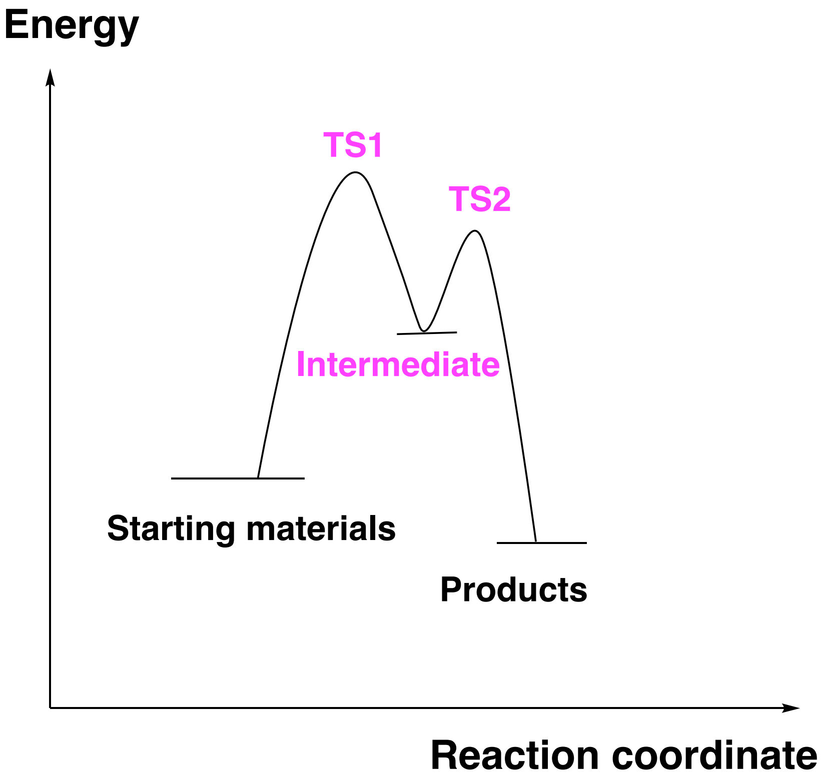

Late TS

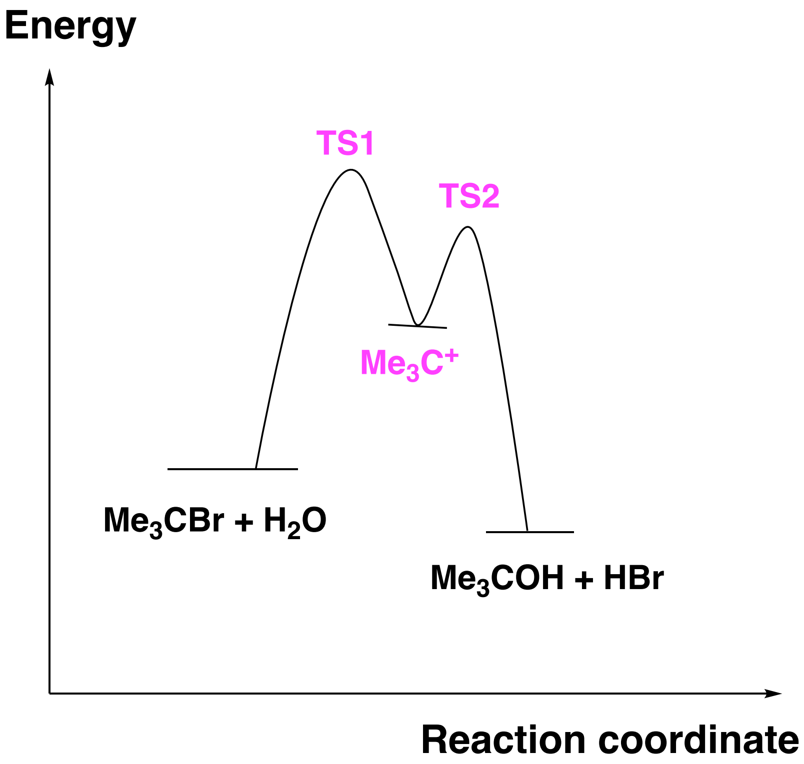
Endothermic reaction

The structure of of TS resembles that of the products

Reaction Involving Intermediate

$$\mathrm{Me_3CBr + H_2O \xrightarrow{S_N1\ mechanism} Me_3COH + HBr}$$





The structure of both TS1 and TS2 resembles that of intermediate

Carbocation is unstable high energy species. Hence, according to Hammond-Leffler Postulate, the transition state should structurally resemble the carbocation. Anything capable of stabilizing the cation will stabilize the TS, hence lowering The E_a and increase the reaction rate.

The Curtin-Hammett Principle

$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} P_B$$

Two limiting cases:

a) Kinetic quench: **The rate of reaction is *faster* than the rate of conformational interconversion: $k_1, k_2 > k_A, k_B$**

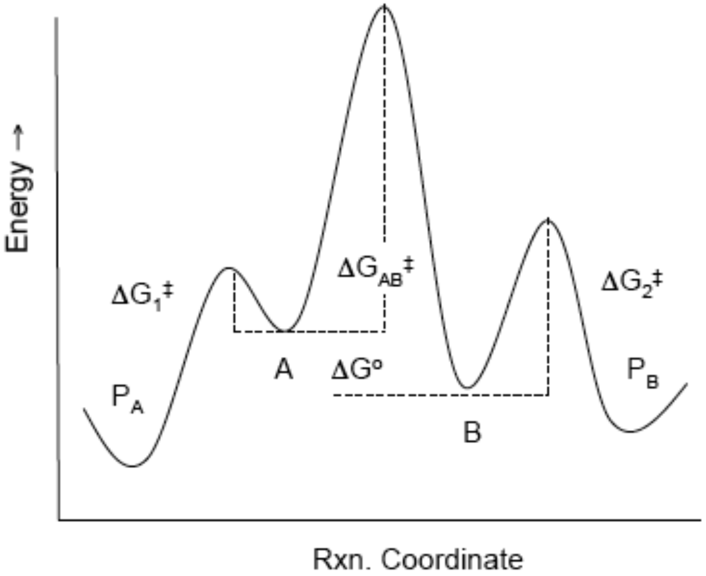
b) Curtin-Hammett scenario: **The rate of reaction is *slower* than the rate of conformational interconversion: $k_1, k_2 < k_A, k_B$**

The Curtin–Hammett principle states that, for a reaction that has a pair of reactive intermediates or reactants *that interconvert rapidly* (as is usually the case for conformers), each going irreversibly to a different product, the product ratio will depend on the difference in the free energy of the transition state going to each product, and not (or not solely) on the equilibrium constant between the intermediates

Kinetic Quench

$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} P_B$$

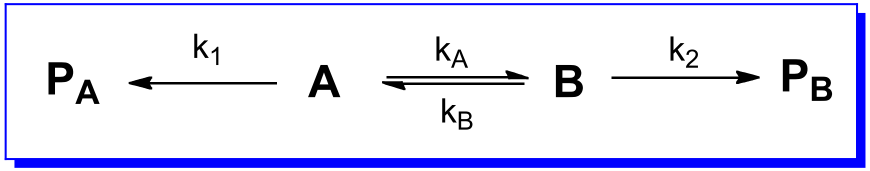
Case 1 Kinetic quench: **The rate of reaction is faster than the rate of conformational interconversion: $k_1, k_2 > k_A, k_B$**



