##### Mechanisms

Mechanism = description of rearrangement of reactants as they proceed to products

## Never can prove a mechanism, only disprove it

covalent bonds are usually broken or formed during a reaction

classifications:

1. heterolytic - electrons on bond remain with one fragment

2. homolytic - each fragment retains one electron

3. pericyclic - cyclic transition state, no intermediates

4. electron transfer – bond making/breaking usually follows

## Predicting products: Thermodynamic Requirements

1. free energy must be negative

2. G = H - TS, G = -RTLnK

3. entropy effect is often small compared to enthalpy except in certain cases

(a) phase change involving gases: gases have higher entropy than liquids and solids

(b) molecularity change

(c) high temperatures

(d) ring formation and breaking

4. enthalpy can be calculated directly from enthalpies of formation of reactions and products

Hrxn = Hf(products) - Hf(reactants)

hydrogenation of butene: – 30.15 (*n*-butane) – 0 (H2) + 2.67 (*t*-2-butene) = – 27.48

experimental heat is –27.5 kcal/mol

5. Reaction enthlapies can be calculated from broken and formed bond energies

H = bond dissociation energies formed – bond dissociation energies broken

only applies if actual values are known

**hydrogenation of ethene**

|  |  |  |  |
| --- | --- | --- | --- |
| Bonds formed |  | Bonds broken |  |
| H-CH2CH3 | 2 x 98.2 | H-H | 103 |
| CH3-CH3 | 88 | C=C | 171 |
| sum | 284.4 |  | 274 |
| H =-10.4 kcal/mol (7.5 from Hf) | | | |

Actual process does not correspond to bond energies used



**Methods of Determining a Mechanism**



**Identification of Products**: mechanism must account for products

**Identify intermediates**

1. stop reaction in progress and isolate intermediate



2. observe intermediate during reaction (hydroxyl amine)

3. trap intermediate with reactive reagent (carbene with olefin)

4. may not be intermediate

5. independently create intermediate under identical conditions (common intermediate)

**Isotopic Labeling** - mechanism requires a label to appear at specific sites



ester hydrolysis with H2O18, example:

**Stereochemistry** - mechanism requires stereochemistry to be preserved or lost



Br2 addition to cyclopentene: explain anti? Syn? mixture products? 1,3 addition?

**kinetic evidence**

#### Rate law - indicates which component contributes to RDS

1. follow appearance of product or disappearance of reactant

|  |  |  |  |
| --- | --- | --- | --- |
| [H+] | [A] | [B] | rate |
| 0.001 | 0.1 | 0.1 | 1 x 10-4 |
| 0.001 | 0.2 | 0.1 | 2 x 10-4 |
| 0.001 | 0.1 | 0.2 | 4 x 10-4 |
| 0.004 | 0.1 | 0.1 | 2 x 10-4 |

2. determine dependence on reactants, catalyst, product

3. rate = d[product]/dt, units are mol/Ls

4. example: rate = ko + k[H+]1/2[A][B]2

order of reaction is 3 1/2, 1/2 in [H+], 1st in [A] and 2nd [B] (sum of exponents)

5. compare rate law with proposed mechanism

inital rates (< 10%) can be determined for complex reaction to avoid change in concentrations

**common rate laws**

1. first-order rate law,  (units of k1?)

2. 2nd-order rate law, 

3. 2nd/3rd-order law





, steady state assumption



for 

for 

for 

a useful rate law is expressed in terms of observable species (reactants)

**Integrated rate expression**

1st-order in A, 



plot ln[Ao/At] versus t, slope is k1, units are s-1

**2nd-order in A**

:  



plot 1/[A] - 1/[A]o versus t

k is the rate constant of the event not the rate of molecules disppearing (units are M-1 s-1)

**mixed second order**

use pseudo-1st order conditions

, units = s-1

plot ln([A]o/[A]t) versus t, slope = k1[B]

**Reaction Half-Life**

1. most useful for 1st-order and pseudo 1st-order processes, independent of concentrations

