

Chap. 6 Methods of Studying Organic Rxns

Determining Reaction Mechanisms

1. Identification of reaction products
2. Determination of Intermediates

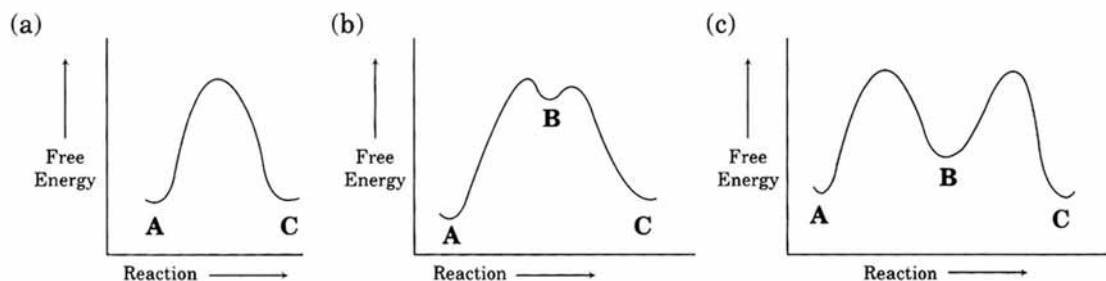
→ Determining no. of steps

(a one step reaction, with reaction \rightarrow T.S. \rightarrow product, is an elementary reaction)

if more than one elementary steps, an intermediate is involved



depending on the magnitude of k_1 , k_2 , the concentration of intermediate can be high or low



→ Isolating intermediate

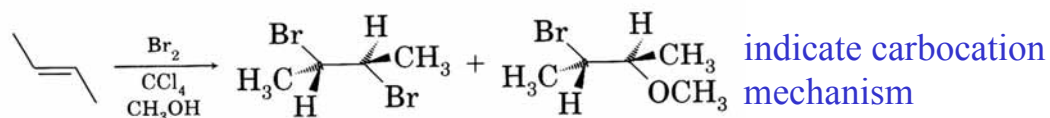
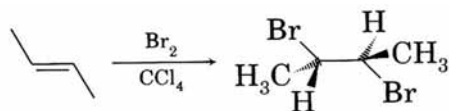
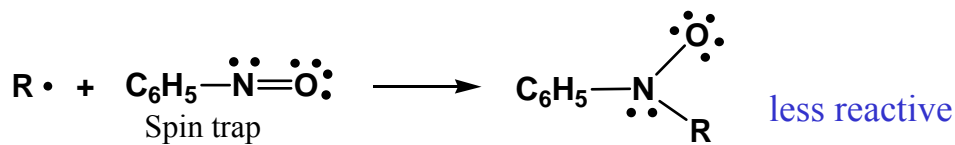
quench the reaction (by cooling, by diluting, by removing catalyst,.....)

→ Spectroscopic characterization

UV-VIS, IR, NMR, ESR.....

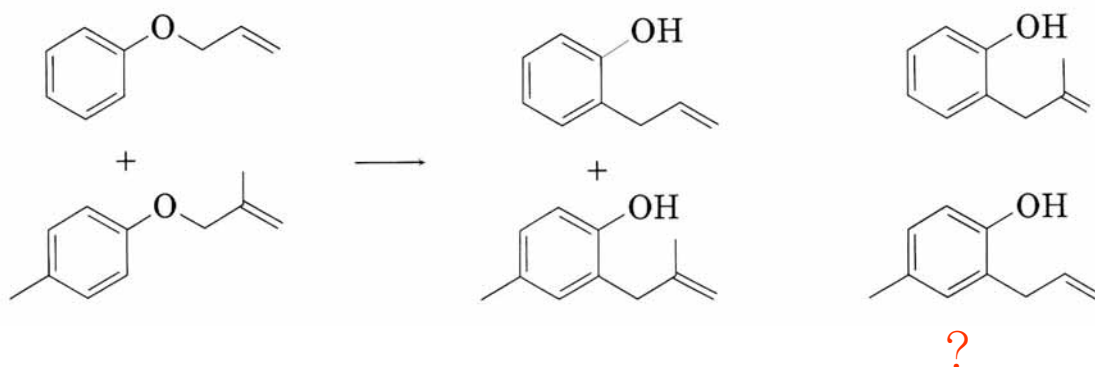
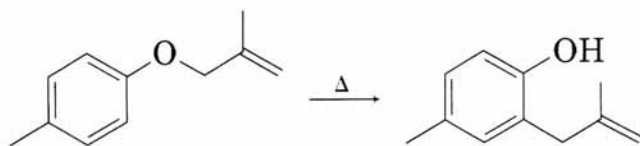
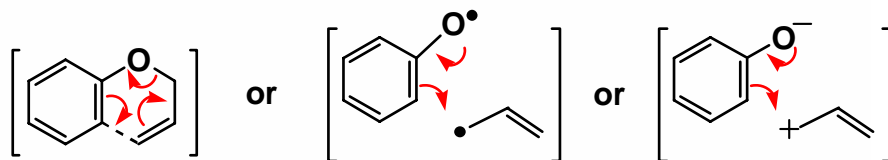
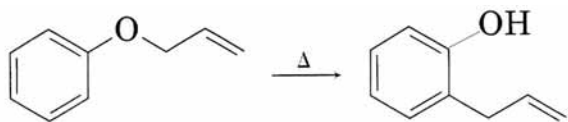
If not isolable, not spectroscopically observable,

→ trap the intermediate by a trapping agent



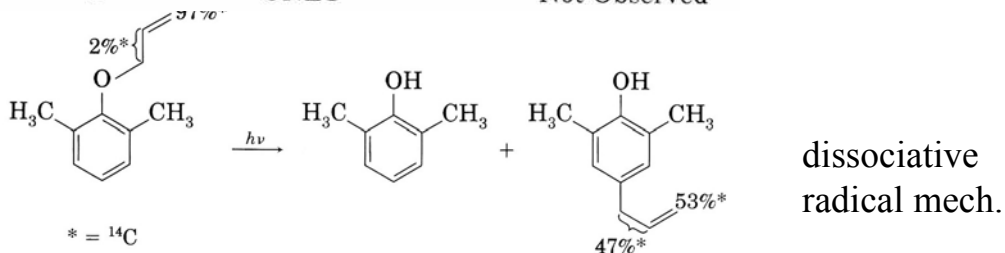
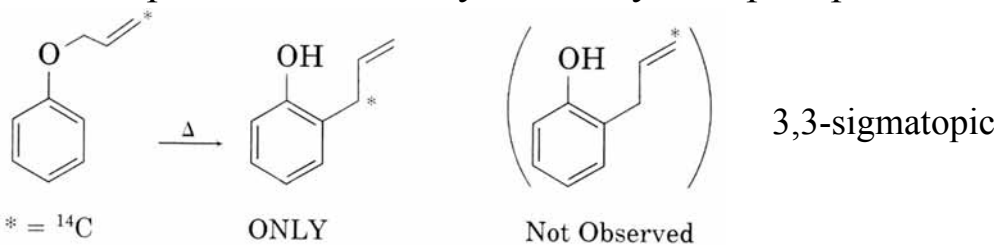
→ Disprove an intermediate
 synthesize a proposed intermediate and compare the reaction properties...

→ Crossover Experiment
 To differentiate intra-molecular or inter-molecular
 (inter fragmental)

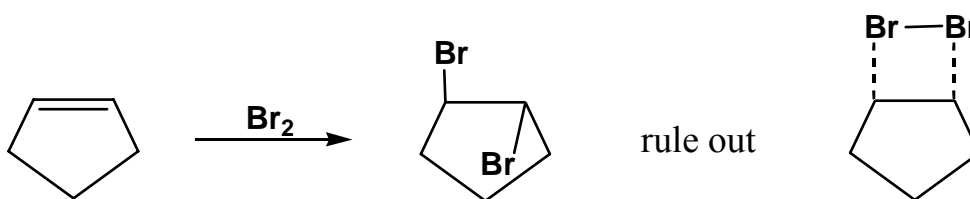
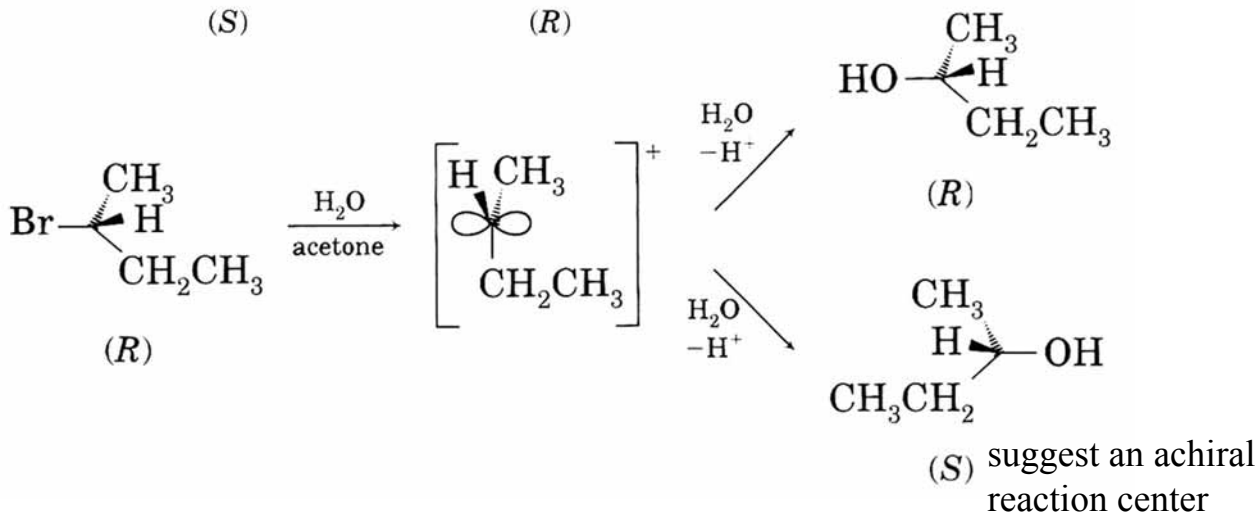
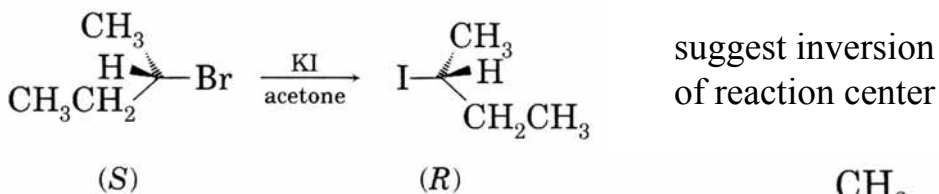


→ Isotope labeling

the least perturbation to a system is by isotope replacement



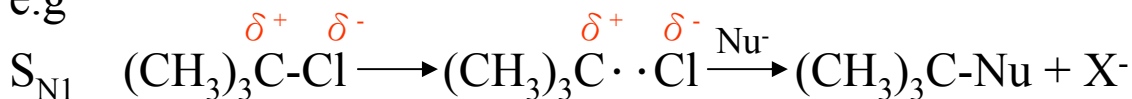
→ Stereochemical Studies



→ Solvent Effect

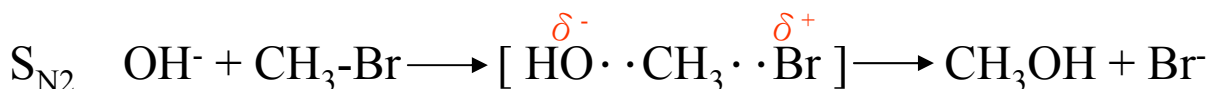
Solvent affects reaction rate through relative stabilization of reactants / transition → deduce T.S. structure

e.g



the rate increases with increasing solvent polarity.

