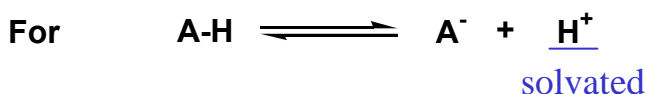
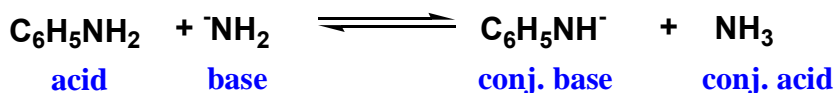
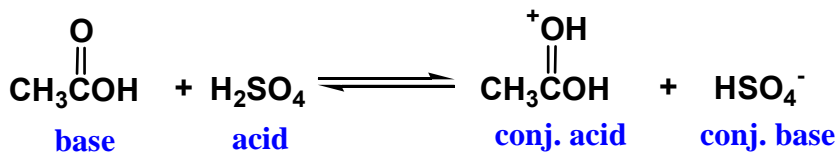
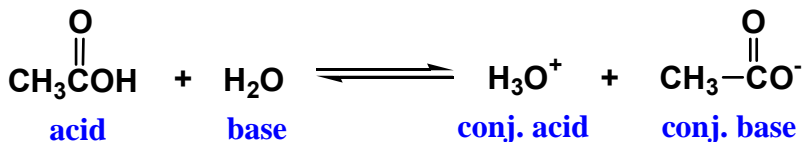


Chap 7. Acid and Bases

Brønsted Acid : Proton donor

Base : Proton acceptor



$$K_a = \frac{[\text{A}^-][\text{H}^+]}{[\text{A-H}]}$$

$$pK_a = -\log K_a = \text{pH} + \log \frac{[\text{A-H}]}{[\text{A}^-]}$$

Solvent usually acts as an acid (to donate H^+) or as base (to accept H^+)

$$\begin{aligned} K_a^* &= \frac{a_{\text{A}^-} \cdot a_{\text{H}^+}}{a_{\text{AH}}} = \frac{r_{\text{A}^-} [\text{A}^-] \cdot r_{\text{H}^+} [\text{H}^+]}{r_{\text{AH}} [\text{A-H}]} \\ &= K_a \frac{r_{\text{A}^-} \cdot r_{\text{H}^+}}{r_{\text{AH}}} \end{aligned}$$

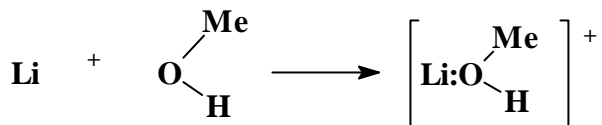
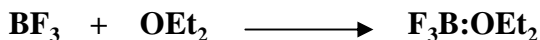
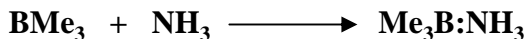
activity
activity coefficient

The stronger the acid is, the weaker the conjugate base is.
The stronger the base is, the weaker the conjugate acid is.

Lewis Acid : electron pair acceptor

Base : electron pair donor

Lewis acid + Lewis base \longrightarrow adduct



Lewis acids: SO_3 , BF_3 , AlCl_3 , SnCl_4 , FeCl_3 , ZnCl_2 , H^+ , Ag^+ , Ca^{+2}

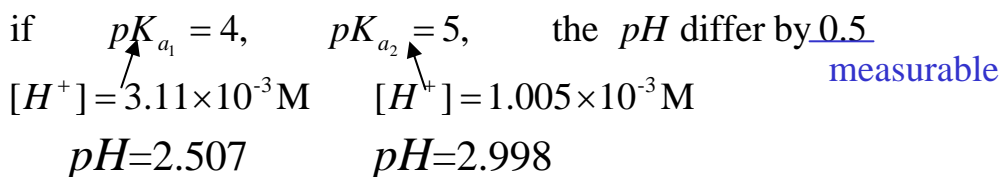
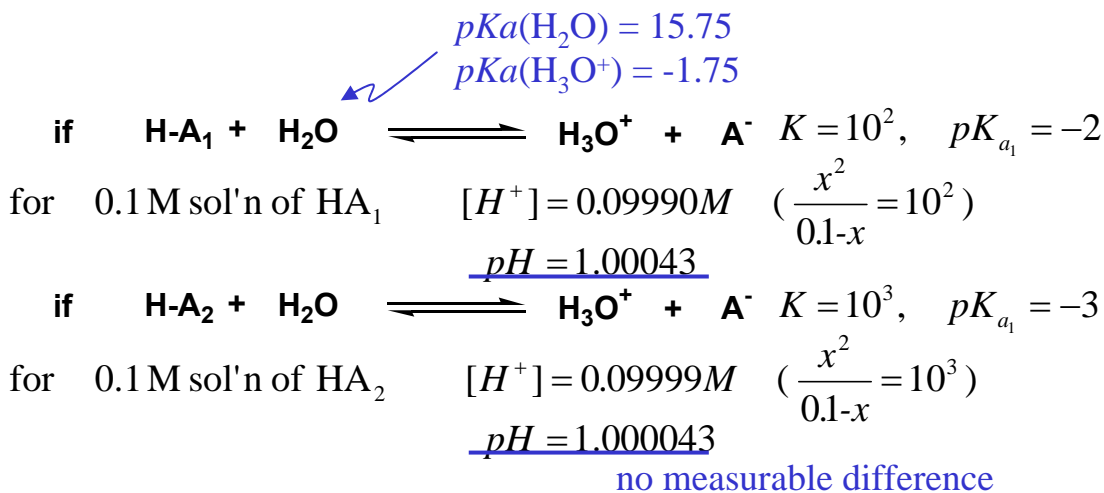
Lewis bases: $\text{C}_6\text{H}_5\text{N}$, $(\text{C}_2\text{H}_5)_2\text{O}$, NH_3 , OH^- , CO_3^{2-} , HCO_2^- , SH^- , CH_3CO_2^-

Brønsted base can be Lewis base, e.g. OH^-

Brønsted acid may not be Lewis acid, e.g. AlCl_3 , or HCl

Leveling effect :

The ionization of an acid (base) depend on the basicity(acidity) of the medium in which it is ionizing.