[A]t1/2 = 1/2 [A]0 ,, ln[2] = 0.693 = k1t1/2

t1/2 = 0.693/k1 1/k1 , *e. g.* 10-9 s 109 s-1 or 10 hr 1/10 hr-1 (t1/2 ≡ 1/k1)

note no concentration dependence

2. higher order processes dependent on initial concentration



*i.e.* increasing A decreases lifetime

**Rates of Molecular processes**

1. unimolecular frequency of vibration (velocity of fragments) 1012 - 1013 s-1

2. bimolecular limited by diffusion, reactant must "meet" diffusion rate 109 - 1011 s-1 in solution, depends on viscosity of media and molecular size

3. termolecular is seldom encountered

**Eyring Equation**

1. theory of transition state decomposition – show rxn coordinate for A+B → TS → product

2. rate of transition state breakdown = kBT/h = 6 x 1012 @ 25 oC

=transmission coefficient =1, kB = Boltzman, T = temp in Kelvin, h = Planck's

rate= [TS]kBT/h

, , rate = K\*[A][B]kBT/h

G\* = -RTlnK\*, = free energy difference between reactants and TS, 

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| G\* | 4.2 | 14 | 24 | 28 |
| k | 1010 | 103 | 10-4 | 10-7 |
| t1/2 | 10-10 | 10-3 | 104 | 107 |
|  | 100 ps | 1 ms | 3 hr | 4 mo |
| assumes B in excess at 1 **M**. | | | | |

rate = , rate constant =  for 

3. log k = 13 - G\*/1.4 @ 25 oC (G\* = kcal/mol)

4. G\* =H\* - TS\* substituting, 

5. ln k/T = ln kB/h + S\*/R - H\*/(RT), plot Ln k/T versus 1/(RT)

slope = H\*, calculate S\* from intercept

6. H\* is almost always positive, larger the more bond breaking in TS

7. S\* is negative if # of components decrease in TS, positive if increased

solvation can make interpretation tricky, *e.g.* SN1 in polar solvents is negative

**Arrhenius equation**

, log k = log A - Ea/(2.303RT)



**Linear Free-Energy Relations**

A. Hammett observed the rate of base hydrolysis of aromatic esters and reactions of other aromatic compounds correlated with the acid dissociation constants of related aromatic acids. x indicates substituent on aromatic ring

B. log kx =  log Kx + C

C. substituents that increase Kx also increase kx: NO2 increases as acidity (stabilizes anion) and rate of hydrolysis (increases the positive charge density at the carbonyl).



D. X = H: log kH =  log KH + C

log kx - log kH = log Kx -  log KH

log kx/kH =  log Kx/KH

x = log Kx/KH is a measure of electronic effects of X, x ≡ Hammett substituent constant

- electron withdrawing groups have positive x and electron donating groups have negative x

- other rates and equilibria can be correlated with x

- the  values indicate sensitivity to substituent changes relative to ionization of benzoic acid derivatives.

x =(log Kx/KH)benzoic acids = (-Gx/RT + GH/RT)benzoic acids

for some reaction sensitive to electronic effects we have

log Kx/KH = (log Kx/KH)benzoic acids = (-Gx/RT + GH/RT) = (-Gx/RT + GH/RT)benzoic acids

similarly

log kx/kH = (log Kx/KH)benzoic acids = (-G\*x/RT + G\*H/RT) = (-Gx/RT + GH/RT)benzoic acids

**E. sign and magnitude of **

1. ionization of benzoic acid derivatives by definition have  =1.