→ more ionic character in T.S. than the reactant



The rate decreases with increasing solvent polarity

→ less ionic character in T.S. than starting material

Measurement of solvent polarity :

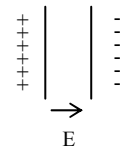
μ : dipole moment (a molecular property)

$$\begin{array}{c} +e \quad -e \\ \cdot \quad \cdot \\ \underbrace{\quad \quad \quad}_r \end{array} \quad +e = 4.8 \times 10^{-10} \text{ esu, for } r = 1 \times 10^{-8} \text{ cm}$$

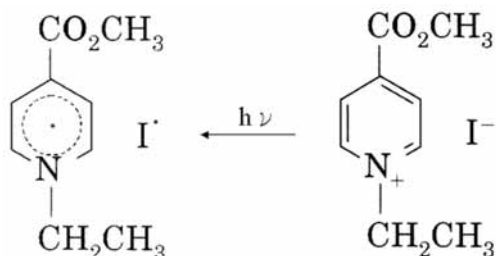
$$\mu = e \cdot r = 4.8 \times 10^{-18} \text{ esu} \cdot \text{cm}$$

$$= 4.8 \text{ D}$$

ϵ : dielectric constant, effect of substance on the E-field between an capacitor, relating to polarity and polarizability

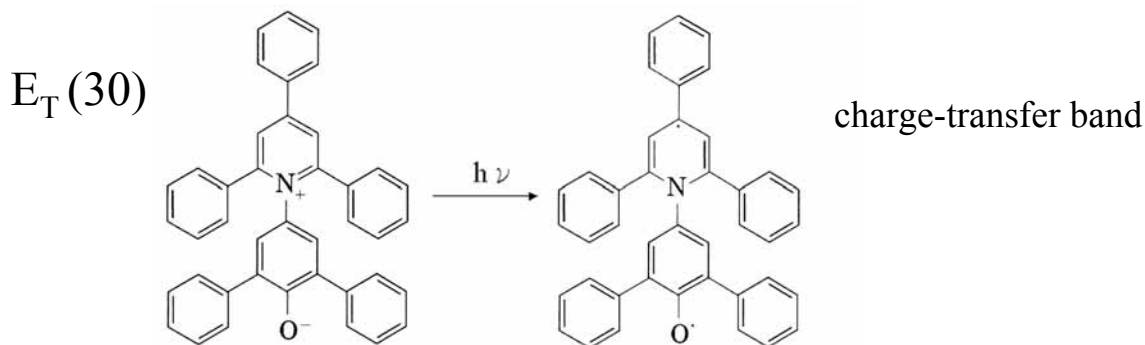
Hexane	1.89	H ₂ O	78.4		$E = \frac{E_0}{\epsilon}$
CCl ₄	2.23	MeOH	32.7		
CHCl ₃	4.8	EtOH	24.5		
		n-PrOH	20.4		

Z : Kosower scale



the charge-transfer band is sensitive to solvent

the transition energy : $Z = E_T$



α : acidity as H-bonding Donor (the ability of the solvent to donate a proton in solvent-solute H-bond)

β : basicity as H-bonded Acceptor

Table 6.1 Solvent parameters.

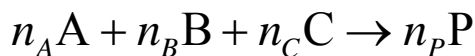
Solvent	ϵ^a	$\mu(D)^a$	Z^b	$E_T(30)^c$	π^*	β	α^f
Formamide	111.0	3.37	83.3	56.6	0.97	0.48 ^g	0.71
Water	78.4	1.8	94.6	63.1	1.09	0.47 ^g	1.17
Formic acid	58.5	1.82		54.3	0.65 ^g	0.38 ^g	1.23 ^g
Dimethyl sulfoxide	46.5	4.06	71.1	45.1	1.00	0.76	0.00
<i>N,N</i> -Dimethylformamide	36.7	3.24	68.5	43.8	1.00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

^aData from the compilation in reference 34. ^bData from reference 38. ^cData from the compilation in reference 39, pp. 365–371. ^dData from the compilation in reference 35, p. 301. ^e(0.13 M EtOH). ^fValues for π^* , β , and α from reference 40. ^gData from the compilation in reference 42.

§ Application of Kinetics in Studying Rxn Mechanism

reaction rate : rate of change of concentration of reactant or product

For a reaction



$$\text{rate} = -\frac{1}{n_A} \frac{dA}{dt} = -\frac{1}{n_B} \frac{dB}{dt} = -\frac{1}{n_C} \frac{dC}{dt} = \frac{1}{n_P} \frac{dP}{dt}$$

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

overall reaction order = a + b + c. ← determined by experiment
not by stoichiometry

(For elementary reaction

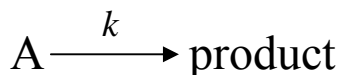
the order of the reaction = the no. of reacting molecule
= molecularity)

Pseudo order : if one reactant doesn't change its concentration significantly, e.g. $[C] \doteq \text{const}$

$$\text{rate} = k' [A]^a [B]^b, \text{ reaction order} = a + b$$



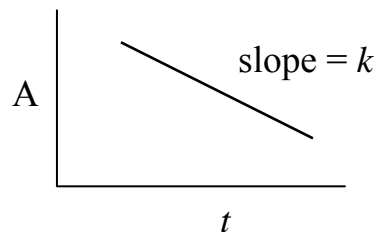
zero order



$$\text{rate} = -\frac{dA}{dt} = k \quad \int -dA = \int k dt$$

Differential rate equation

$$A - A_0 = -kt \quad \text{Integration rate equation}$$

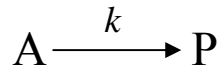


e.g. Saturation reaction on the surface of a metal

half life $t^{1/2} = \text{the time for } A = \frac{A_0}{2}$

$$\frac{A_0}{2} - A_0 = -kt^{1/2}, \quad t^{1/2} = \frac{A_0}{2k}$$

First order reaction



$$-\frac{d[A]}{dt} = k[A], \quad \int \frac{d[A]}{[A]} = -\int k dt$$

$$\ln \frac{[A]}{[A]_0} = -kt, \quad [A] = [A]_0 e^{-kt}, \quad t_{1/2} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

plot $\ln[A]$ v.s $t \rightarrow$ straight line, slope $= -k$

Second order reaction



$$\frac{d[P]}{dt} = -\frac{d[A]}{2dt} = k[A]^2,$$

$$\frac{d[A]}{2[A]^2} = -k dt, \quad \int \frac{d[A]}{[A]^2} = -\int 2k dt, \quad \frac{1}{[A]} - \frac{1}{[A]_0} = 2kt$$

plot $\frac{1}{[A]}$ v.s $t \rightarrow$ straight line slope $= 2k$

$$t_{1/2} : \quad \frac{2}{[A]_0} - \frac{1}{[A]_0} = 2kt_{1/2} \quad t_{1/2} = \frac{1}{2k[A]_0}$$

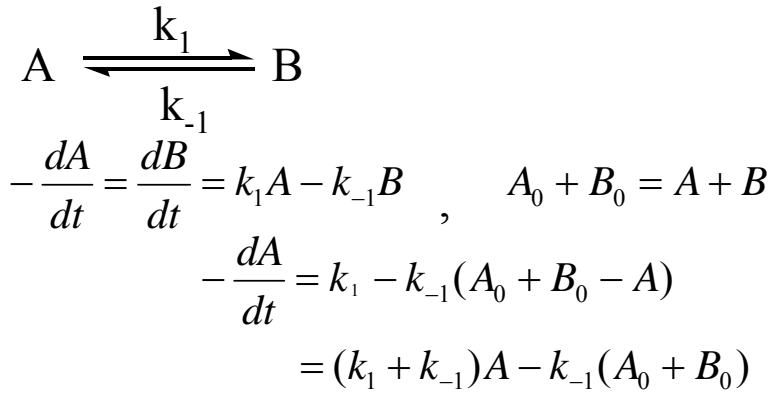


$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_2[A][B],$$

$$\ln \frac{[A]}{[B]} + \ln \frac{[B]_0}{[A]_0} = ([A]_0 - [B]_0)k_2 t,$$

plot $\ln \frac{[A]}{[B]}$ v.s $t \rightarrow$ straight line slope $= ([A]_0 - [B]_0)k_2$

Reversible reaction



$$\int \frac{dA}{(k_1 + k_{-1})A - k_{-1}(A_0 + B_0)} = \int -dt \quad \because \int \frac{dx}{a+bx} = \frac{1}{b} \ln(a+bx)$$

$$\frac{1}{k_1 + k_{-1}} \ln[(k_1 + k_{-1})A - k_{-1}(A_0 + B_0)] = -t + \text{const.}$$

at $t=0$

$$\text{const.} = \frac{1}{k_1 + k_{-1}} \ln[(k_1 + k_{-1})A_0 - k_{-1}(A_0 + B_0)]$$

subst. into above eq.

$$\ln \frac{(k_1 + k_{-1})A_0 + k_{-1}(A_0 + B_0)}{(k_1 + k_{-1})A - k_{-1}(A_0 + B_0)} = (k_1 + k_{-1})t$$

$$\ln \left(\frac{k_1 A_0 + k_{-1} B_0}{k_1 A + k_{-1} A - k_{-1} A_0 - k_{-1} B_0} \right) = (k_1 + k_{-1})t$$

at $t = \infty$ $A = A_\infty$, $B = B_\infty$ $k_{eq} = \frac{B_\infty}{A_\infty} = \frac{k_1}{k_{-1}}$ $k_1 = k_{-1} \frac{B_\infty}{A_\infty}$

$$\ln \frac{k_{-1} \frac{A_0}{A_\infty} B_\infty - k_{-1} B_0}{k_{-1} \frac{B_\infty}{A_\infty} A - k_{-1} B} = (k_1 + k_{-1})t$$

$$\ln \left(\frac{A_0 B_\infty - A_\infty B_0}{B_\infty A - B A_\infty} \right) = (k_1 + k_{-1})t$$

plot left hand side v.s. $t \rightarrow$ slop = $k_1 + k_{-1}$

$$\rightarrow k_1, k_{-1} \text{ from } k_1 = k_{-1} \frac{B_\infty}{A_\infty}$$

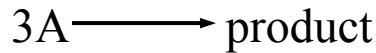
more common simplification : Pseudo first order



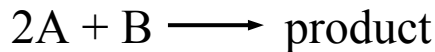
$$-\frac{d[A]}{dt} = k'[A] \quad \text{where } k' = k_2[B]$$

$$\Rightarrow \ln \frac{[A]}{[A_0]} = -k't$$

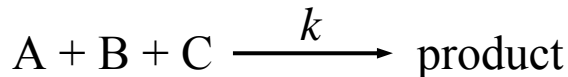
third order reaction



$$\text{rate} = -\frac{d[A]}{3dt} = k[A]^3$$

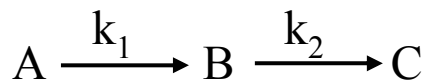


$$\text{rate} = -\frac{1}{2} \frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A]^2[B]$$



$$\text{rate} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = -\frac{d[C]}{dt} = k[A][B][C]$$

For consecutive and irreversible reaction



$$\text{rate} = \frac{d[C]}{dt} = k_2[B]$$

$$\frac{d[B]}{dt} = k_1[A] - k_2[B], \quad -\frac{d[A]}{dt} = k_1[A], \quad [A] = [A]_0 e^{-k_1 t}$$

$$\Rightarrow C = A_0 - A_0 e^{-k_1 t} - \frac{k_1 A_0}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t})$$

Figure 6.15
 Variation of [A], [B],
 and [C] with time for
 $k_1/k_2 = 3.0$.