- 1. No acid stronger than the conjugate acid of a solvent can exist in appreciable concentration in that solvent.
 - 2. No base stronger than the conjugate base of a solvent can exist in appreciable concentration in that solvent
 - Relative strengths of acids stronger than the conjugate acids of a solvent cannot be determined in that solvent.
 - Relative strengths of bases stronger than the conjugate bases of the solvent cannot be determined in that solvent
- (acidity can be measured for acid stronger than H₂O, and weaker than H₃O⁺)

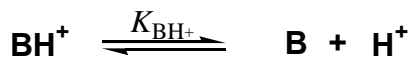
The acidity range varies dramatically. strong acid HI, HClO₄...

weak acid methane, 

To measure very strong acid → use mix of H₂O/H₂SO₄

To measure very weak acid → NH₃, DMSO...

Acidity Function, H₀



$$K_{\text{BH}^+} = \frac{a_{\text{B}} \cdot a_{\text{H}^+}}{a_{\text{BH}^+}} = \frac{r_{\text{B}}[\text{B}] \cdot r_{\text{H}^+}[\text{H}^+]}{r_{\text{BH}^+}[\text{BH}^+]}$$

$$\log K_{\text{BH}^+} = \log \frac{[\text{B}]}{[\text{BH}^+]} + \log[\text{H}^+] + \log \frac{r_{\text{B}} \cdot r_{\text{H}^+}}{r_{\text{BH}^+}}$$

$$pK_{\text{BH}^+} = \underbrace{\log I + pH}_{H_0} - \log \frac{r_{\text{B}} \cdot r_{\text{H}^+}}{r_{\text{BH}^+}}, \quad I = \frac{[\text{BH}^+]}{[\text{B}]}$$

H₀, if activity co. r_B, r_{BH⁺}, r_{H⁺} → 1
then H₀ → pH

For a base with known pK_{BH⁺}, in a series of acid sol'n
measure I → H₀ for the series of acid sol'n

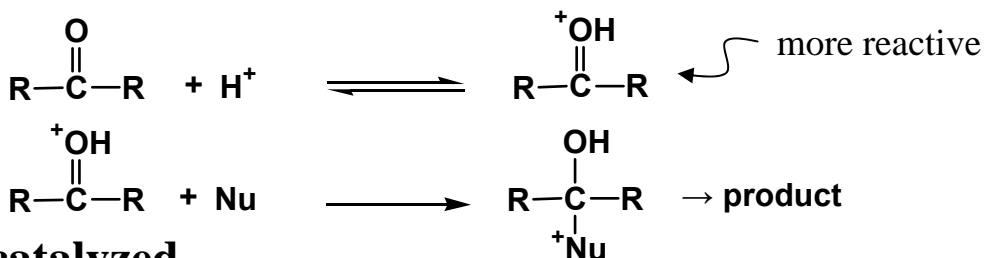
use H₀ to measure the pK_{B₂H⁺} of a weaker base

from pK_{B₂H⁺} to measure H₀ for even more acidic sol'n

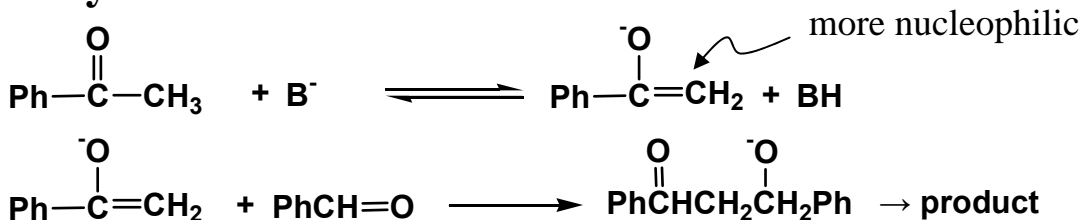
from H₀ of these sol'n to measure pK_{B₃H⁺} even weaker base

Acid-Base Catalyzed Reactions

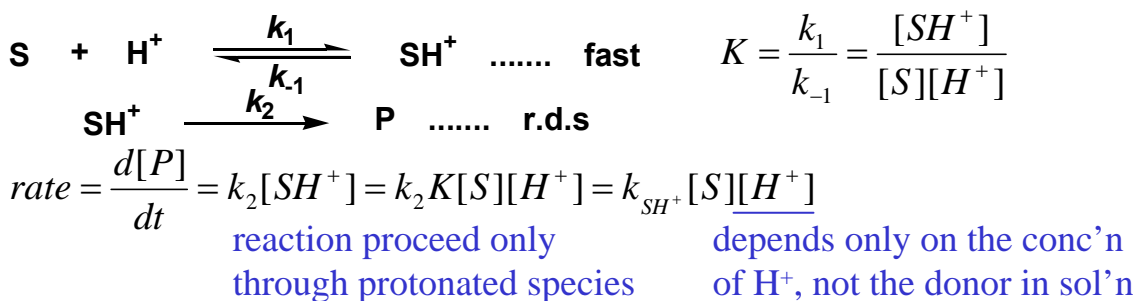
acid-catalyzed



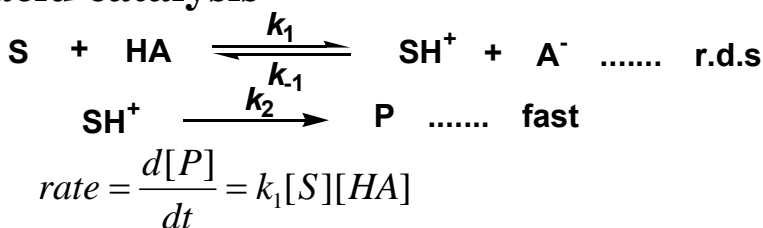
base-catalyzed



Specific acid catalysis



General acid catalysis



if more than one acid available in sol'n,

$$\frac{d[\text{P}]}{dt} = \sum_i = k_1[\text{S}][\text{HA}_i] \quad \text{general}$$

Similar for general base (or specific base catalysis)

To differentiate specific or general acid catalysis

- use buffer to keep [H⁺] const, with changing buffer
- constant rate → specific acid catalysis
- changing rate → general acid catalysis

Brønsted Catalysis Law

For general acid catalysis, the acidity of each acid will affect the rate.

