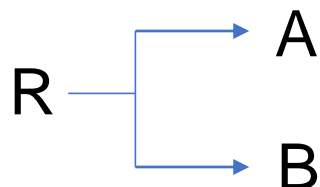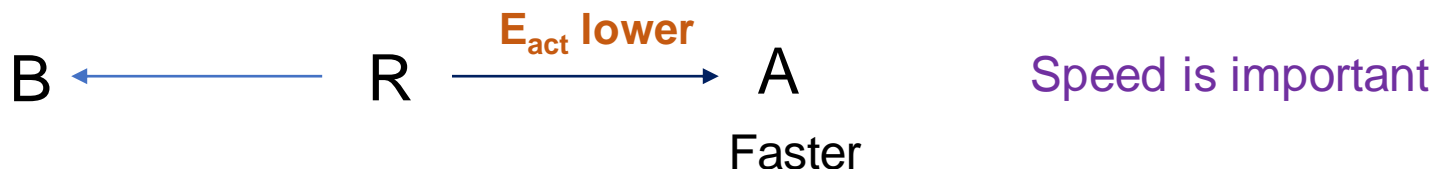# Last lecture: Kinetic versus Thermodynamic Control
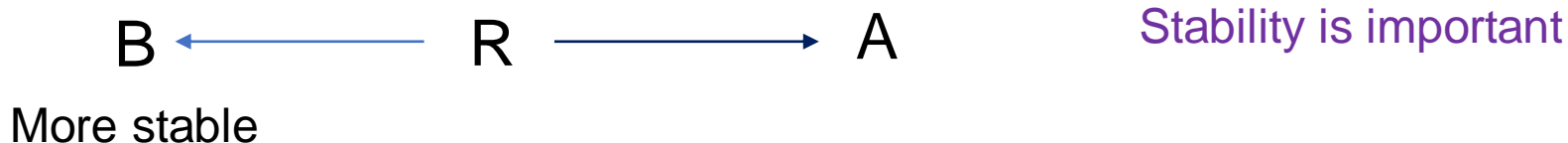
R → A
R → B

If multiple products are possible for a reaction, ratio of products can be dictated by

- Relative energy of transition states – Kinetic control (KC)

$$B \longleftarrow R \xrightarrow{\textbf{E}_{act} \textbf{ lower}} A$$

Faster

Speed is important

- Relative energy of products – thermodynamic control (TC)

$$B \longleftarrow R \longrightarrow A$$
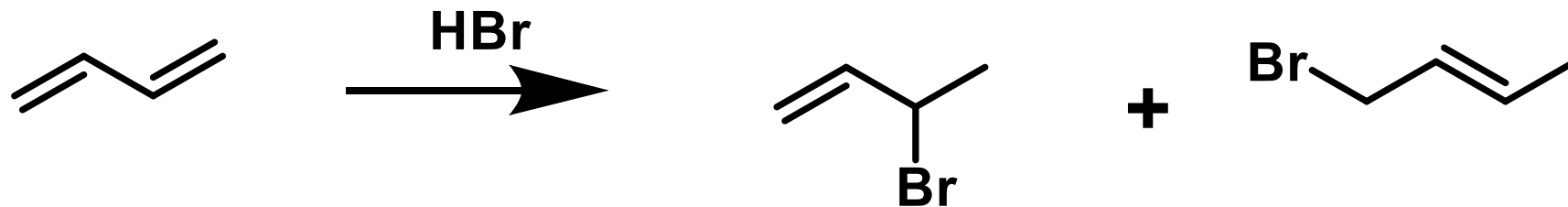
More stable

Stability is important

Write the plausible mechanism

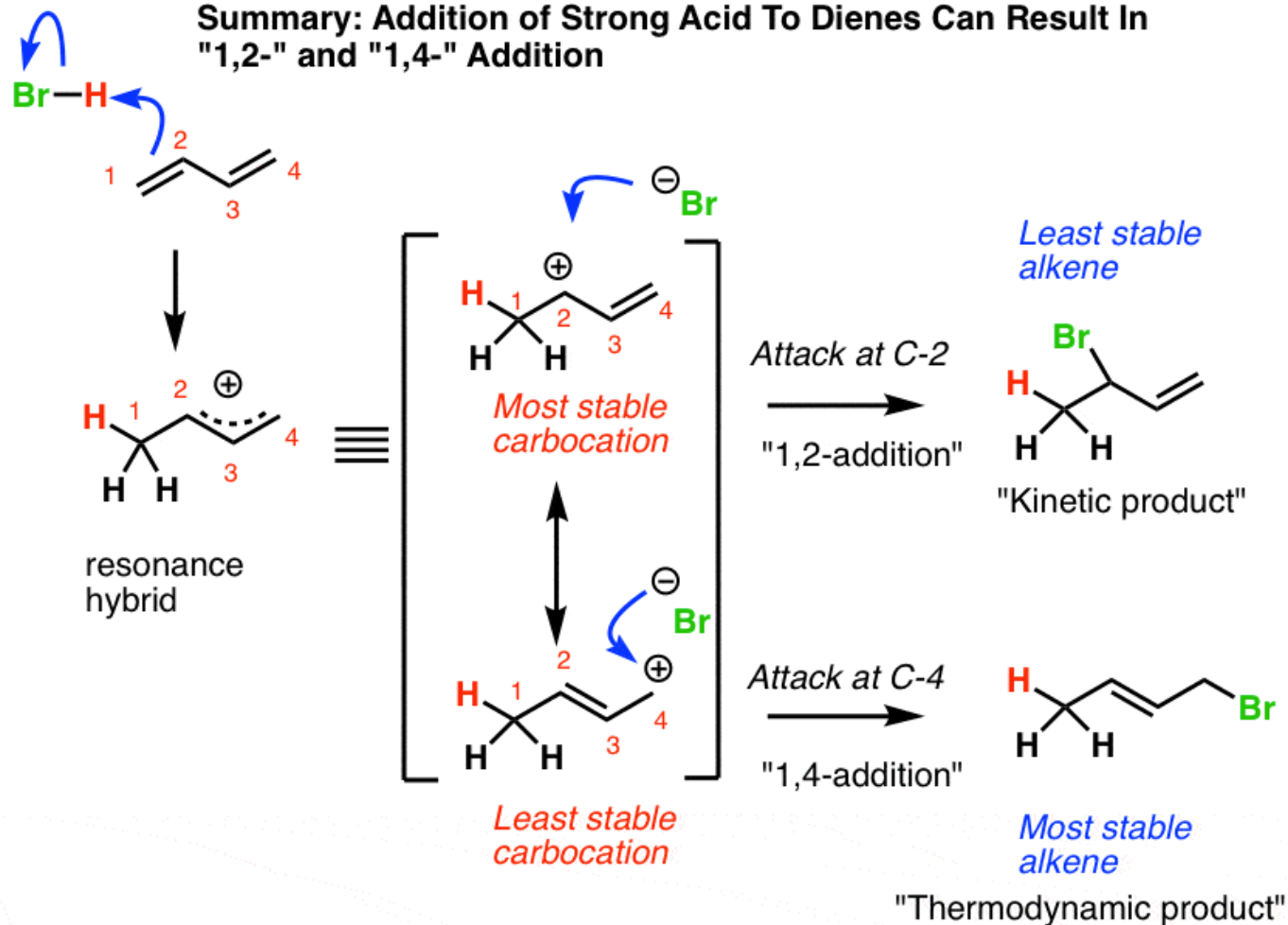**Draw reaction coordinate diagram for both the products**

Identify thermodynamically controlled product and kinetically controlled product

What conditions should be used to get preferentially one over the other

ΔG is negative!!

Summary: Addition of Strong Acid To Dienes Can Result In "1,2-" and "1,4-" Addition

Br—H

Most stable carbocation

Least stable alkene

Attack at C-2

"1,2-addition"

"Kinetic product"

resonance hybrid

Least stable carbocation

Attack at C-4

"1,4-addition"

Most stable alkene
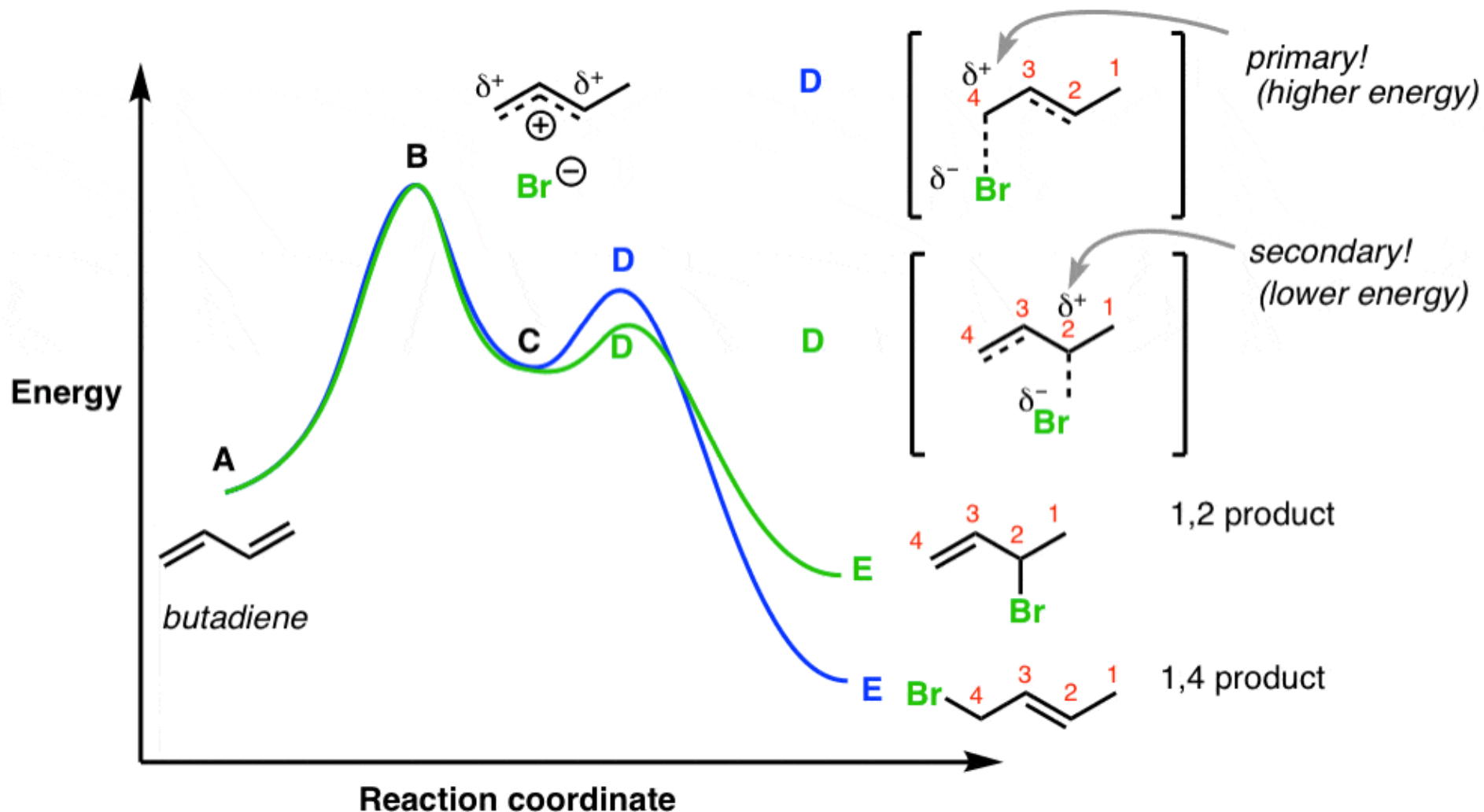
"Thermodynamic product"

In this case, the major product can be controlled with temperature:

• At low temperatures, the reaction is irreversible and the lowest-energy transition state will determine the major product (i.e. addition to the carbon best able to stabilize positive charge). This is **kinetic contro**l.