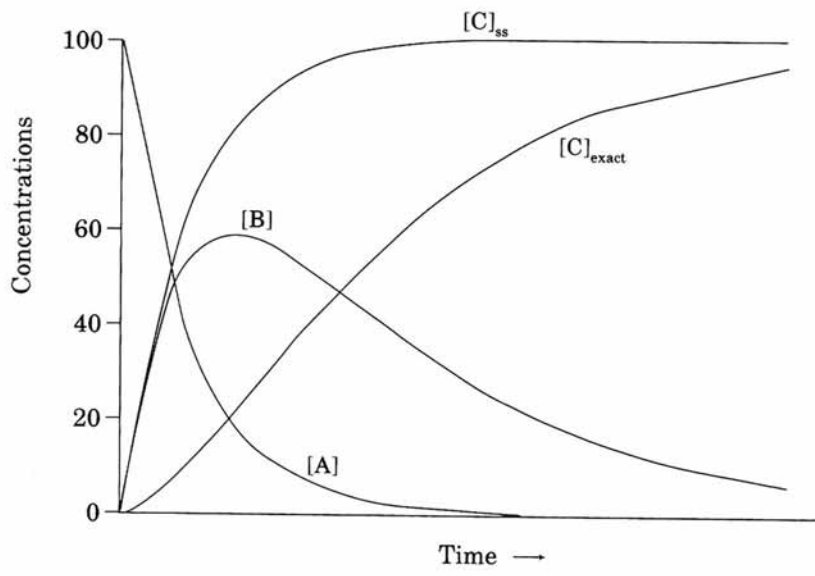


Figure 6.16
 Variation of [A], [B],
 and [C] with time for
 $k_1/k_2 = 0.33$.

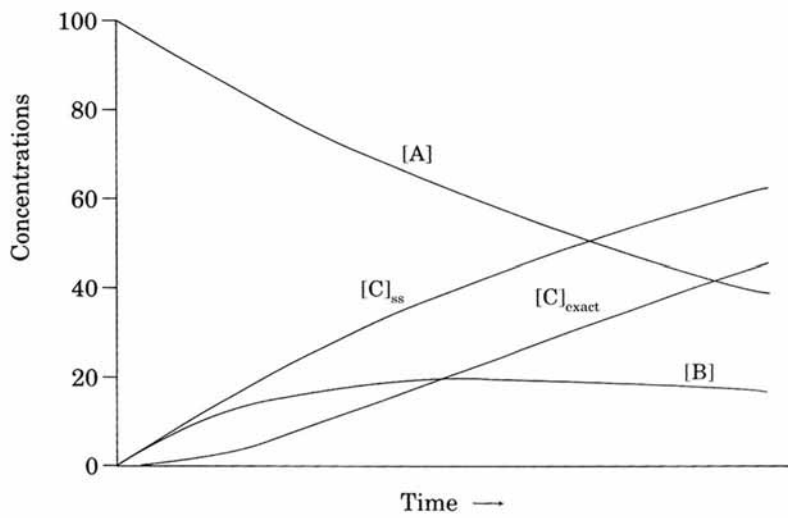
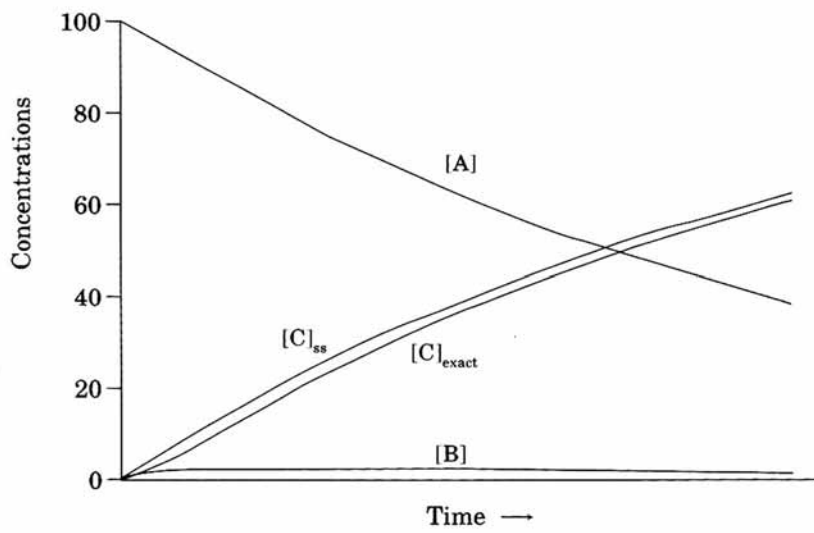


Figure 6.17
 Variation of [A], [B],
 and [C] with time for
 $k_1/k_2 = 0.033$.



Apply steady state approximation to [B] in the case $k_2 \gg k_1$

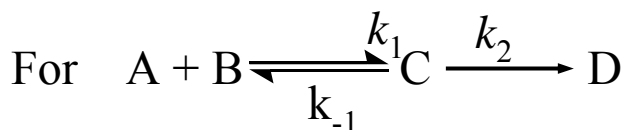
$$\frac{d[B]}{dt} = k_1[A] - k_2[B] = 0$$

i.e. the first step is slower

$$k_1[A] = k_2[B]$$

$$\text{rate} = \frac{d[C]}{dt} = k_2[B] = k_1[A]$$

the s.s.a. is more accurate if $k_1/k_2 \ll 1$



$$\text{rate} = \frac{d[D]}{dt} = k_2[C]$$

applying steady state approximation

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

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

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

if $k_2 \ll k_{-1}$, $k_2 + k_{-1} \approx k_{-1}$ (the reverse reaction is fast)

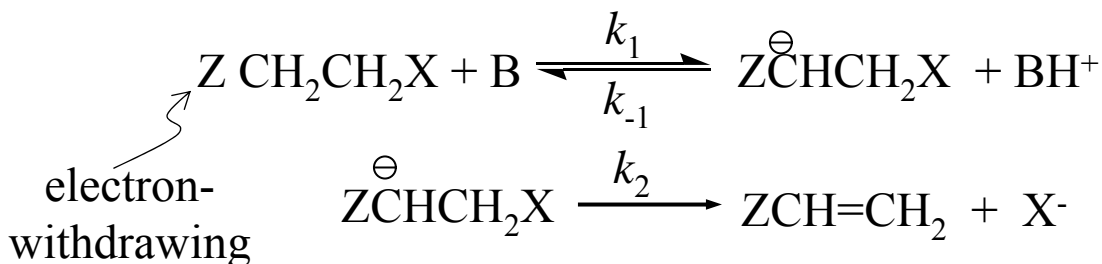
$$\text{rate} = k_2 \left(\frac{k_1}{k_{-1}} \right) [A][B] = k_2 K [A][B]$$

if $k_2 \gg k_{-1}$

$$\text{rate} = k_1 [A][B]$$

Pre-equilibrium
const.

e.g. E_{1cb} rxn



$$\begin{aligned} \text{s.s.a. } \frac{d[\text{Z}\overset{\ominus}{\text{C}}\text{HCH}_2\text{X}]}{dt} = 0 &= k_1[\text{ZCH}_2\text{CH}_2\text{X}][\text{B}] \\ &\quad - k_{-1}[\text{Z}\overset{\ominus}{\text{C}}\text{HCH}_2\text{X}][\text{BH}^+] \\ &\quad - k_2[\text{Z}\overset{\ominus}{\text{C}}\text{HCH}_2\text{X}] \end{aligned}$$

$$[\text{Z}\overset{\ominus}{\text{C}}\text{HCH}_2\text{X}] = \frac{k_1[\text{ZCH}_2\text{CH}_2\text{X}][\text{B}]}{k_{-1}[\text{BH}^+] + k_2}$$

$$\text{rate} = \frac{d[\text{ZCH}=\text{CH}_2]}{dt} = \frac{k_2 \cdot k_1[\text{ZCH}_2\text{CH}_2\text{X}][\text{B}]}{k_{-1}[\text{BH}^+] + k_2}$$

(1) assume $k_2 \gg k_{-1}[\text{BH}^+]$ (formation of carbanion is slow, destruction is fast)

$$\text{rate} = k_1[\text{ZCH}_2\text{CH}_2\text{X}][\text{B}]$$

(2) assume $k_{-1}[\text{BH}^+] \gg k_2$ (the destruction of anion is slow)

$$\text{rate} = \frac{k_2 \cdot k_1}{k_{-1}} \frac{[\text{ZCH}_2\text{CH}_2\text{X}][\text{B}]}{[\text{BH}^+]}$$

To distinguish between (1) or (2), one can use a buffer.

Experimental methods for determination of reaction orders

(1) method of integration

$$-\frac{dA}{dt} = k[A]^a[B]^b[C]^c \quad \text{evaluation of } a, b, c \text{ by integration plot}$$

(2) method of half life

$$t_{1/2} \propto A_0^{1-n}, \quad n \text{ is the order}$$

determine the relationship between $t_{1/2}$ and $A_0 \Rightarrow$ order

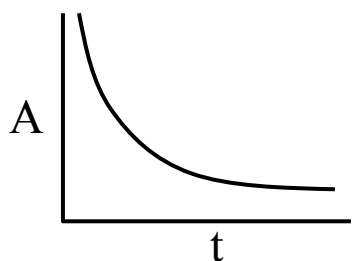
(3) method of isolation -----Pseudo orders

$$-\frac{dA}{dt} = k[A]^a[B]^b[C]^c$$

make the concentration of B and C extremely large

so that they don't change with progress of rxn.

(4) Differential method



monitor the conc. of A v.s. t

$$-\frac{dA}{dt} \approx \frac{\Delta A}{\Delta t}$$

$$\text{if } -\frac{dA}{dt} = kA^n \quad \log\left(-\frac{dA}{dt}\right) = \log k + n \log A$$

determine several $-\frac{dA}{dt}$, plot $\log\left(-\frac{dA}{dt}\right)$ v.s. $\log A$

the slope is the order of A

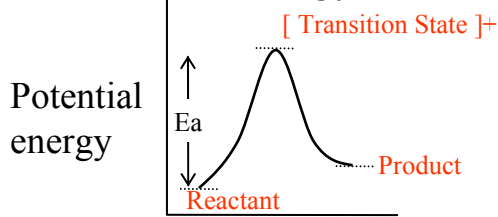
no matter what the order is,

$\log\left(-\frac{dA}{dt}\right)$ v.s. $\log A$ is always a straight line, with slope n

§ Arrhenius Theory & Transition State Theory

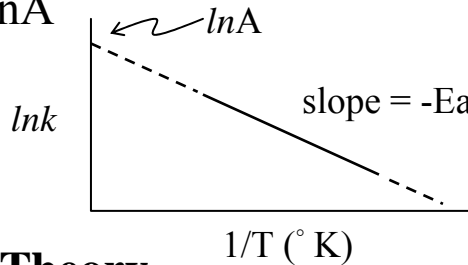
rate constant is a function of temperature

activation energy



Arrhenius equation : $k = A \exp(-E_a/RT)$

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



E_a : activation energy
 A : pre exponential factor
 relate to probability

Transition state Theory

The starting material is in equilibrium with activated complex

treat the TS as a species, rate = $[AB]^\ddagger \times$ frequency of T.S passing over

$$k_r = \left(\frac{\kappa kT}{h} \right) e(-\Delta G^\ddagger / RT) = \left(\frac{\kappa kT}{h} \right) e(\Delta S^\ddagger / R) e(-\Delta H^\ddagger / RT)$$

transmission coefficient, to account for probability of reactant to product

for $\Delta G^\ddagger = \Delta H^\ddagger - T \Delta S^\ddagger$ ($E_a = \Delta H^\ddagger + RT$)

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

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

from k_r , T , ΔH^\ddagger
 at one temp.

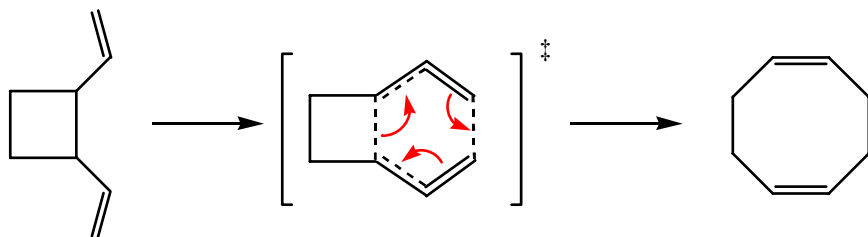
plot $\ln \left(\frac{k_r}{T} \right)$ v.s. $\frac{1}{T}$ $\rightarrow \Delta H^\ddagger$, then ΔS^\ddagger
 from slope

ΔS^\ddagger reflects the change in the order of the system from reactants to activated complex (T.S.)