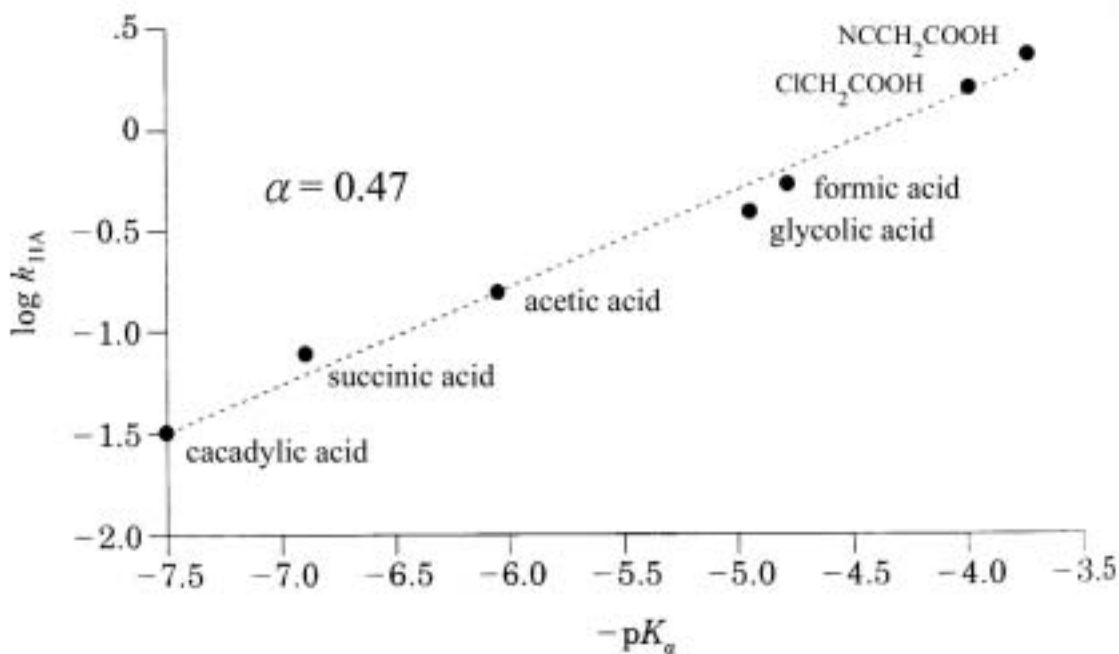
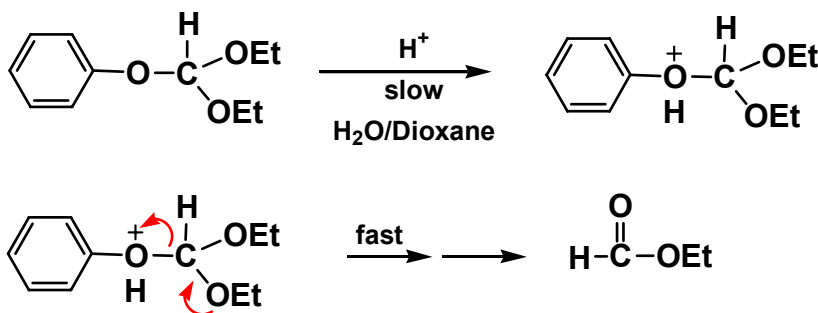
$$k_a = G_a(K_a)^\alpha$$

plot $\log k_a$ v.s $\log K_a$ for a series of related acid gives a linear curve with slope of α

$$\log k_{\text{HA}} = \alpha \log K_a + \text{constant}$$

sensitivity of the rate constant to structural change

$$(\log k_{\text{HB}} = \beta \log K_b + \text{constant})$$

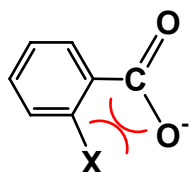


Substituent Effect on acidity

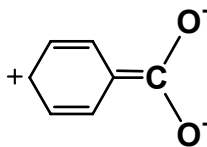
Table 7.1 pK_a data for selected organic compounds in aqueous solution.