• At higher temperatures, the reaction is reversible and the product distribution will favor the more stable product (the more substituted alkene, in this case). This is called **thermodynamic control.**
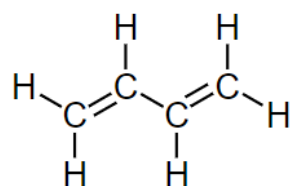
Kinetic versus Thermodynamic Control

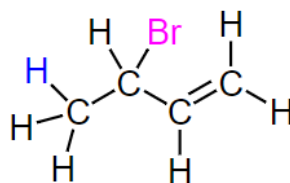Energy Diagram for 1,2- versus 1,4- additions to butadiene

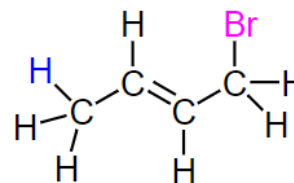# Kinetic versus Thermodynamic Control

Example: 2 step reaction

1,3-Butadiene → (HBr) → 1,2-Addition Product + 1,4-Addition Product

	1,2-Addition Product	1,4-Addition Product	
At -80 °C:	80%	20%	**Kinetic Control**
At 0 °C:	70%	30%	**Kinetic Control**
At 40 °C:	15%	85%	**Thermodynamic Control**
At 60 °C:	10%	90%	**Thermodynamic Control**

CH 209 – Basic Organic Chemistry

Reaction mechanisms: Acids, bases and factors affecting pK$_a$ and nucleophilicity

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Why is it necessary to understand acids and bases in organic chemistry?

Acids and Bases

- Many organic and biological reactions are catalyzed by acids or bases

- If the first step in a reaction is the protonation or deprotonation of one of the reactants, it is necessary to know where the compound would be protonated or deprotonated and what strength acid or base would be needed.

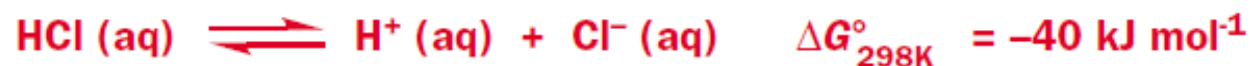Can you name few reactions where the first step of the reaction is protonation or deprotonation?

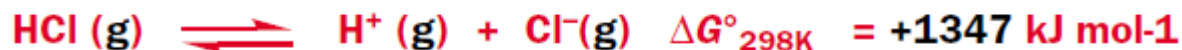- **Acid or base catalysed hydrolysis of proteins, peptides, sugars**

- **Aldol additions**

Acids and Bases

Bronsted definitions of acids and bases

- **An acid is a species having a tendency to lose a proton**

- **A base is a species having a tendency to accept a proton**

$HCl\ (aq) \rightleftharpoons H^+\ (aq)\ +\ Cl^-\ (aq)$ $\Delta G^{\circ}_{298K} = -40\ kJ\ mol^{-1}$ The equilibrium lies well over to the right

$HCl\ (g) \rightleftharpoons H^+\ (g)\ +\ Cl^-(g)$ $\Delta G^{\circ}_{298K} = +1347\ kJ\ mol^{-1}$ HCl does not ionize in the gas phase readily

Why then is HCl such a strong acid in water?

Why the equilibrium is well over to right in aqueous media?

Acids

- In aqueous solution the proton is strongly attached to a water molecule to give the very stable **hydronium ion**, H_3O^+, and the ions are no longer isolated but solvated.

- Solvated hydronium ions are stabilized by hydrogen-bonding
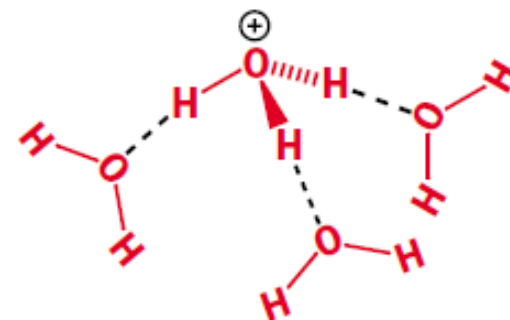
a structure for a solvated hydronium ion in water the dashed bonds represent hydrogen bonds

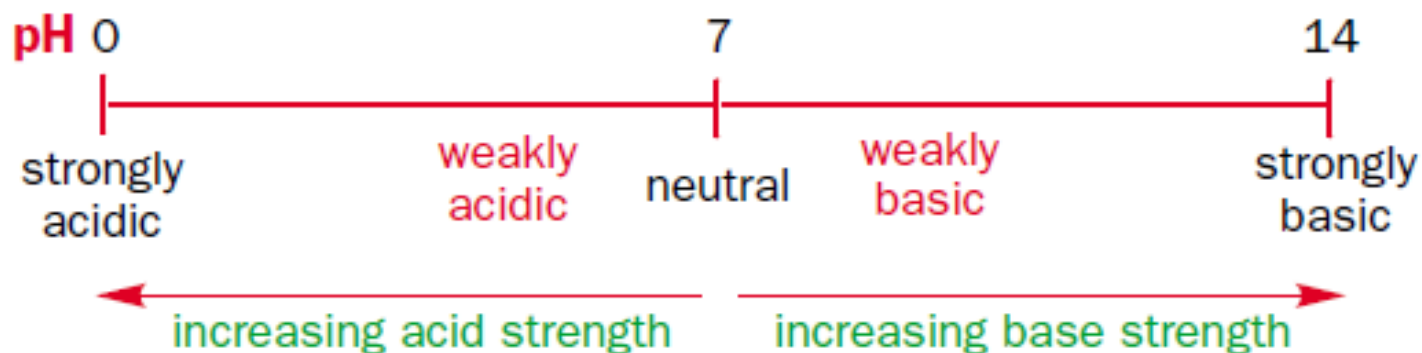**Every acid has a conjugate base associated with it and every base has a conjugate acid associated with it!!**

$$HCl\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + Cl^-(aq)$$

Acid   Base   Conjugate acid   Conjugate base

$$CH_3COOH + NH_3 \rightleftharpoons NH_4^+ + CH_3COO^-$$

Acid   Base   Conjugate acid   Conjugate base

Water can behave as an acid or as a base

- If a strong acid is added to water, the water acts as a base and is protonated by the acid to become H_3O^+.

- If we add a strong base to water, the base would deprotonate the water to give hydroxide ion, OH^-, and here the water would be acting as an acid.

- Compounds that can act as either an acid or a base are called **amphoteric**.

Do you know any other molecular species that act as amphoteric?

basic group   O   acidic group

H_2N

OH

R

Amino acids

⊕
H_3N

O

O⊖

R

an amino acid zwitterion
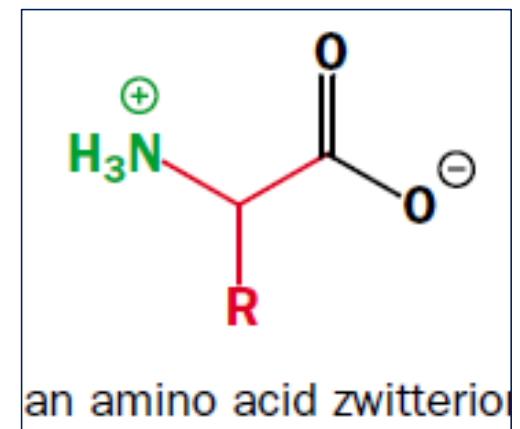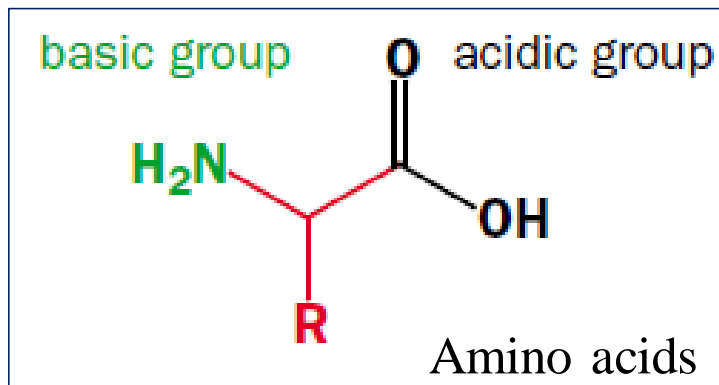
Strength of an acid is not indicated by pH

- The pH of a solution is only a measure of the acidity of the solution

- pH does not tell about how strong one acid might be relative to another

- The pH of a solution of a given acid varies with its concentration: as we dilute the solution, the acidity falls and the pH increases

- As we decrease the concentration of HCl in an aqueous solution from 1 to 0.1 to 0.01 to 0.001 mol dm^{-3}, the pH changes from 0 to 1 to 2 to 3.

$$pH = -\log[H_3O^+]$$

pH of a solution depends on the acid

Do 0.1 M HCl and 0.1 M CH$_3$COOH in an aqueous solution have the same pH?

- 0.1 M HCl has a pH of 1

- The same concentration of acetic acid has a pH of 3.7

- HCl is a strong acid and completely dissociates in water

- Acetic acid is not fully dissociated—the solution contains both acetic acid and acetate ions.

$$HCl\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq)\ +\ Cl^-\ (aq)$$

$$CH_3COOH\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + CH_3COO^-\ (aq)$$

Definition of pK_a

- To measure the strength of an acid relative to water and find out how effective a proton donor it is, we must look at the equilibrium constant for the reaction

$$AH\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + A^-\ (aq)$$

$$K_{eq} = \frac{[H_3O^+][A^-]}{[AH][H_2O]}$$

- With dilute solutions of acids, a new equilibrium constant, K_a, is defined and called the **acidity constant**.

$$K_a = \frac{[H_3O^+][A^-]}{[AH]}$$

- Like pH, K_a is also expressed in a logarithmic form, pK_a.

$$pK_a = -\log K_a$$

Definition of pK_a

$$pK_a = -\log K_a$$

- **The lower the pK_a, the larger the equilibrium constant, K_a, is and hence the stronger the acid.**

- The pK_a of the acid is the pH where it is exactly half dissociated.

$$K_a = \frac{[H_3O^+][A^-]}{[AH]}$$

$$[H_3O^+] = K_a \times \frac{[AH]}{[A^-]}$$

$$pH = pK_a + \log\left(\frac{[A^-]}{[AH]}\right)$$

When an acid is 50% ionised:

$$pH = pK_a$$

0.1 M CH_3COOH aqueous solution has a pH of 3.7

If we raise its pH to 4.76, the resultant solution would contain equal concentrations of acetic acid and acetate ion.