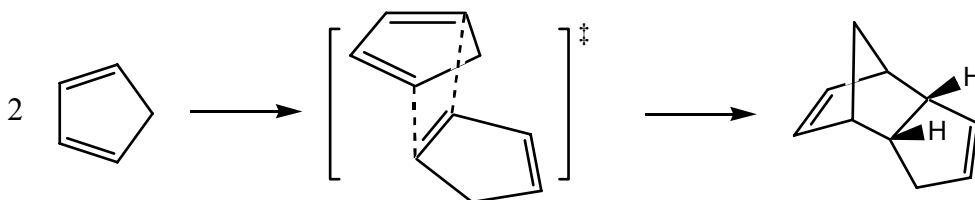
$$\Delta S^\ddagger = 13.8 \text{ eu}$$

one molecule becomes two



$$\Delta S^\ddagger = -11.7 \text{ eu}$$

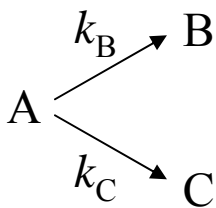
two fragments connected together



$$\Delta S^\ddagger = -26 \text{ eu}$$

two molecules combine to one

For competing reaction



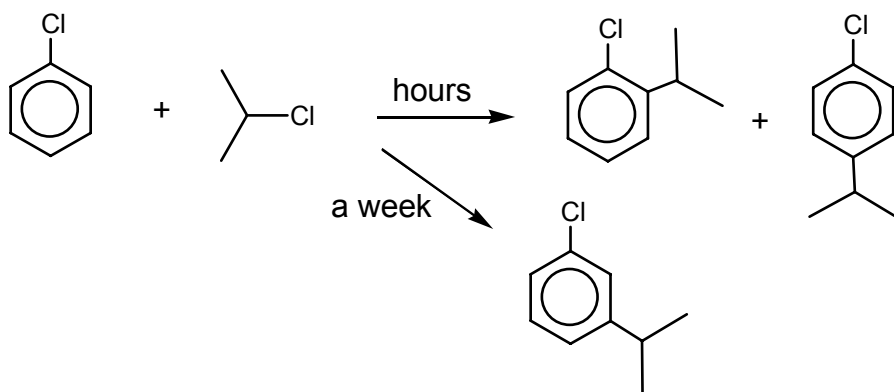
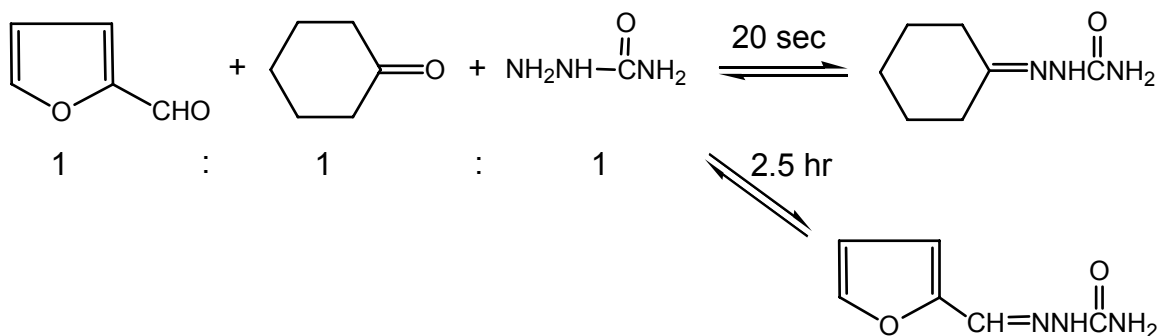
if irreversible, the product ratio is the rate constant ratio.

$$\frac{k_B}{k_C} = \frac{[B]}{[C]} = e^{\Delta\Delta G^\ddagger / RT}$$

activation free energy difference

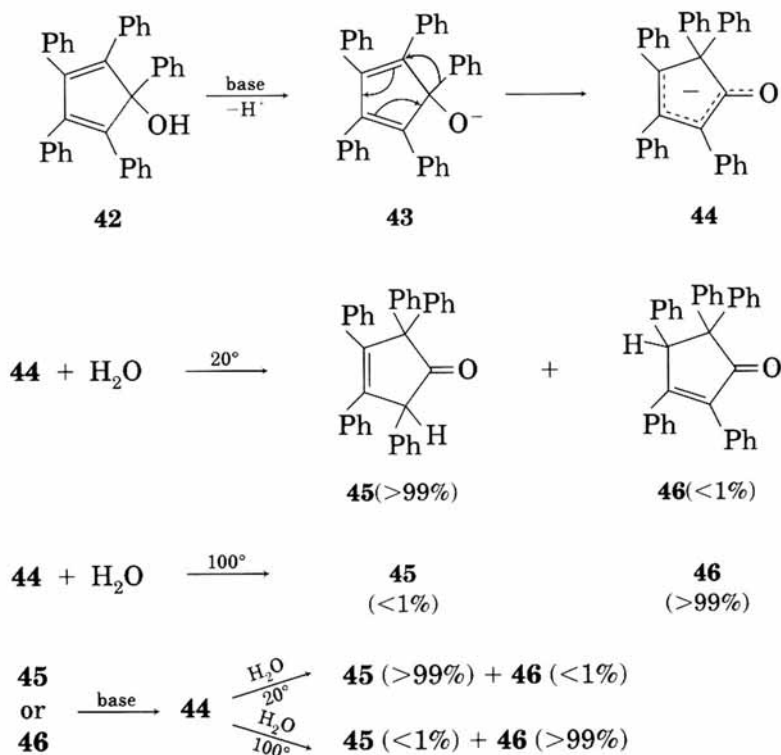
$\frac{[B]}{[C]}$	$\Delta\Delta G^\ddagger$ (kcal/mol)
1	0
100	2.73
1000	4.09
10000	5.45

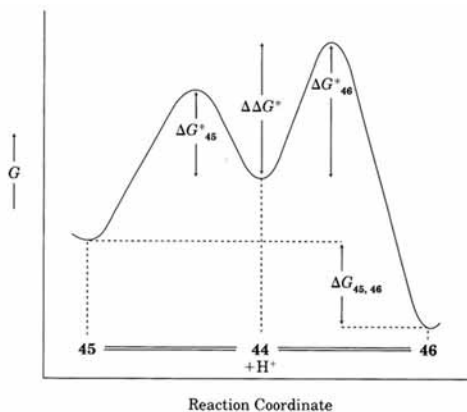
Different product ratio for diff. reaction time (or temperature)
for reversible reaction



different prod. ratio at diff. temperature

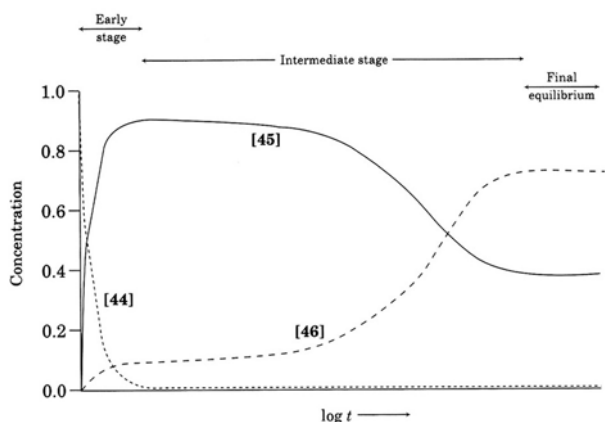
Figure 6.26
Temperature effects
on the reaction of
44 with water.



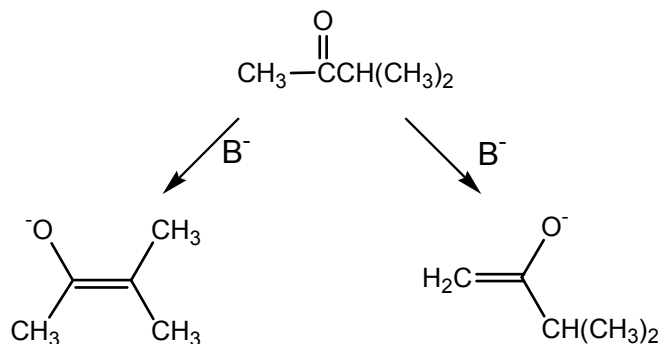


Kinetic control v.s
Thermodynamic control

Both time effect and temperature effect are of same origin → the time required to reach the equilibrium



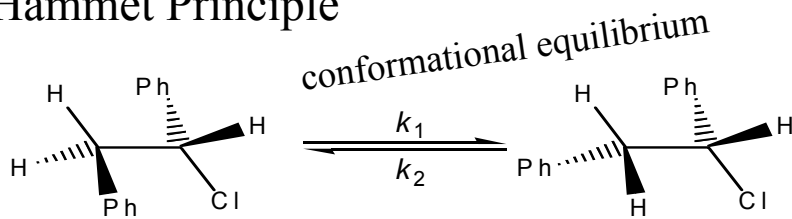
Kinetic enolate v.s
Thermodynamic enolate



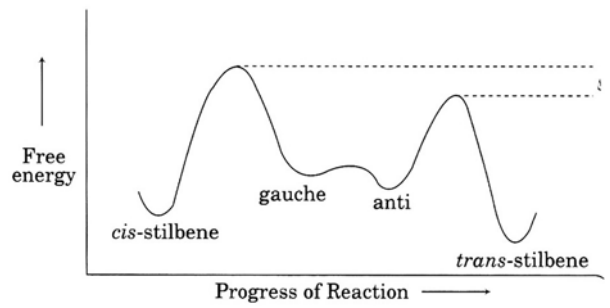
If a bulky base used, non-hydroxylic solvent used,
low temperature used → less substituted enolate dominates
(Kinetic enolate)

If hydroxylic solvent used, or higher temperature equilibrium
reached → more substituted enolate dominates
(Thermodynamic enolate)

Curtin-Hammett Principle



This product is favored, but not due to a favored anti-conformation



For two equilibrium conformational isomer, each leading to different product, the product ratio is determined by the activation energy difference, not by the population of the isomer.

$$B \rightleftharpoons A \quad K_c = \frac{[A]}{[B]}$$

$$\text{rate of Product } P_A = \frac{dP_A}{dt} = k_a[A] = k_a K_c[B]$$

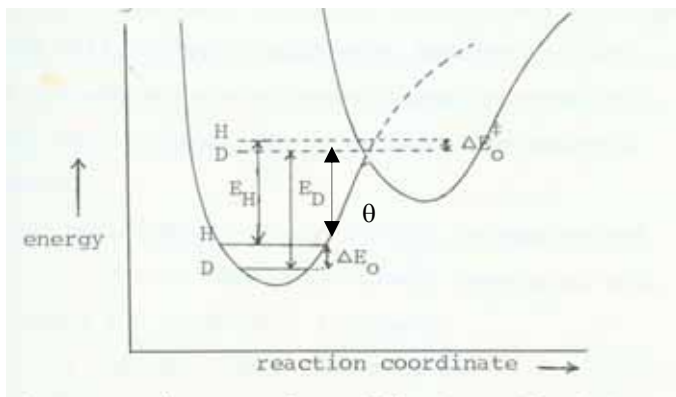
$$\text{Product } P_B = \frac{dP_B}{dt} = k_b[B]$$

$$\text{Product ratio} = \frac{dP_A/dt}{dP_B/dt} = \frac{k_a K_c[B]}{k_b[B]} = \frac{k_a K_c}{k_b}$$

$$k_r = \frac{\kappa k T}{h} e^{-\Delta G^\ddagger / RT}, \quad K_c = e^{-(-\Delta G / RT)}$$

$$\begin{aligned} \text{product ratio} &= \frac{(\kappa k T / h) e^{-\Delta G^\ddagger_a / RT} e^{\Delta G_c / RT}}{(\kappa k T / h) e^{-\Delta G^\ddagger_b / RT}} = e^{(-\Delta G^\ddagger_a + \Delta G^\ddagger_b + \Delta G_c) / RT} \\ &= e^{\Delta G^\ddagger_b - \Delta G^\ddagger_a} \end{aligned}$$