Compound	pK_a	Compound	pK_a
Carboxylic acids			
Formic acid	3.75 ^a	Cyclohexanecarboxylic acid	4.90 ^a
Performic acid	7.1 ^b	Benzoic acid	4.20 ^a
Acetic acid	4.76 ^c	2-Methylbenzoic acid	3.91 ^d
Fluoroacetic acid	2.59 ^a	3-Methylbenzoic acid	4.27 ^d
Chloroacetic acid	2.87 ^a	4-Methylbenzoic acid	4.37 ^d
Bromoacetic acid	2.90 ^a	2- <i>t</i> -Butylbenzoic acid	3.54 ^d
Iodoacetic acid	3.18 ^a	2-Bromobenzoic acid	2.85 ^d
Cyanoacetic acid	2.47 ^a	3-Bromobenzoic acid	3.81 ^a
Methoxyacetic acid	3.57 ^a	4-Bromobenzoic acid	4.00 ^a
Nitroacetic acid	1.48 ^d	2-Chlorobenzoic acid	2.91 ^d
Mercaptoacetic acid	3.56 ^d	3-Chlorobenzoic acid	3.83 ^a
2-Hydroxyacetic acid (Glycolic acid)	3.38 ^a	4-Chlorobenzoic acid	3.99 ^a
Phenylacetic acid	4.31 ^b	2-Fluorobenzoic acid	3.27 ^d
Phenoxyacetic acid	3.16 ^b	3-Fluorobenzoic acid	3.86 ^d
Difluoroacetic acid	1.34 ^d	4-Fluorobenzoic acid	4.14 ^d
Dichloroacetic acid	1.35 ^d	2-Iodobenzoic acid	2.86 ^d
Dibromoacetic acid	1.48 ^b	3-Iodobenzoic acid	3.85 ^d
Trifluoroacetic acid	0.52 ^b	4-Iodobenzoic acid	4.00 ^d
Trichloroacetic acid	0.51 ^b	2-Hydroxybenzoic (Salicylic) acid	2.97 ^a
Tribromoacetic acid	0.72 ^b	3-Hydroxybenzoic acid	4.07 ^d
Propanoic acid	4.87 ^a	4-Hydroxybenzoic acid	4.58 ^a
Acrylic acid ($H_2C=CH-CO_2H$)	4.25 ^b	2-Cyanobenzoic acid	3.14 ^e
Propiolic acid ($HC\equiv C-CO_2H$)	1.89 ^d	3-Cyanobenzoic acid	3.60 ^e
Pyruvic acid (CH_3COCO_2H)	2.39 ^b	4-Cyanobenzoic acid	3.55 ^a
2,2,3,3,3-Pentafluoropropanoic acid	-0.41 ^b	2-Nitrobenzoic acid	2.21 ^d
Butanoic acid	4.82 ^c	3-Nitrobenzoic acid	3.49 ^d
<i>cis</i> -2-Butenoic acid	4.42 ^b	4-Nitrobenzoic acid	3.44 ^a
<i>trans</i> -2-Butenoic acid	4.70 ^b	Acetylsalicylic acid	3.38 ^b
2-Butynoic acid ($CH_3-C\equiv C-CO_2H$)	2.59 ^b	Pentafluorobenzoic acid	1.75 ^b
3-Butynoic acid ($HC\equiv C-CH_2CO_2H$)	3.32 ^b	1-Naphthoic acid	3.60 ^b
Cyclopentanecarboxylic acid	4.99 ^a	2-Naphthoic acid	4.14 ^b
		Alcohols and Phenols	
		(Water)	15.74 ^d
		Methanol (CH_3OH)	15.5 ^d
		Ethanol	15.9 ^d

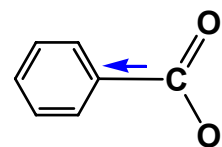
the acid strengthening effect of ortho-substituent



the ortho group
remove the planarity



resonance effect :
decrease the acidity



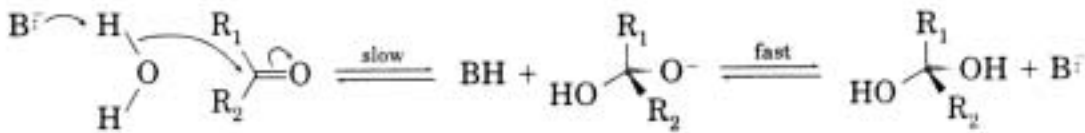
inductive effect :
acid strengthening

Addition to Carbonyl Group

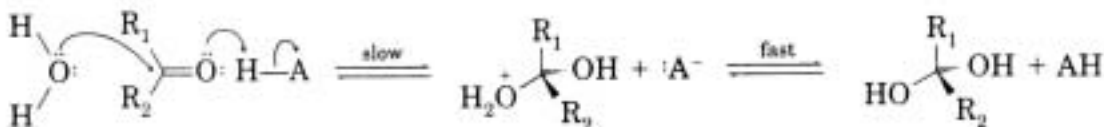
Hydration of aldehyde and ketone

General base catalysis and general acid catalysis

base-catalysis

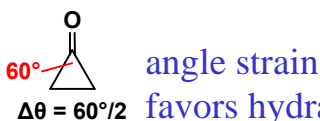
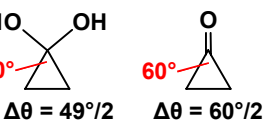
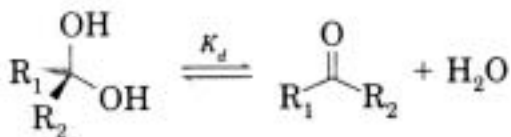


acid-catalysis



the catalytic efficiency depends on acid strengthening

for the equilibrium



angle strain favors hydrate

e^- -withdrawing group favors hydrate

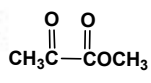
bulky group favors ketone

Steric effect

conjugate aromatic group favors ketone

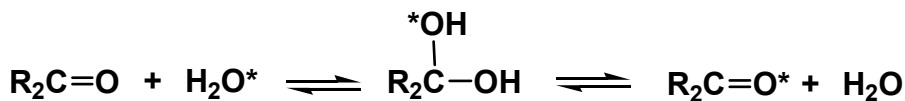
Table 7.6 Equilibrium constants for dissociation of hydrates of carbonyl compounds.¹²⁹

Compound	K_d^{129}
Cyclopropanone ¹²⁴	very small
Chloral (α,α,α -Trichloroacetaldehyde)	3.6×10^{-5}
Formaldehyde ¹²⁷	4.5×10^{-4}
α -Chloroacetaldehyde	2.7×10^{-3}
α -Chlorobutyraldehyde	6.3×10^{-2}
α,α' -Dichloroacetone	0.10
α,α -Dibromobutanal	0.11
α -Chloroheptanal	0.16
2-Chloro-2-methylpropanal	0.19
Methyl pyruvate ¹³²	0.32
α,α -Dichloroacetone ¹³²	0.35
α -Bromobutyral	0.35
Pyruvic acid ¹³²	0.42
Biacetyl ¹³²	0.50
Acetaldehyde ¹²⁴	0.83
Propanal	1.4
Butanal	2.1
2-Methylpropanal	2.3
Pivaldehyde ¹³²	4.1
α -Chloroacetone ¹³²	9.1
Sodium pyruvate ¹³²	18.5
Benzaldehyde ¹²⁶	120
Acetone ¹²⁹	720
Acetophenone ¹³⁴	1.5×10^5
Benzophenone ¹³⁴	8.5×10^6