A and B can not equilibrate during the course of the reaction, and the product ratio (P_A/P_B) will reflect the initial composition of two conformers and depend solely on the initial ratio of two conformers

$P_A/P_B = [A]/[B]$

The Curtin-Hammett Principle



$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} P_B$$

Three Curtin-Hammett Scenarios (k_1, k_2 < k_A, k_B):

a) **If both conformers react *at the same rate*, the product distribution will be the same as the ratio of conformers at equilibrium.**

a) **If the *major conformer* is also the faster reacting conformer, the product from the major conformer should prevail, and will not reflect the equilibrium distribution.**

b) **If the *minor conformer* is the faster reacting conformer, the product ratio will depend on all three variables, and the observed product distribution will not reflect the equilibrium distribution.**

***You can potentially isolate a product which is derived from a conformer you cannot observe in the ground state*.**

The Curtin-Hammett Principle

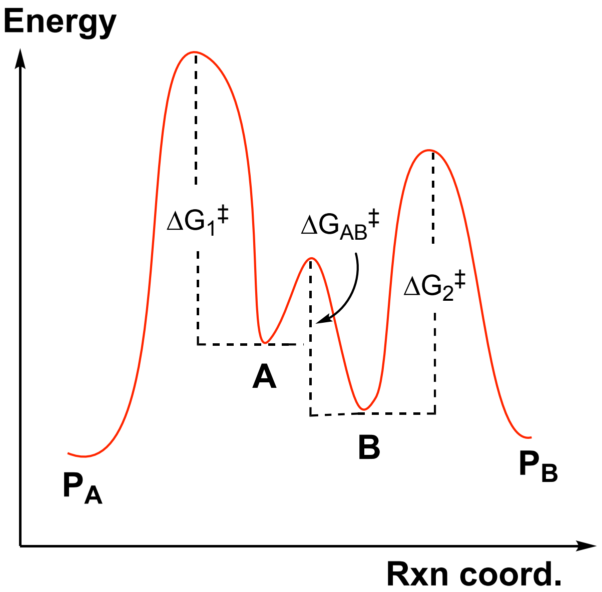
$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} P_B$$

Three Curtin-Hammett Scenarios (k_1, k_2 < k_A, k_B):

a) **If both conformers react *at the same rate*, the product distribution will be the same as the ratio of conformers at equilibrium.**

$$\Delta G_1^{\ddagger} = \Delta G_2^{\ddagger}$$

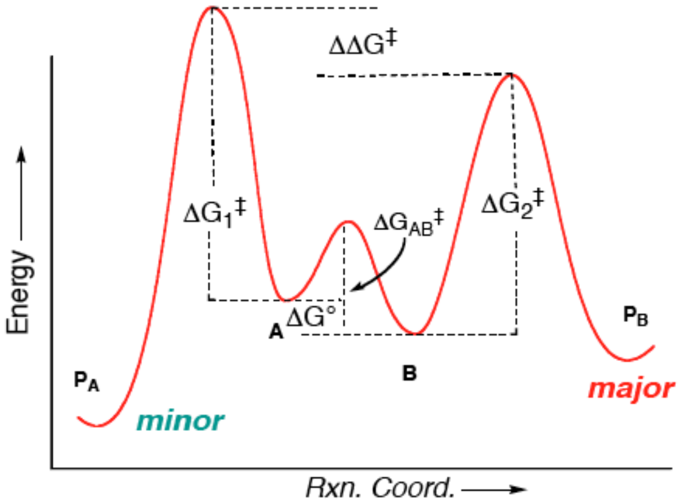
$$P_A/P_B = [A]/[B]$$



The Curtin-Hammett Principle

$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} P_B$$

Curtin-Hammett conditions: $k_1, k_2 << k_A, k_B$



$$\frac{d[P_A]}{dt} = k_1[A] \quad \text{and} \quad \frac{d[P_B]}{dt} = k_2[B]$$

$$\therefore \frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]} \qquad d[P_B] = \frac{k_2[B]}{k_1[A]} d[P_A]$$

$$\int d[P_B] = \frac{k_2[B]}{k_1[A]} \int d[P_A]$$

$$\therefore \frac{[P_B]}{[P_A]} = \frac{k_2[B]}{k_1[A]} = \frac{k_2}{k_1} K_e$$

$$\because k_2 > k_1; \quad Ke > 1$$

$$\therefore \quad P_B\text{: Major Product}$$

B is a more stable conformer, leads to major product P_B.

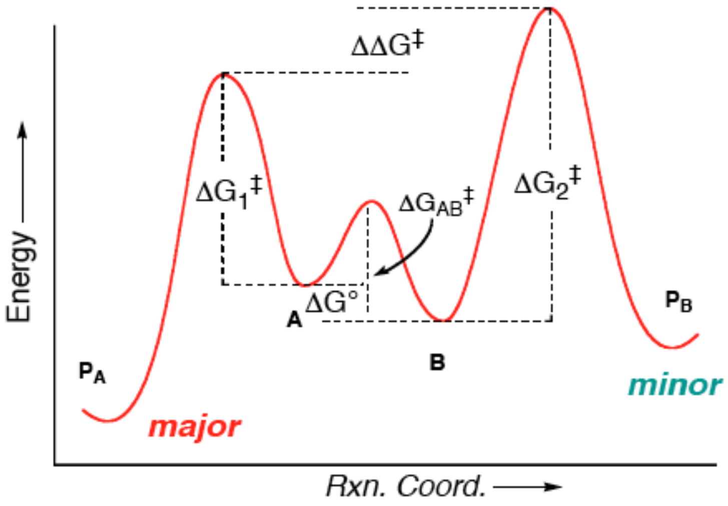
$\Delta G_2^\ddagger < \Delta G_1^\ddagger$, P_B is kinetic product.

