

*A Discussion of Reaction Kinetics
and their Application to Organic Chemistry*

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MacMillan Group Meeting
June 11, 2007

Lead Reference:

Modern Physical Organic Chemistry; Anslyn E. V., Dougherty, D., A.; University Science Books: Sausalito, 2006; Chapter 7

Overview

■ The Basics

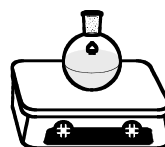
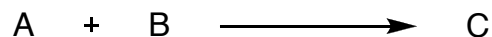
- What is kinetics?
- Energy Surfaces
- Reaction Coordinate Diagrams
- Principles and Postulates
- Rates and Rate Constants

■ Kinetics experiments

- Elementary Reactions
- Multi-Step Reactions (Steady-State Approximation)
- Bringing it All Together, a Kinetic Analysis of Selectivity Trends

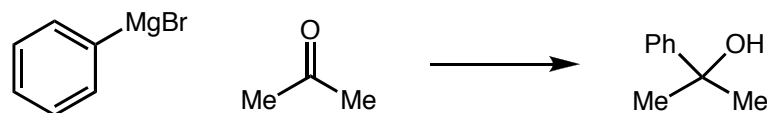
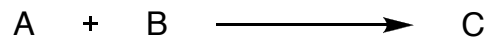
What Do We Mean When We Talk About Reaction Kinetics?

- Kinetics: the experimental measurement of the macroscopic properties of a reaction mixture and how the concentration of product and reactants changes over time, ie, reaction rate



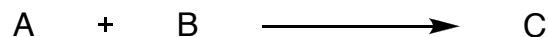
How fast does a solution of A and B at a given concentration go to a solution of C and what does this tell us about the mechanism?

- Dynamics: the molecular scale analysis of reaction rates



How fast does a molecule of A and B go to a molecule of C and what does this tell us about the mechanism?

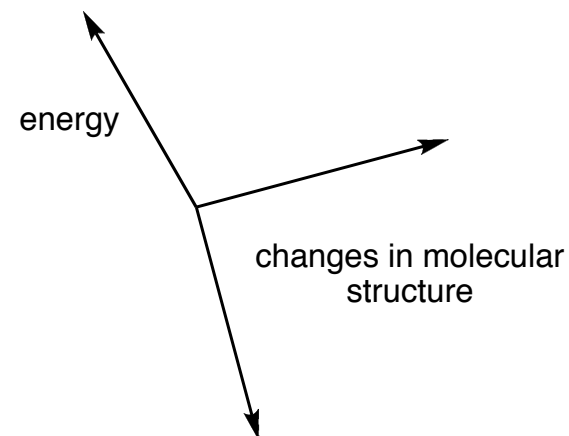
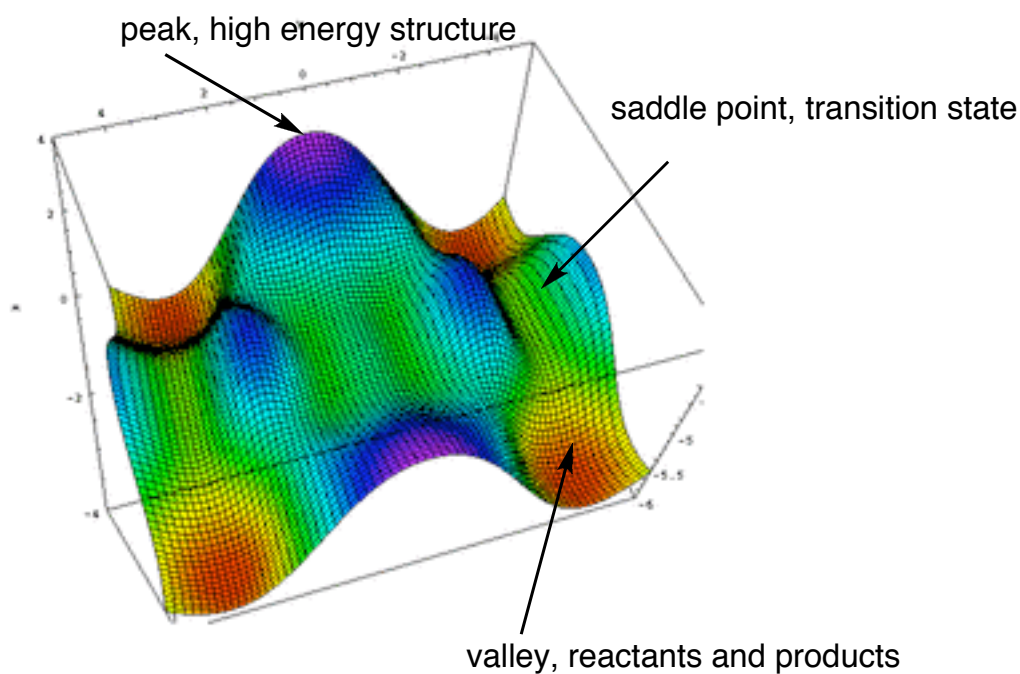
- Thermodynamics: concerned only with the final state of a system, mechanism of transformation does not matter



What is [A], [B] and [C] when the system is at equilibrium?

Energy Surfaces

- Energy Surfaces are a way to visualize the energy involved in a chemical transformation



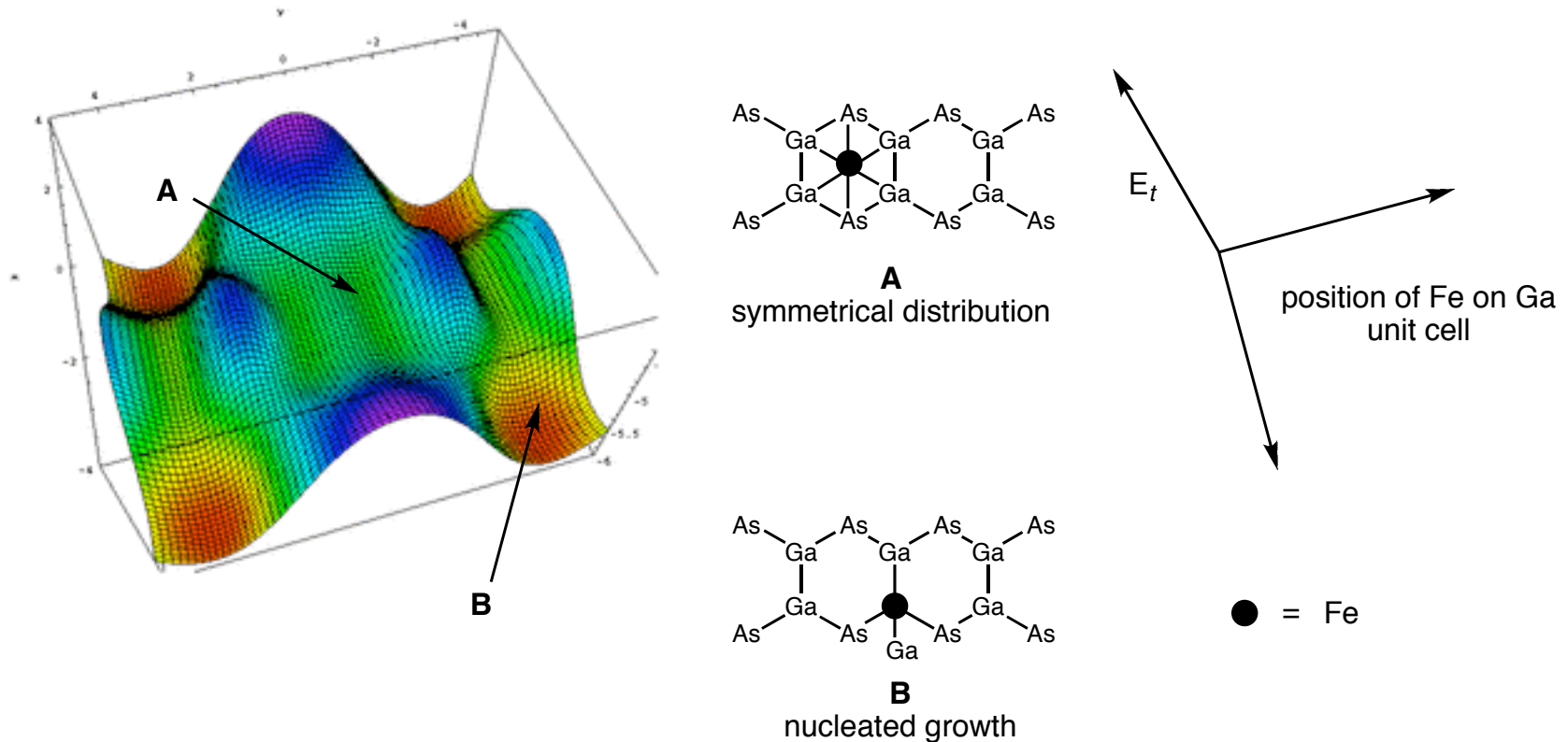
- The unit along the Z-axis is energy

- The X and Y-axes represent a continuum of molecular structures that encompasses:

- stable reactants and products (valleys)
- high energy structures that are seldom obtained (peaks)
- highest energy points that must be traversed during the transformation of reactant to product (saddle point)

Energy Surfaces

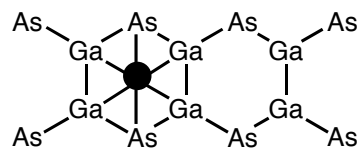
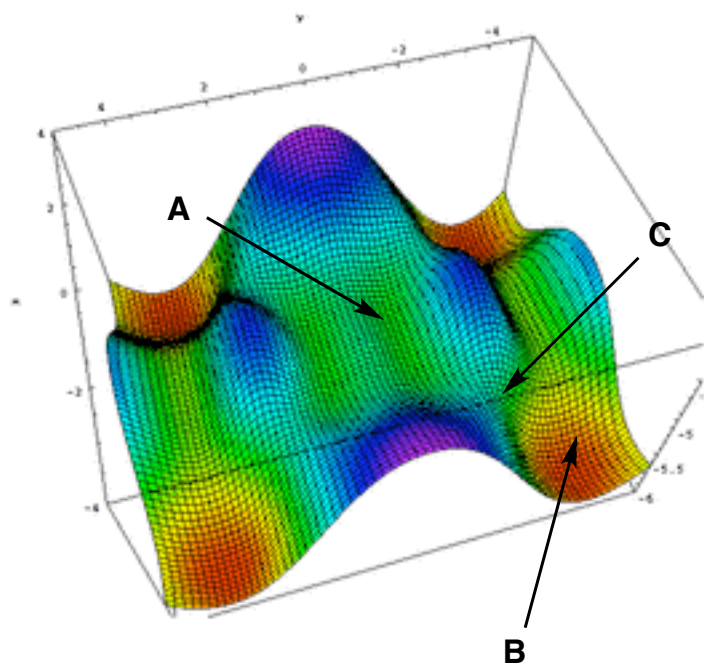
■ Modelling the growth of Fe on a GaAs surface using density functional theory, total energy (E_t) plotted against adsorbate position within the surface unit cell



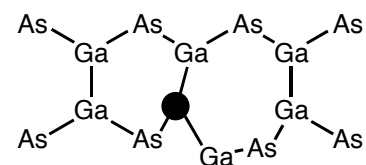
■ The potential energy surface explains why they observe non-symmetrical deposition of Fe on the GaAs surface

Energy Surfaces

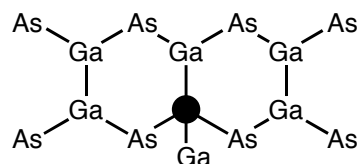
■ The **activated complex** is the molecular structure that exists at the **transition state**



A
symmetrical distribution



C
activated complex



B
nucleated growth

● = Fe

■ Though often used interchangeably "transition state" refers to the point on the energy surface while "activated complex" refers to the molecular structure

What Comprises the Energy on an Energy Surface?

