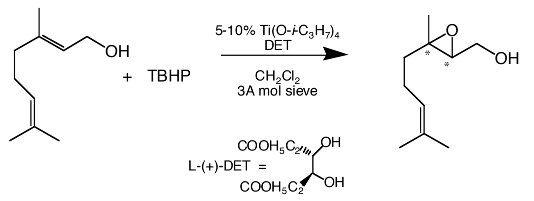
Reaction Kinetics in Organic Reactions

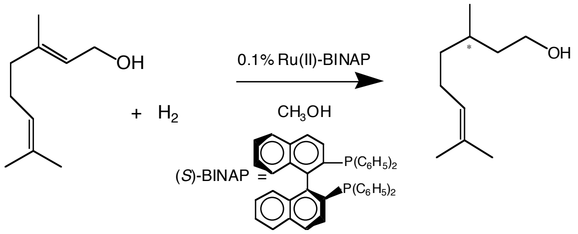
Why are kinetic analyses important?

- Consider two classic examples in asymmetric catalysis:

geraniol epoxidation



geraniol hydrogenation

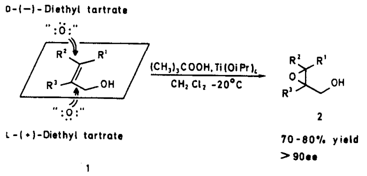


- In both cases, high enantioselectivities may be achieved. However, there are fundamental differences between these two reactions which kinetics can inform us about.

Kinetics of Asymmetric Catalytic Reactions

geraniol epoxidation:

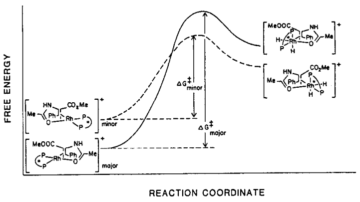
- *enantioselectivity is controlled primarily by the preferred mode of initial binding of the prochiral substrate and, therefore, the relative stability of intermediate species. The transition state resembles the intermediate species.*



Finn and Sharpless in Asymmetric Synthesis, Morrison, J.D., ed., Academic Press: New York, 1986, v. 5, p. 247.

geraniol hydrogenation:

- *enantioselectivity may be dictated by the relative reactivity rather than the stability of the intermediate species. The transition state may not resemble the intermediate species.*



for example, hydrogenation of enamides using Rh^+(dipamp) studied by Landis and Halpern (*JACS*, **1987**, *109*,1746)

Kinetics of Asymmetric Catalytic Reactions

> “Asymmetric catalysis is four-dimensional chemistry. Simple stereochemical scrutiny of the substrate or reagent is not enough. The high efficiency that these reactions provide can only be achieved through a combination of both an ideal three-dimensional structure (*x,y,z*) and suitable kinetics (*t*).”

R. Noyori, *Asymmetric Catalysis in Organic Synthesis*,Wiley-Interscience: New York, 1994, p.3.

> “Studying the photograph of a racehorse cannot tell you how fast it can run.”

J. Knowles, *Angew. Chemie Int. Ed. Eng. 1977.*

Transition State Theory

- Intermediate species are energy wells; they tell us about ***stability***

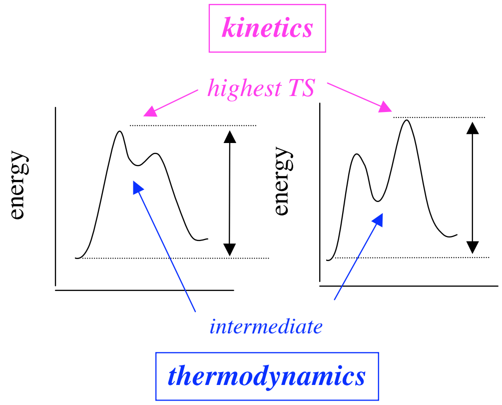
  The more stable an intermediate species, the higher its concentration

  this tells us nothing about how fast it reacts!

- Transition states are energy maxima; they tell us about ***reactivity***

  The lower in energy a transition state, the faster the reaction

  this tells us nothing about the population of intermediate species!