Since there is no equilibrium possible between P_A and P_B, P_B is the major product, although it is thermodynamically less stable than P_A

The Curtin-Hammett Principle

$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} P_B$$

Curtin-Hammett conditions: **The rate of reaction is slower than the rate of conformational interconversion: $k_1, k_2 << k_A, k_B$**

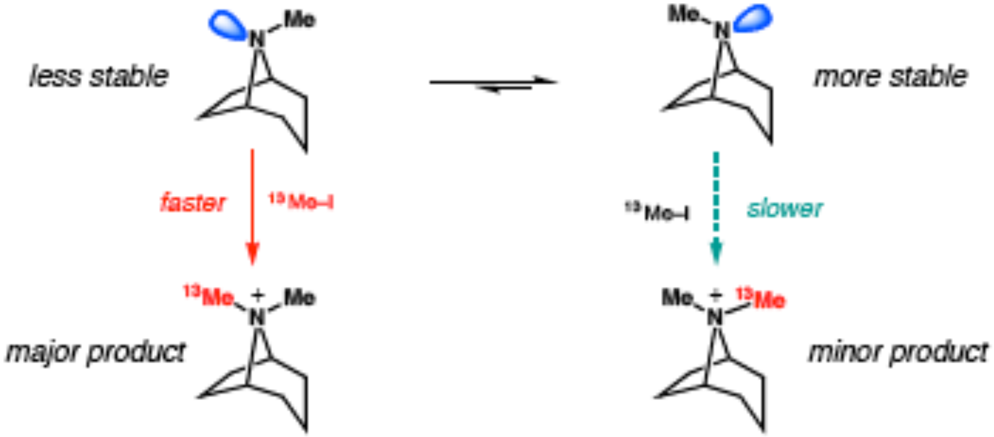


A is a less stable conformer, leads to Major product P_A.
$\Delta G_1^‡ < \Delta G_2^‡$, P_A is kinetic product. P_A is also thermodynamically more stable than P_B. The product ratio depend on k_1, k_2 and K_e.

$$\frac{[P_B]}{[P_A]} = \frac{k_2[B]}{k_1[A]} = \frac{k_2}{k_1} K_e$$

When A and B are in rapid equilibrium, we must consider the rates of reaction of the conformers as well as the equilibrium constant when analyzing the product ratio.

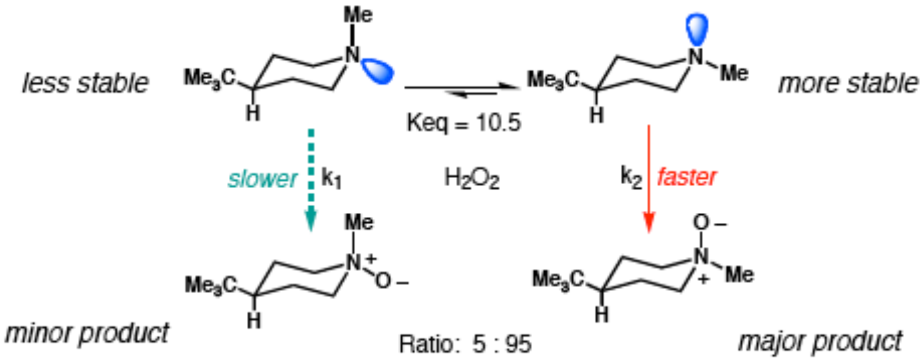
The Curtin-Hammett Principle: Examples



The less stable conformer reacts much faster than the more stable conformer, resulting in an unexpected major product!

Draw the reaction coordinate diagram of these two reactions

Oxidation of piperidines:



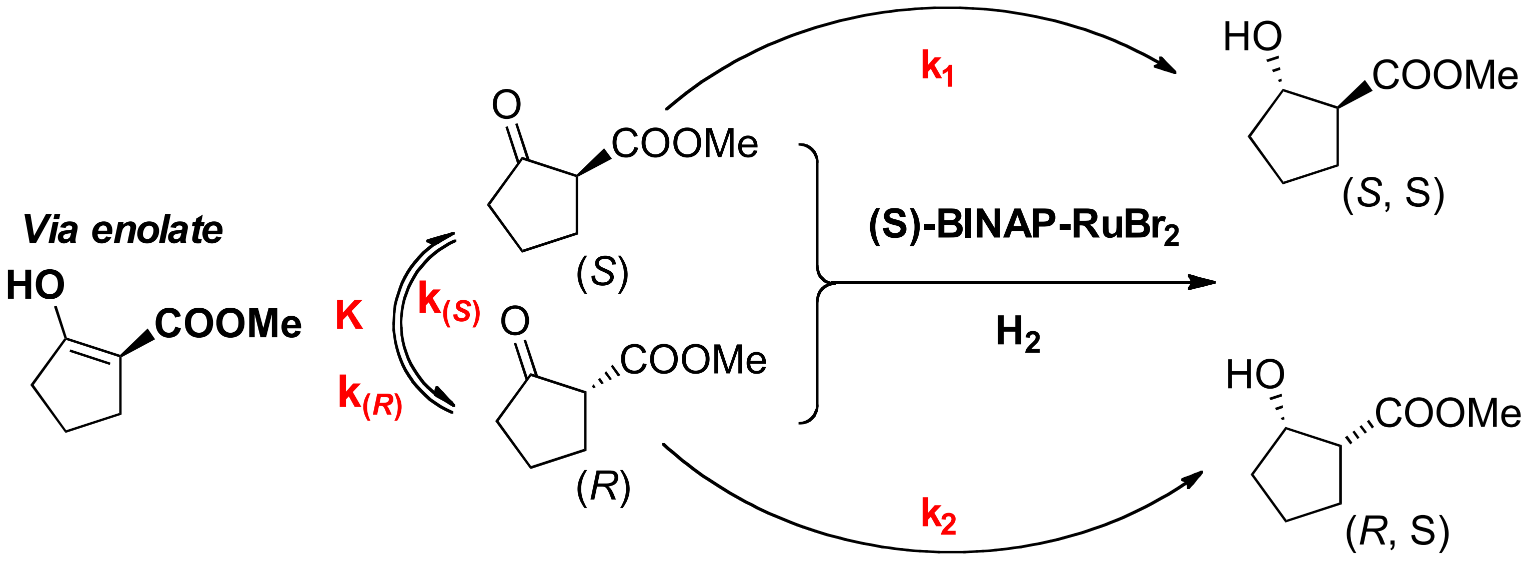
When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

Note that in this case, the more stable conformer is also the faster reacting conformer!

$$\frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq}$$

$$\frac{k_2}{k_1} = 1.8$$

The Curtin-Hammett Principle: Dynamic Kinetic Resolution



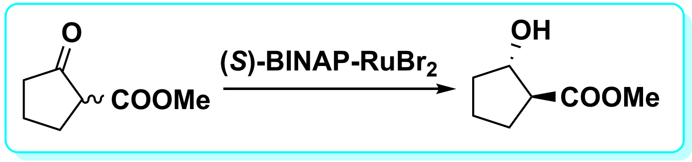
(*S*) to (*S*, *S*) **OK**
(*R*) to (*S*, *S*) **How?, need to be converted first to (*S*)-enantiomer**