Kinetic Isotope Effect



the KIE results from the zero point energy difference for H- or D-substituted species

$$\text{zero point energy } E_0 = \frac{1}{2} h \nu_0$$

$$E_D - E_H = (\theta + \Delta E_0) - (\theta + \Delta E_0^\ddagger) = \Delta E_0 - \Delta E_0^\ddagger$$

due to anharmonicity

$$\nu_0 = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}}$$

force const. \leftarrow
reduced mass \leftarrow

e.g. for a C-H bond, $\nu_{\text{C-H}} \sim 3000\text{cm}^{-1}$

replaced by D, $\nu_{\text{C-D}} \sim 2100\text{cm}^{-1}$

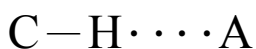
In ground state, the zero point energy differs by ΔE_0 , in transition state, zpe differs by ΔE_0^\ddagger , (usually $\Delta E_0^\ddagger < \Delta E_0$) depend on the extent of C-H bond breakage, k_H/k_D may vary.

$$k_H/k_D = \exp \{ (\Delta E_0 - \Delta E_0^\ddagger) / RT \}$$

for C-H k_H/k_D maximum value at room temp. ~ 7 for primary KIE depend on the ext. of bond cleavage, $1 < k_H/k_D < 7$

Information provided by primary KIE :

- $k_H/k_D > 2 \rightarrow$ strong evidence that the C-H bond is broken in T.S.
- the magnitude of k_H/k_D provides qualitative indication of where the T.S. lies relative to S.M. or Product



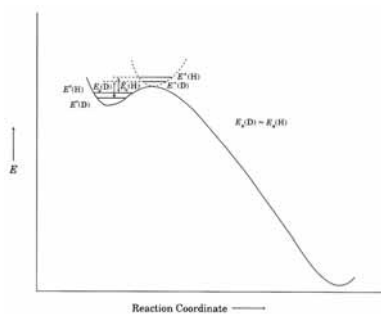
symmetric

k_H/k_D small

large

small

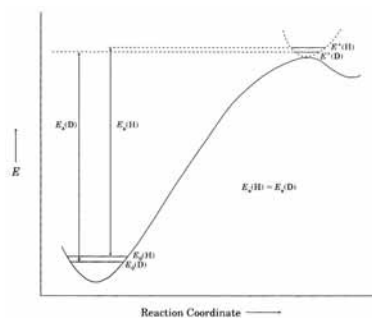
early transition state



$$k_H/k_D \sim 1$$

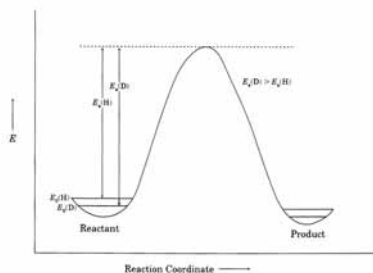
C-H (or C-D) bond is slightly broken in the T.S.

late transition state



$$k_H/k_D \sim 1 \text{ (small)}$$

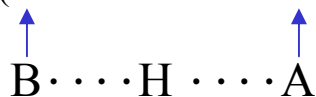
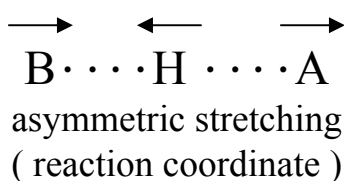
C-H (or C-D) is nearly fully broken away from S.M., but nearly fully from in product.



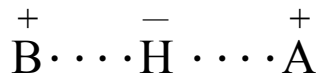
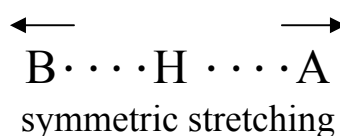
Symmetric T.S

C-H (or C-D) is half-broken \rightarrow large k_H/k_D

[Transition State Theory Description :]



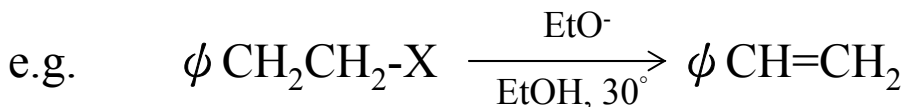
in plane bending



out-of-plane bending

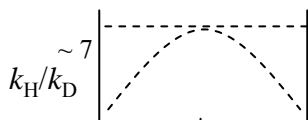
of low energy & cancel similar bending in S.M.

contribute to Zero Point energy in T.S.

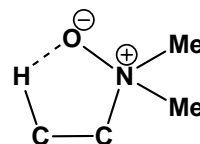


X =	Br	OTs	SMe ₂	NMe ₃
k_H/k_D	7.11	5.67	5.07	2.98

for non-linear T.S. KIE is also smaller



50% H-transfer



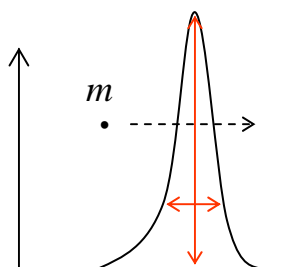
usual range of Primary Kinetic Isotope Effects 5~8

Some KIE are much larger than expected maximum

Because oversimplifications :

1. C-H bending vibration (~ 48 if considered)
2. Tunneling of H will increase k_H/k_D

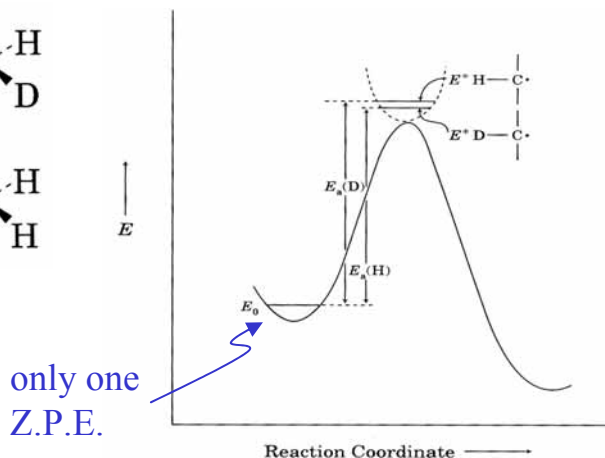
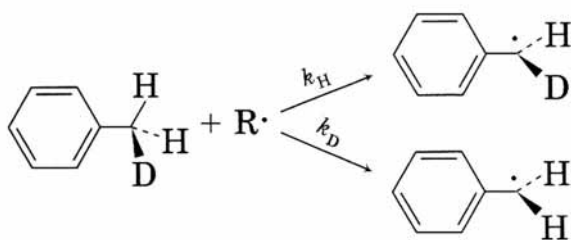
Tunneling Effect



by Classical mechanical Theory
the probability of finding m in the other side is zero.

by Quantum mechanical Theory
There is finite probability on the other side of the barrier

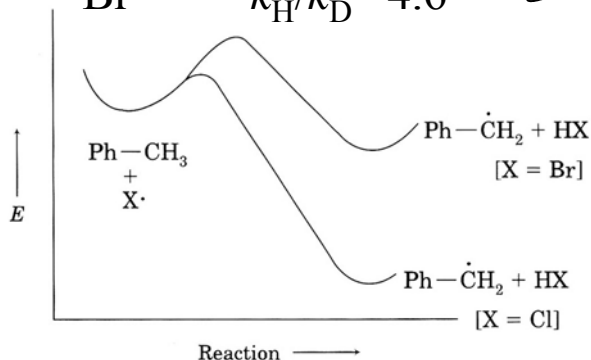
Intra molecular KIE :



if $R \cdot = Cl \cdot$ $k_H/k_D = 1.3$

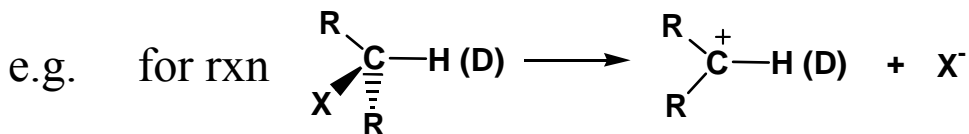
$R \cdot = Br \cdot$ $k_H/k_D = 4.6$

Transition State lies to the right
(occurs later)

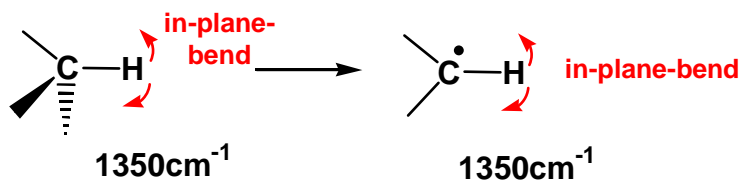
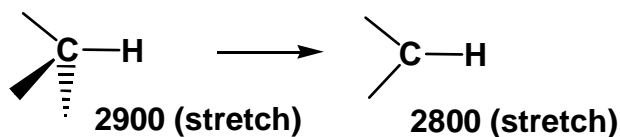


Secondary Isotope Effect

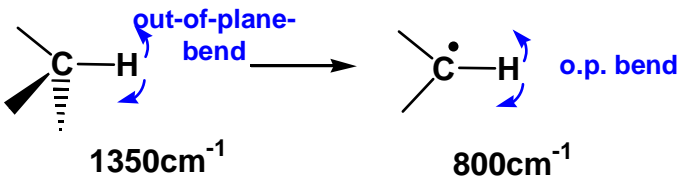
The effect of isotope substitution at a bond not broken in the transition state. \rightarrow result from zero-point-energy difference due to change of force constant in a vibration in going from reactant to T.S. (α -, β - 2° KIE)



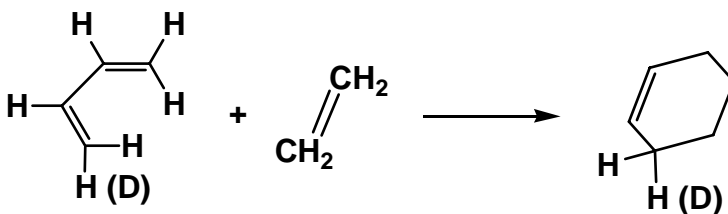
in going from $sp^3 \rightarrow sp^2$, C-H bond will experience a decreased resistance to C-H bending. The effect is greater for C-H bond than C-D bond (C-H longer than C-D by 0.009 \AA) $k_H/k_D > 1$ (normal secondary isotope effect).



$$k_H/k_D \doteq 1.41$$



For

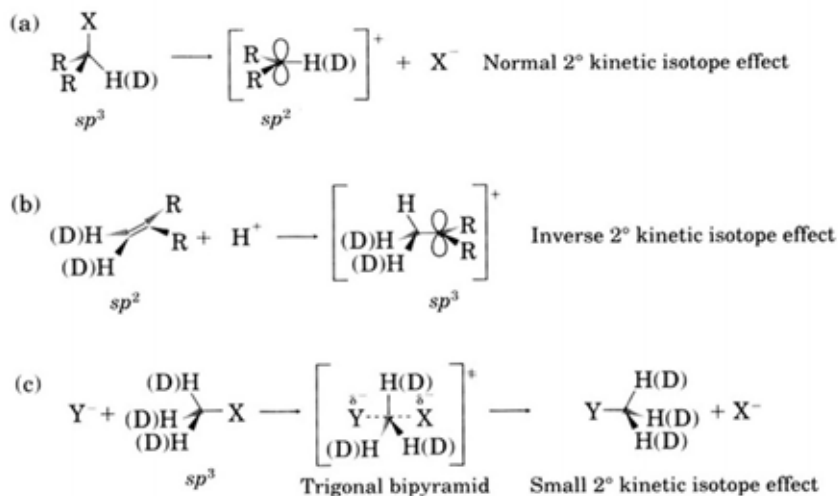


The exact value depend on the location of T.S.