pK_a of acetic acid = 4.76

Graphical description of the pK_a of acids
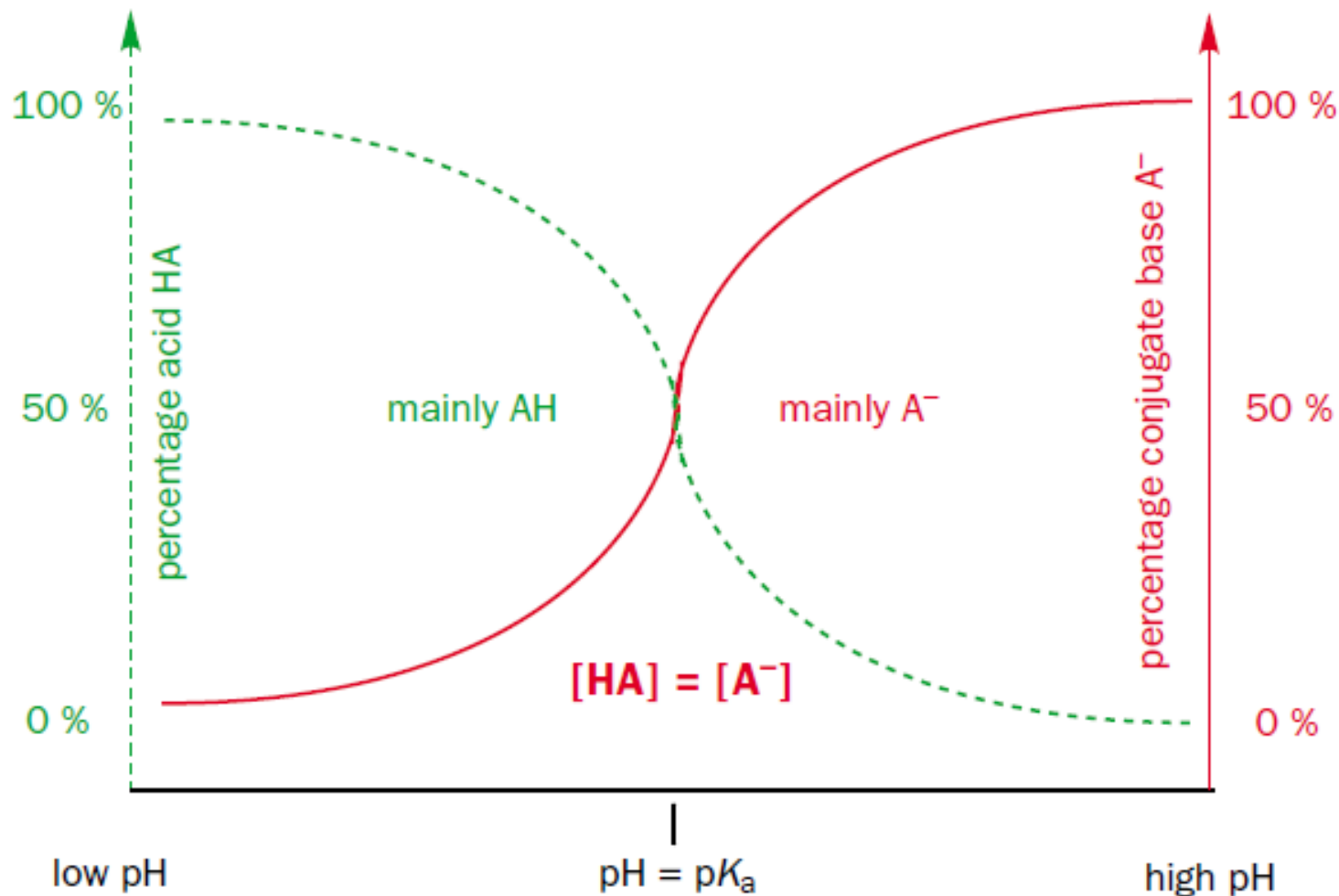
At low pH the compound exists entirely as AH and at high pH entirely as A⁻. At the pK_a the concentration of each species, AH and A⁻, is the same. At pHs near the pK_a the compound exists as a mixture of the two forms.

Ionization of an acid – 2,4-dinitrophenol
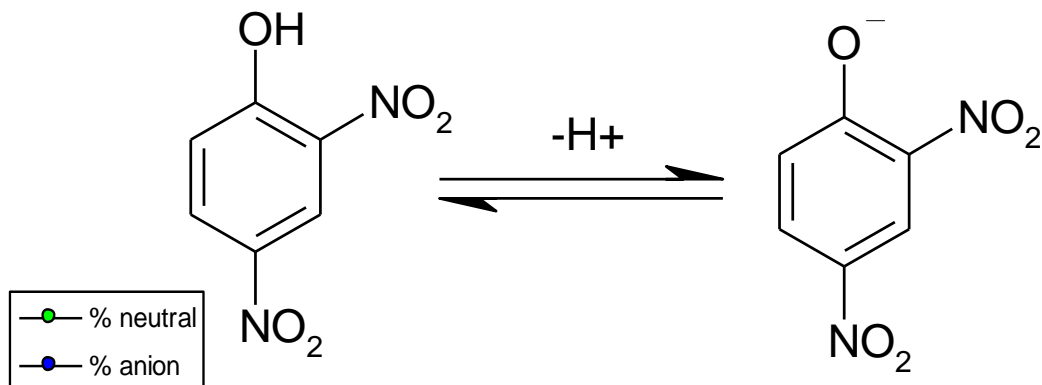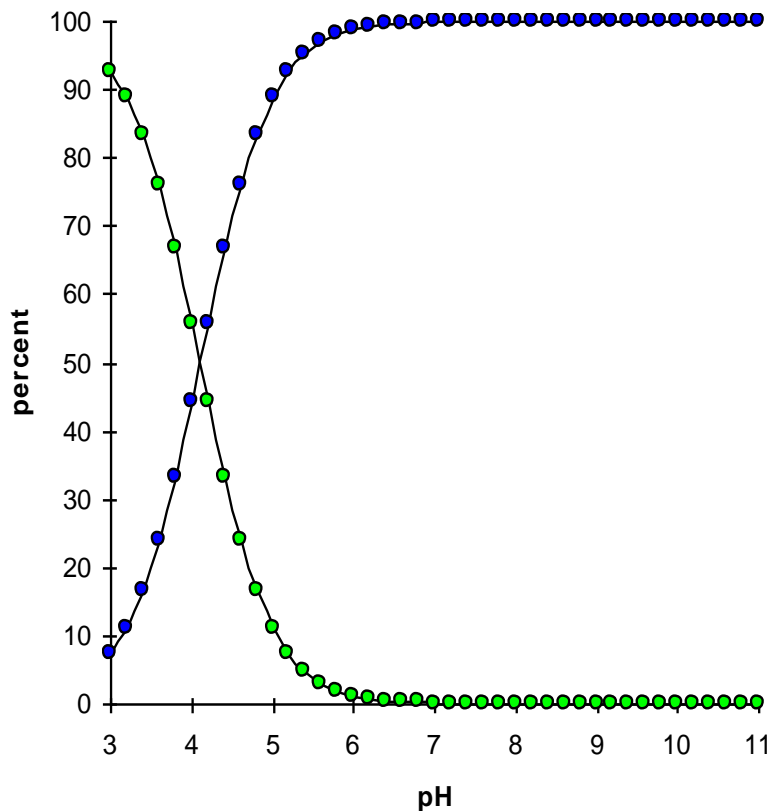
pK$_a$ = 4.1

Ionization of an base – 4-aminopyridine
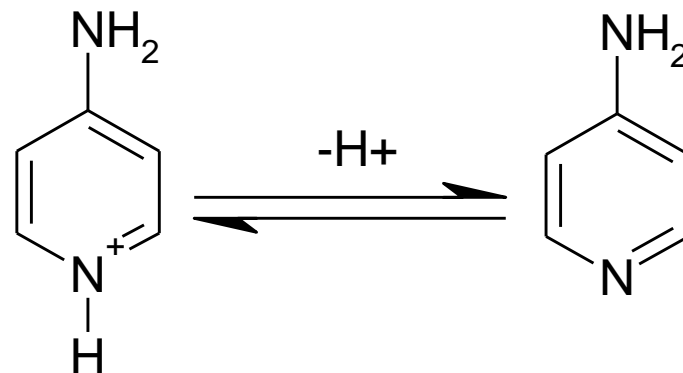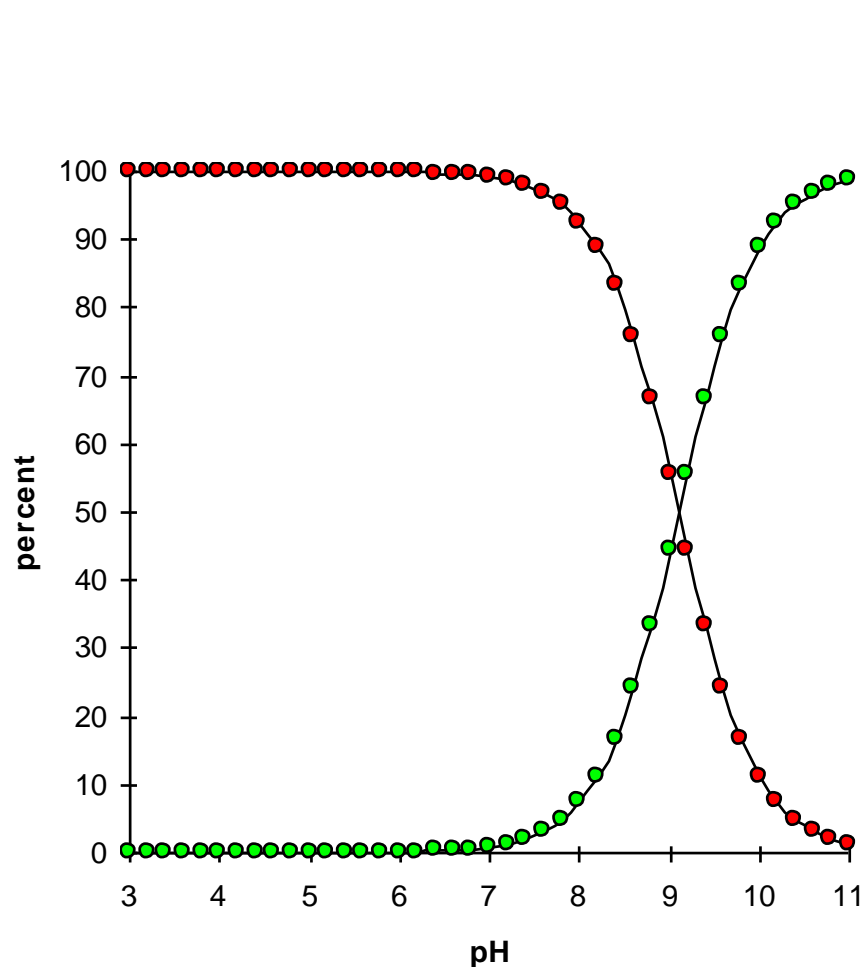
Solubility, pH and pK_a

- At pHs above the pK_a of the acid, it will be more soluble in water.

- Ionic groups considerably increase a compound's solubility and so the ion A⁻ is much more soluble in water than the undissociated acid HA.

- Water can solvate both cations and anions

- We can increase the solubility of a neutral acid in water by increasing the proportion of its conjugate base present
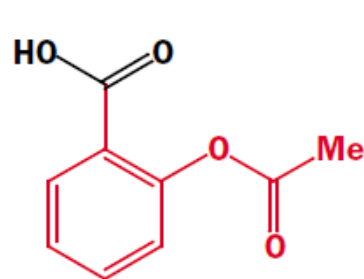
aspirin
not very soluble in water
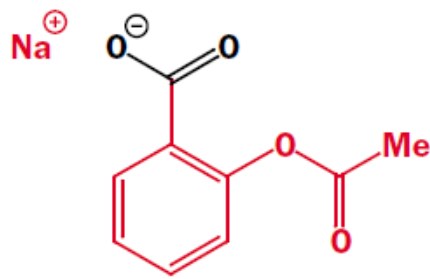
the sodium (or calcium) salt of
aspirin is more soluble in water
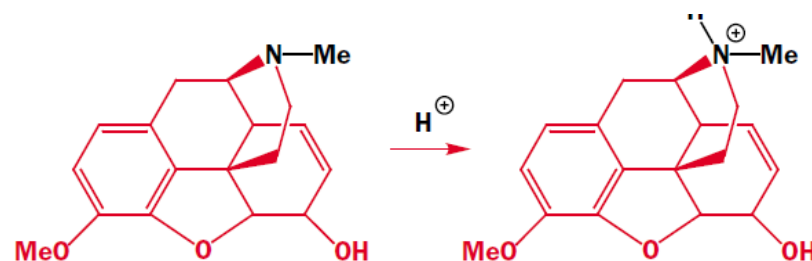
neutral codeine
sparingly soluble in water

the conjugate acid is much
more soluble in water

- **Tuning the drug's solubility is a critical field in the pharmaceutical industry.**