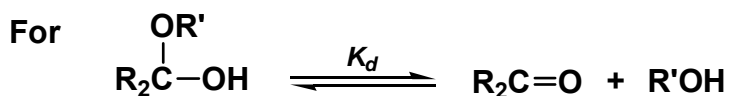
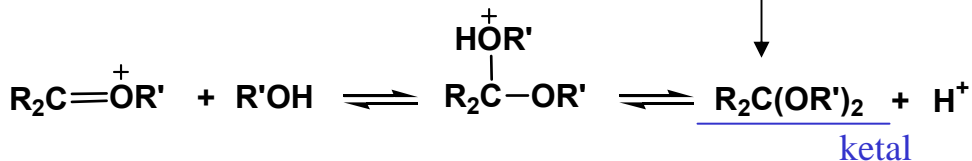
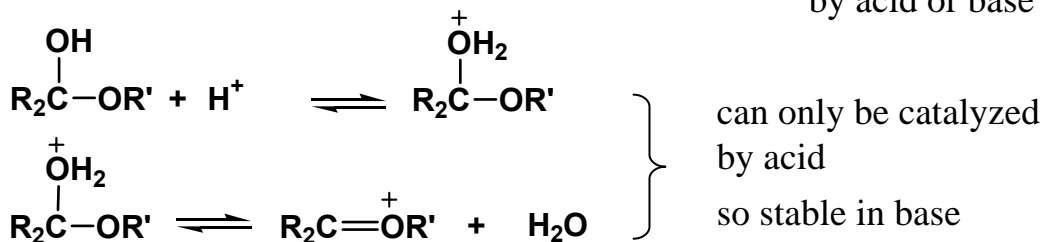
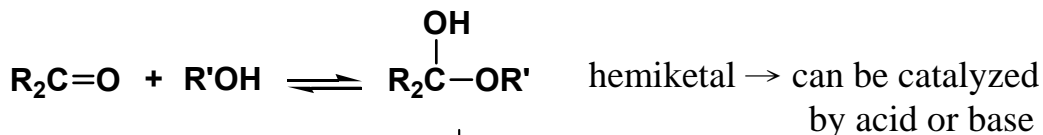
increasing alky substitution

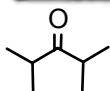

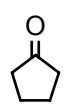
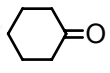
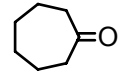
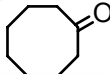
The hydration may be unfavorable, but the equilibrium is established fast



$t_{1/2} \sim 1$ min in neutral condition
 $\ll 1$ min in acidic or basic condition

hemiketal, hemiacetal, ketal, acetal

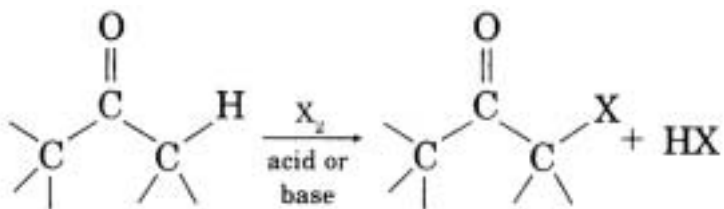


Ketone	K_d (methanol)	K_d (ethanol)
 Dipropyl ketone	89.0	
 Cyclobutanone	1.11	327
 Cyclopentanone	15.1	810
 Cyclohexanone	2.16	237
 Cycloheptanone	53.5	
 Cyclooctanone	268	

in general less favorable than methanol for steric reason

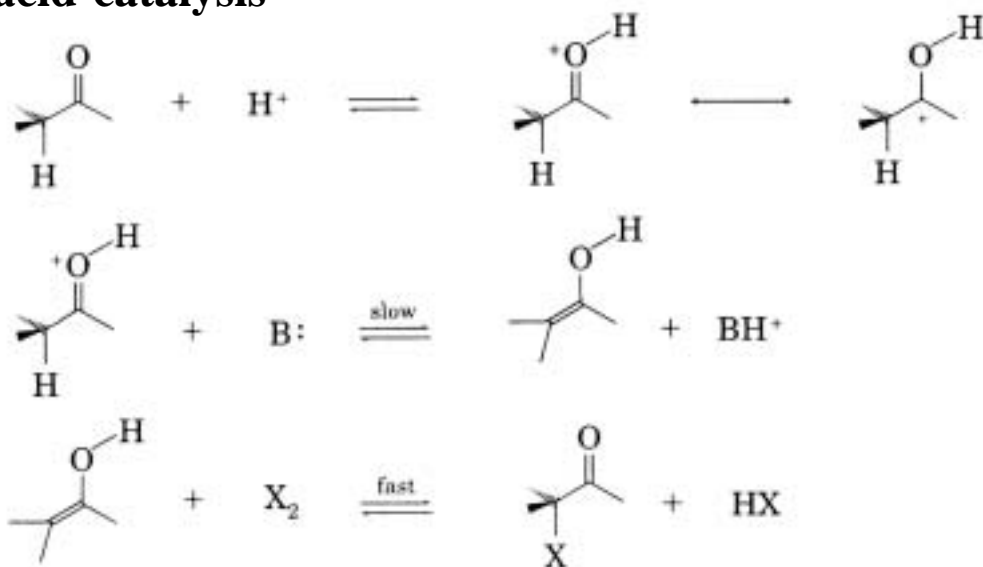
To drive equilibrium to ketal, dehydration or azeotrope are used