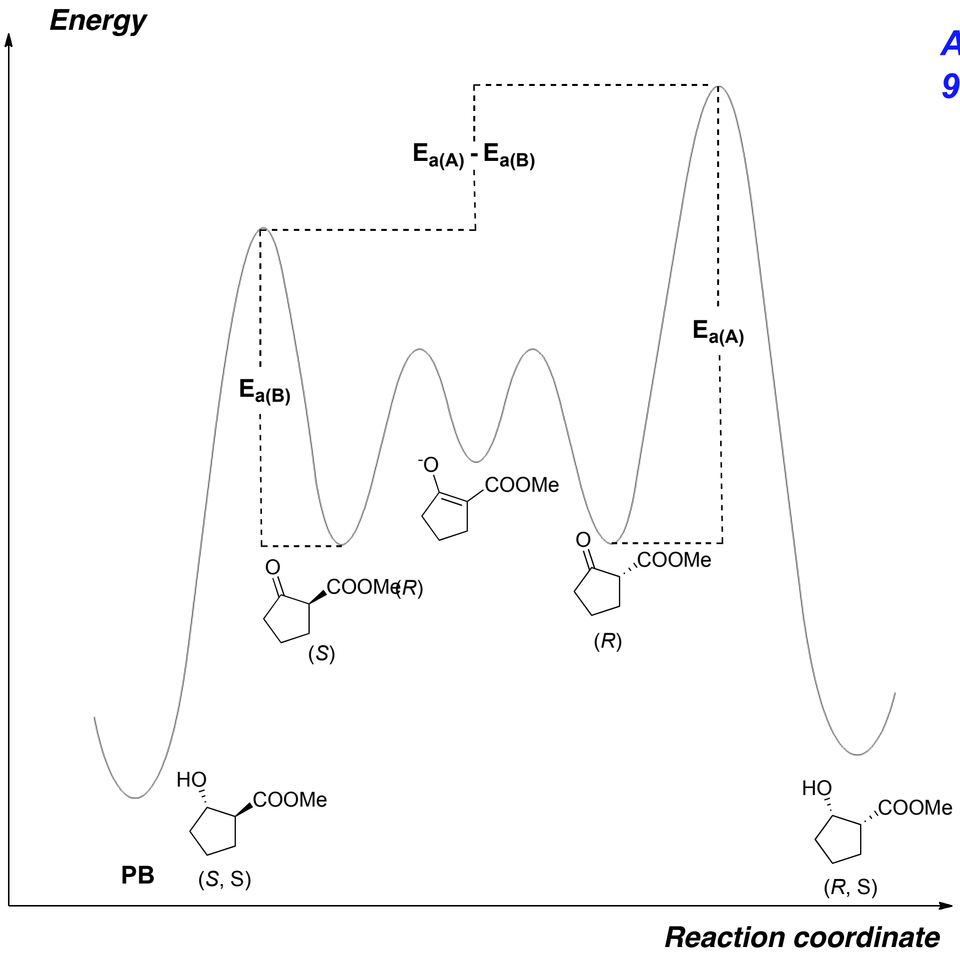
To obtain high yield and high enantio- and diastereoselectivity:

a) hydrogenolysis of (*S*)-enantiomer (k_1) should be faster than that of the (*R*)-enantiomer (k_2).
b) equilibrium between two enantiomers should be much faster than hydrogenolysis.

$k_{(S)}, k_{(R)} >> k_1 > k_2$

Energy Diagram of Dynamic Kinetic Resolution





Assuming enantiomeric excess of this reaction is 99/1 at 25 ° C, i.e. PB/PA = 99/1, calculate the ΔE_a

$P_B/P_A = (k_B/k_A)\ K_{eq}$

$K_{eq} = 1$ (for two enantiomers)

$k_B/k_A = P_B/P_A = 99$

$$\frac{Ae^{-Ea(B)/RT}}{Ae^{-Ea(A)/RT}} = 99$$

$$\frac{E_{a(A)}}{RT} - \frac{E_{(B)}}{RT} = \ln 99$$

$E_{a(A)}\text{-}E_{(B)} = RT \ln 99 = 2.7$ kcal/mol

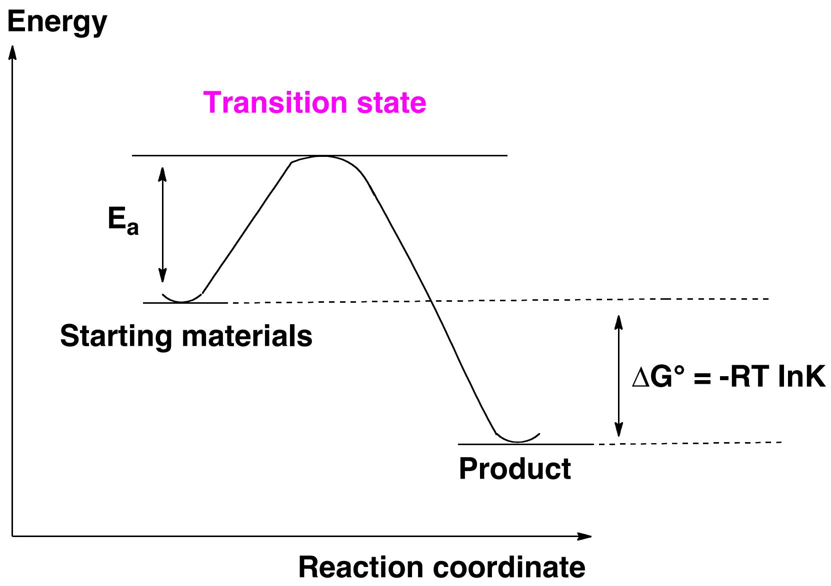
The Curtin-Hammett Principle:

The product ratio is not solely dependent on relative proportions of the conformational isomers in the substrate

Never assume that the most stable conformation of a compound is the most reactive. It may be, but it may not be.

Conversely, never assume that the less sable conformer is the most reactive. It may be, but then again, it may not be

Thermodynamics: Equilibrium Constant



Gibbs free energy: $\Delta G°$

$\Delta G° = \Delta H - T\Delta S$
ΔH: Enthalpy change
ΔS: Entropy change

$\Delta G° = \sum \Delta G_{products} - \sum \Delta G_{reactants}$

If $\Delta G° < 0$, products will be favored at equilibrium. Reaction is exergonic.

If $\Delta G° > 0$, reactants will be favored at equilibrium. Reaction is endogonic.

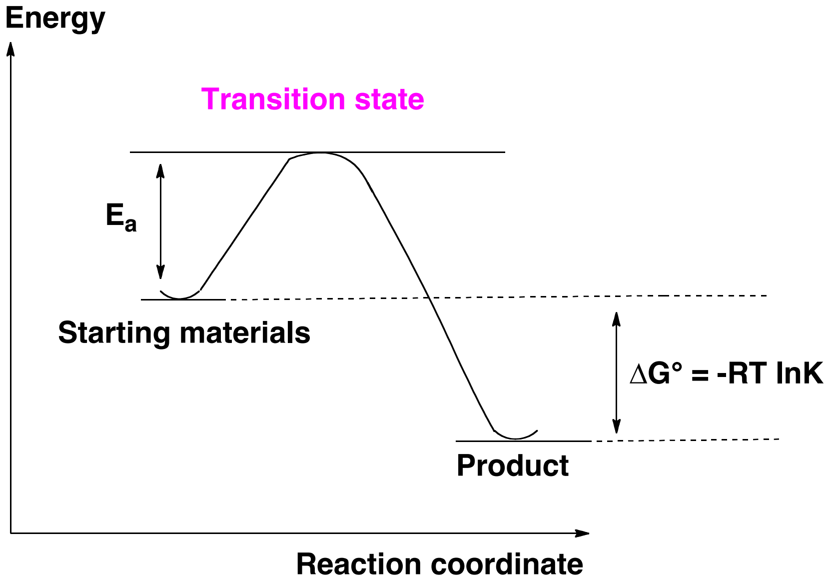
If $\Delta G°$ is zero, $K_e = 1$.