Solubility, pH and pK_a : Lab procedures

- Charged compounds can be separated by acid–base extraction

insoluble in water + insoluble in water → NaOH → insoluble in water + soluble in water
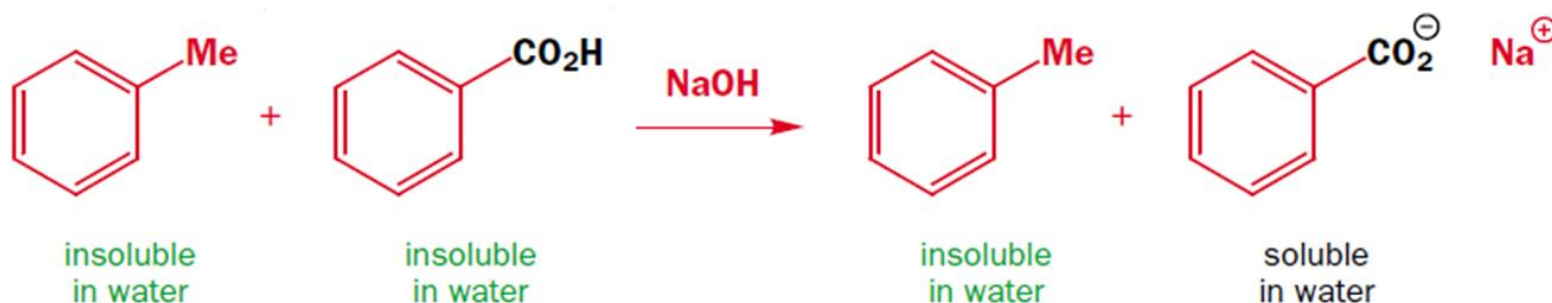
Adjust the pH to acidic to the blow pK_a of benzoic acid

- Water is quite difficult to evaporate due to its high boiling point

Benzoic acid
(water insoluble)

Factors affecting the pK_a

- An acid's pKa depends on the stability of its conjugate base

- The pK_a of HCl is around –7 compared to 4.76 for acetic acid.

$$\text{HCl (aq)} + \text{H}_2\text{O (l)} \rightleftharpoons \text{H}_3\text{O}^+ \text{ (aq)} + \text{Cl}^- \text{ (aq)} \qquad K_a = 10^7$$

$$\text{CH}_3\text{COOH (aq)} + \text{H}_2\text{O (l)} \rightleftharpoons \text{H}_3\text{O}^+ \text{ (aq)} + \text{CH}_3\text{COO}^- \text{ (aq)} \qquad K_a = 1.74 \times 10^{-5}$$
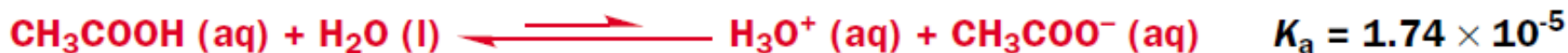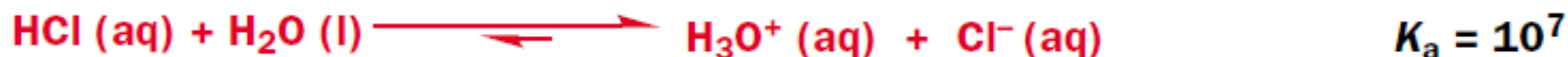
Why are the equilibria so different? Why does hydrogen chloride fully dissociate but acetic acid do so only partially?
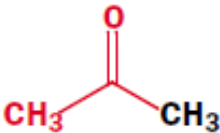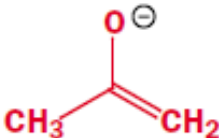
- The chloride ion is not a strong enough base to deprotonate the hydronium ion.

- Acetate, on the other hand, is easily protonated by H_3O^+ to give neutral acetic acid

● **Acid and conjugate base strength**
  - The stronger the acid HA, the weaker its conjugate base, A$^-$
  - The stronger the base A$^-$, the weaker its conjugate acid AH

pK_a values

Table 8.1 The pK_a value of some compounds

Acid	pK_a	Conjugate base
HI	ca. −10	I$^-$
HCl	ca. −7	Cl$^-$
H_2SO_4	ca. −3	HSO_4^-
HSO_4^-	2.0	SO_4^{2-}
CH_3COOH	4.8	CH_3COO^-
H_2S	7.0	HS^-
NH_4^+	9.2	NH_3
C_6H_5OH	10.0	$C_6H_5O^-$
CH_3OH	15.5	CH_3O^-
	20.0	
CH≡C—H	25	CH≡C$^\ominus$
NH_3	33	NH_2^-
C_6H_6	ca. 43	$C_6H_5^-$
CH_4	ca. 48	CH_3^-

Aqueous solutions and the pK_a

- The strongest base in aqueous solution is OH⁻ and the strongest acid in aqueous solution is H_3O^+. Remember that:

- Addition of stronger bases than OH⁻ just gives more OH⁻ by the deprotonation of water

- Addition of stronger acids than H_3O^+ just gives more H_3O^+ by protonation of water

Also remember that:
The pH of pure water at 25°C is 7.00 (not the pK_a)
The pK_a of H_2O is 15.74
The pK_a of H_3O^+ is –1.74
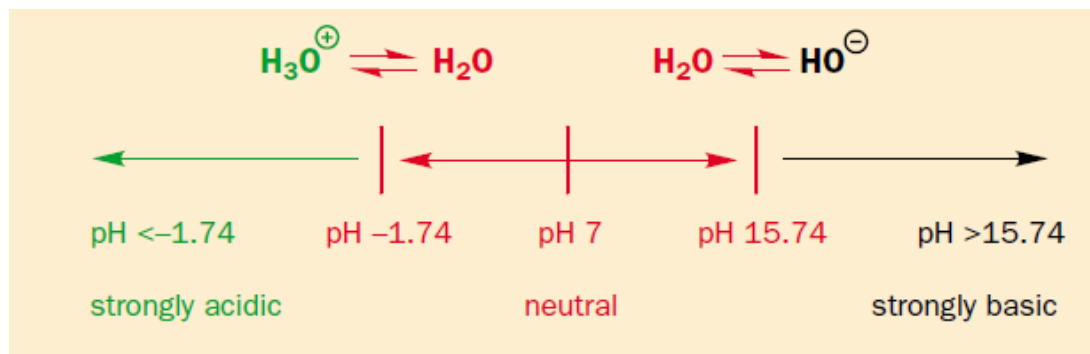
The choice of solvent limits pK_a range

- In water, effective pK_a range is only -1.74 to 15.74, that is, it is determined by the solvent. This is known as the **levelling effect** of the solvent.

- If we want to remove the proton from something with a high pK_a, say 25–30, it would be impossible to do this in water since the strongest base we can use is hydroxide.

- If we do need a stronger base than OH⁻, we must use a different solvent system.

$$CH \equiv C-H \ + \ NH_2^{\ominus} \ \underset{\longleftarrow}{\overset{NH_3 \, (l)}{\longrightarrow}} \ CH \equiv C^{\ominus} \ + \ NH_3$$

pK_a ~25
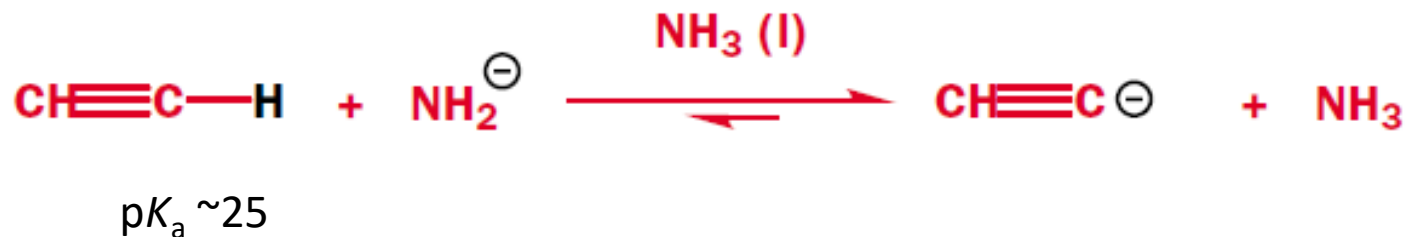
- We must use a different solvent that does not have a pK_a less than 25

Constructing a pK_a scale

- The negative charge on an electronegative element stabilizes the conjugate base

  - The pKa values for second row hydrides CH_4, NH_3, H_2O, and HF are about 48, 33, 16, and 3, respectively.
  - Due to increased electronegativity

- Weak A–H bonds make stronger acids

  - Acid strength HI > HBr > HCl > HF (pK_as: -10, -9, -7, 3 respectively)
  - Does not obey electronegativity rule here
  - Bond weakens down the group

- Delocalization of the negative charge stabilizes the conjugate base

  - The acids HClO, $HClO_2$, $HClO_3$, and $HClO_4$ have pKa values 7.5, 2, –1, and about –10, respectively
  - the acidic proton is on an oxygen attached to chlorine, that is, *we are removing a proton from the same environment in each case*.

With each successive oxygen, the charge can be more delocalized, and this makes the anion more stable
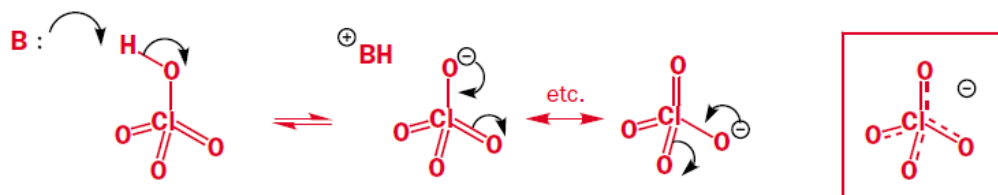
the negative charge on the perchlorate anion can be delocalized equally over all four oxygens

Constructing a pK_a scale

How do you explain the following observation of pK_a values?

H_3C—OH

pK_a~15.9

H_3C—$C(=O)$—OH

pK_a~4.76

$O=S(=O)(Me)$—OH

pK_a~ -1.79
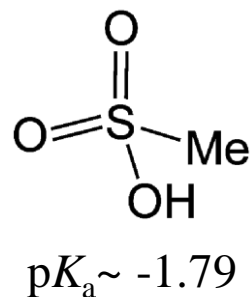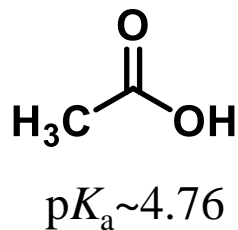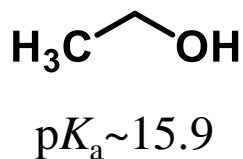
ethoxide
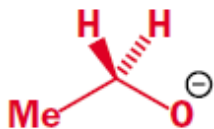
charge localized on one oxygen

acetate
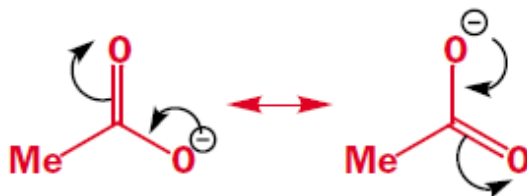
charge delocalized over two oxygens
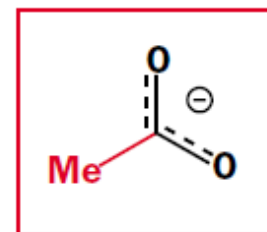
methane sulfonate
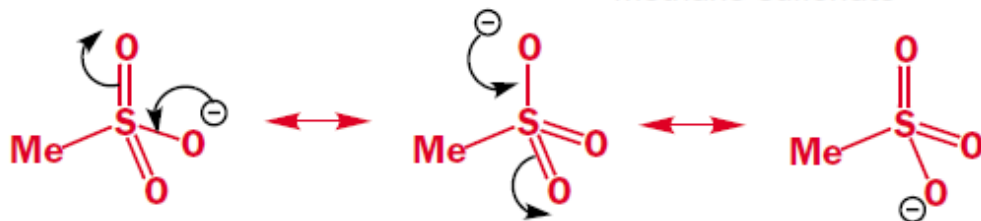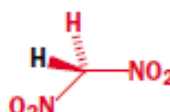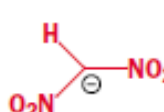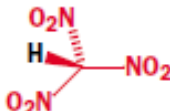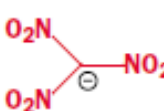
charge delocalized over three oxygens
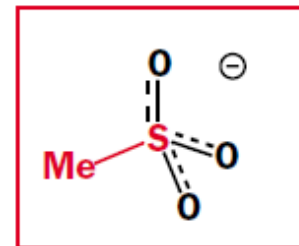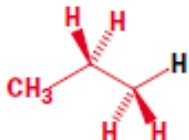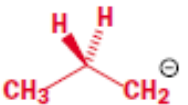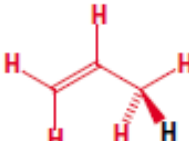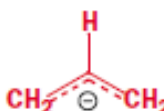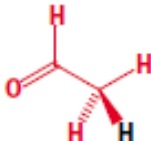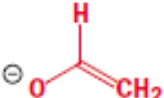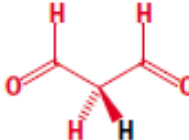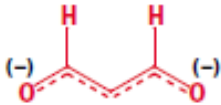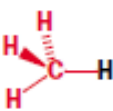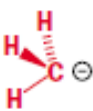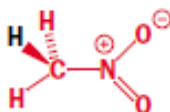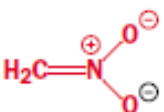
Constructing a pK_a scale