■ The energy coordinate is the **potential energy** of the system, it's Gibb's free energy

■ Gibbs free energy (G) is comprised of two components, enthalpy (H) and entropy (S) related by:

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

enthalpy: describes the energy associated with conformation, bond strength, vibrational states and how changes in these properties affect the overall energy of the system

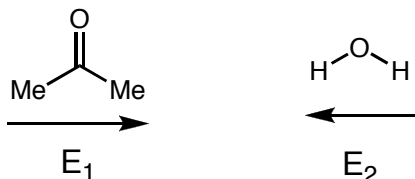
entropy: describes the degrees of freedom of a molecule, i.e., what sort of rotational, translational and internal motions can it undergo

■ On an energy surface, enthalpy can be related to the height of the surface while entropy is related to the width of the channels leading from one energy well to another

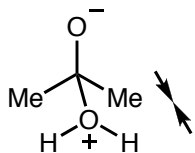
■ Thinking about the energy surface as potential energy helps us think about what is really happening during a chemical reaction

Thinking About a Reaction in Terms of Energy Transformations

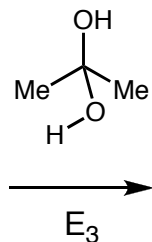
- Reactions occur due to molecular collisions, for example, carbonyl hydrolysis



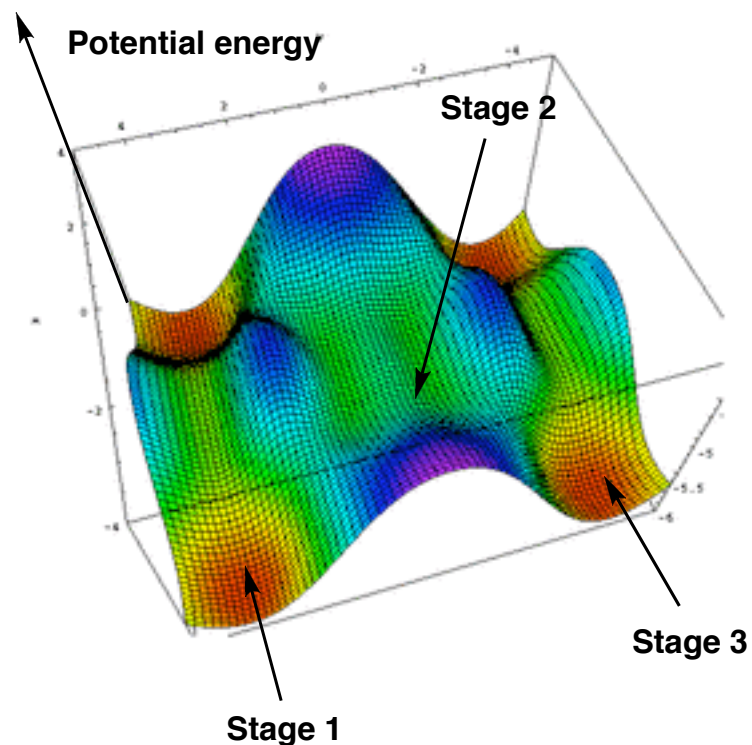
Stage 1: energy exists primarily as kinetic energy, two molecules moving in solution



Stage 2: molecules collide and distort, kinetic energy is converted to potential energy



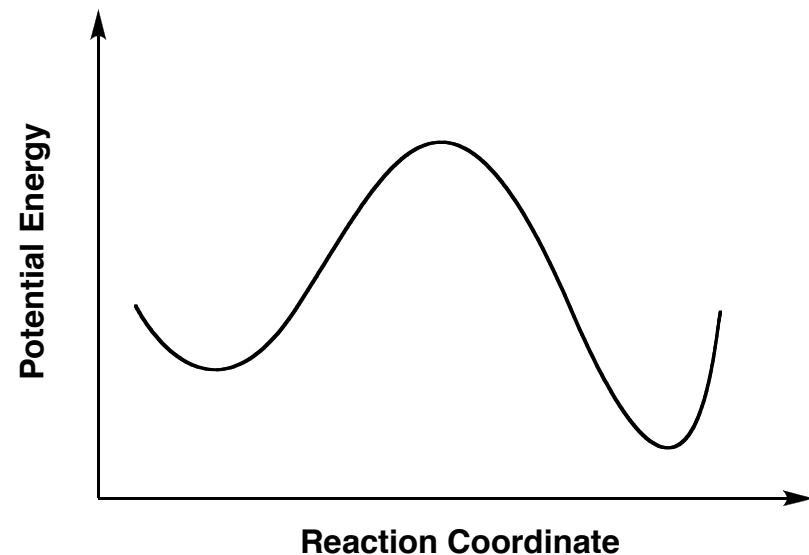
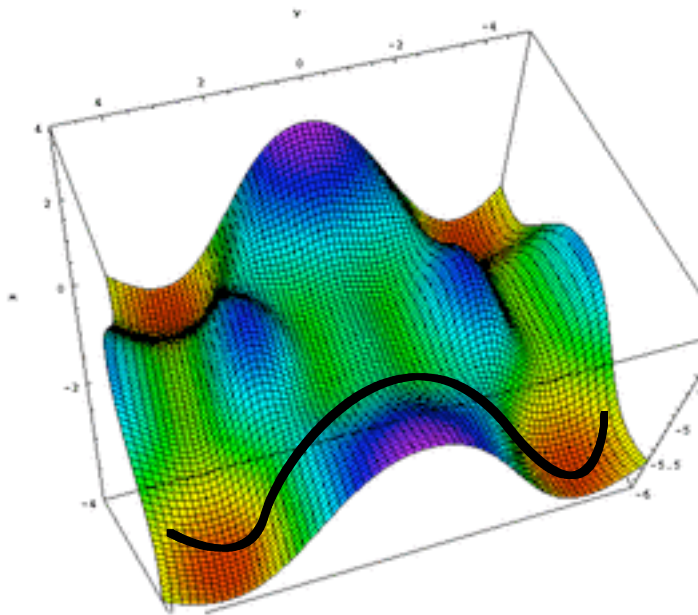
Stage 3: new molecule moves off with a new kinetic energy



- If the energy of the collision is high enough and distortion is severe enough to achieve the structure of the activated complex, the collision leads to a chemical reaction

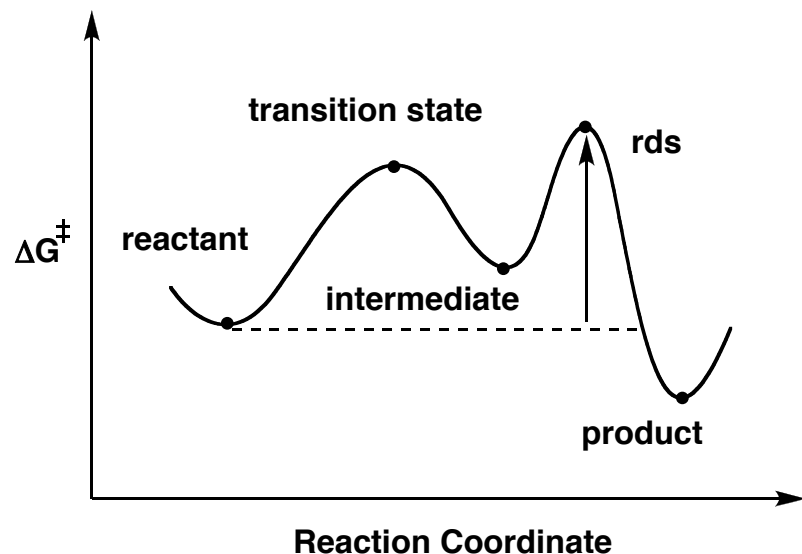
Energy Surfaces vs. Reaction Coordinate Diagrams

- Something that cannot be represented in the three dimensional energy surface below is the differentially populated vibrational modes of the molecules
- There are also multiple pathways across the energy surface for molecules to take from reactant to product, thus a reaction rate is actually a weighted average of the rates of all possible pathways
- Reaction coordinate diagrams are used to simplify the situation, they represent a composite picture of all the reaction pathways giving a curve of the lowest energy path for a molecule to follow



Reaction Coordinate Diagrams

- Reaction coordinate diagrams show the energies of transition states, intermediates, reactants and products



intermediate any chemical structure that lasts longer than the time of a typical bond vibration, 10^{-13} to 10^{-14} s

rate-determining step (rds) the step of the reaction whose rate determines the observed rate of product formation, **usually** the step containing the highest energy transition state but also concentration dependent (steady state approximation)