Thermodynamics is not about things moving and changing but instead about how stable they are in one state versus another

The equilibrium constant (capital K), is a thermodynamic quantity. It depends *only* on the overall reaction.

Endothermic/exothermic: only ΔH is considered.
Endergonic/exergonic: $\Delta G°$ is concerned (both enthalpy and entropy factors).

Thermodynamics: Equilibrium Constant



$\Delta G^\circ = \Delta H - T\Delta S$
ΔH: Enthalpy change
ΔS: Entropy change

As K is exponential to ΔG° , A small change in ΔG° makes a big difference in K, hence the product distribution.

ΔG° (kJ/mol)	Keq	% of more stable state at equilibrium (T = 298 K)
0	1.0	50
1	1.5	60
2	2.2	69
3	3.5	77
4	5.0	83
5	7.5	88
10	57	98
15	430	99.8
20	3200	99.97
50	580 000 000	99.9999998

Applying ΔG° = - RTlnK, knowing K, one found ΔG; knowing ΔG, one found K.

Equilibrium Constant (K) and Temperature

$$\Delta G = -RT\ln K = \Delta H - T\Delta S,\ \text{hence: } \ln K = \Delta H - T\Delta S/(-RT) = \frac{-\Delta H}{RT} + \frac{\Delta S}{R}$$

For endothermic reaction, $\Delta H\ [\sum\Delta H(_{\text{bonds broken in Reactants})}-\Delta H_{\text{(bonds made in Products)}}]$ is positive, increase T, increase K, increase product formation. This can also be understand according to Le Chaterlier's Principle:

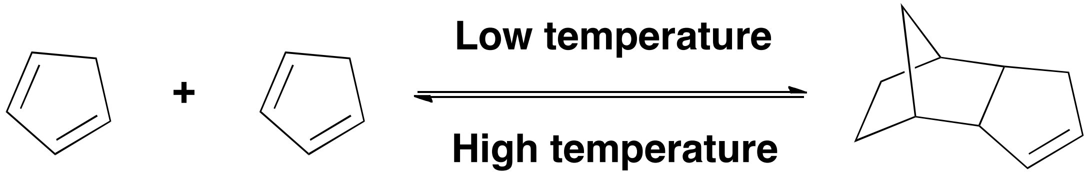
$$A + \text{heat} \longrightarrow B$$ ***endothermic reaction***

$$A \longrightarrow B + \text{heat}$$ ***exothermic reaction***

In endothermic reaction, increase T, push the reaction towards the right (product).

In exothermic reaction, increase T, push the reaction towards left (SM). The enthalpy term alone determine how K varies with temperature.

Example of making reaction reversible on heating



Enthalpy

Break chemical bonds: Need to supply energy
Creat chemical bond: Release energy
Therefore, the change in enthalpy of any chemical reactions in terms of bond energies is given by: ΔH^0 = Bond energies of reactants - Bond energies of products

$$\boxed{2\,H_2O \longrightarrow 2\,H_2 + O_2}$$

Energy required to break 4 O-H bonds = 4 x 460 kJ/mol = 1840 kJ/mol

Energy released to form 2 H-H bonds = 2 x 436.4 kJ/mol = 872.8 kJ/mol
Energy released to form 1 O=O bond = 1 x 498.7 kJ/mil = 498.7 kJ/mol

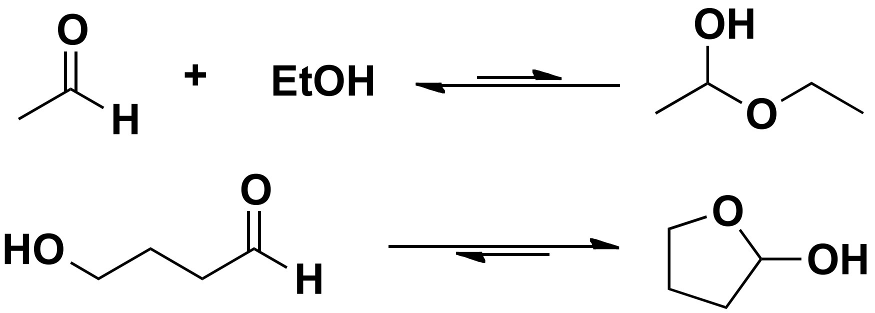
Total input energy = 1840 kJ/mol
Total output (released) energy = 872.8 kJ/mol + 498.7 kJ/mol = 1371.5 kJ/mol

ΔH^0 = Bond energies of reactants - Bond energies of products
= 1840 kJ/mol -1371.5 kJ/mol = 468.5 kJ/mol
The reaction is endothermic $\Delta H^0 > 0$
it means that 469 kJ of heat need to be supplied in order to carry out this reaction.

Reminder: The *Bond Energy* is the amount of energy (enthalpy) required to break or form a bond in 1 mole of gaseous molecules, which is expressed as kJ/mol.

Entropy vs Enthalpy

Enthalpy change depends on the bond broken and bond formed and is inherent to a given reaction
Entropy can became a dominant factor when dealing with two similar reactions: one intermolecular and the other intramolecular.



eq 1

eq 2

The hemi-acetal formation in both equation has similar enthalpy changes. However, eq 1 has tendance to go to the left side, while eq 2 moves more to the left, so why?

Both reaction loose entropy, however, the bimolecular reaction (eq 1) loose more entropy than the intramolecular one shown in eq 2).

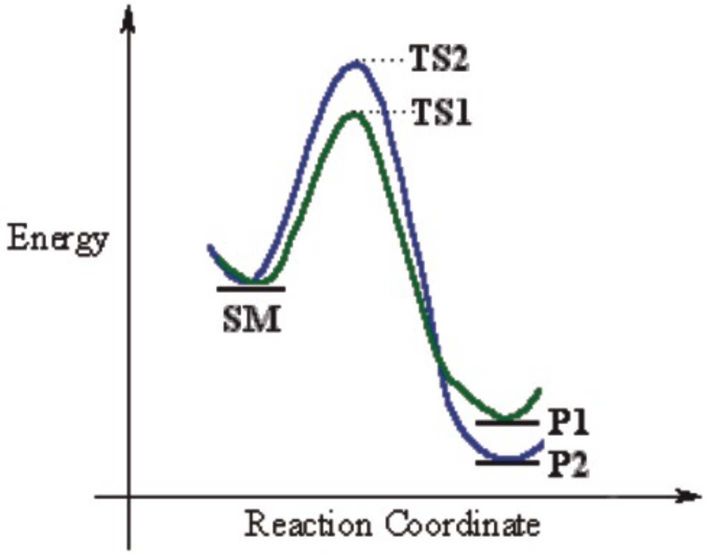
Note: 5- and 6-membered rings are always easy to form. However, macrocyclization is difficult to realize although intramolecular, due to the significant lose of entropy.

Kinetic and Thermodynamic Control

The potential outcome of a reaction is usually influenced by two factors:

a) the relative stability of the products (*i.e. thermodynamic factors)*

b) the rate of product formation (*i.e. kinetic factors)*



Consider the case where a starting material, SM, can react to give two different products, P1 and P2 via different pathways (represented by green and blue lines).