$sp^2 \rightarrow sp^3$

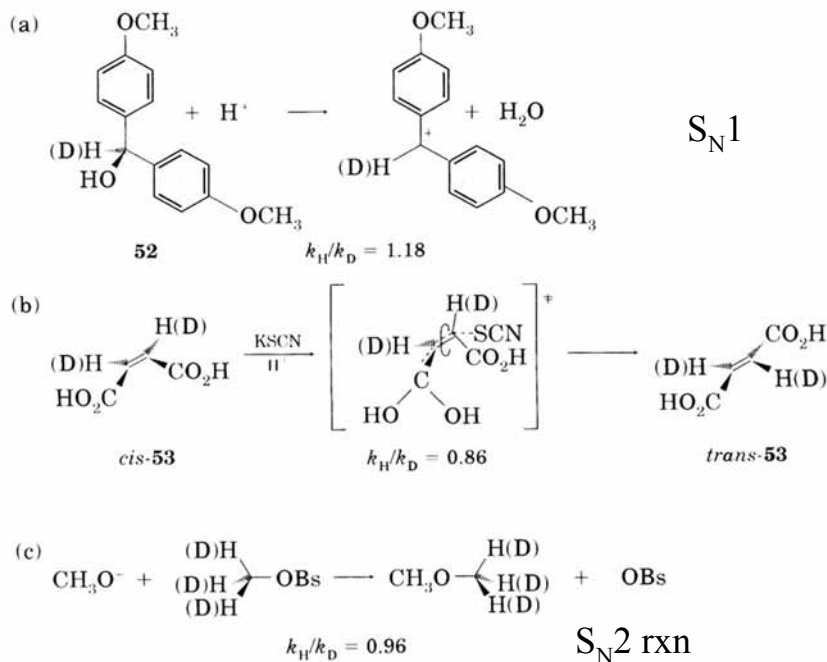
$$k_H/k_D < 1 \approx \frac{1}{1.41} = 0.71 \quad (\text{Inverse IE})$$

Figure 6.42
Types of secondary kinetic hydrogen isotope effects.

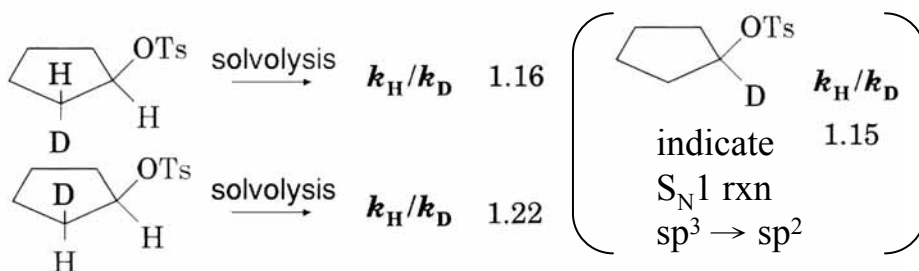


α -isotope effect

Figure 6.43
Examples of secondary hydrogen kinetic isotope effects.

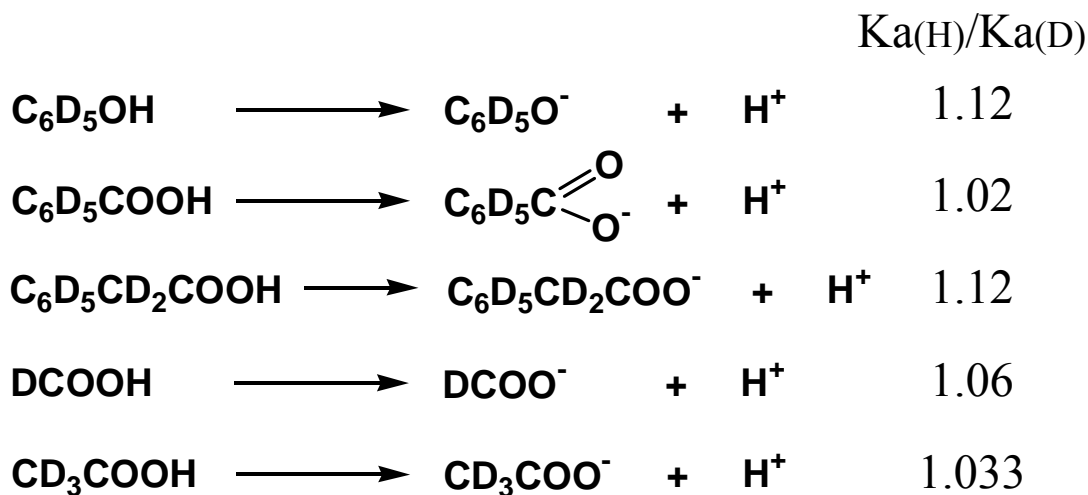


β -secondary isotope effect : the isotope bond to a position next to reaction center

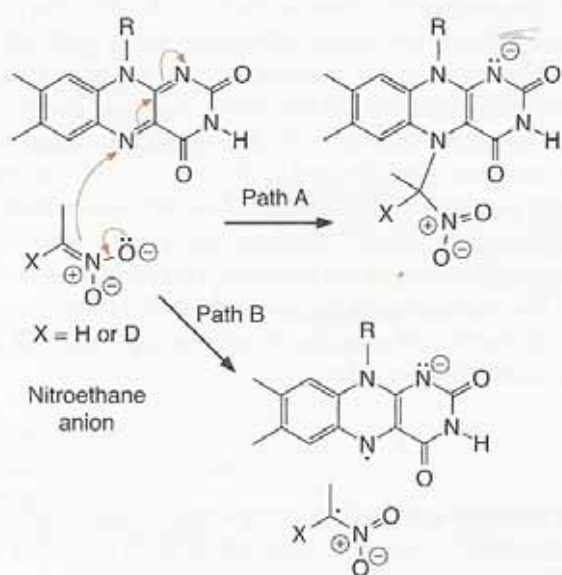


The hyperconjugation weakens β -H (or β -D) bond, thus a small ZPE contribution. \rightarrow faster for H- species (C-H > C-D)

Isotope effect on Acidity (Not Kinetic IE, but equilibrium IE)



\therefore The C-D bond is shorter than C-H by 0.009Å, the electron-density is closer to C, equivalent to a e⁻-donating group. (+I effect, C-D > C-H)



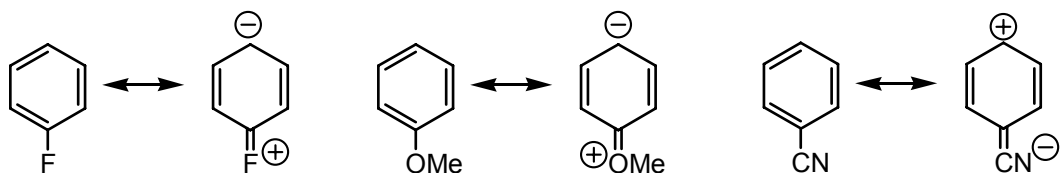
Probing radical vs. nucleophilic mechanisms

Path A: nucleophilic addition
 Path B: electron transfer followed
 by combination of radicals
 $k_{\text{H}}/k_{\text{D}} = 0.84$, implying rehybridization

§ Substituent Effect and Linear Free Energy Relationship

A substituent can influence a reaction rate, equilibrium or property via inductive, resonance, steric effect.

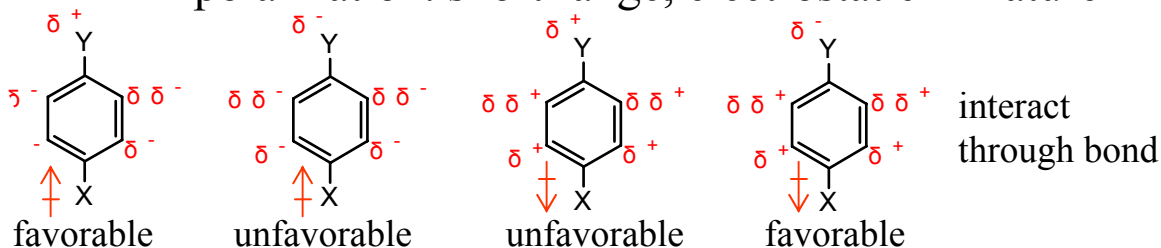
Resonance Effect : Polarization of charge density through π - bond formation (or π -system) in a structure



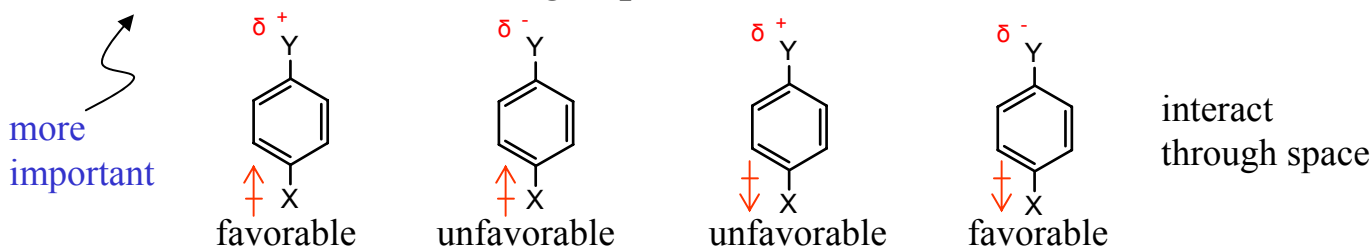
+ R : e-donating : halogen, OR, NR₂, alkyl

- R : e-withdrawing : -NO₂, -CN, -CO₂R, -C₆H₅

Inductive Effect : Due to polarization of a σ -bond, the bond dipole, transmit through bonds by successive polarization. short range, electrostatic in nature



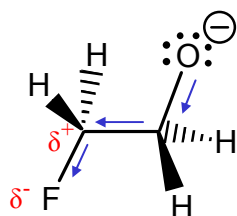
Field Effect : Through space electrostatic interaction



+ I : alky

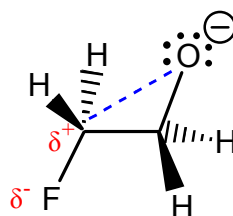
- I : halogen, -⁺NR₃, -⁺SR₂, -CX₃

higher acidity for 2-fluoroethanol



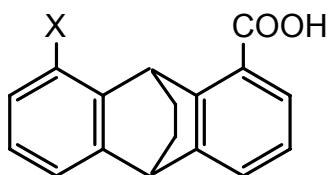
Stabilized by inductive withdrawal through bond

or

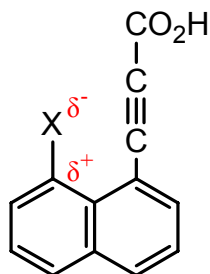


Stabilized through space field effect

the importance of through space effect

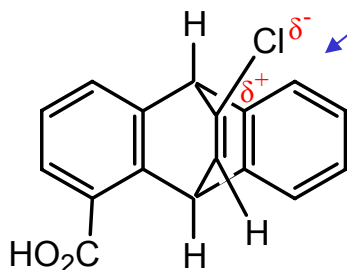


X = H	pKa = 6.04	↓ decr. acidity 6.25 → the δ^- end of C-Cl bond close to the carboxylate through space effect
Cl	6.25	

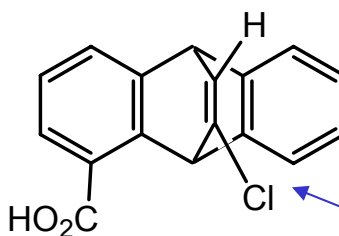


X = H	pKa = 4.42	↓ decr. acidity
Br	4.70	
Cl	4.90	

field effect in right orientation



pKa = 5.72

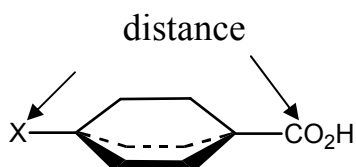


pKa = 5.90

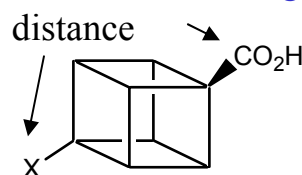
closer to CO₂H, by inductive effect through bond, should be stronger acid

Similar effect for X on acidity on the two type cpd.