The pK_a of cyclohexanol is 16 and phenol is 10. How can you explain this difference?

cyclohexanol
pK_a 16

localized
anion

phenol
pK_a 10

phenoxide

delocalization increases the
electron density on the ring
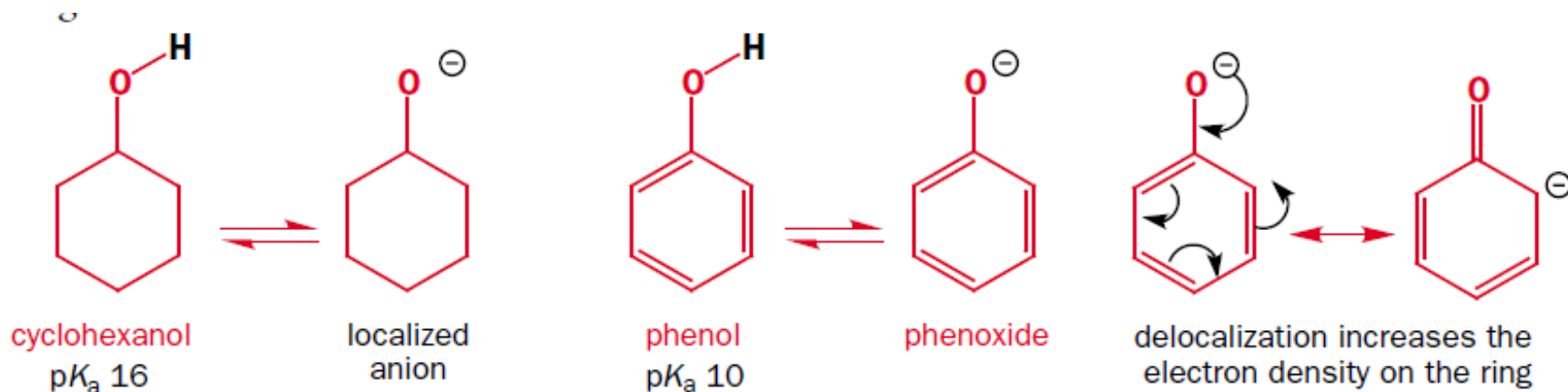
- In phenol, PhOH, the OH group is directly attached to a benzene ring.

- On deprotonation, the negative charge can be delocalized into the aromatic ring.

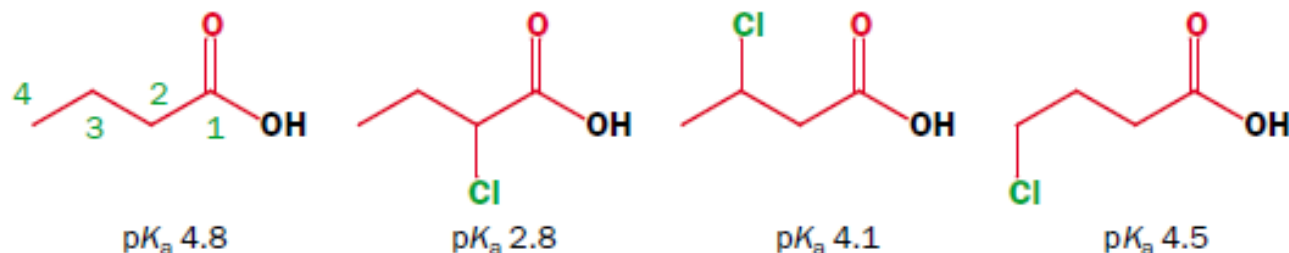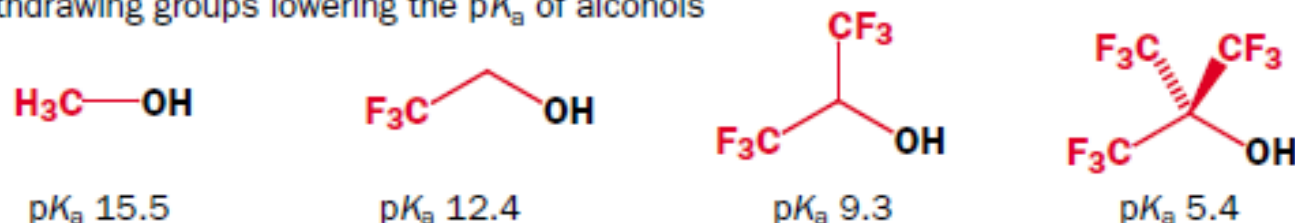| Acid	Conjugate base	pK_a	Comments
		~50	charge is localized on one carbon—difficult since carbon is not very electronegative
		~43	charge is delocalized over π system—better but still not really good
		13.5	charge is delocalized over π system but is mainly on the electronegative oxygen—much better
		5	charge delocalized over π system but mainly over two oxygens—better still
		~48	charge is localized on one carbon—again very unsatisfactory
		10	charge is delocalized but mainly on oxygens of nitro group
		4	charge can be delocalized over two nitro groups—more stable anion
		0	charge can be delocalized over three nitro groups—very stable anion

Electron withdrawing groups increase acidity

- Any group that withdraws electrons will help to stabilize the conjugate base and therefore increase the strength of the acid.

electron-withdrawing groups lowering the pK_a of carboxylic acids

pK_a 4.76   pK_a 1.7   pK_a 1.8   pK_a 2.4   pK_a 3.6
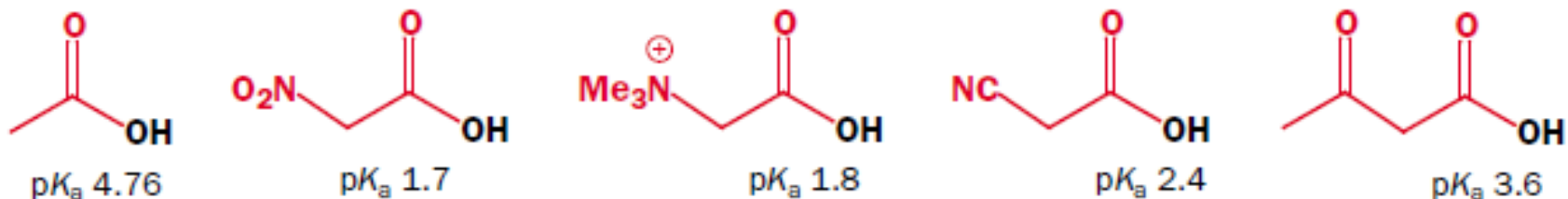
electron-withdrawing groups lowering the pK_a of alcohols

pK_a 15.5   pK_a 12.4   pK_a 9.3   pK_a 5.4

pK_a 4.8   pK_a 2.8   pK_a 4.1   pK_a 4.5

Inductive effects become less significant as the electron-withdrawing group gets further away

Electron donating groups decrease acidity

- Electron donating groups destabilize the conjugate base because, instead of helping to spread out the negative charge, they actually put more in.
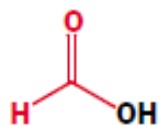
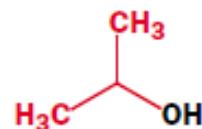formic (methanoic) acid
pK_a 3.7
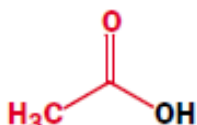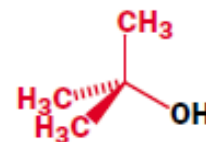
acetic (ethanoic) acid
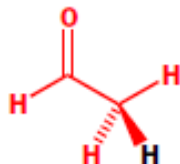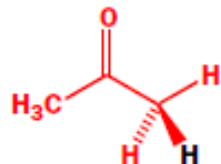pK_a 4.8

methanol
pK_a 15.5

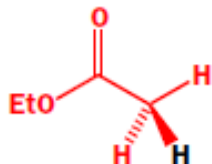ethanol
pK_a 16.0

isopropyl alcohol
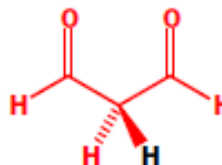pK_a 17.1

tert-butyl alcohol
pK_a 19.2

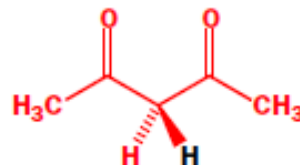acetaldehyde
(ethanal)
pK_a 13.5

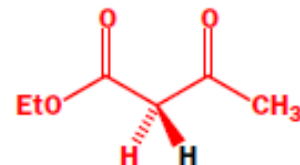acetone
(propanone)
pK_a 20
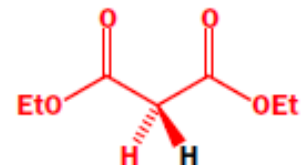
ethyl acetate
(ethyl ethanoate)
pK_a 25

propandial
pK_a ca. 5

acetylacetone
(2,4-pentanedione)
pK_a 8.9

ethyl acetoacetate
(ethyl 3-oxobutanoate)
pK_a 10.6

diethyl malonate
(diethyl propanedioate)
pK_a 12.9

Hybridization affects the pK_a

- S orbitals are held closer to the nucleus than P orbitals, the electrons in them are lower in energy, that is, more stable.

- Consequently, the more S character an orbital has, the more tightly held are the electrons in it.

- This means that electrons in an sp orbital (50% S character) are lower in energy than those in an sp^2 orbital (33% s character), which are, in turn, lower in energy than those in an sp^3 orbital (25% s character).
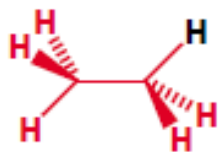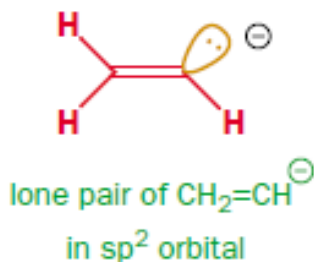

pK_a ca. 50   pK_a ca. 44   pK_a ca. 26
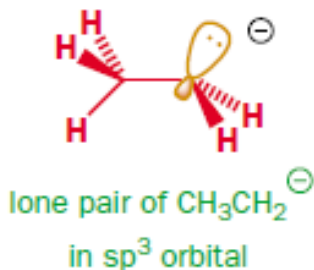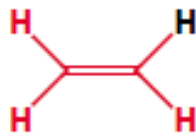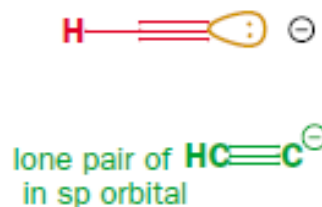
lone pair of CH$_3$CH$_2^{\ominus}$ lone pair of CH$_2$=CH$^{\ominus}$ lone pair of HC≡C$^{\ominus}$
in sp^3 orbital   in sp^2 orbital   in sp orbital