- The rate of the overall reaction is determined by the energy difference between that of the ***highest*** transition state and that of the reactant.

$\Delta G^{\ddagger}$ = *standard free energy of activation*

Reaction Rate

Consider the reaction:

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

How do we define the *rate* of the reaction?

First, we define something called the *extent* of the reaction:

$$\xi = \text{extent of reaction} = \frac{n_i - n_{i0}}{\nu_i}$$

Subscript i refer to the reactants and products
(A, B, C, and D)
n_{i0} means the number of moles of species i initially present
ν_i means the stoichiometric coefficient of species i
(-1,-1,1, and 1)

Reaction rate is defined as the instantaneous change in the extent of reaction per unit reaction volume:

$$\boxed{rate = \frac{1}{V} \cdot \frac{d\xi}{dt} = \frac{1}{\nu_i} \frac{1}{V} \cdot \frac{dn_i}{dt}}$$

Reaction Rate

$$\boxed{rate = \frac{1}{V} \cdot \frac{d\xi}{dt} = \frac{1}{\nu_i} \frac{1}{V} \cdot \frac{dn_i}{dt} = \frac{1}{\nu_i} \cdot \frac{dC_i}{dt}}$$

- For reactions in the liquid phase, the volume doesn't change very much over the course of the reaction: V ≅ constant. We can use the instantaneous change in species **concentration** as the variable we measure. Concentration ($C_i = n_i/V$) is given in units of molarity (moles/liter).
- This definition of reaction rate is the overall or global reaction rate, and it doesn't depend on which species i we choose.
- We can also define the reaction rate of a particular species i as follows:

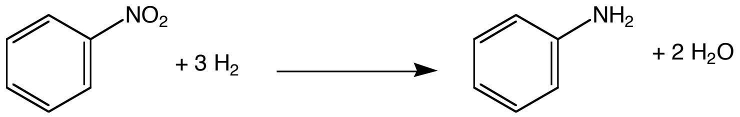
$$\boxed{\text{rate of reaction of species } i = rate \cdot \nu_i = \frac{dC_i}{dt}}$$

Reaction Rate

$$rate = \frac{1}{\nu_i}\frac{dC_i}{dt}$$

$$rate\ of\ reaction\ of\ species\ i\ =\ rate \cdot \nu_i = \frac{dC_i}{dt}$$

- Consider the following example:



- How do we measure rate?
  - By FTIR monitoring of $PhNO_2$ disappearance
  - By hydrogen pressure uptake
  - By monitoring production of water
- We get a different “species rate” for each of these.

Elementary Reactions

- an elementary reaction is one which occurs on a molecular level exactly as it is written
  - *this means that the rate expression for an elementary reaction may be written on inspection*
- the number of chemical species involved as reactants is referred to as the molecularity of the reaction
  - *almost all elementary reactions are either unimolecular or bimolecular*
- a reaction which is unimolecular in one direction may be bimolecular in the other direction!

Unimolecular reaction: $A \xrightarrow{k_1} B + C \qquad r = k_1 \cdot C_A$

Bimolecular reaction: $M + N \xrightarrow{k_2} P \qquad r = k_2 \cdot C_M \cdot C_N$

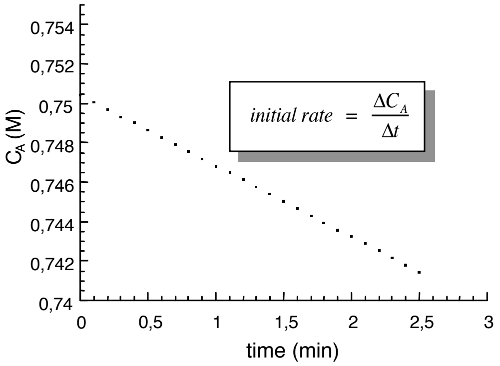
Empirical Kinetic Methods

- Experimental observations show that chemical reactions often depend on the concentrations of reactants.
- Empirical methods have been developed with the aim to determine the mathematical dependence of each substrate’s concentration.
- This mathematical relationship between rate and concentration is known as a reaction rate equation or reaction rate law.
- The most common approach is to look for a “**power law**” form of the rate law:

$$\text{reaction rate} = f(\text{concentration}) = k \cdot C_A^x C_B^y$$

Initial Rate Methods

- Holding the concentration of one substrate constant, we measure the change in concentration of second substrate over a brief period of time at the beginning of the reaction.
- If the change is concentration of the substrate is not too large, then we can say that $\Delta C_A/\Delta t$ approximates the instantaneous change dC_A/dt at that value of C_A.
- We repeat this experiment using different initial concentrations of substrate A (still holding substrate B constant).



$$\text{initial rate} = \frac{\Delta C_A}{\Delta t}$$

- From this set of experiments, we can build a plot of rate ($\Delta C_A/\Delta t$) vs. C_A.
- Then we carry out the same procedure again, this time holding C_B constant and varying C_A.

Initial Rate Methods

- Consider these nucleophilic substitution reactions of alkyl halides:

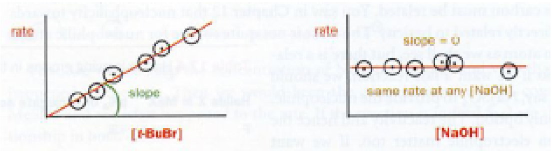
$$t\text{-}BuBr + NaOH \xrightarrow{k_1} t\text{-}BuOH + NaBr \qquad MeI + NaSMe \xrightarrow{k_2} MeSMe + NaI$$

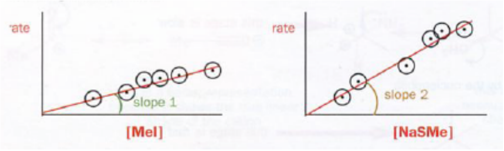
Monitor rate at:

constant [NaOH] constant [*t*-BuBr]

Monitor rate at:

constant [NaSMe] constant [MeI]





first order in [*t*-BuBr] zero order in [NaOH]

first order in [NaSMe] first order in [MeI]

S_N1 **S_N2**

Methods for Non-Integer Order

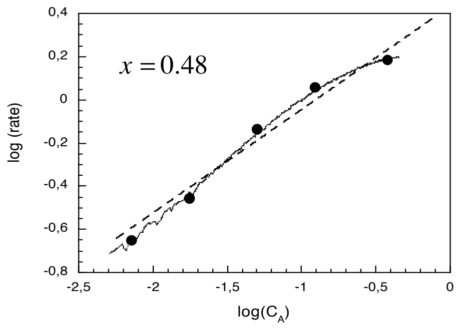
- If we don't get a straight line plotting rate vs. C_A, we can plot the data differently to determine the reaction order in species A.
- The orderin substrate A may be obtained by plotting a different relationship to obtain a straight line:

$$rate = k \cdot C_A^x C_B^y$$
$$\log(rate) = \log(k \cdot C_A^x C_B^y)$$
$$= \log(k \cdot C_B^y) + \log(C_A^x)$$

$$\log(rate) = \boxed{\log(k \cdot C_B^y)} + \boxed{x} \cdot \log(C_A)$$

constant (y-intercept)

reaction order in C_A (slope)



IntegraTed Rate Equations

- Mathematical characterization of simple cases (for example, where x and y are 0, 1, or 2).

$$\text{reaction rate} = -\frac{dC_A}{dt} = k\cdot C_A^x C_B^y$$

We can integrate these equations analytically:

$$r = \frac{-dC_A}{dt} = k \longrightarrow C_A = C_{A0} - k\cdot t$$

$$r = \frac{-dC_A}{dt} = kC_A \longrightarrow \ln(C_A) = \ln(C_{A0}) - k\cdot t$$