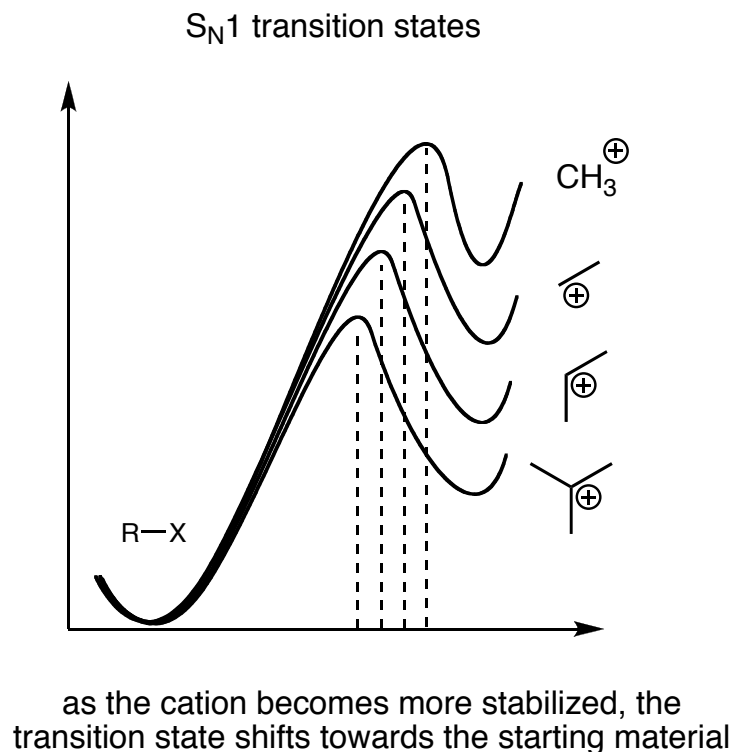
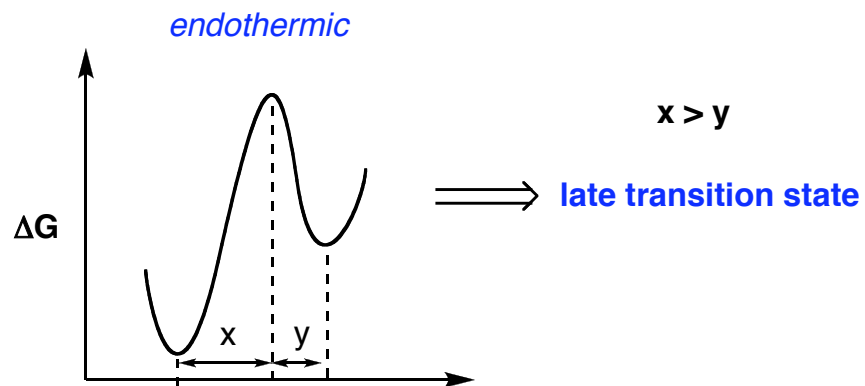
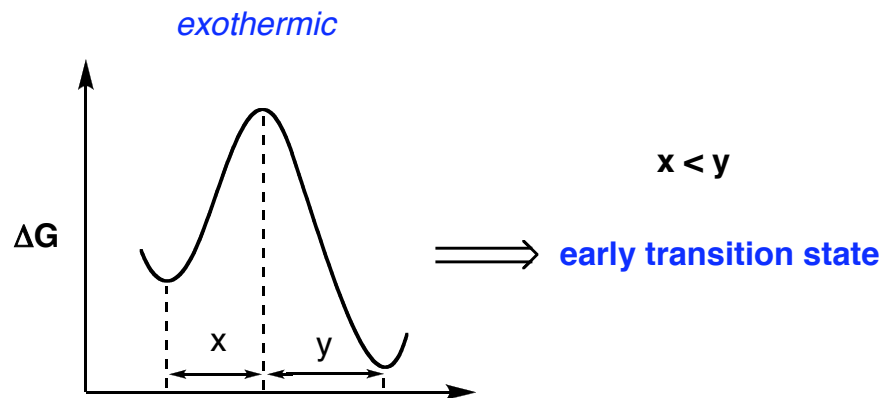
- The peaks and valleys of a reaction coordinate diagram are not necessarily in a straight line along the energy surface, molecules can "turn" within a valley but not at a saddle point

- Reaction coordinate diagrams can be drawn using either intuition according to classic postulates and principles or using more rigorous methods such as computation and Marcus theory

The Hammond Postulate

"If two states, as for example a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures"

- The most widely used physical organic principle for estimating the structures of activated complexes, assumes that structural changes occur along a continuum
- The postulate is most clearly demonstrated by comparing an endothermic reaction with an exothermic reaction

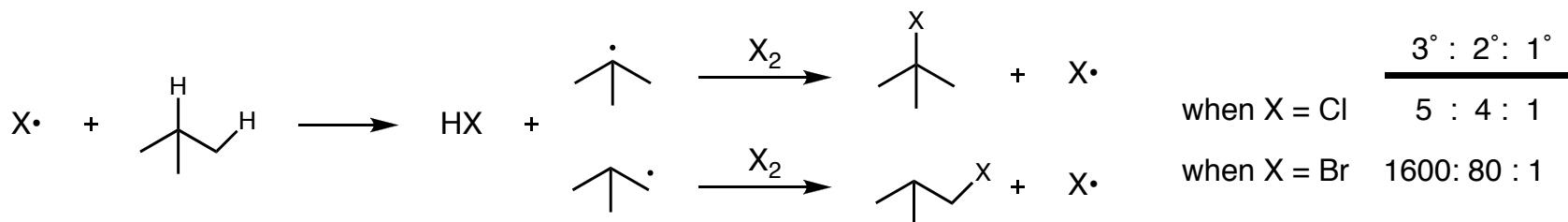


Reactivity vs. Selectivity Principle

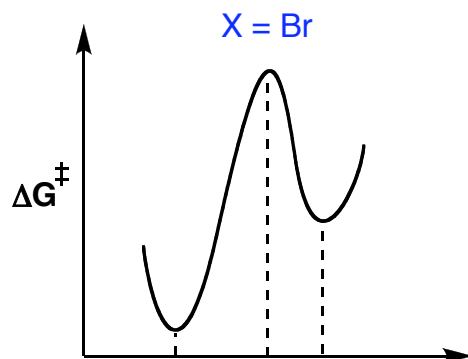
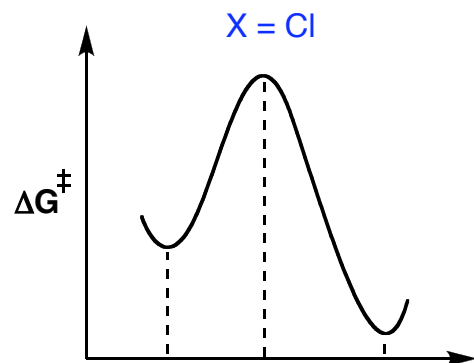
"The more reactive a compound is, the less selective it will be"

■ Really just an application of the Hammond postulate where "more reactive" means higher in energy or exothermic

■ Classic example: Free Radical Halogenation



■ Hydrogen abstraction by Cl• is exothermic while abstraction by Br• is endothermic

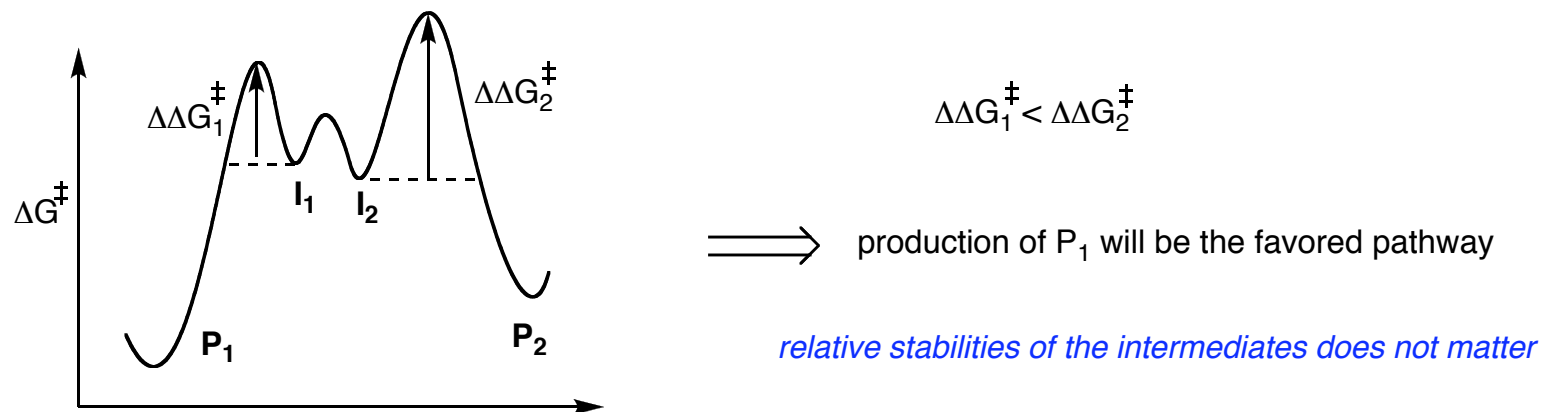


due to the late transition state when X = Br, the differences between alkyl radical stabilities has a greater effect on product distribution

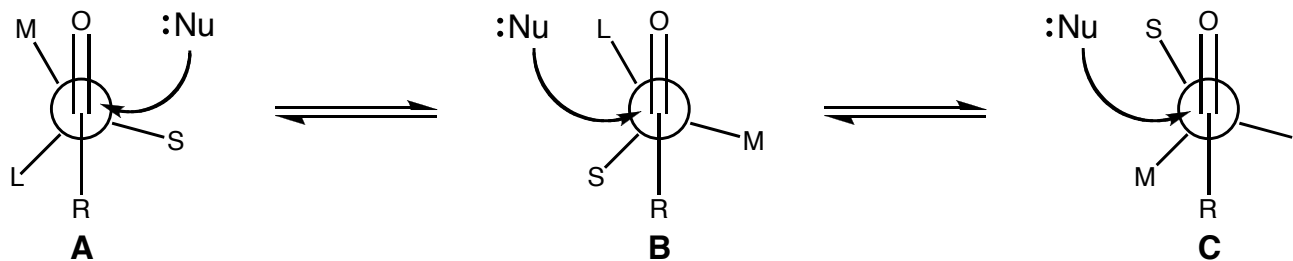
Curtin–Hammett Principle

"When there are competing pathways leading from interconverting intermediates, the product ratio is determined by the relative heights of the highest energy barriers leading to the products"

■ Curtin-Hammett applies only when the barrier to interconversion is much less than the barrier to product formation



■ Allows us to predict the stereochemistry of nucleophilic addition into carbonyls



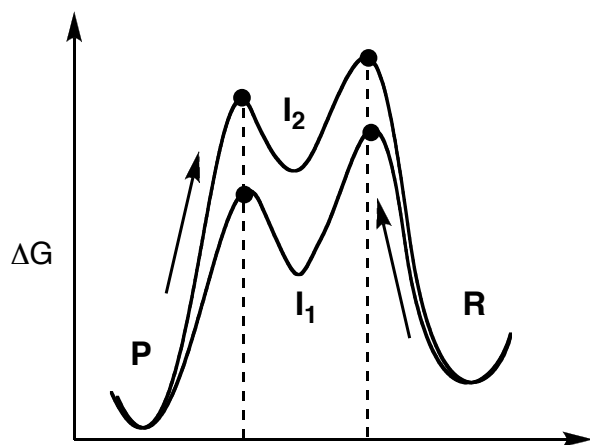
$E_{a \text{ nuc addn}} \gg E_{a \text{ bond rotation}}$

Situation **A** will predominate because the trajectory is lower in energy due to minimized steric interactions

Microscopic Reversibility

"The pathway for conversion of the product back to the reactant is the exact microscopic reverse of the forward pathway"