Hybridization affects the pK_a

More remote hybridization is also important
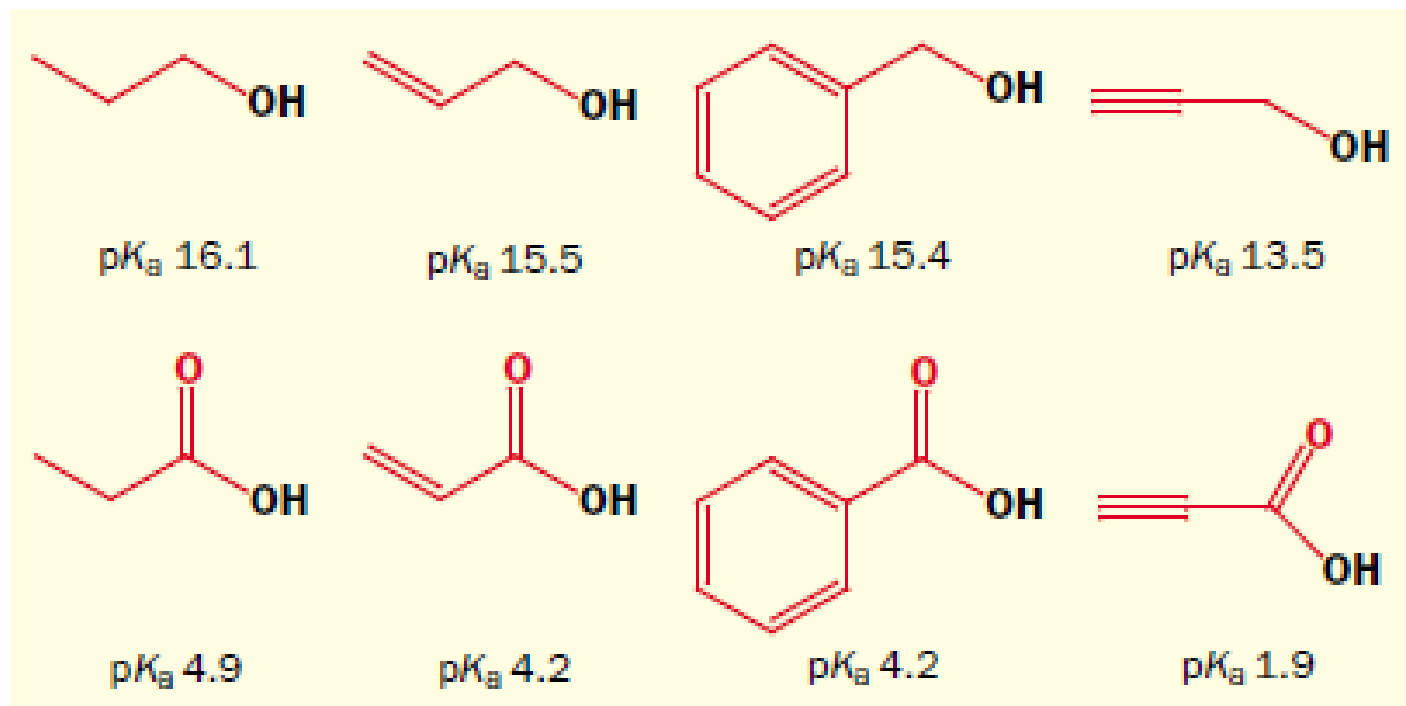
pK$_a$ 16.1   pK$_a$ 15.5   pK$_a$ 15.4   pK$_a$ 13.5

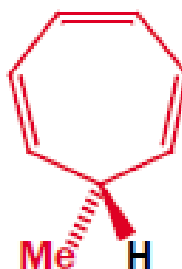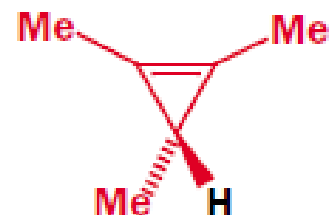pK$_a$ 4.9   pK$_a$ 4.2   pK$_a$ 4.2   pK$_a$ 1.9

Effect of Gaining aromaticity on pK_a

cyclopentadiene
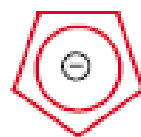pK_a 15.5

cycloheptatriene
pK_a ca. 36

trimethylcyclopropene
pK_a ca. 62

anion is planar
6π electrons
make it aromatic
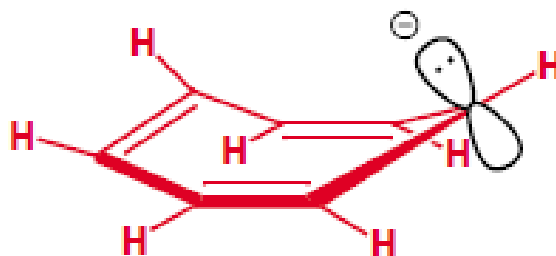
anion not planar
neither aromatic or anti-aromatic
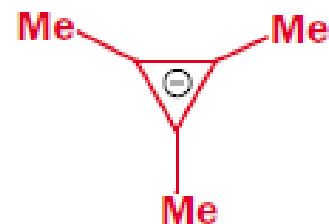
anion is planar
4π electrons
make it anti-aromatic

If you wanted to separate a mixture of naphthalene, pyridine, and *p*-toluic acid, how would you go about it?
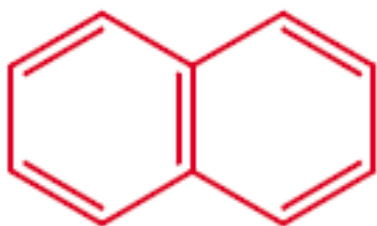
naphthalene
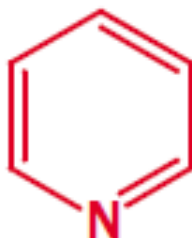
pyridine

para-toluic acid

Summary: Factors affecting pK_a of acids

The more stabilized the conjugate base, A⁻, the stronger is the acid, HA. Ways to stabilize A⁻ include:

- Having the charge on an electronegative element

- Delocalizing the negative charge over other carbon atoms, or even better, over more electronegative atoms

- Spreading out the charge over electron-withdrawing groups by the polarization of σ bonds (inductive)

- Electron donating groups decrease acidity

- Having the negative charge in an orbital with more s character

- Becoming aromatic

# Effect of Gaining aromaticity on pK_a
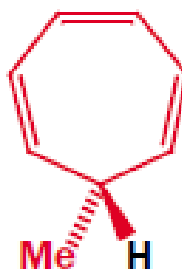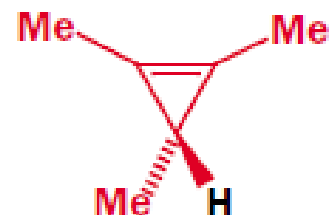
cyclopentadiene
pK_a 15.5

cycloheptatriene
pK_a ca. 36

trimethylcyclopropene
pK_a ca. 62
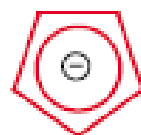
anion is planar
6π electrons
make it aromatic
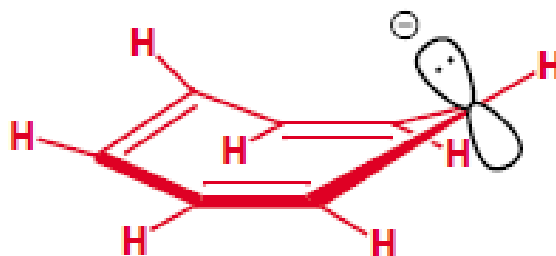
anion not planar
neither aromatic or anti-aromatic
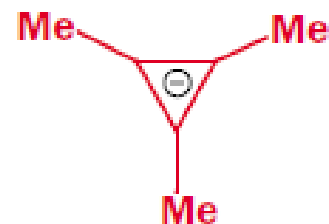
anion is planar
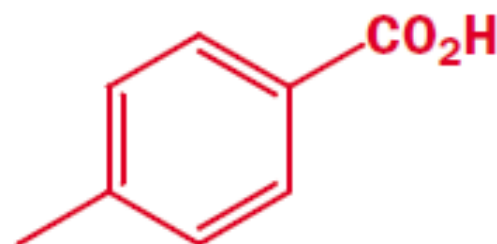4π electrons
make it anti-aromatic

If you wanted to separate a mixture of naphthalene, pyridine, and *p*-toluic acid, how would you go about it?
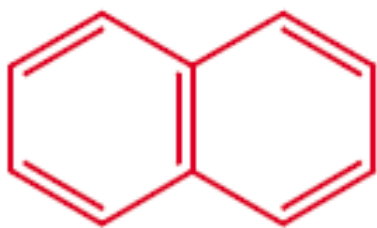
naphthalene
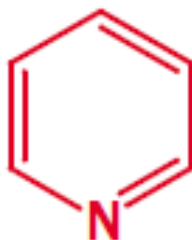
pyridine
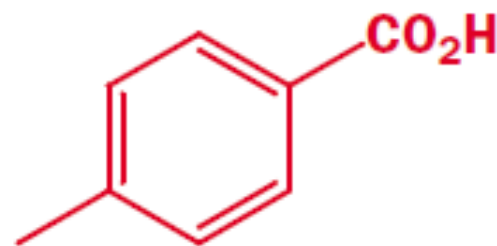
para-toluic acid

The phenols shown here have approximate pK_a values of 4, 7, 9, 10, and 11. Suggest with explanations which pK_a value belongs to which phenol.
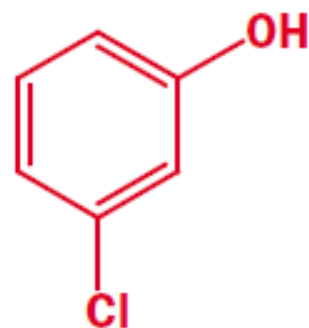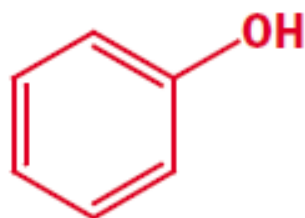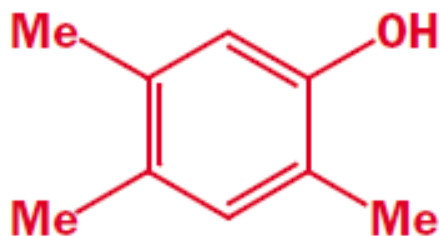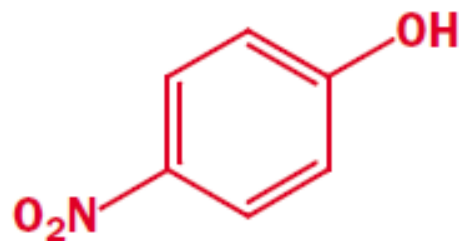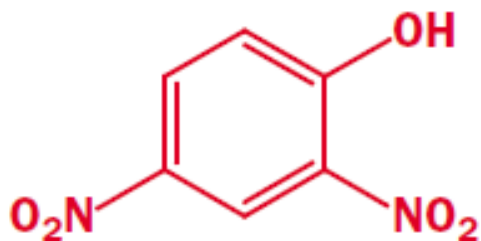
Basicity

- A **base** is a substance that can accept a proton by donating a pair of electrons

Example: ammonia, water, the acetate anion, and the methyl anion

How can we measure a base's strength? To what extent does a base attract a proton?

- For example, if we want to know which is the stronger base—formate anion or acetylide anion—we look up the pK_as for their conjugate acids

- the pK_a for formic acid (HCO_2H) is 3.7, whilst the pK_a for ethyne (acetylene) is around 25.

- Ethyne is much more reluctant to part with its proton, that is, acetylide is much more basic than formate.