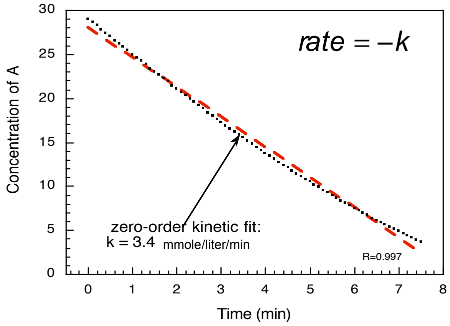
$$r = \frac{-dC_A}{dt} = kC_A^2 \longrightarrow \frac{1}{C_A} = \frac{1}{C_{A0}} + k\cdot t$$

$$r = \frac{-dC_A}{dt} = kC_AC_B \longrightarrow \ln\left(\frac{C_B}{C_A}\right) = \ln\left(\frac{C_{Bo}}{C_{Ao}}\right) + \left(C_{Ao}\upsilon_B - C_{Bo}\upsilon_A\right)kt$$

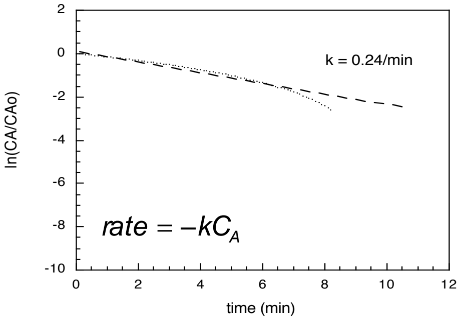
$$\ln\left(\frac{C_B}{C_A}\right) = \ln\left(\frac{C_{Bo}}{C_{Ao}}\right) + \left(C_{Bo} - C_{Ao}\right)kt \qquad \text{when } \upsilon_A, \upsilon_B = -1$$

Following reactions as a function of time

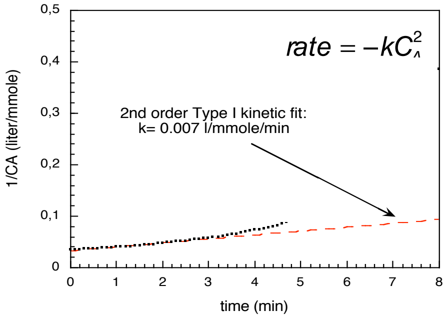
Zero order



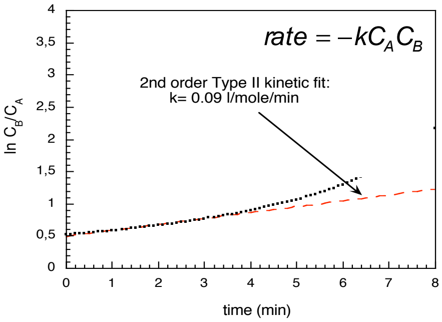
First order



Second order Type I



Second order Type II



Limitations of Empirical Methods

- These mathematical descriptions are simply and solely mathematical constructs to help reveal trends in the experimental data
- The reaction order obtained with any of these methods may have no physical meaning or relationship to the intrinsic reaction processes occurring on the molecular level
- These methods may be useful for thinking about reactions for which not much is known about the *reaction mechanism*

the more we know about how the reaction proceeds on the molecular level, the better we will be able to model its behavior so that we may carry it out under any conditions of scale, temperature and composition

➪ ***REACTION MECHANISM!***

Reaction Mechanisms

- a *reaction mechanism* is a series of elementary steps through which it is proposed that a reaction proceeds
- a mechanism is a hypothetical construct and cannot be proven! At best, it may be said that a proposed reaction mechanism is *consistent with the experimental evidence*
- elementary steps in a proposed reaction mechanism often contain *intermediate species* which may be impossible to isolate or even to detect
- the reaction mechanism must represent the overall observed reaction stoichiometry *via* a linear combination of the proposed elementary steps (this just means that we add up the steps we need to get the overall rate expression)
- any intermediates produced in the elementary steps in the mechanism must be eliminated to obtain the final rate expression
- a postulated mechanism for a reaction in the forward direction must also hold for the reverse reaction (*principle of microscopic reversibility*)

Observed Reactions: Rate-Limiting Step

- What we observe are almost *never* elementary reactions, but instead a combination of elementary reactions
- *How can we describe the rate of these global reactions?*