Field effect outweighs

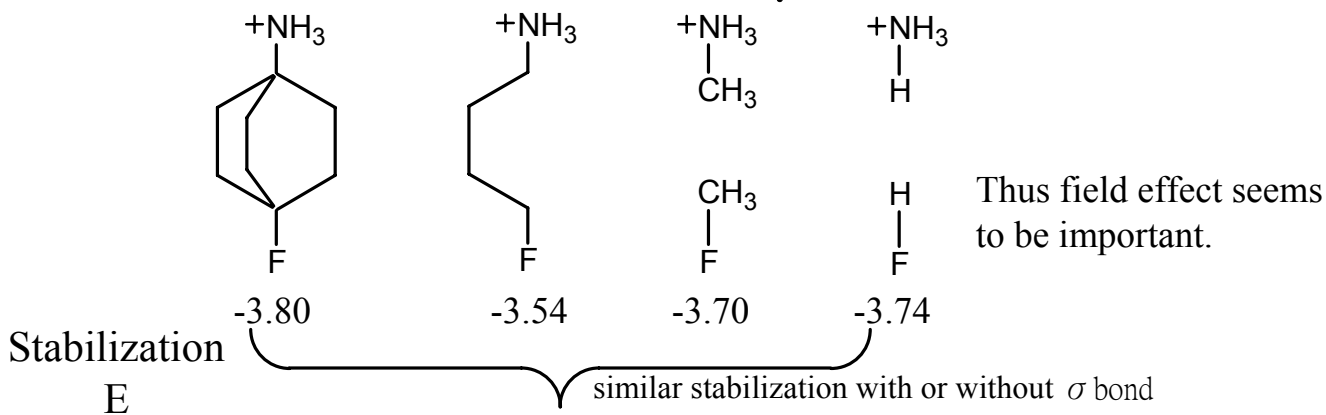


three 3-bond path between X and CO₂H

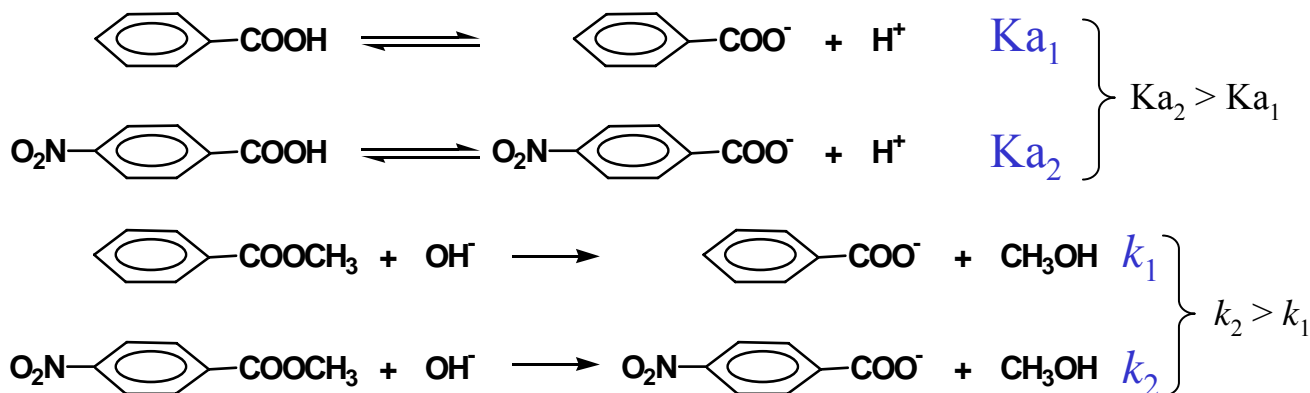


six 3-bond path between X and CO₂H, through bond effect should be more effective

Transmission of electronic properties through σ -framework ?



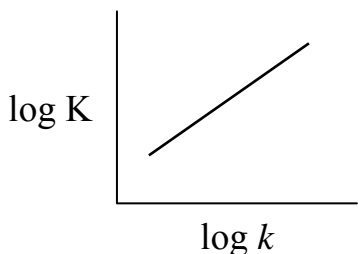
Linear Free Energy Relationship



$$\Delta \Delta G^\circ \propto \Delta \Delta G^\ddagger$$

the free energy change of the rxn by the structure change

the free energy change of the T.S by the structure change



from $\Delta G^\circ = -RT \ln K$, $\Delta G^\ddagger = -RT \ln k$

$$\log k = \rho \log K + A$$

with no substituent $\log k_0 = \rho \log K_i^\circ + A$

$$\log \frac{k}{k_0} = \rho \log \frac{K}{K_i^\circ} \quad \text{let} \quad \log \frac{K}{K_i^\circ} = \sigma$$

then $\log \frac{k}{k_0} = \rho \sigma \Rightarrow$ Hammett equation

σ : substituent constant $= \log \frac{K_i}{K_i^\circ}$

A measure of the electronic effect of the substituent S at a particular position.

at 25°C in H₂O

substituted Benzene
 unsubstituted

ρ : reaction constant

A measure of sensitivity of the reaction to the electronic effect of a substituent

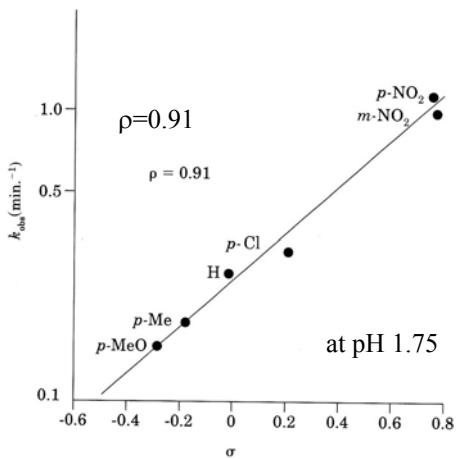
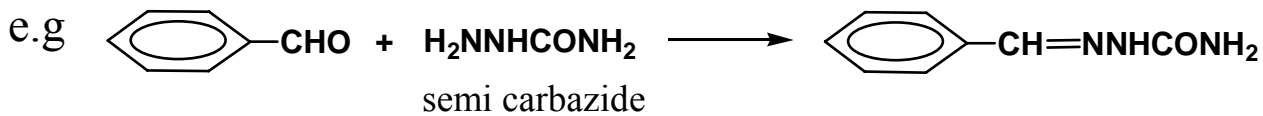
$= 1$ for ionization of benzoic acid (the reference system)

ρ : “+” for rxn favored by e⁻-withdrawing
 “-” for rxn favored by e⁻-donating

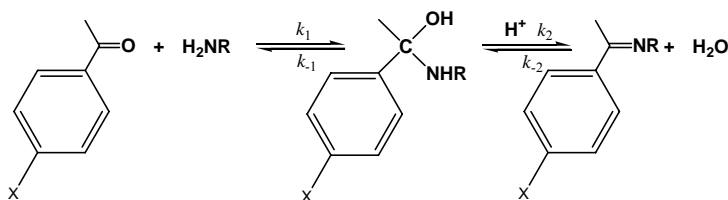
σ : “+” for e⁻-withdrawing
 “-” for e⁻-donating

substituted Benzoic acid	σ
P-NH ₂	-0.66
P-CH ₃	-0.17
H	0
P-Cl	0.23
P-CN	0.66
P-NO ₂	0.78

For a particular rxn, plot rates v.s σ , if a linear curve is obtained, a linear free energy relationship exists.

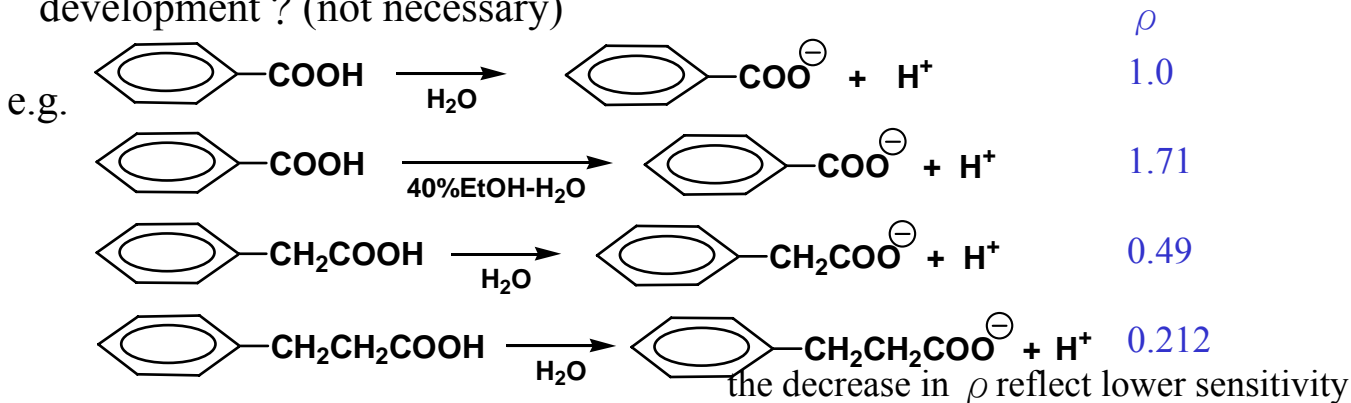


$\rho = 0.91$ means there is negative charge developed in the T.S.



at pH 1.75, the first step is rate-determining

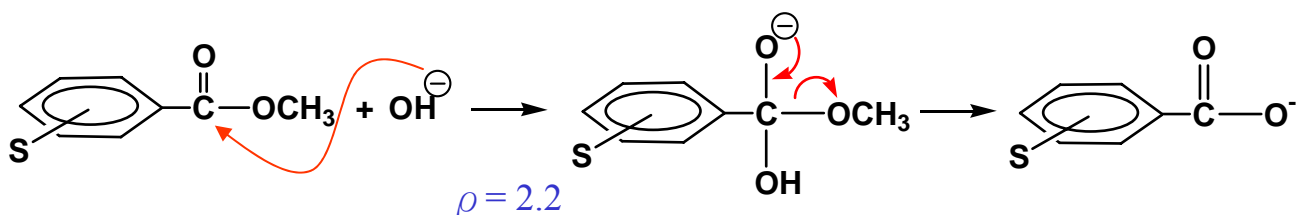
magnitude of $\sigma \rightarrow$ sensitivity to the substituent \rightarrow extent of charge development? (not necessary)