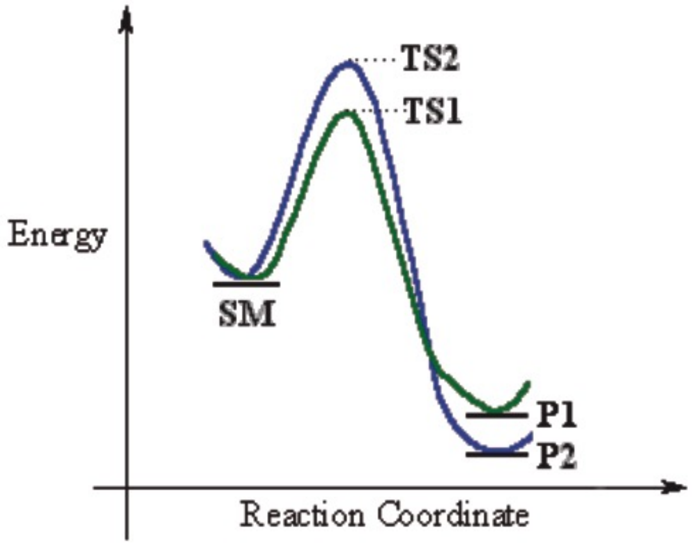
Reaction 1 via pathway 1 (green) generates P1.

This will be the *faster reaction* since it has a more stable transition state, TS1, and therefore a lower activation barrier. So P1 is the kinetic product.

Reaction 2 via pathway 2 (blue) generates P2.

P2 is the more stable product since it is at lower energy than P1. So P2 is the thermodynamic product.

Kinetic and Thermodynamic Control



Now consider what happens as we alter the reaction temperature and therefore the *average* energy of the molecules changes.

1. At low temperature, the reaction preferentially proceeds along the green path to P1 and stops since they lack sufficient energy to reverse to SM, *i.e. it is irreversible*, so the product ratio of the reaction is dictated by *the rates of formation of* P1 and P2, k_1: k_2.

2. At some slightly higher temperature, reaction 1 will become reversible while reaction 2 remains irreversible. So although P1 may form initially, over time it will revert to SM and react to give the more stable P2.

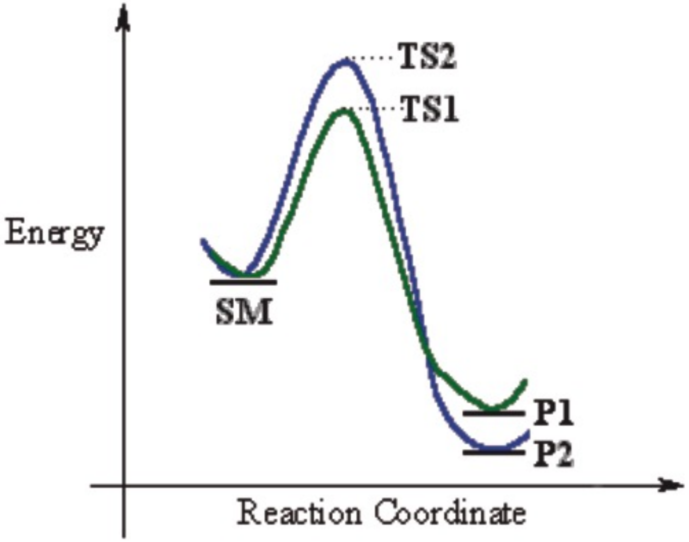
3. At high temperature, both reaction 1 and 2 are reversible and the product ratio of the reaction is dictated by the *equilibrium constants for* P1 and P2, $K_1 : K_2$ which is in turn depend on the $\Delta G°_{(P1-SM)}$ and $\Delta G°_{(P2-SM)}$.

Kinetic and Thermodynamic Control

Summary

At low temperature, the reaction is under kinetic control (rate, irreversible conditions) and the major product is that from fastest reaction (lower E_a or $\Delta G^{\ddagger}$).

At high temperature, the reaction is under thermodynamic control (equilibrium, reversible conditions) and the major product is the more stable system.



In the lab: When two potentially interchangable products are produced, How to know if the observed selectivity is under kinetic or thermodynamic control (by a simple experiment)?

Answer: isolate each products and resubmit them separately to the reaction conditions and check if they isomerize.
Kinetic selectivity: depending on the $\Delta G^{\ddagger}$ of each reaction pathway.
Thermodynamic selectivity: depending on the ΔG^0 of each product.

Thermodynamically Favorable but Kinetically Unfavorable

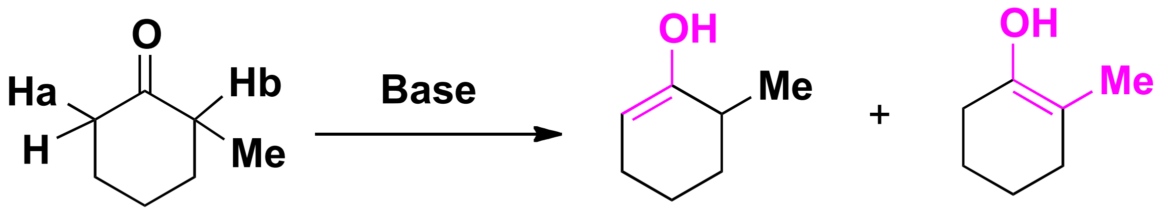
Graphite and diamond are both forms of carbon, but graphite has a lower free energy. Therefore, diamond wants to convert into graphite (nature always tries to get things as stable as they can be). However, it doesn't seem to occur ("Graphite is forever" is in fact more correct in thermodynamic term than "diamond is forever").

So even though the conversion of diamond to graphite is thermodynamically favorable, it is slow (and actually never occur, difficult to break all the C-C bonds of diamond and re-form them in a different, more stable graphite Configuration). The activation energy is too high !

(Conversely, it would be even more difficult to convert graphite to diamond…)

Therefore, even though the reaction *should go thermodynamically*, it does not because it is *kinetically* unfavorable.

Kinetic and Thermodynamic Control: Enolate Formation



	Enolate A	Enolate B
Base = LDA	99%	1%
Base = Et_3N	22%	78%

A is a kinetic product since Ha is more acidic than Hb, and is less hindered. B is thermodynamically more stable than A as the double bond in B is more substituted than in A.

LDA being a strong base, it abstracts the least hindered hydrogen with greater ease, hence forming enolate A which is the Kinetic Product of the reaction.

Triethylamine being a weak base, it abstracts the alpha-hydrogen on the less hindered side, but need higher temperature. the reaction is reversible. Thus there will be an equilibrium between the reactants and products and thermodynamically more stable enolate B will be produced predominantly.