Example: S_N1 reaction mechanism

$$Ph_2CHCl + X^- \longrightarrow Ph_2CHX + Cl^-$$

$$Ph_2CHCl \underset{\longleftarrow}{\xrightarrow{slow}} Ph_2CH^+ + Cl^-$$

$$Ph_2CH^+ + X^- \xrightarrow{fast} Ph_2CHX$$

The reaction rate is <u>*controlled*</u> or <u>*limited*</u> by the rate of formation of the carbocation intermediate:

$$rate = k_{slow} \cdot \left[Ph_2CHCl\right]$$

Experimental Observations:

- Rate is independent of nucleophile concentration
- Rate is independent of nucleophile identity

- Therefore the addition of X^- must be much faster than the formation of the carbocation

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Rate-Limiting Step: Common Misconceptions

- Do we need to know the rate-limiting step to write a rate expression for a proposed mechanism?

  No! We can always write the reaction simply as the rate of appearance of product, using the last step. Defining a rate-limiting step may help to simplify the general rate expression.

- Do all reactions have a rate-limiting step?

  No! In many reactions, several steps contribute more or less equally to the total time required to produce a molecule of product.

- Can the rate-limiting step change as the reaction progresses?

  Yes! Especially in catalytic reactions with intermediate species, different steps may dominate in different concentration ranges

- Is the rate-limiting step always the same for all products formed?

  No! In reactions where several products may be formed, the rate-limiting step may be different for each one, or the rate-limiting step for each product may change differently with changes in reactant concentration

- Does the rate-limiting step describe the concentration dependence of the reaction?

  Not necessarily. Completion of the reaction can depend on species which are not included in the rate law for the rate-limiting step.

Rate-Limiting Step: Reading Material

K. J. Laidler:

Is the Rate-Limiting Step a Necessary or Useful Construction?

J. Chem. Ed., **1988**, vol. 65, p. 250.

J. J. Murdoch:

What is the Rate-Limiting Step of a Multi-Step Reaction?

J. Chem. Ed., **1981**, vol. 58, p. 32.

Reaction Rate Expressions

- We can always write the rate in terms of the rate of the elementary step in which the product is formed:
- For S_N1 reaction mechanism, this is:

$$Ph_2CHCl + X^- \longrightarrow Ph_2CHX + Cl^-$$

$$Ph_2CHCl \mathrel{\substack{\xrightarrow{slow} \\ \longleftarrow}} Ph_2CH^+ + Cl^- \qquad rate = k_{fast} \cdot \left[Ph_2CH^+\right] \cdot \left[X^-\right]$$

$$Ph_2CH^+ + X^- \xrightarrow{fast} Ph_2CHX$$

- The problem is that we don't know how to measure the concentration of intermediate species.
  - Reaction rate expressions must be written only in terms of species present in the global reaction expression.
- How can we put the concentrations of intermediate species in terms of concentrations of species we can measure?

Solving for Intermediate Species

We need to make an assumption to solve for the concentration of the intermediate species [Ph$_2$CH$^+$]

$$Ph_2CHCl \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} Ph_2CH^+ + Cl^-$$

$$Ph_2CH^+ + X^- \xrightarrow{k_2}{}^{-} Ph_2CHX$$

- Bodenstein Steady-State Approximation

If the intermediate concentration is very small compared to the substrate concentration, then the rate of change in concentration of the intermediate species will also be very small, and we may set this rate equal to zero.

$$\frac{d\left[Ph_2CH^+\right]}{dt} \approx 0 = \overset{\textit{production}}{\overbrace{k_1[Ph_2CHCl]}} - \overset{\textit{consumption}}{\overbrace{k_{-1}\left[Ph_2CH^+\right]\left[Cl^-\right]}} - \overset{\textit{consumption}}{\overbrace{k_2\left[Ph_2CH^+\right]\left[X^-\right]}}$$