■ Understanding this principle via reaction coordinate diagrams

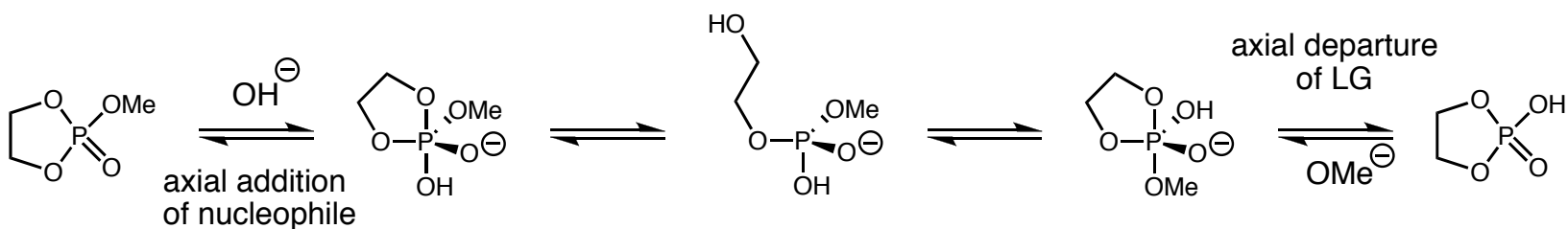


Assume **R** is converted to **P** via **I₁**

Conversely, **P** is converted to **R** via **I₂**

⇒ *The same transition states are formed in the forward and reverse direction along both pathways*

■ Organic chemists often use this principle without realizing it



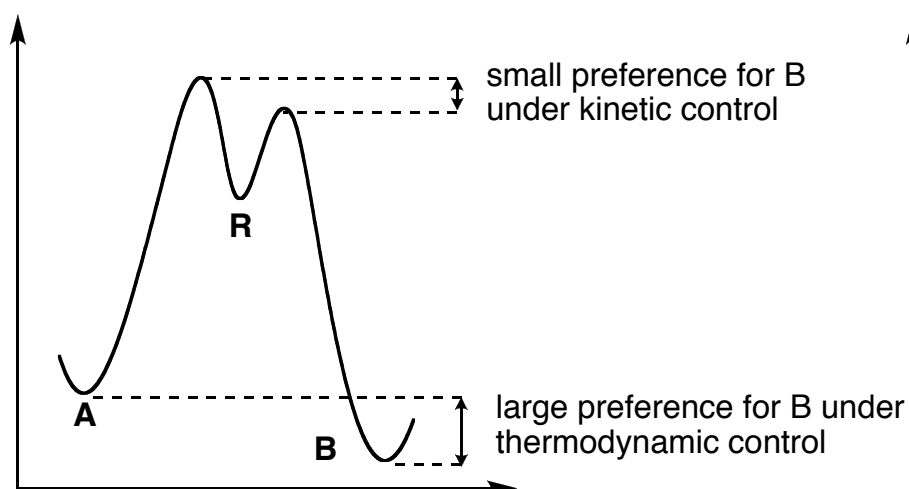
As leaving group departure occurs solely from the axial position, according to the principle of microscopic reversibility nucleophile addition must occur axially as well

Kinetic vs. Thermodynamic Control

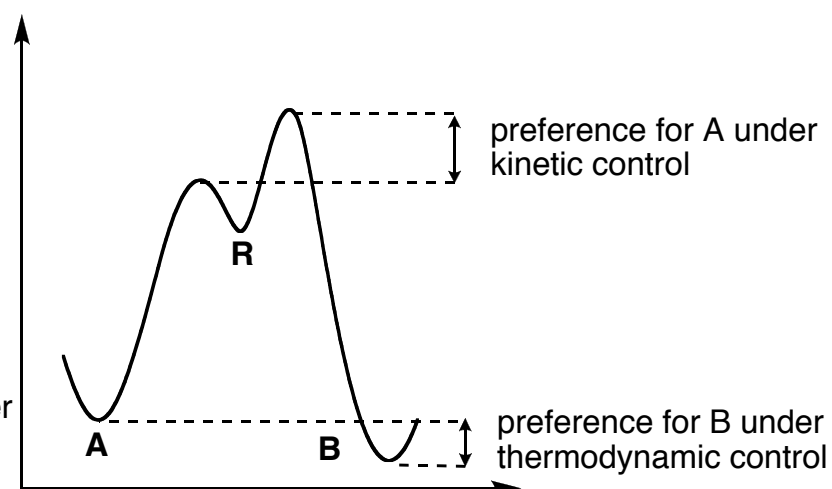
"When a reaction is under **kinetic control**, product ratios are determined by the relative barrier heights of the transition states. When a reaction is under **thermodynamic control**, product ratios are determined by the relative stabilities of the products"

■ Thermodynamic control occurs only when the reaction is easily reversible or the products can interconvert via a second chemical pathway

Case 1: **B** is both the kinetic and thermodynamic product



Case 2: **A** is the kinetic product while **B** is the thermodynamic product



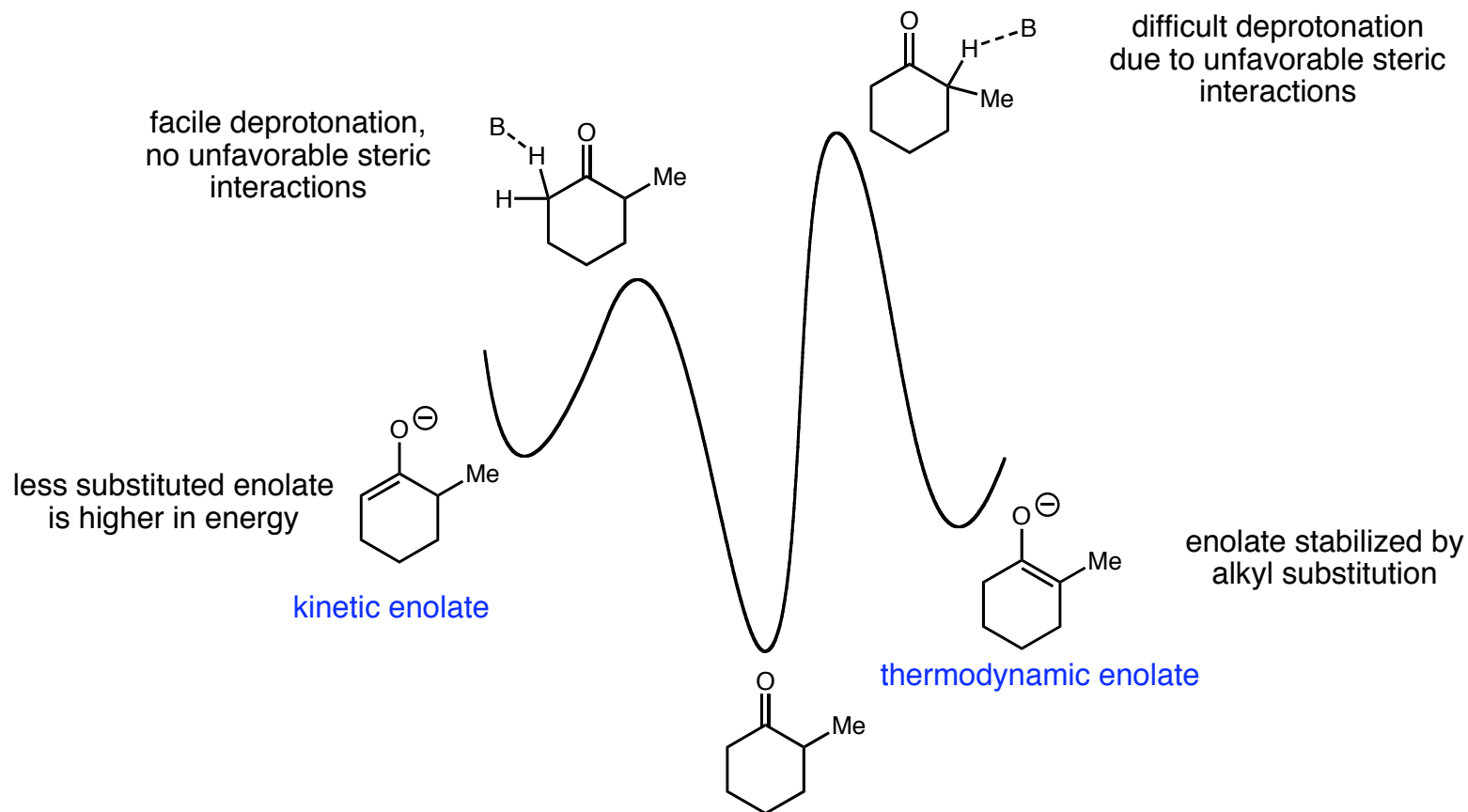
■ The best way to partition a reaction between the kinetic and thermodynamic product is through temperature.

lower temps \implies irreversible reaction \implies *kinetic product*

higher temps \implies reversible reaction \implies *thermodynamic product*

Kinetic vs. Thermodynamic Control: Enolate Geometry

■ A synthetically useful example of kinetic vs. thermodynamic control is the selective formation of enolates



■ Working at low temps favors the kinetic enolate as the system cannot equilibrate to form the more stable thermodynamic enolate

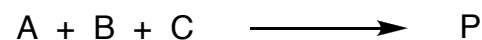
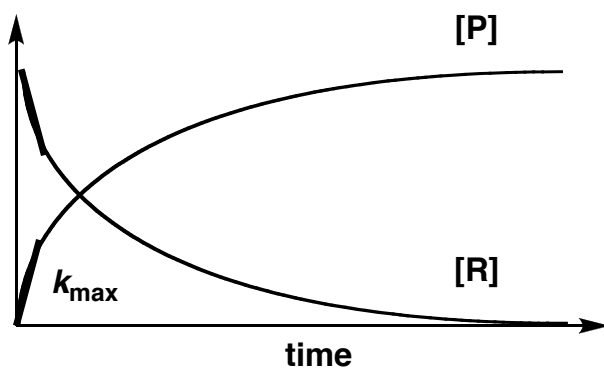
Rates and Rate Constants

■ Reaction rates are dependent on reactant concentration and a proportionality constant called the *rate constant* (k)

$$\text{rate} = k [R]$$

k represents the barrier height of an energy surface and temperature

■ Dependence on $[R]$ implies that rates are time dependent with the rate being greatest when $[R]$ is at a maximum, leading to differential rate equations known as *rate laws*



$$\text{rate} = -d[R] / dt = d[P] / dt$$

$$= k [A]^a [B]^b [C]^c$$

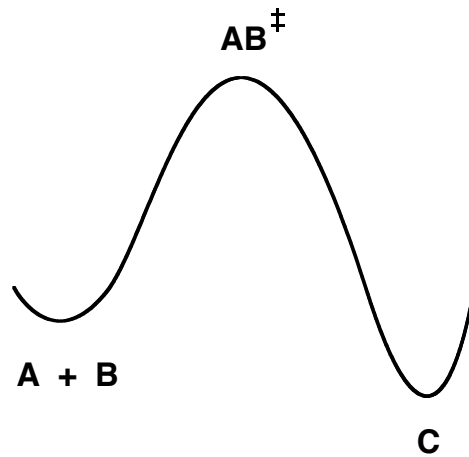
reaction order the mathematical dependence of the rate law on reactant concentration

molecularity the number of molecules involved in the transition state of elementary reactions

reaction order can be used to describe a complicated reaction involving several steps but *molecularity* applies only to elementary reactions