2. reactions with positive  have increase in charge density in TS (or product)

3. reactions with negative  have decrease in charge density in TS (or product)

|  |  |  |
| --- | --- | --- |
| group | p | m |
| O- | -0.81 | -0.47 |
| OH | -0.38 | 0.13 |
| OMe | -0.28 | 0.10 |
| H | 0 | 0 |
| F | 0.15 | 0.34 |
| Cl | 0.24 | 0.37 |
| Br | 0.26 | 0.37 |
| I | 0.28 | 0.34 |
| NH3+ | 0.60 | 0.86 |
| N2+ | 1.93 | 1.65 |

4.  is negative for the protonation of anilines

5. | > 1 if reaction is more sensitive to substitutent effects that ionization of benzoic acids (reverse is also true, e.g. 2-phenylethanoic acid derivative)

**Compare x**

Deviation from LFER indicates change in mechanism (see figure above) or electronic effect different than reference reaction.



**Taft Ingold equation**

Ingold noted that acid and base hydrolysis of aliphatic esters are nearly equal in sensitivity to steric effects and that acid hydrolysis was insensitive to electronic effects



thus log(kx/kH)A = Es (Es is steric parameter,  indicates sensitivity to steric effects)

and I = 0.181[log(kx/kH)B -log(kx/kH)A] (electonic parameter)

in general for alkyl systems: **log kx/kH = II + Es**

the more negative Es the greater the steric bulk of X

consider thiol adition to aldehydes versus ketones.

**Isotope Effects**



1. rate can change if reactant has isotopic substitution (chlorination of ketone)

2. deuterium for hydrogen most popular, kH/kD

3. rate is usually slower due to difference in 0-point vibrational energy

4. position in potential energy for vibration determined by reduced mass

5. maximum is 7 for CH, 11 for OH and 6 for NH+

6. for CH, kH/kD = 2-7 for primary isotope effect, kH/kD = 1-2 for secondary

primary: bond broken in TS, timing effects magnitude

secondary: broken before or change in bonding (*e.g.* hybridization)



7. iodination of phenol

(a) rate =

(b) k2 [B] >> k-1[I-] then secondary isotope effect (kH/kD = 1-2)

(c) k-1[I-] >> k2[B] , second step is RDS, then **primary isotope** effect

(d) observed kH/kD 4

8. hydrolysis of benzyl chloride

, kH/kD 1.4 ( secondary isotope effect)

, kH/kD 1.1 ( secondary isotope effect)

9. **inverse isotope effect** - greater bonding in TS



10. in following hydrogen transfer from Mn, kH/kD 0.4

R2C=CH2 + HMn(CO)4 → •Mn(CO)4 + R2•CCH3

###### CH bond forming in TS, C-H is stronger than Mn-H

11. rigorous treatment requires consideration of all bond vibration changes



= exp[0.1865/T], for CH bonds,  in cm-1

**Kinetic versus Thermodynamic control**

1. low temperatures favor product with lowest activation energy even if not most stable

2. high temperature favors most stable product even if barrier is higher, higher temperature allows access over higher barrier

## 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.”*

*“In highly exothermic steps it will be expected that the transition states will resemble reactants closely and in endothermic steps the products will provide the best models for the transition states.'*

**Curtin-Hammett Postulate (Move)**



absolute height difference between transition states determines relative rates for products formed

**Microscopic reversibility (Move)**



reaction always follows lowest energy path so path is same in reverse as it is in forward direction. Critique the following mechanism.

ACIDS and BASES

A. many reactions are acid and/or base catalyzed

B. reactive intermediates are often acids and bases

C. extent of formation of intermediates can be determined from pKas

1. strength of acid or base related to pKa of acid or conjugate acid

2. Ka defined by ability to protonate water  

3.  **pKeq = pKa = pKa1 - pKa2**, a1 = acid, a2 = conjugate acid, pKa = -logKa

4. strong acid (a1) + strong base weak acid (a2) + weak base

5 strongest acid in water is hydronium and strongest base is hydroxide

6. pKas are determined by the relative stability of acid and conjugate base

electronegativity: CH4 (48) NH3 (38) H2O (18) HF (5)

charge/field: NH3 (38) vs. NH4+ (9) CH3CO2H (5) vs. CF3CO2H (0)

delocalization: CH3CO2H (5) vs. CH3CH2OH (16)

hybridization: HCCH (25) H2C=CH2 (44) CH3CH3 (50)

overlap: HI > HBr > HCl > HF

solvation: H2O v *t*-BuOH in solution and gas-phase

**see list of pKa's**

D. proton transfer is diffusion controlled if pKa is 2 for transfer between heteroatoms

1. hydrogen bond is formed first

2. proton transter to and from carbon are almost always slower than diffusion control because of poor hydrogen bonding (why?) and reorganization