Formation of enolate is essentially non-reversible with LDA, but reversible with Et_3N, why? (Using your knowledge of acid-base reaction)

Getting Selectivity For either Kinetic or Thermodynamic Product

Kinetic products are in general, more easily formed than thermodynamic products due to the lower energetics required. To form a thermodynamic product, you will have to supply enough energy to the system which is greater than that for the kinetic product, you will always get some of the kinetic product in the reaction.
But there are some tricks you could use while doing these reactions

To Get Kinetic Product (using enolate formation shown in previous slide as an example):
A kinetic product is favored under non-equilibrium conditions.
1. Shortening the reaction time – this will ensure that there is not enough time for a reversible reaction to occur to lead to the formation of more stable thermodynamic product.
2. Using highly reactive reagents (stronger base in this case) – This will ensure that the process is not reversible at the intermediate step.
3. Doing the reaction at lower temperatures – that way you do not provide more energy to cross the E_A of the thermodynamic product.
4. Using of Bulky reagent (hindered base in this case) - This point refers to the above example of 2-methylcyclohexanone where abstraction of less hindered and more acidic proton would result in formation of kinetic product. Therefore, if we use a bulky base, the more hindered proton would not be readily taken up by the base, thus favoring the kinetic enolate.

Getting Selectivity For either Kinetic or Thermodynamic product

To Get Thermodynamic Product:

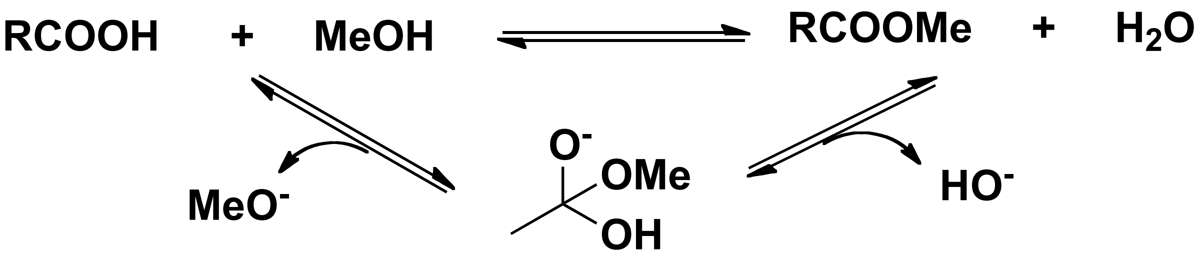
In order to get thermodynamic control, you need conditions of reversibility at some stage of the reaction. If that exists then you can try the following:

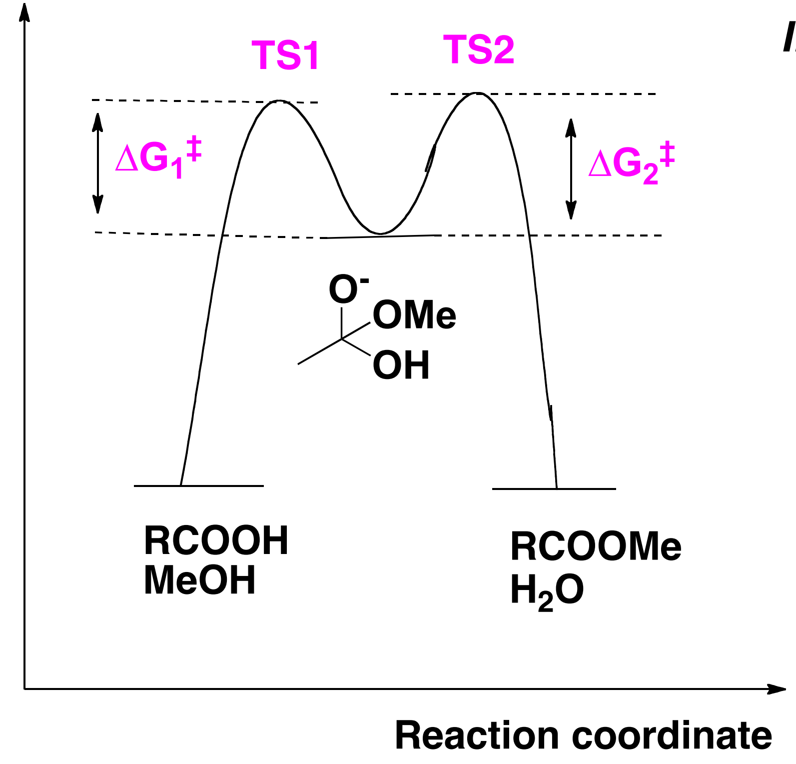
1. Lengthening the reaction time – longer reaction times will ensure that the equilibrium favors formation of more stable product.

2. Use of milder reagents – This will ensure a greater equilibrium stage allowing reactions to occur in a reversible manner in the mechanism.

3. Use of higher temperatures.

How to Drive the Equilibrium to Product
Example of Esterification



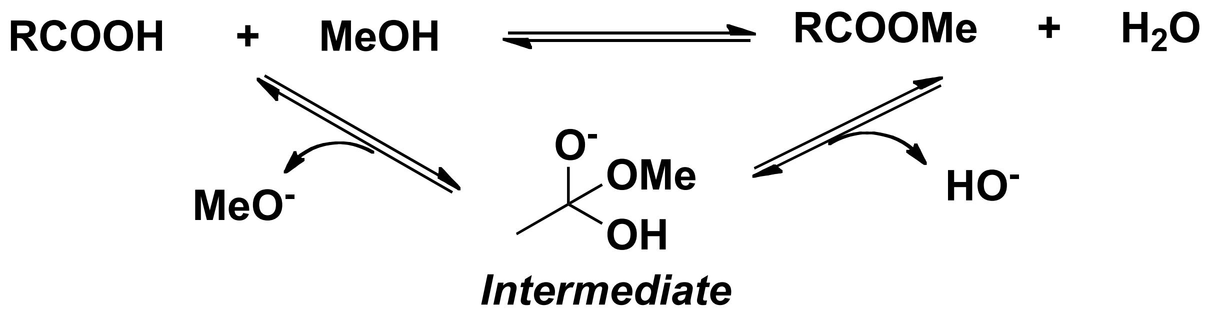


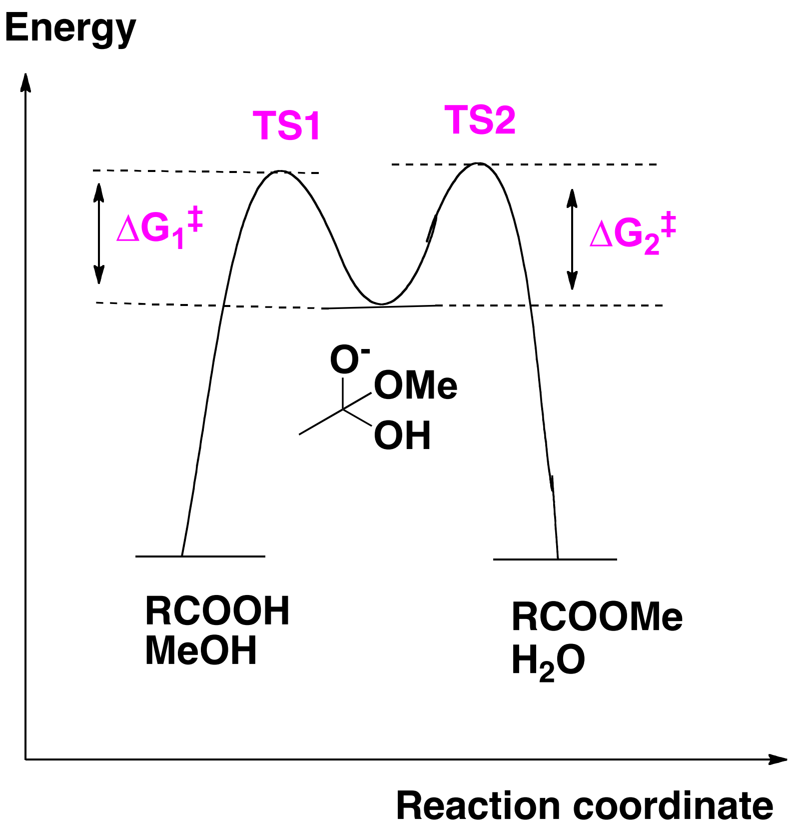
RCOOH and RCOOMe has similar thermostability $\Delta G° \approx 0$ KJ/mol.
Kinetically, fragmentation of intermediate to acid and to ester has similar rate $\Delta G_1^\ddagger \approx \Delta G_2^\ddagger$. Indeed, MeO- and HO- have similar leaving abilities since pK_a (H_2O) = 15.7, pK_a (MeOH) = 16.0