Enolization of Carbonyl Compounds

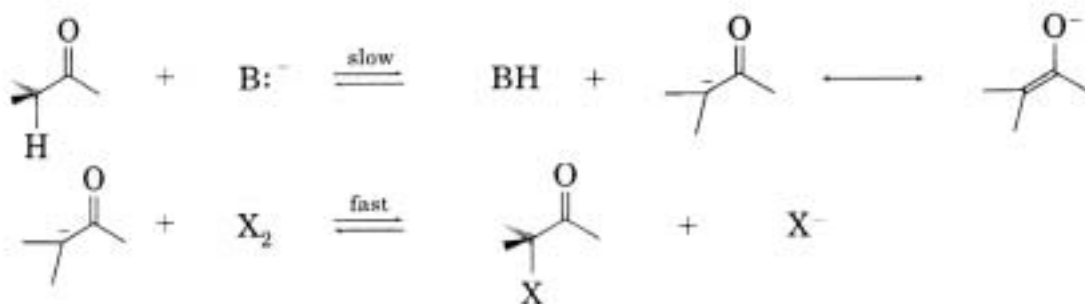


1. catalyzed by acid or base
2. first order in ketone, zero order in X₂
3. if chiral at α-carbon, the rate of bromination is the same as rate of racemization and rate H-exchange
 → rate-determining step is the formation of enol or enolate

in acid-catalysis

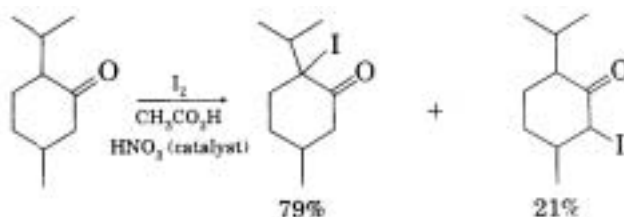


in base-catalysis

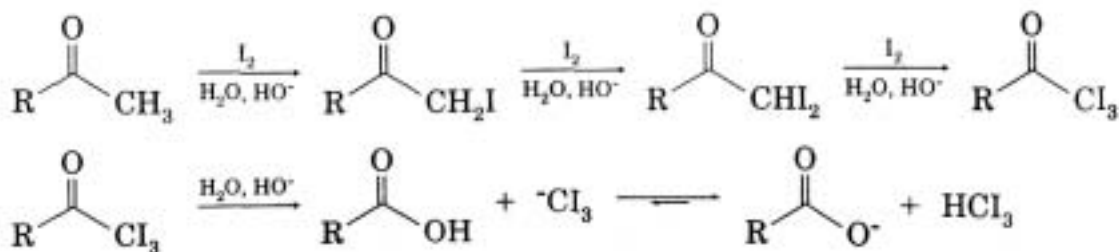


For unsymmetrically substituted ketone, the enolization / halogenation depends on condition

in acid-catalysis, more substituted enol is formed



in base-catalysis, less substituted enolate is formed

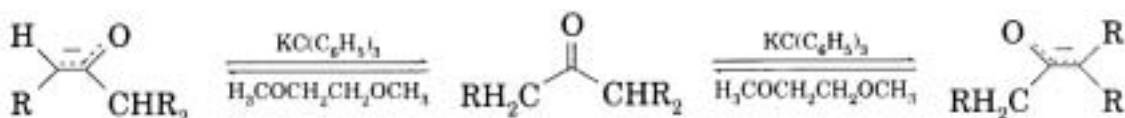


the preference is based on both kinetic and thermodynamic reasons

Kinetic reason :

	<u>R₁</u>	<u>R₂</u>	<u>Relative Rate</u>
	H	H	238
	H	CH ₃	37
	H	CH ₂ CH ₃	29
	CH ₃	CH ₃	7

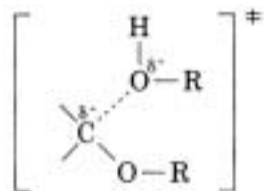
Thermodynamic reason :



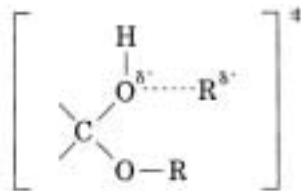
favored

Hydrolysis of Acetal by acid-catalysis

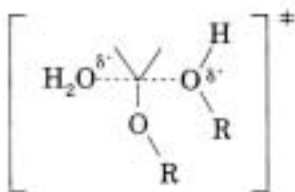
Possible Transition State



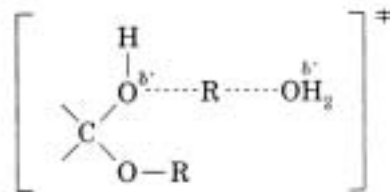
A1: unimolecular



A1: unimolecular



A2: bimolecular

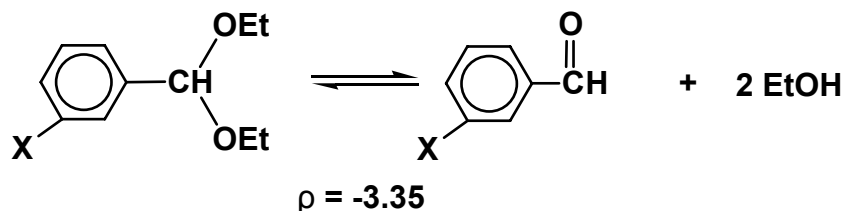


A2: bimolecular

Mechanistic Evidences

1. C-O cleavage between carbonyl C and O is shown by isotope labeling experiment, stereochemistry of R group. (no racemization or inversion)