This is all very well for anions—we simply look up the pK_a value for the neutral conjugate acid, *but what if we want to know the basicity of ammonia?*

Basicity

- If we want to know the *basicity* of ammonia, we must look up the pK_a of its conjugate acid, the ammonium cation, NH_4^+, protonated ammonia

- Its pK_a is 9.24 which means that ammonia is a weaker base than hydroxide—the pK_a for water (the conjugate acid of hydroxide) is 15.74.
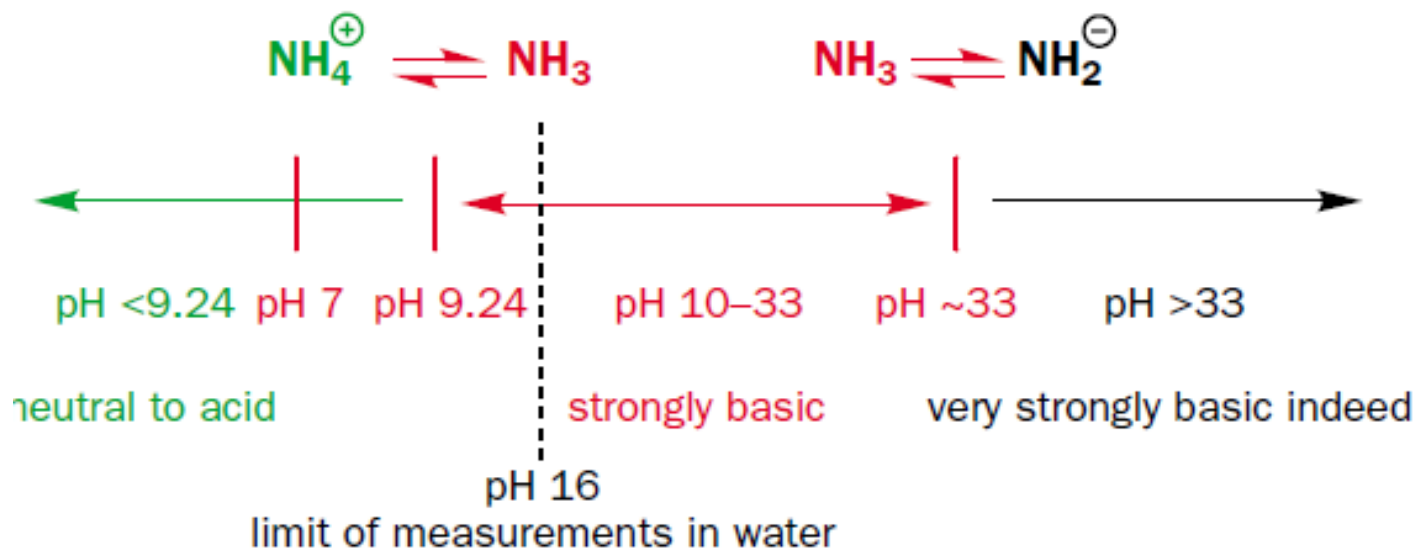
Factors affecting basicity

- The more accessible the electrons are, the stronger the base is.

- A negatively charged base is more likely to pick up a proton than a neutral one.

- A compound in which the negative charge is delocalized is going to be less basic than one with a more concentrated, localized charge, and so on.

- Carboxylic acids are stronger acids than simple alcohols because the negative charge formed is delocalized over two oxygens in the carboxylate but localized on just one oxygen for the alkoxide

- The alkoxide is a stronger base because its electrons are more available to be protonated.

Let us look at strength of neutral base!!

Factors affecting basicity

- Accessibility of the lone pair and to what extent can the resultant positive charge formed be stabilized either by delocalization or by the solvent.

- The accessibility of the lone pair depends on its energy—it is usually the HOMO of the molecule and so, the higher its energy, the more reactive it is and hence the stronger the base.

- The lone pair is lowered in energy if it is on a very electronegative element or if it can be delocalized in some manner.

Why do you think ammonia is more basic than water?

- Ammonia is 10^{10} times more basic than water: since oxygen is more electronegative than nitrogen, its lone pair is lower in energy.

- The pK_{aH} for ammonia is 9.24 whilst the pK_{aH} for water is -1.74.

pK_{aH} simply means the pK_a of the conjugate acid

Factors affecting basicity

- Ammonia is the simplest nitrogen base and has a pK_{aH} of 9.24.

- Any substituent that increases the electron density on the nitrogen therefore raises the energy of the lone pair thus making it more available for protonation and increasing the basicity of the amine

- Conversely, any substituent that withdraws electron density from the nitrogen makes it less basic

- Substituting one hydrogen of ammonia increases the basicity by more than a factor of ten, substituting two has less effect and in the trisubstituted amine the pK_{aH} is actually *lower*.

Table 8.4 pK_{aH} values for primary, secondary, and tertiary amines

| R	pK_{aH} RNH$_2$	pK_{aH} R$_2$NH	pK_{aH} R$_3$N
Me	10.6	10.8	9.8
Et	10.7	11.0	10.8
n-Pr	10.7	11.0	10.3
n-Bu	10.7	11.3	9.9

Why the basicity is reduced?

Factors affecting basicity: Amines case

- Substituting one hydrogen of ammonia increases the basicity by more than a factor of ten, substituting two has less effect and in the trisubstituted amine the pK_{aH} is actually *lower*.

Table 8.4 pK_{aH} values for primary, secondary, and tertiary amines

R	pK_{aH} RNH$_2$	pK_{aH} R$_2$NH	pK_{aH} R$_3$N
Me	10.6	10.8	9.8
Et	10.7	11.0	10.8
n-Pr	10.7	11.0	10.3
n-Bu	10.7	11.3	9.9

(1) the increased availability of the lone pair and the stabilization of the resultant positive charge, which increases with successive replacement of hydrogen atoms by alkyl groups; and

(2) the stabilization due to solvation, an important part of which is due to hydrogen bonding and this effect decreases with increasing numbers of alkyl groups.

more stabilization of positive charge from alkyl groups

more stabilization of positive charge from hydrogen bonding with solvent
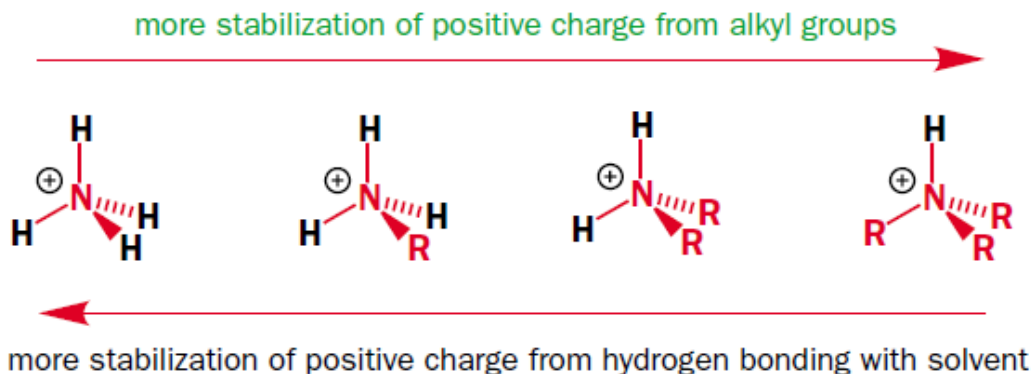
Factors affecting basicity

If the lone pair on nitrogen is *less* available for protonation, and that amine is *less* basic. If,

- the nitrogen atom is attached to an electron-withdrawing group

- the lone pair is in an SP or SP^2 hybridized orbital

- the lone pair is conjugated with an electron-withdrawing group

- the lone pair is involved in maintaining the aromaticity of the molecule

Cl_3C–$\ddot{N}H_2$
pK_{aH} 5.5

Cl_3C–$\ddot{N}H_2$
pK_{aH} 9.65

F_3C–$\ddot{N}H_2$
pK_{aH} 5.7

F_3C–$\ddot{N}H_2$
pK_{aH} 8.7
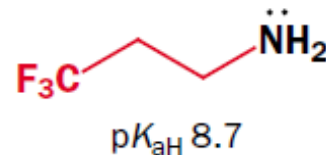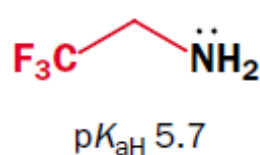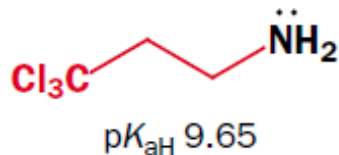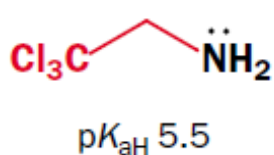
Inductive effects fall off rapidly with distance.

Factors affecting basicity

- The more S character an orbital has, the more tightly it holds on to its electrons and so the more electron-withdrawing it is.

Table 8.5 pK_{aH}s of unsaturated primary, secondary, and tertiary amines
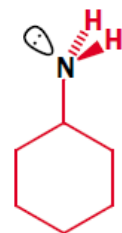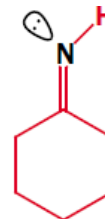
R	RNH_2	R_2NH	R_3N
$H_3C-CH_2-CH_2-$	10.7	11.0	10.3
$H_2C=CH-CH_2-$	9.5	9.3	8.3
$HC\equiv C-CH_2-$	8.2	6.1	3.1

- If the lone pair itself is in an SP^2 or an SP orbital, it is more tightly held (the orbital is lower in energy) and therefore much harder to protonate.

lone pair in sp³ orbital
pK_{aH} 10.7

lone pair in sp² orbital
pK_{aH} 9.2
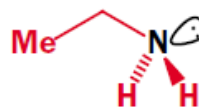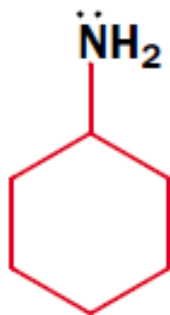
lone pair in sp³ orbital
pK_{aH} 10.8
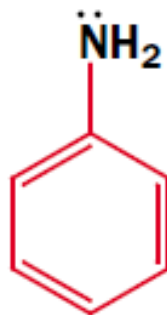
lone pair in sp orbital
pK_{aH} ca. −10

Why aniline is less basic?

cyclohexylamine
pK_{aH} 10.7

aniline
pK_{aH} 4.6

NH_2 is attached to SP^2 carbon

Conjugation effect

Factors affecting basicity: Amide case

- Amides are weak bases protonated on oxygen
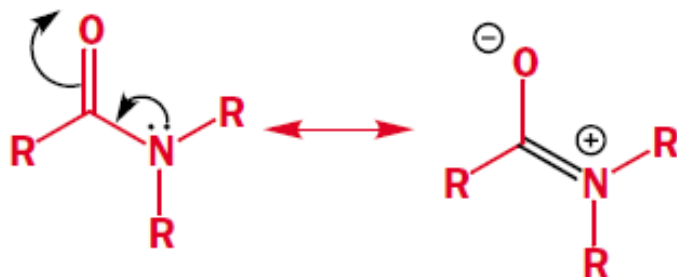
delocalization of nitrogen's
lone pair into π system

The pK_{aH} for an amide is typically between 0 and −1.
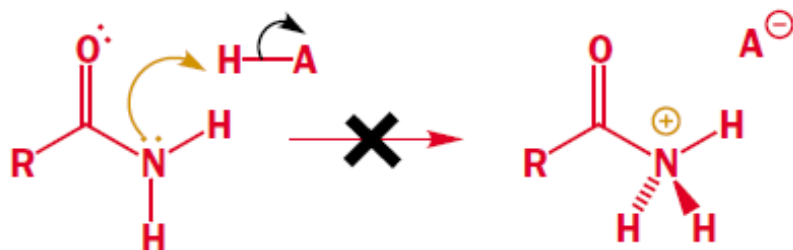
no protonation occurs on the nitrogen atom

- Protonation at nitrogen would result in a positive charge on the nitrogen atom.

- Since this is adjacent to the carbonyl, whose carbon is also electron-deficient, this is energetically unfavourable.

- If the amide were protonated at nitrogen, the positive charge could not be delocalized on to the oxygen but would have to stay localized on the nitrogen

Factors affecting basicity: Amide case

- Protonation occurs on the carbonyl oxygen atom.