E. determination of pKa for very strong acids (conjugate acids of very weak bases)

1. Two problems:
   1. Typical determination of Ka for strong acid does not work, no HA: 
   2. Need acidic medium (conc. H2SO4) to inhibit dissociation: incomplete solvation H+, non-ideal behavior, concentrated acids or bases have greater activity if not completely solvated

2. create acidity function HO equivalent to pH, determined using indicators of known pKa in water

a. in a concentrated acid solution (*e.g*. 2 M H2SO4), effective concentration of acid will be greater than the apparent concentration

, , , 

from known Ka and a measurement of [HI]/[I-], a calculation of [H+] is greater than added acid!!!!, define new measure of acid strength (H0) to avoid confusion

b. H0 is defined for specific solvent and concentration of acid

c. pKa of stronger acid can be determined using new H0

d. series of H0 are determined with increasingly acidic indicators

e. similar functions can be obtained for basic solutions

**F. acid/base catalysis**

1. specific acid/base - rate dependent directly on pH, independent of acid or base used to adjust pH

2. general acid/base - rate depends on added acid or base even at constant pH

3. Bronsted acid catalysis law – GA or GB rate constant is proportional to acidity of acid

log k =  log Ka + C,  can be 0-1, indicates extent of proton transfer in TS?

4. if reaction is general acid/base catalyzed then proton transfer occurs in RDS



**Separation of catalytic terms**

rate expression for scheme at left 



plot kobs v. [HA] at constant [H+]

slope = kHA (assuming not GB), intercept = k0 + kH+[H+]

repeat at other [H+]

plot intercepts versus [H+]

slope = kH+, intercept = k0

what if 

then  and plot kobs v. [HA] at constant [H+]

slope =  and intercept = k0 + kH+[H+], determine k0 + kH+ as above

plot slope v. 1/[H+], intercept is kHA and slope is kA-Ka

## GA equivalent ot SA + GB and GB is equivalent to SB + GA



comparison of kinetic expressions:

, , A = amide







if water addition is rds then k-1 >> k2[X-] and 

where , then rearrange to  and substituting for X-

 which is kinetically indestinguishable from the GA rate expression:

**Lewis Acids and bases**

A. Lewis acid - vacant or electron deficient orbital

B. Lewis base - pair of electrons (lone-pair,  and -electrons)

C. Hard Soft Acid Base Theory

1. soft acids and bases have low electronegativity and high polarizability

2. hard acids and bases have high electronegativity and low polarizability

3. **hard acids prefer to bond to hard bases and soft acids prefer to bond to softs bases**

4. hard acids and bases tend to form ionic bonds and soft acids and bases tend to form covalent bonds

**Marcus Theory (for single step processes)**

activation energy is composed of two parts

1.kinetic part - intrinsic free energy of activation G\*int: barrier that would occur if G of reaction was zero

2. thermodynamic part - results from G of reaction, wR and wP (work required to bring together reactant or products

3. for 

(a) G\* for OH- + MeOH (41.8 kcal/mol) and Br- + MeBr (23.7 kcal/mol)

(b) approximate symmetrical potential energy surface with parabolas facing up

-point of intersection corresponds to activation energies

-use average parabolas to create intersection at averaged barrier (32.3 kcal/mol)

-adjust vertically to reflect free energy of reaction (G = -23.4 kcal)

(c) 

(d) assume work terms are small



(e) 

Kurtz, J. L. *J. Org Chem.* **1983**, *48,* 5117.