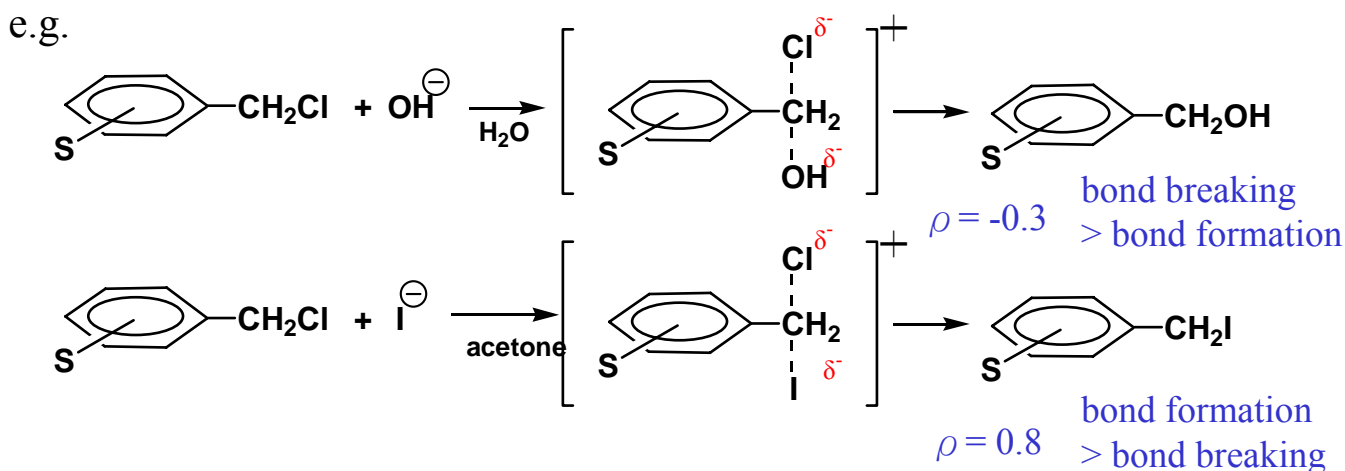
the decrease in ρ reflect lower sensitivity

not different charge formation

Inferring mechanism from Hammett ρ value

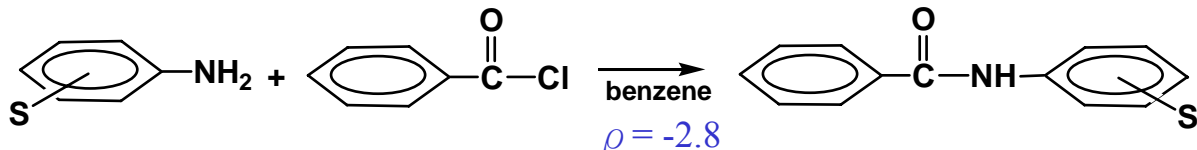
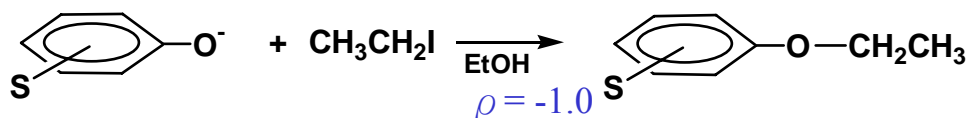
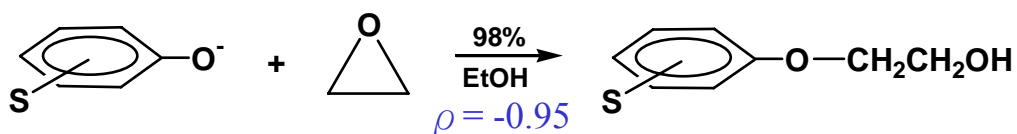


typical S_N2 reaction has low ρ values



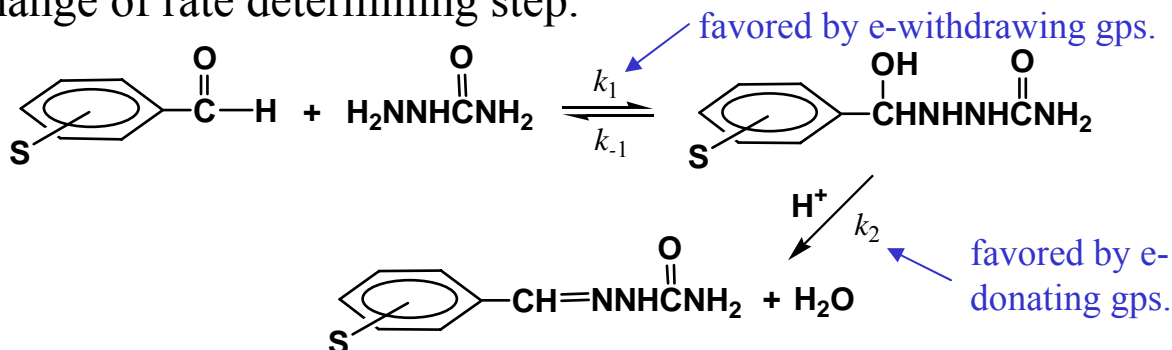
the large value of 2.2 for ester hydrolysis rules out a S_N2 mechanism

However

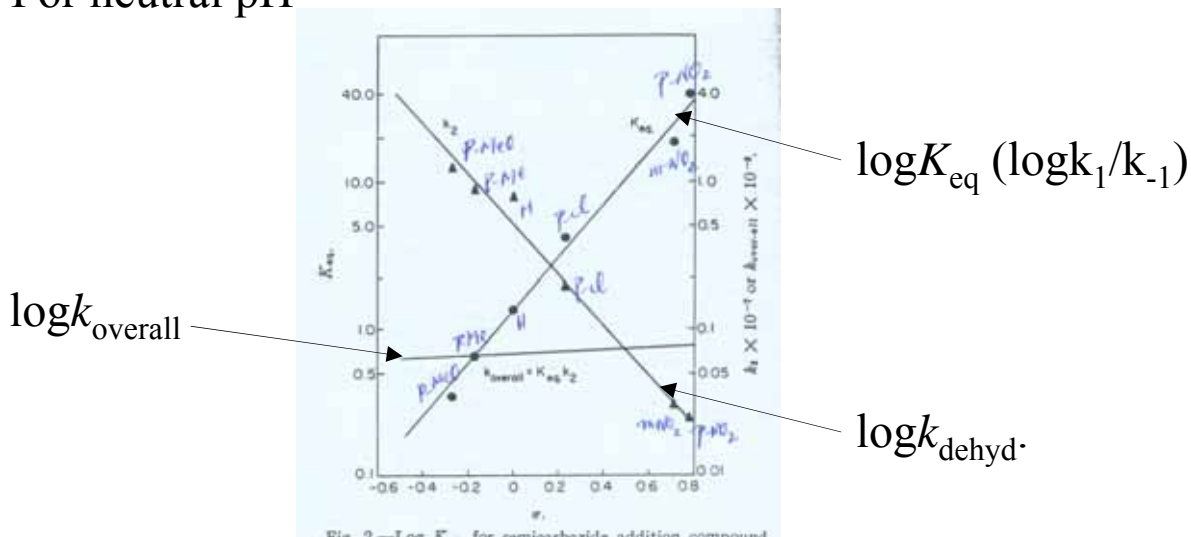


Nonlinear Hammett Correlation

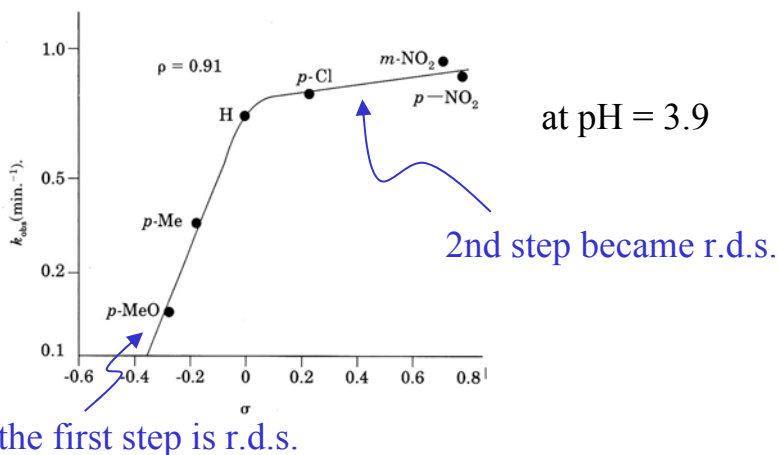
If not due to expt'l error, if not due to impurity, if not due to side reactions. → may due to change of mechanism or change of rate determining step.



For neutral pH

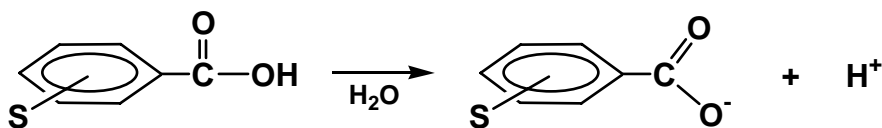


at Neutral pH, the observed rate is the resultant of two → insensitive to σ



Substituent Constants

σ : defined with respect to



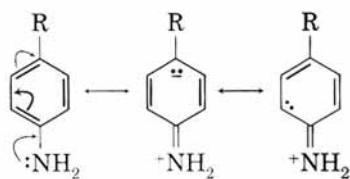
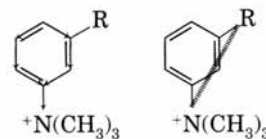
substituent constant depends on position

no direct resonance between S and Carboxyl carbon

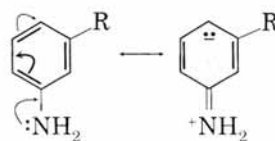
Substituent	σ_p	σ_m	
-I determine	F	.06	.34
	NMe ₃ ⁺	.82	.88
R + I	NH ₂	-.66	-.16
	COCH ₃	.50	.38
	OCH ₃	-.27	.12

$\sigma_m > \sigma_p$ the inductive effect (and field effect) are distance-dependent. the closer, the stronger

$$|\sigma_p| > |\sigma_m|$$

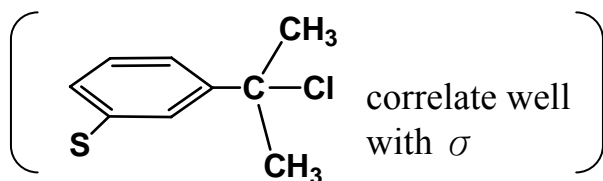
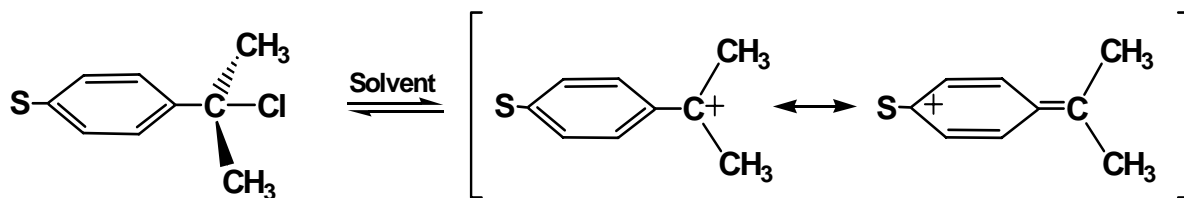


stronger interaction due to resonance



resonance did not bring stronger interaction

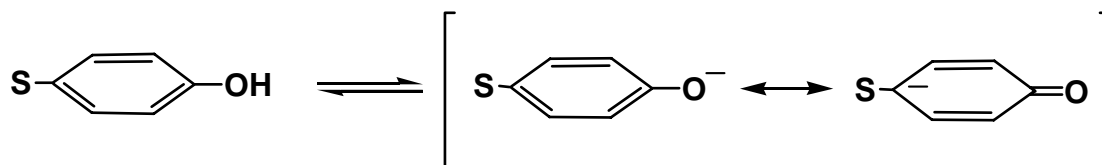
σ^+ : defined with respect to



direct resonance interaction with reaction center.

more sensitive for those can interact through resonance

σ^- : defined with respect to



Which sets of σ^- 's correlate better will depend on the nature of the reaction center.

Yukawa-Tsuno equation

$$\log \frac{K}{K_0} = \rho\sigma + \overbrace{\rho r(\sigma^+ - \sigma)}^{\text{a term to correct for the additional contribution from resonance}}$$

\uparrow
 depend on rxn, large $r \rightarrow$ large resonance contribution
 $r \rightarrow 0$, original Hammett eq.

Swain-Lupton

$$\log \frac{k_x}{k_v} = f \underbrace{F}_{\substack{\text{field effect} \\ \text{(Polar)}}} + r \underbrace{R}_{\text{resonance effect}} \quad \left(\text{dual-substituent parameter} \right)$$

$\rho_I \sigma_I + \rho_R \sigma_R$

for ortho-substituents, steric effect may involve.

σ^* : a measure of polar effect of alkyl substituent in aliphatic system.

$$\sigma^* = [(\log \frac{k_x}{k_o})_B - (\log \frac{k_x}{k_o})_A] / 2.48$$

Taft equation

$$\log \frac{k_x}{k_v} = \rho^* \sigma^* - S \underline{E}_S$$

steric substituent constant

$$E_S = \log \left(\frac{k}{k_0} \right)_A$$

acid-hydrolysis of aliphatic ester $\text{RCO}_2\text{R}'$, only related to steric effect