So reaction will reach equilibrium with equal amount of acid and ester (K = 1).

How to drive the reaction towards the formation of ester?

How to Drive the Equilibrium to Product
Example of Esterification



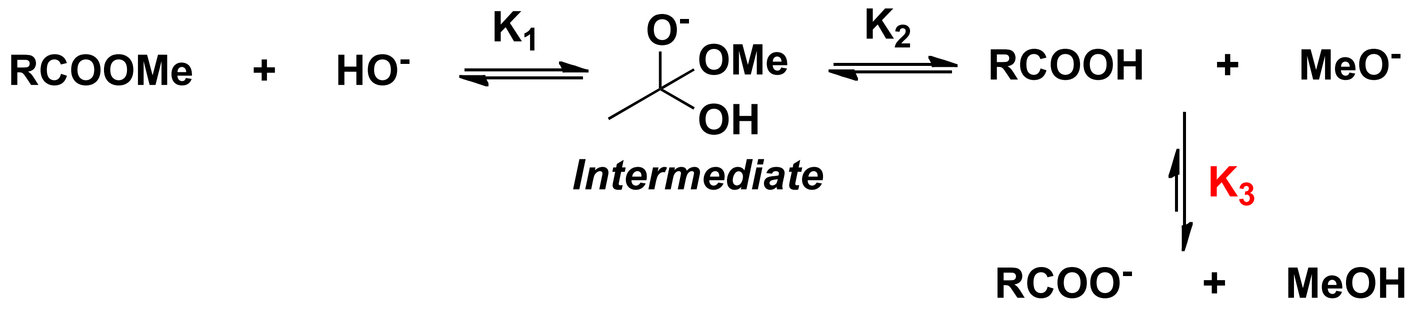


Adding strong acid (conc. H_2SO_4) catalyze the reaction. Reaction reaches equilibrium more rapidly ($\Delta G_1^\ddagger$ and $\Delta G_2^\ddagger$ reduced and rate constant (k) increased, but *This did not change the equilibrium constant*. At Equilibrium, the amount of ester remained the same (K = 1).

So catalyst speed up the reaction but doesn't change the product ratio.

Trick: Applying Le Chatelier's Principle:
Increase the amount of MeOH (eg using MeOH as solvent)

Hydrolysis of Ester under Basic Conditions. How Does It Work?


RCOOMe + HO⁻ $\underset{}{\overset{K_1}{\rightleftharpoons}}$ Intermediate $\overset{K_2}{\rightleftharpoons}$ RCOOH + MeO⁻

RCOO⁻ + MeOH

RCOOH and RCOOMe has same thermostability $\Delta G^\circ \approx 0$ KJ/mol.
Kinetically, fragmentation of intermediate to acid and to ester has similar rate $\Delta G_1^\ddagger \approx \Delta G_2^\ddagger$.
Indeed, MeO^- and HO^- have similar leaving abilities since pK_a (H_2O) = 15.7, pK_a (MeOH) = 16.0

So reaction will reach equilibrium with equal amount of acid and ester (K = 1) as in the case of the esterification of carboxylic acid. However, this is not true, because an additional step is operating that convert the carbocylic acid to carboxylate, driving hence the reaction to the right (Le Chaterlier's Principle).

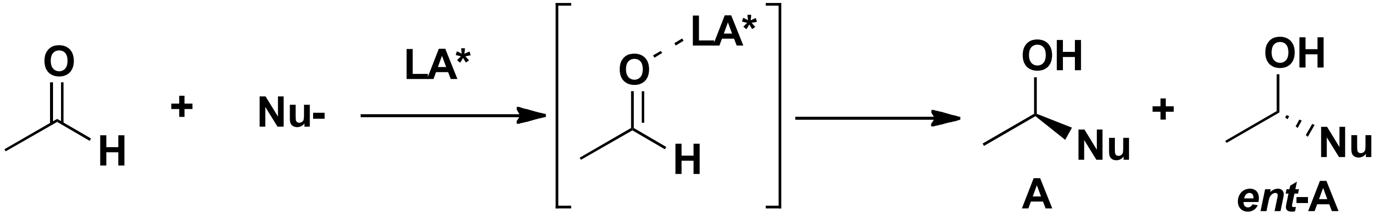
Assuming the pKa of carbocylic acid is 5 and that of MeOH 16, calculate the equlibrilium constant K_3:

$$K_3 = \frac{[RCOO^-]\,[MeOH]}{[RCOOH]\,[MeO^-]} = \frac{[RCOO^-]\,[MeOH]}{[RCOOH]\,[MeO^-]} \times \frac{[H^+]}{[H^+]} = \frac{K_a\,(RCOOH)}{K_a\,(MeOH)}$$

$$= \frac{10^{-pka\,(RCOOH)}}{10^{-pka\,(MeOH)}} = 10^{11}$$

Irreversible Reaction: ΔG‡ vs Product Distribution

Considering an enantioselective addition of nucleophile to aldehyde. For a selectivity of *R/S* = 98/2 at 25 ° C, what would be the difference of E_a for the reaction leading to these two enantiomers.



For a good enantioselective process, the reaction better to be irreversible and thus under kinetic control. In this case, the product distribution would depend on the rate of their formation, *ie*: R/S ratio parallels to k_1/k_2 ratio.

$$\frac{k_1}{k_2} = \frac{Ae^{-\frac{E_a}{RT_1}}}{Ae^{-\frac{E_a}{RT_2}}} \Longrightarrow \ln\frac{k_1}{K_2} = -\frac{E_{a1}}{RT} + \frac{E_{a2}}{RT} = \frac{1}{RT}\left(E_{a2} - E_{a1}\right)$$

$$\ln\frac{98}{2} = \frac{1}{RT}\left(E_{a2} - E_{a1}\right)$$

$\Delta E_a = E_{a2} - E_{a1} = 8.314 \times 298 \times \ln 49$
= 9642.2 J = 9. 64 KJ/mol = 2.30 Kcal/mol

Note: 2.30 kcal/mol is just nothing as energy required for rotating the C-C bond in ethane is about 2.87 kcal/mol