Transition State Theory (TST)

- TST is a molecular dynamical analysis for determining the energy values of barrier heights on energy surfaces, *ie*, rate constants



the rate at which C is produced is dependent upon the rate of activated complex decomposition

$$\text{rate} = d[C] / dt = k[A][B] = k^{\ddagger}[AB^{\ddagger}]$$

key assumption: reactant and activated complex are in equilibrium

$$K^{\ddagger}[A][B] = [AB^{\ddagger}]$$

$$K^{\ddagger}k = k^{\ddagger}$$

$$\kappa \nu = k^{\ddagger}$$

κ transmission coefficient, the probability of an oscillation of the activated complex leading to product

ν vibration frequency of activated complex

- To solve for K^{\ddagger} statistical mechanics is invoked to define the transition state population

$$K^{\ddagger} = \left(\frac{k_B T}{h\nu} \right) K^{\ddagger'}, \quad \text{where} \quad K^{\ddagger'} = \exp\left(\frac{\Delta G^{\ddagger}}{RT} \right)$$

*substitution leads to the **Eyring** equation*

$$k = \kappa \left(\frac{k_B T}{h} \right) \exp\left(\frac{\Delta G^{\ddagger}}{RT} \right)$$

Eyring Equation

■ The Eyring equation is most useful for experimental chemists when given in terms of activation parameters

$$k = \kappa \left(\frac{k_B T}{h} \right) \exp \left(\frac{\Delta G^\ddagger}{RT} \right)$$

$$k = 2.083 \times 10^{10} T \exp \left(\frac{\Delta G^\ddagger}{RT} \right)$$

$$\Delta G^\ddagger = 4.576 T [10.319 + \log (T / k)] \text{ kcal / mol}$$

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

$$k = 2.083 \times 10^{10} T \exp \left(\frac{\Delta S^\ddagger}{R} \right) \exp \left(\frac{-\Delta H^\ddagger}{RT} \right)$$

note that the rate constant and activation parameters obtained are for a given temperature

An Apparent Contradiction in TST

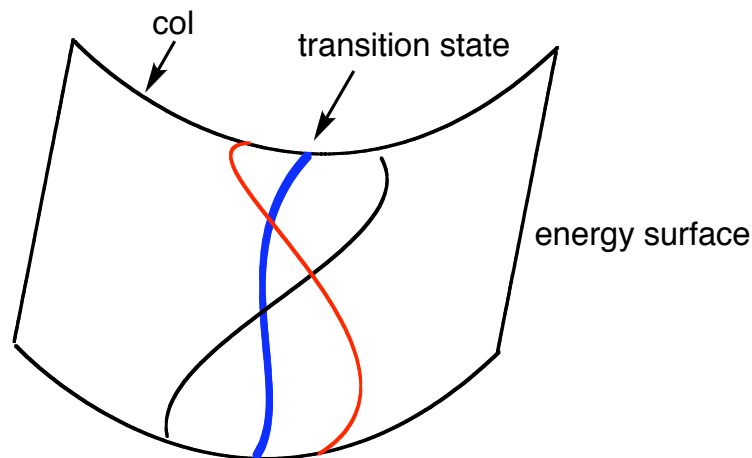
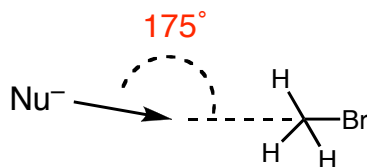
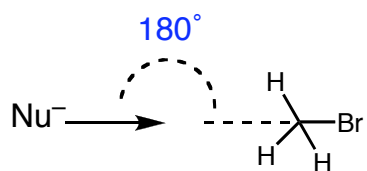
■ We used statistical mechanics to allow us to solve for K^\ddagger assuming a Boltzmann distribution of energies for the population of molecules at the transition state.

$$K^\ddagger = \left(\frac{k_B T}{h\nu} \right) K^{\ddagger, \prime} \quad \text{where} \quad K^{\ddagger, \prime} = \exp\left(\frac{\Delta G^\ddagger}{RT} \right)$$

■ However, Boltzmann distributions assume that molecules are long lived enough to undergo full energy exchange through rotations and vibrations, this is by definition untrue for activated complexes

■ This substitution is still valid and actually represents the average of all possible ways for a molecule to undergo transformation as it approaches the saddle point representing the transition state

S_N2 displacement



differing angles of nucleophile approach leads to a distribution of energies of molecules as they cross over the col

The Arrhenius Rate Law

- Came out of empirical observations by Arrhenius that reaction rates increase exponentially as a function of temperature

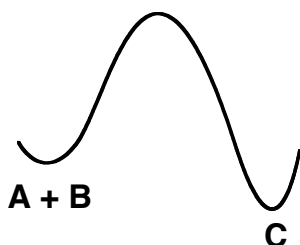
$$k = A \exp\left(\frac{-E_a}{RT}\right)$$

A exponential factor

E_a activation energy (barrier height)

- Despite their similar forms, Eyring and Arrhenius treatments are not the same

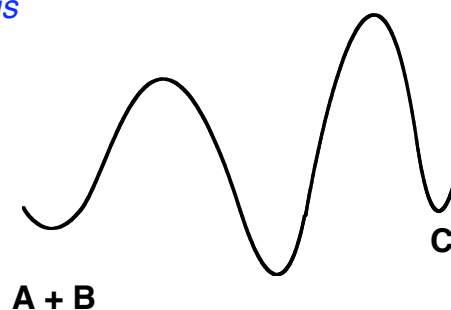
Eyring



$$k = \kappa \left(\frac{k_B T}{h}\right) \exp\left(\frac{\Delta G^\ddagger}{RT}\right)$$

- a microscopic rate constant for a fundamental step
- derived theoretically from TST

Arrhenius



$$k = A \exp\left(\frac{-E_a}{RT}\right)$$

- a macroscopic rate constant for an entire transformation
- derived empirically from experimental observation

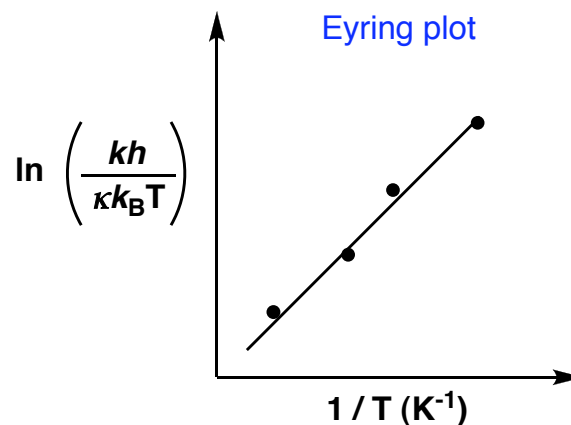
Experimental Determinations of Activation and Arrhenius Parameters

■ The Eyring equation can be mathematically manipulated to give the equation of a line with a dependence on temperature

$$k = \kappa \left(\frac{k_B T}{h} \right) \exp \left(\frac{\Delta S^\ddagger}{R} \right) \exp \left(\frac{-\Delta H^\ddagger}{RT} \right)$$

$$\ln k = \ln \left(\frac{\kappa k_B T}{h} \right) - \frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R}$$

$$\ln \left(\frac{kh}{\kappa k_B T} \right) = - \frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R}$$



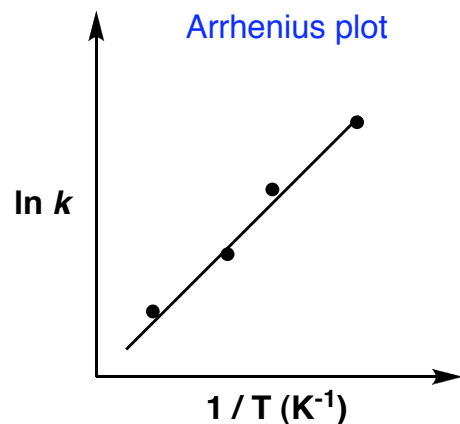
slope $\implies \Delta H^\ddagger$

y-intercept $\implies \Delta S^\ddagger$

■ Similar manipulation of the Arrhenius equation allows one to experimentally determine values for E_a and A

$$k = A \exp \left(\frac{-E_a}{RT} \right)$$

$$\ln k = \ln A - \left(\frac{E_a}{RT} \right)$$

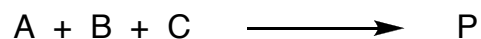


slope $\implies E_a$

y-intercept $\implies A$

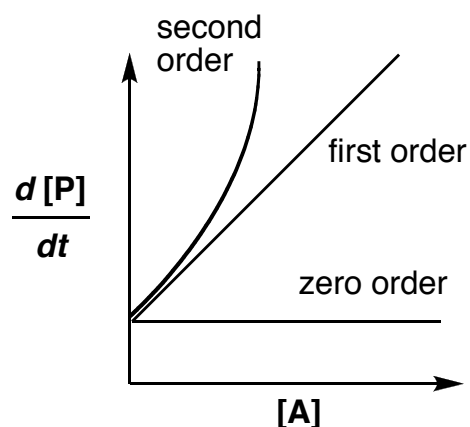
Kinetics Experiments: Keys to Keep in Mind

■ The goal of a kinetics experiment is to establish a quantitative relationship between reactant concentration and reaction rate in the hopes that it will lend insight into the reaction mechanism



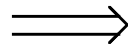
$$d[P] / dt = k [A]^a [B]^b [C]^c$$

■ The order of each reactant needs to be determined in order to find the rate law and rate constant for the overall transformation



[B], [C] kept constant

the slope of the line of $d[P] / dt$ vs. $[A]$ tells us the order of the reactant



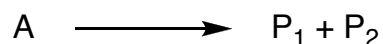
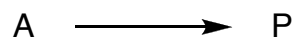
if a reactant is involved in a step after the rds, its order will be zero

■ Reaction rate changes over time so rates need to be compared at equivalent points for the data to have any value. This is done either one of two ways:

1. Use initial rate kinetics
2. Plot rate constants as a function of concentration (pseudo-first order kinetics)

Kinetics Experiments: Elementary Reactions

First Order Kinetics: deriving the rate law



$$\frac{d[P]}{dt} = -\frac{d[A]}{dt} = k[A]$$

rearrange and integrate:

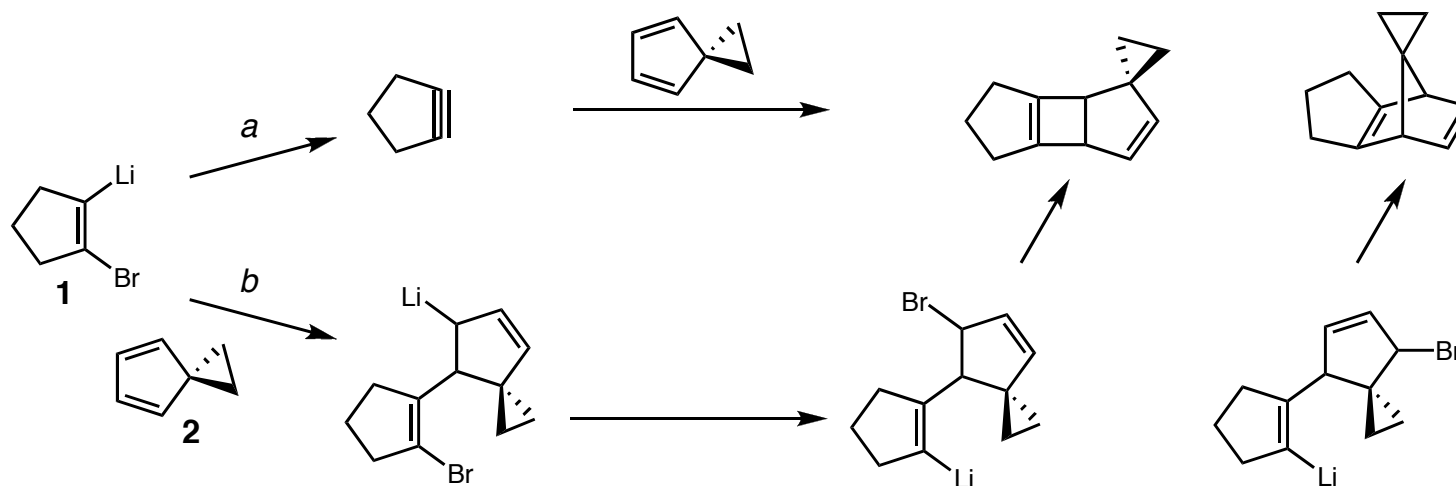
$$\ln [A] = \ln [A]_0 - kt$$

$[A]_0$ = starting concentration

Monitoring $[P]$ instead of $[A]$:

$$\ln \left(\frac{[A]_0}{[A]_0 - [P]} \right) = kt$$

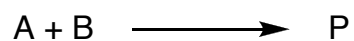
Distinguishing between unimolecular and bimolecular pathways: pentyne



found to be first order in **1** and zero order in **2** \implies pathway A is operating

Kinetics Experiments: Elementary Reactions

■ Second Order Kinetics: deriving the rate law

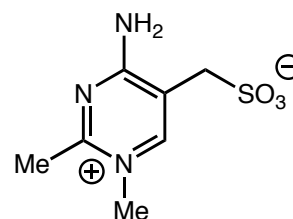
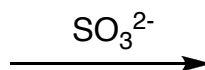
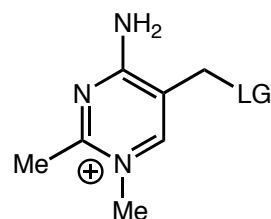
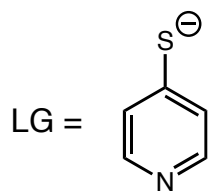


$$\frac{d[P]}{dt} = k[A][B]$$

rearrange and integrate:

$$\left(\frac{1}{[B]_0 - [A]_0} \right) \ln \left(\frac{[A]_0 [B]}{[B]_0 [A]} \right) = kt$$

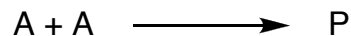
Nucleophilic Substitution of a Thiamine Analog



second order dependence
on sulfite

Kinetics Experiments: Elementary Reactions

■ Second Order Kinetics: deriving the rate law

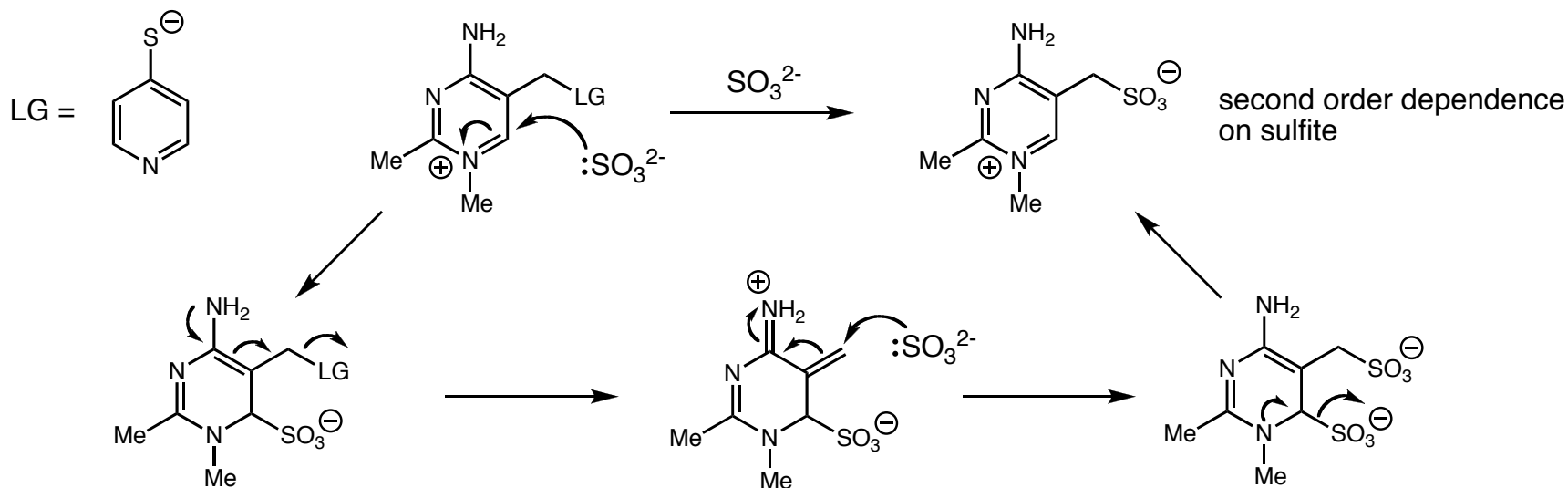


$$\frac{d[P]}{dt} = k[A][B]$$

rearrange and integrate:

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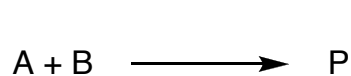
Nucleophilic Substitution of a Thiamine Analog



■ For a bimolecular reaction, one must be able to monitor both [A] and [B]. As this is not always experimentally easy, people often turn to pseudo-first order kinetics to prove bimolecularity

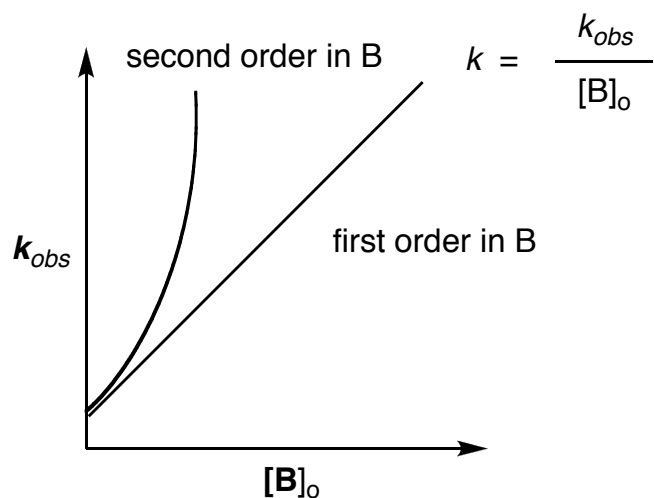
Kinetics Experiments: Pseudo-First Order Kinetics

■ By using a large excess (>10 equiv) of B, [B] can be considered constant, $[B]_0$, leading to a simplified rate expression



$$\frac{d[P]}{dt} = k[A][B] = k[A][B]_0 = k_{obs}[A]$$

a first order rate law



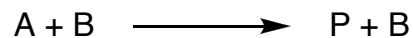
the slope of a plot of k_{obs} vs $[B]_0$ is the rate constant k

commonly used for determining kinetic order

linear dependence on $[B]_0 \implies$ first order in B

quadratic dependence on $[B]_0 \implies$ second order in B

■ Pseudo-first order kinetics are generally seen with catalytic reactions

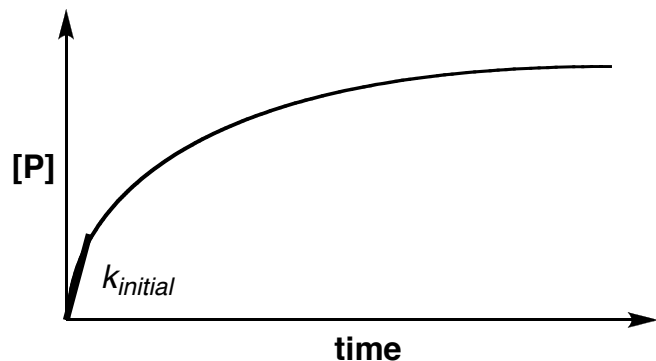


if B is a catalyst, then [B] remains constant

■ It is important to remember that in spite of the name, pseudo-first order kinetics actually describes bimolecular or more complex reaction mechanisms

Kinetics Experiments: Initial Rate Kinetics

- The most common technique used by organic chemists, it is used when reactions have longer half lives or when competing pathways are an issue



half-life

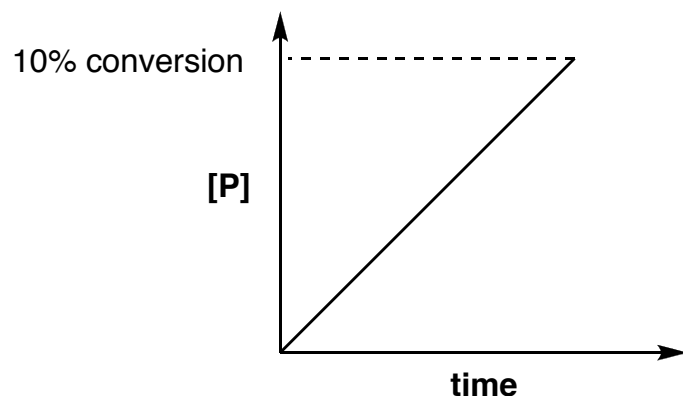
the time required for 50% of the starting material to be consumed



$$\frac{d[P]}{dt} = -k[A] = -k[A]_0$$

[A] can be approximated as a constant

- Reactions are generally followed to 5-10% completion where the graph of [P] vs time is linear



Following the reaction while $[A] \gg [P]$ prevents deviations in ideal behavior due to competing reaction pathways

$$k = \text{slope} \quad : \text{ in units of } M / \text{ time}$$

$$k = \frac{\text{slope}}{[A]_0} \quad : \text{ in units of } \text{time}^{-1}$$

- It is important to use an analytical technique that can accurately measure low concentrations of product or slight decreases in starting material concentration