2. Hammett ρ value

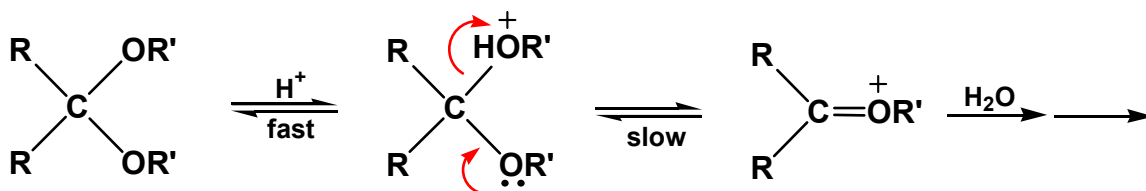


3. ΔS^\ddagger nearly zero or slightly positive

4. kinetic solvent isotope effect $k_{D_3O^+}/k_{H_3O^+} \sim 2-3$

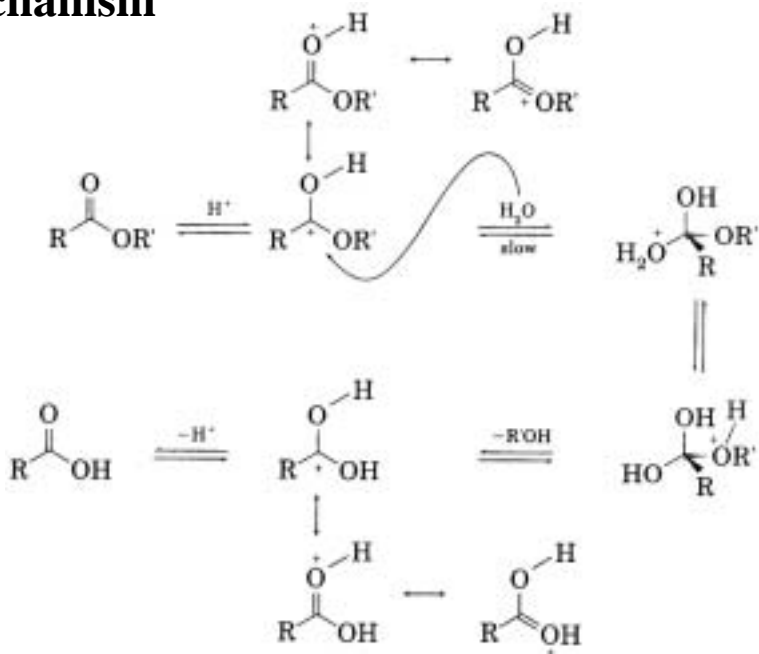
5. the reaction is specific acid catalyzed

→ a pre-equilibrium exist for protonation of ketal/acetal

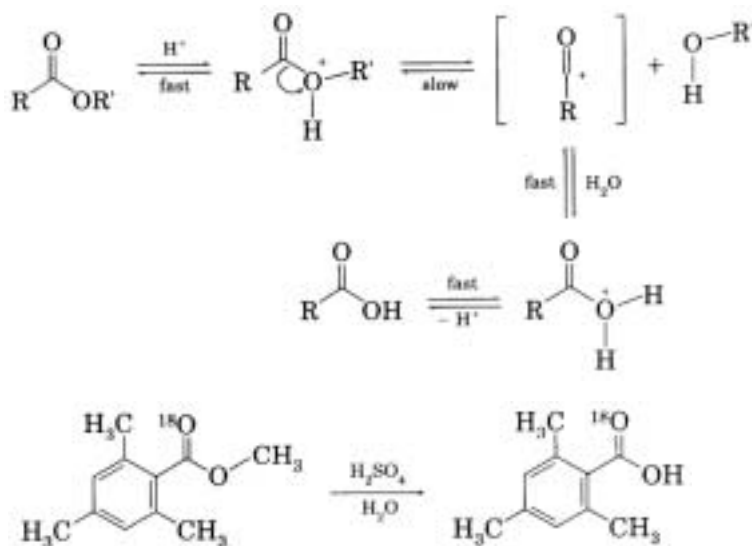


Acid-catalyzed Hydrolysis of Ester

A_{Ac}2 Mechanism



A_{Ac}1 Mechanism



at 9.8M H_2SO_4 , $\Delta S^\ddagger +17eV$ (support A_{Ac}1)

$\Delta H^\ddagger 28.4kcal$

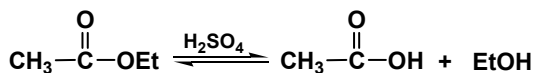
No carbonyl oxygen exchange (rule out A_{Ac}2)

A_{Al}1 Mechanism

the hydrolysis mechanism depends on structure and condition



evidence for switching
of mechanism kinetic
parameters, exchange
experiment



% H ₂ SO ₄	ΔH ⁺	ΔS ⁺
40.0	16.9	-15.3
62.2	16.3	-17.0
98.4	2.7	2.3

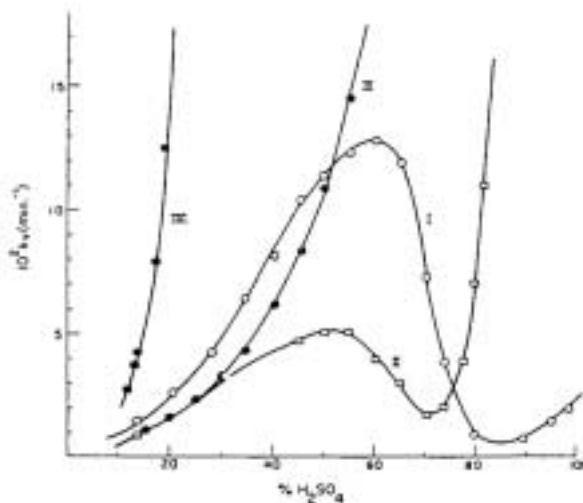


Figure 1. Typical rate profiles for acetate hydrolysis: type I, methyl; II, *sec*-butyl; III, phenyl; IV, *tert*-butyl.

Base-Catalyzed Hydrolysis of Ester

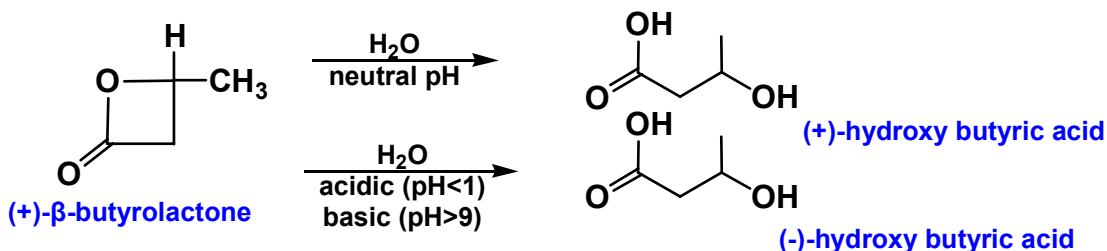
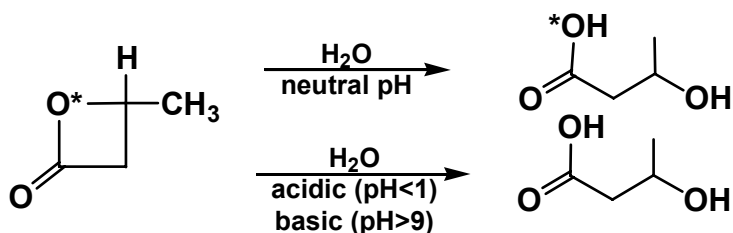
B_{Al}2 Mechanism