Solving for Intermediate Species

Rate is equal to the rate of the final step:

$$rate = k_2\left[Ph_2CH^+\right]\left[X^-\right]$$

$$Ph_2CHCl \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} Ph_2CH^+ + Cl^-$$

$$Ph_2CH^+ + X^- \xrightarrow{k_2} Ph_2CHX$$

Bodenstein Steady-State Approximation

$$\frac{d\left[Ph_2CH^+\right]}{dt} \approx 0 = k_1[Ph_2CHCl] - k_{-1}\left[Ph_2CH^+\right]\left[Cl^-\right] - k_2\left[Ph_2CH^+\right]\left[X^-\right]$$

$$\left[Ph_2CH^+\right] = \frac{k_1[Ph_2CHCl]}{k_{-1}\left[Cl^-\right] + k_2\left[X^-\right]} \xrightarrow{\textit{substitute}} \boxed{rate = \frac{k_1k_2[Ph_2CHCl]\left[X^-\right]}{k_{-1}\left[Cl^-\right] + k_2\left[X^-\right]}}$$

Solving for Intermediate Species

Can we reconcile our two rate expressions?

$$rate = k_1\left[Ph_2CHCl\right]$$

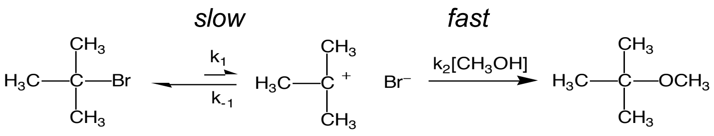
$$rate = \frac{k_1 k_2\left[Ph_2CHCl\right]\left[X^-\right]}{k_{-1}\cancel{\left[Cl^-\right]} + k_2\left[X^-\right]}$$

If $k_{-1}[Cl^-] << k_2[X^-]$, then the two expressions are the same.

- This means that the backwards rate of the first step is ***much slower*** than the forward rate of step 2.

- The S_N1 reaction will only be zero-order in nucleophile concentration if the k_{-1} term is ***small.***

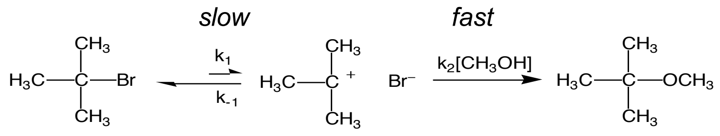
S_N1 Reaction Mechanism Revisited



- Conclusion: the S_N1 reaction will only be zero-order in nucleophile concentration if the k_{-1} term is very small in magnitude.
- Then why do the books write the backwards arrow longer than the frontwards arrow?
  - The forward reaction is a first order reaction.
  - The reverse reaction (for solvent-separated pairs) is a second-order reaction.
  - Rate constants for first and second order reactions have different units:

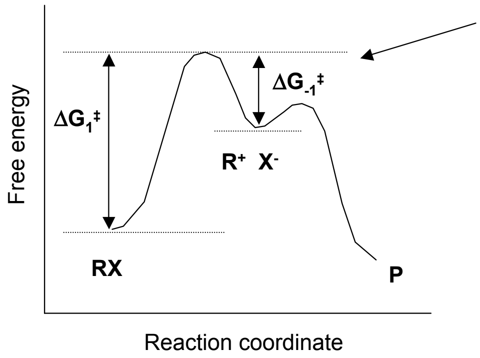
    k_1: s^{-1} k_{-1}: $M^{-1}s^{-1}$
  - Most textbooks set an arbitrary "standard state" in which the concentration of the second substrate (X^- in this case) equals 1 M so that they can compare k_1 with a "pseudo-first-order rate constant k_{-1}*(1 M).
  - However, $[X^-]$ = 1 M is highly unrealistic (by many orders of magnitude!) in this case.

S_N1 Reaction Mechanism Revisited



RX **R^+** **X^-** **P**

- Free energy diagrams also perpetuate the myth of the backwards arrow.



This makes it look like the reverse reaction ($k_{-1}[Br^-]$) is much faster than carbocation formation ($k_1[(CH_3)_3CBr)]$)

Activation energies are directly related to reaction rates *only* for unimolecular reactions.

Energy diagrams are designed for a unimolecular world!