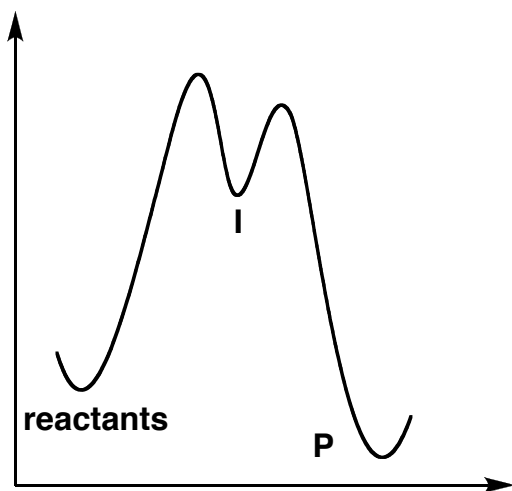
Kinetics Experiments: Steady State Kinetics

■ Most mechanisms are comprised of more than one step involving reactive intermediates and so cannot be described by the rate laws for elementary steps given previously. In these cases we turn to steady state kinetics to determine rate laws

steady state approximation (SSA)

the concentration of the reactive intermediate is constant during the reaction

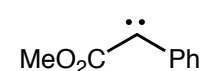
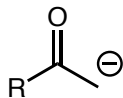
$$\frac{d[I]}{dt} = 0$$



SSA is valid if:

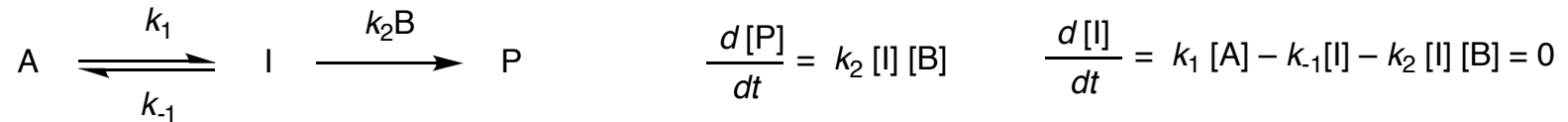
1. The absolute change in [I] is small compared to the change in [P] and [reactants]
2. The barrier for conversion of I to reactants and product is small relative to the barriers in the reverse direction
3. The conversion of I to P is irreversible, this prevents equilibration between P and I
4. The energy of I is significantly higher than that of the reactants and the product, ensures that [I] remains small

■ Steady state kinetics are often used when studying organic mechanisms as they often involve high energy intermediates such as carbocations, radicals, carbanions and carbenes



Steady State Kinetics: Possible Scenarios

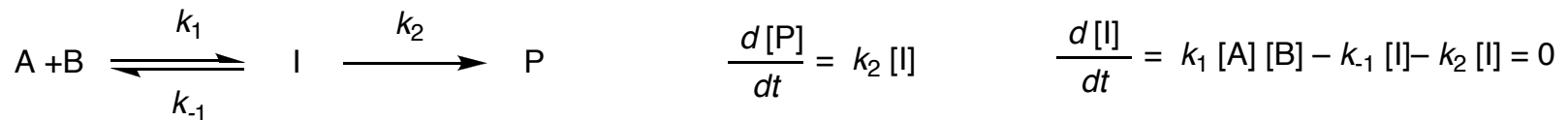
■ First order intermediate formation followed by second order product formation



Solving for [I] lets us write the rate law:

$$[I] = \frac{k_1 [A]}{k_{-1} + k_2 [B]} \quad \frac{d[P]}{dt} = \frac{k_1 k_2 [A] [B]}{k_{-1} + k_2 [B]} \quad \text{In this scenario, there is a first order dependence on [A] and a more complicated dependence on [B]}$$

■ Second order intermediate formation followed by first order product formation

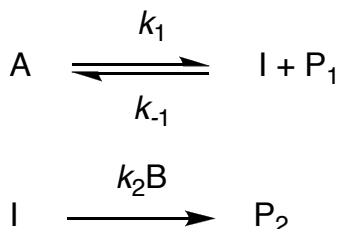


Solving for [I] lets us write the rate law:

$$[I] = \frac{k_1 [A] [B]}{k_{-1} + k_2} \quad \frac{d[P]}{dt} = \frac{k_1 k_2 [A] [B]}{k_{-1} + k_2} \quad \text{In this scenario, there is a first order dependence on [A] and [B]. It is important to realize that it is impossible to differentiate kinetically between this case and a second order elementary reaction}$$

Steady State Kinetics: Possible Scenarios

■ First order intermediate and product formation followed by a second order reaction with another reactant to form a second product



$$\frac{d[\text{P}_2]}{dt} = k_2 [\text{I}] [\text{B}]$$

$$\frac{d[\text{I}]}{dt} = k_1 [\text{A}] - k_{-1}[\text{I}] [\text{P}_1] - k_2 [\text{I}] [\text{B}] = 0$$

Rearrange to solve for [I]:

$$[\text{I}] = \frac{k_1 [\text{A}]}{k_{-1}[\text{P}_1] + k_2[\text{B}]}$$

Substitution for [I] gives the rate law:

$$\frac{d[\text{P}_2]}{dt} = \frac{k_1 k_2 [\text{A}] [\text{B}]}{k_{-1}[\text{P}_1] + k_2[\text{B}]}$$

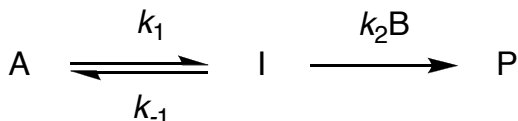
In this scenario, there is a first order dependence on [A], a less than first order dependence on [B] and the reaction will be retarded by [P₁]

■ Working out the expected order of each reactant for a variety of scenarios allows one to draw mechanistic conclusions based on experimental results

Steady State Kinetics: Observations about Rate Laws

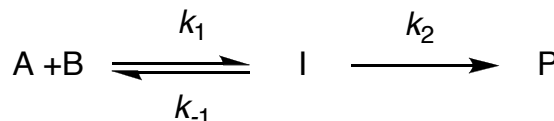
■ A comparison of the rate laws for the three scenarios leads to a series of interesting conclusions

Case 1



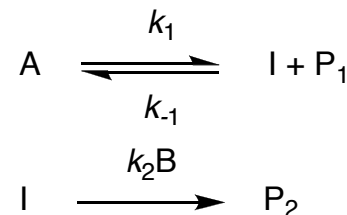
$$\frac{d[P]}{dt} = \frac{k_1 k_2 [A] [B]}{k_{-1} + k_2 [B]}$$

Case 2



$$\frac{d[P]}{dt} = \frac{k_1 k_2 [A] [B]}{k_{-1} + k_2}$$

Case 3

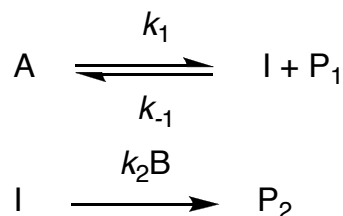


$$\frac{d[P_2]}{dt} = \frac{k_1 k_2 [A] [B]}{k_{-1} [P_1] + k_2 [B]}$$

1. The numerator is the **product** of all the forward rate constants and concentrations of all reactants required to form the product. The denominator is the **sum** of terms reflecting another route by which I can react
2. For the terms in the denominator, first order elementary steps are represented solely by a rate constant. Second order elementary steps are represented by the product of the rate constant and concentration
3. Terms in the denominator are not necessarily of comparable magnitude. If one of the denominator terms is dependent on concentration, often experimental conditions can be altered that lead to a simplification of the overall rate law

Steady State Kinetics: Saturation Kinetics

- Often experimental conditions can be used to simplify the rate expression for a given reaction



$$\frac{d[\text{P}_2]}{dt} = \frac{k_1 k_2 [\text{A}] [\text{B}]}{k_{-1} [\text{P}_1] + k_2 [\text{B}]}$$

if we add excess P_1 :

$$\frac{d[\text{P}_2]}{dt} = \frac{k_1 k_2 [\text{A}] [\text{B}]}{k_{-1} [\text{P}_1]}$$

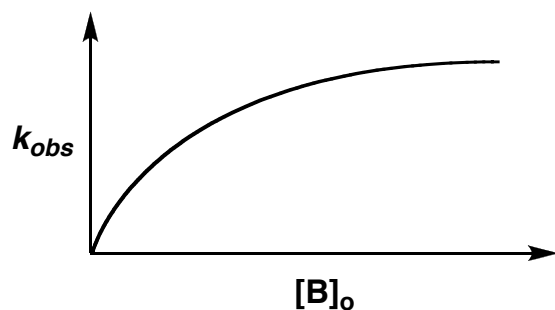
the reaction is now first order in A and B

if we add excess B:

$$\frac{d[\text{P}_2]}{dt} = \frac{k_1 k_2 [\text{A}] [\text{B}]}{k_2 [\text{B}]} = k_1 [\text{A}]$$

the reaction is now first order in A and zero order in B

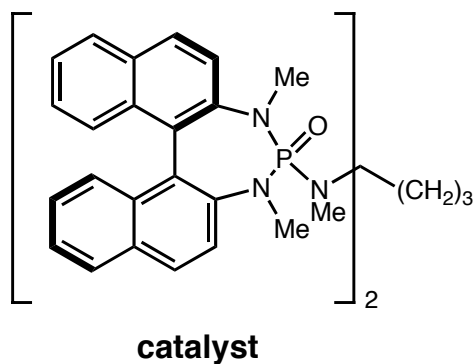
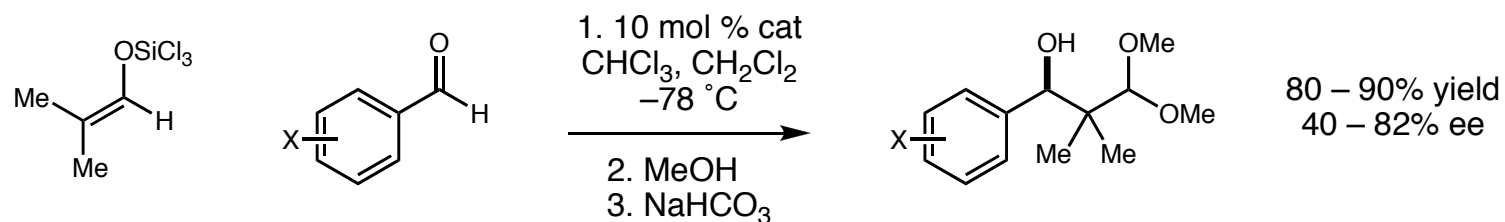
- This will lead to observed saturation kinetics with a first order dependence on B when $[\text{B}]$ is low and a zero order dependence when $[\text{B}]$ is large