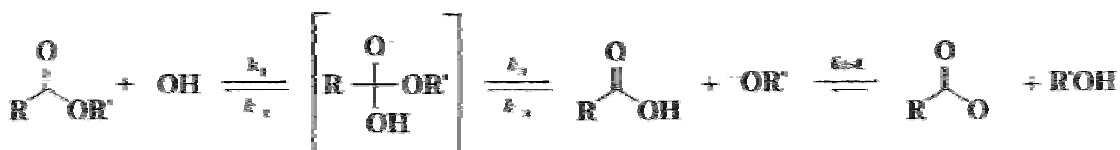
Ruled out for most ester by labeling experiment



but in highly strained case



B_{Ac}2 Mechanism



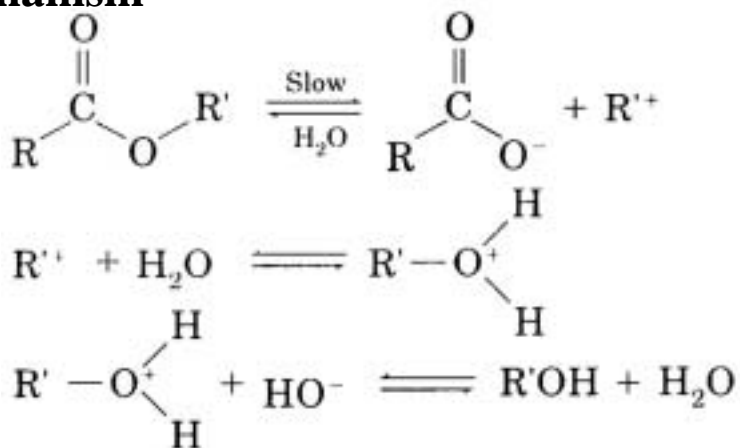
Evidences : kinetics, isotope labeling

dependence of [OH-],
activation parameters

Acyl-O cleavage,
exchange with
solvent...

Substituent effect : Electron-withdrawing groups in R and R'
favor hydrolysis

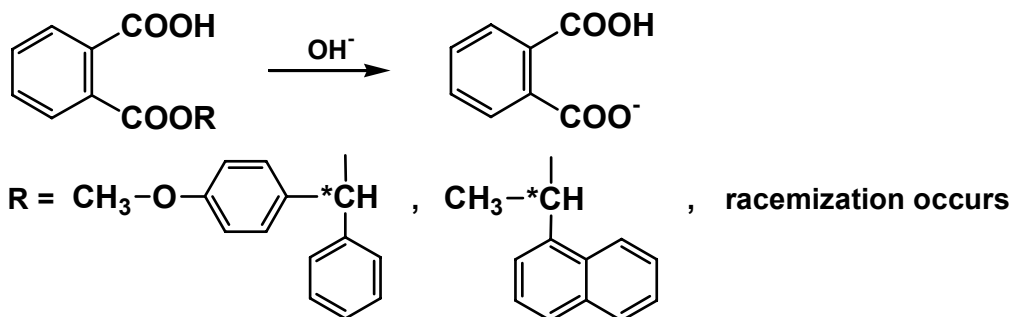
B_{Al}1 Mechanism



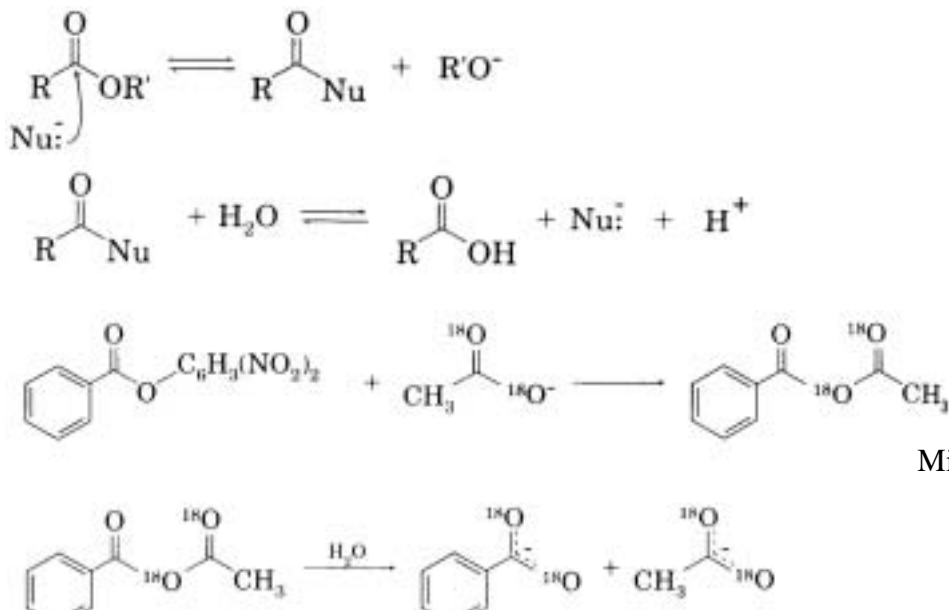
for ester from a strong acid (carboxylate ion stable)

for R' a tertiary or benzylic alkyl group (carbocation stable)
or conc'n of base too low

with B_{Al}1 mechanism, R'OH will be racemized



Nucleophilic Catalysis



Mixed anhydride