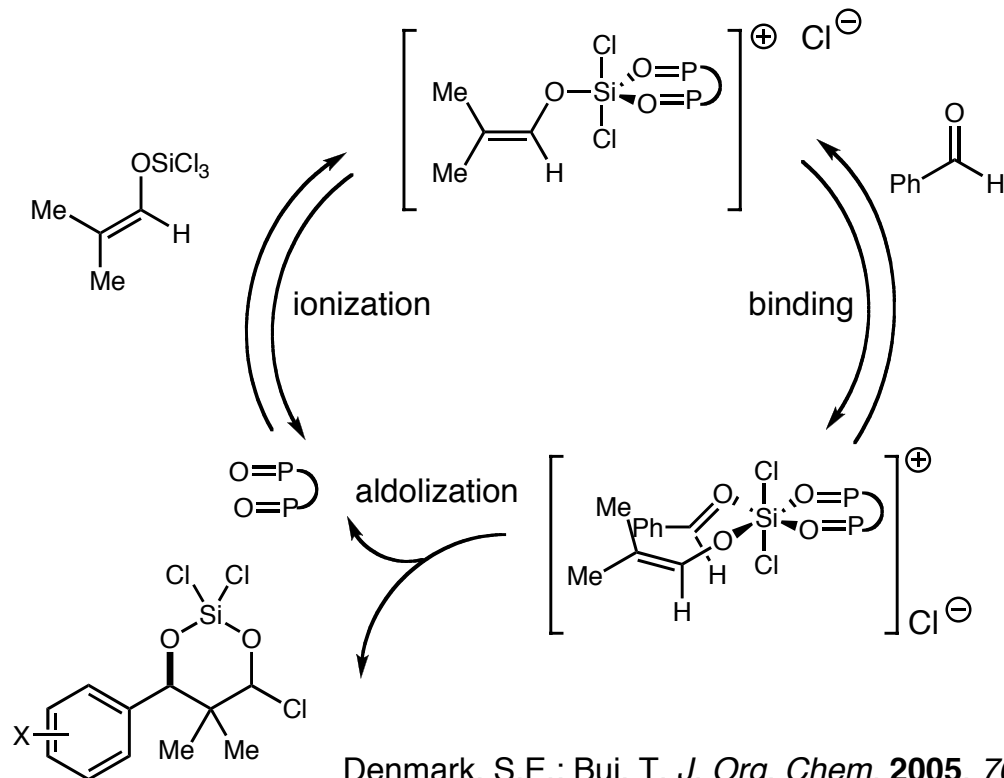
saturation kinetics are observed in all cases where B is involved **after** a pre-equilibrium step

Using Kinetics to Interpret Selectivity Trends

■ An interesting enantioselectivity trend in Denmark's phosphoramidate catalyzed aldol reaction leads to an investigation into origin of stereoselectivity and analysis of reaction mechanism

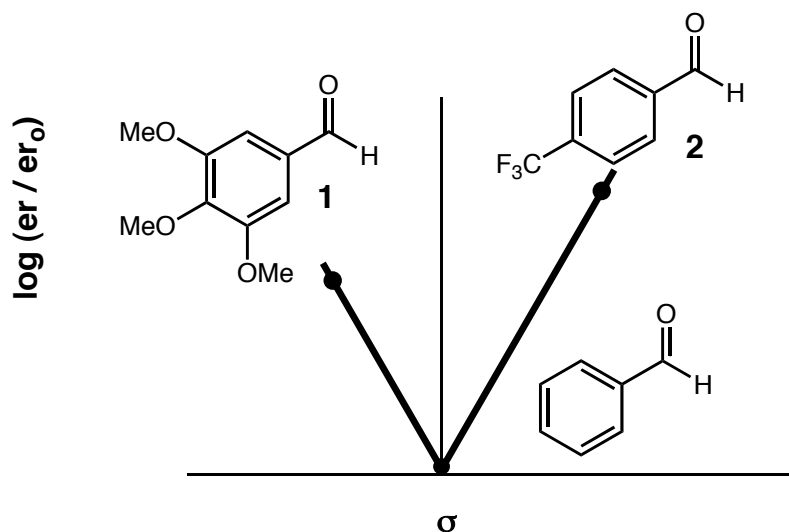


KIE studies show that aldolization is the rds for aldehydes with EWG and EDG



Using Kinetics to Interpret Selectivity Trends

■ A Hammett plot reveals that enantioselectivity is greatest for substrates with strong electron withdrawing or donating substituents



As the rds is the same for both classes of substrates, perhaps changes in activation parameters is the source of enantiodivergence

■ Arrhenius study showed that the activation parameters are similar for both classes of substrates

	1	2
E_a (kcal/mol)	1.6	3.3
A ($M^{-1}S^{-1}$)	13.4	3.39×10^4
ΔH^\ddagger	1.2	2.9
ΔS^\ddagger	-54.6	-39.0
ΔG^\ddagger	12.1	10.7

Conclusions:

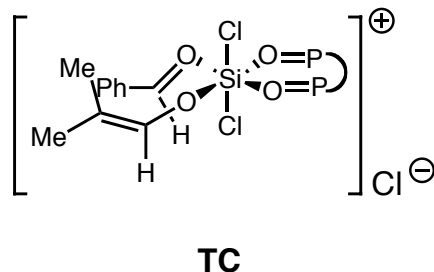
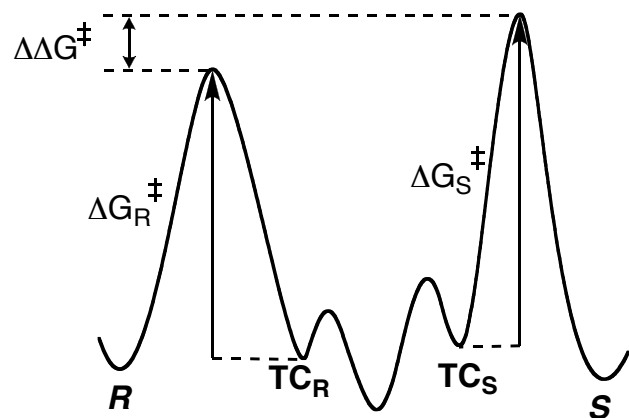
1. Large, negative ΔS^\ddagger indicates a highly ordered activated complex at the transition state
2. The similarities in activation parameters suggest that both classes of substrates undergo the same mechanistic pathway

⇒ *The difference in enantioselectivities must arise from a change in other factors affecting selectivity*

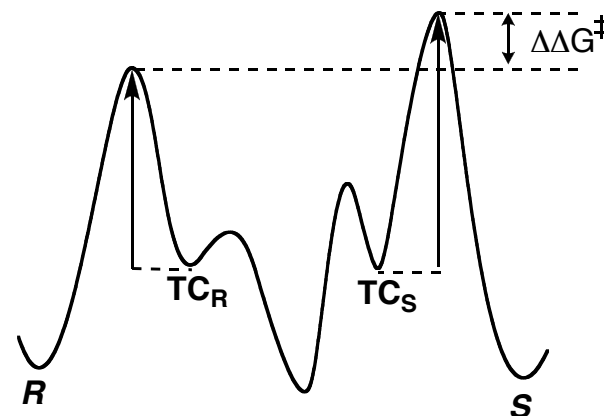
Using Kinetics to Interpret Selectivity Trends

■ The authors invoke the Hammond postulate, Curtin-Hammett principle and reaction coordinate diagrams to try and rationalize the observed selectivity trend.

Case 1: aldolization is stereochemistry determining

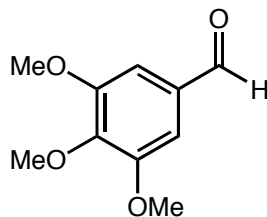


Case 2: binding is stereochemistry determining



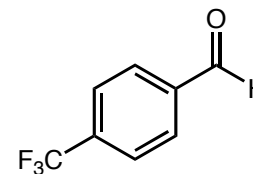
● aldehyde binding is fast (early TS) while aldolization is slow (late TS)

● this scenario is under Curtin-Hammett control



the more electron rich the aldehyde, the later the transition state for aldehyde binding and the better the selectivity

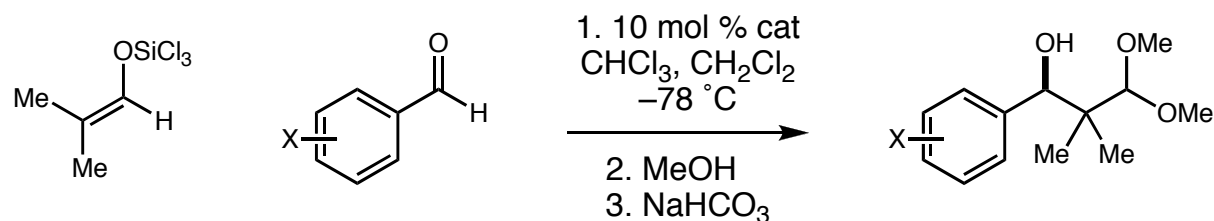
● aldehyde binding is slow (late TS) while aldolization is fast (early TS)



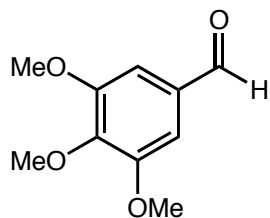
the more electron deficient the aldehyde, the later the transition state for aldehyde binding and the better the binding stage

Using Kinetics to Interpret Selectivity Trends

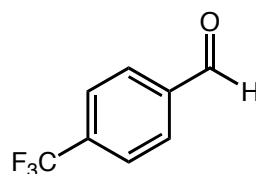
■ As seen from the previous example, applying kinetic analyses to multi-step organic reactions is not always straightforward



need to invoke two scenarios to explain the observed selectivity



selectivity from aldolization



selectivity from aldehyde binding

■ It is easy to make mistakes and use analyses that are inappropriate for the situation, ie, using an Eyring analysis in an Arrhenius situation

E_a , A: can be obtained for any reaction

$$E_a = \Delta H^\ddagger + RT$$

ΔG^\ddagger , ΔS^\ddagger , ΔH^\ddagger : only for elementary reactions

this is true only for single step,
unimolecular reactions

■ Most organic mechanisms are complicated and contain several steps whereas kinetic analyses are often for simplified systems

Conclusions

■ Terminology is important, using the correct words and phrases is key to communication and is imperative in a field where slight differences of phrasing can make a huge difference

■ Reactions are all about energy and the theoretical basis for analyzing reaction kinetics are energy surfaces and reaction coordinate diagrams.

■ The physical organic postulates and principles that we use provide us with a way to think about how and why reactions take place and allow us to predict chemical behavior

■ A variety of kinetic scenarios have been described and it is important to always use an analysis that is appropriate to what is actually happening

■ Kinetics can become very complicated very quickly as one moves from the realm of elementary reactions to the multi-step organic transformations we encounter every day

■ A kinetic analysis by itself is often not enough to determine mechanism, however, when used in conjunction with LFER techniques, they can lend enormous insight into the mechanistic basis of reactivity and selectivity trends