- We can draw the mechanism for this using either a lone pair on oxygen or on nitrogen.

protonation occurs
on the oxygen atom

these structures are just two different
ways to draw the same delocalized cation

these arrows emphasise
the contribution of the
nitrogen's lone pair.
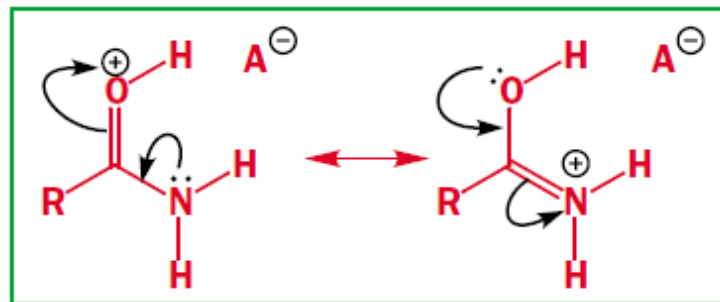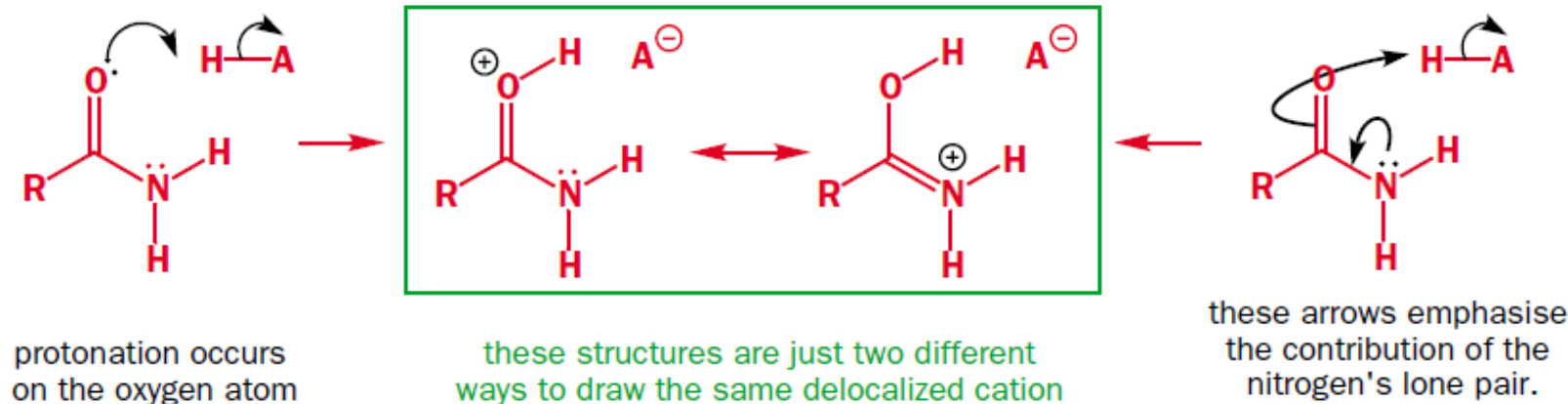
Factors affecting basicity: Amidines

- Amidines are stronger bases than amides or amines

an amidine pK_{aH} 12.4

- An amidine has two nitrogen atoms that could be protonated—one is SP^3 hybridized, the other SP^2 hybridized.
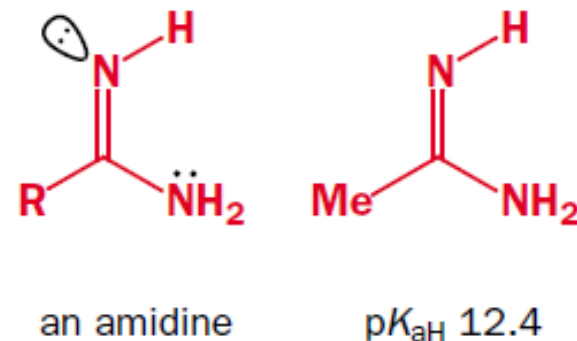
- We might expect the SP^3 nitrogen to be more basic but protonation occurs at the SP^2 nitrogen atom.

- Only if we protonate on the SP^2 nitrogen can the positive charge be delocalized over both nitrogens.

- We are using *both* lone pairs when we protonate on the SP^2 nitrogen.
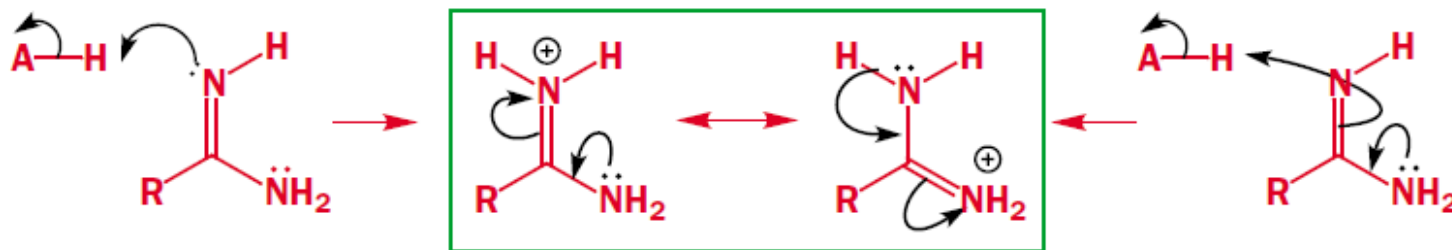
Factors affecting basicity: Guanidines

- Guanidines are very strong bases

- All three nitrogen lone pairs cooperate to donate electrons but protonation occurs, as before, on the SP^2 nitrogen atom.
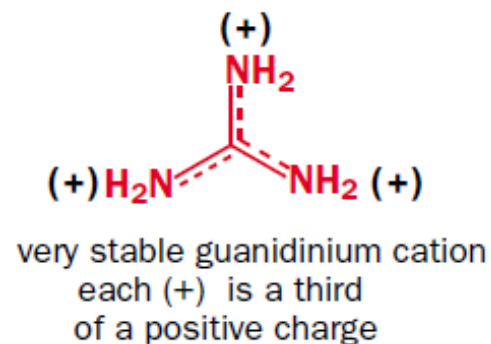

guanidine: pK_a 13.6

very stable guanidinium cation
each (+) is a third
of a positive charge
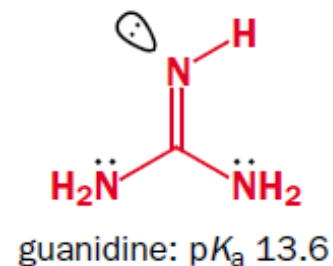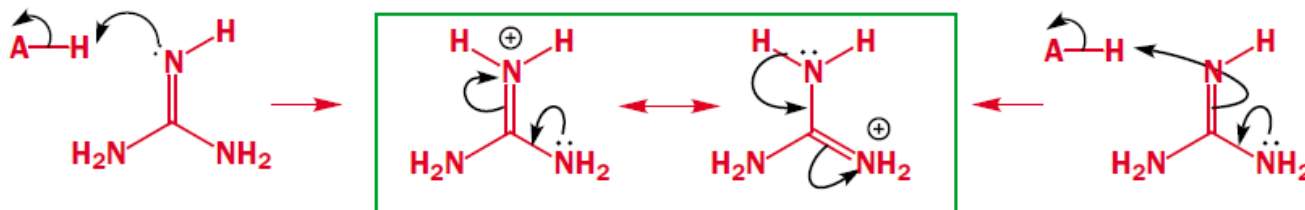
- All three C–N bonds are the same length in the guanidinium ion and each nitrogen atom has the same charge (about one-third positive)

How can you explain the following observations?
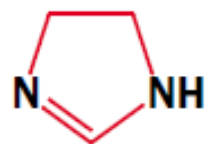
imidazoline
pK_{aH} 11

imidazole
pK_{aH} 7.1

imidazolium
cation
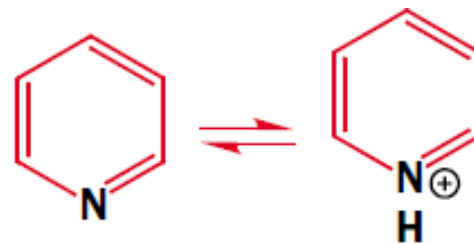
pyridine
pK_{aH} 5.2

pyridinium
cation

Imidazoline is a simple cyclic amidine and its pK_{aH} value is just what we expect, around 11

Imidazole, on the other hand, is less basic (pK_{aH} 7.1) because both nitrogens are attached to an electron-withdrawing sp^2 carbon

However, imidazole, with its two nitrogen atoms, is more basic than pyridine (pK_{aH} 5.2) because pyridine only has one nitrogen on which to stabilize the positive charge.
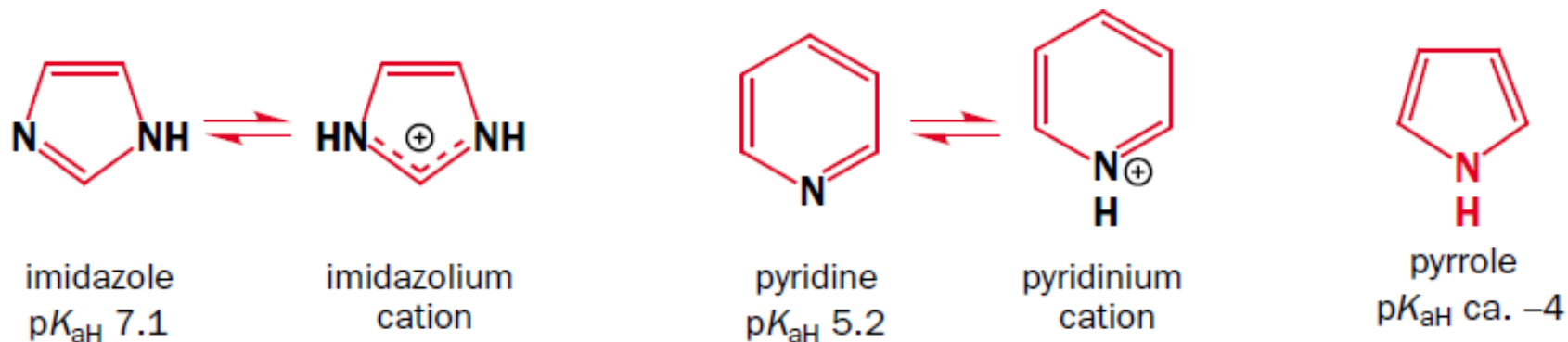
How can you explain the following observations?

imidazole
pKaH 7.1

imidazolium
cation

pyridine
pKaH 5.2

pyridinium
cation

pyrrole
pKaH ca. −4

Both imidazole and pyridine are aromatic—they are flat, cyclic molecules with 6 π electrons in the conjugated system. Imidazole has one lone pair that is and one that is not involved in the Aromaticity.

This contrasts to pyrrole in which the lone pair on the only nitrogen atom is needed to complete the six aromatic π electrons and is therefore delocalized around the ring.

Generally, pK_a values are determined in water. How would the pK_a values of carboxylic acids, alcohols, ammonium ions, phenol, and an anilinium ion change if they were determined in a solvent less polar than water?

Suggest a plausible mechanism
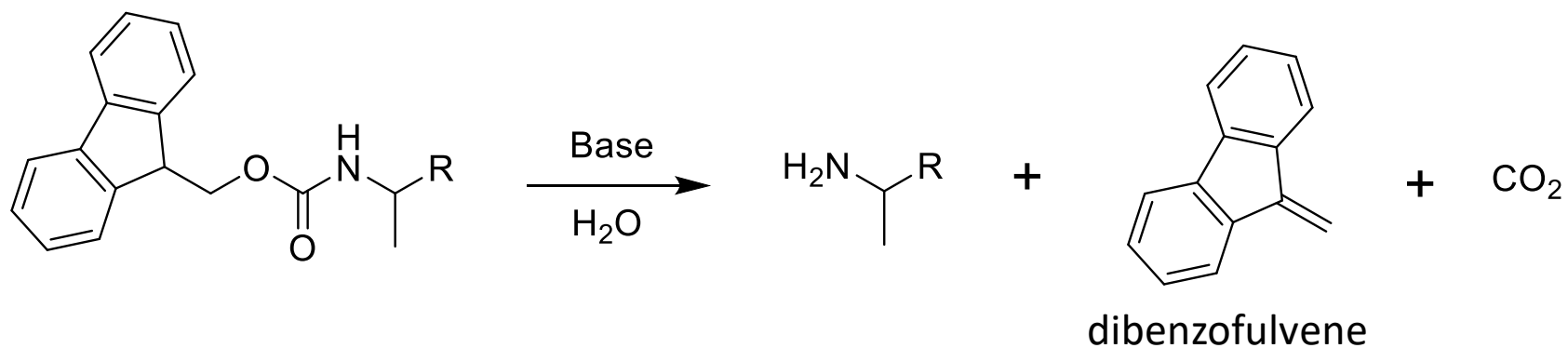
Aromaticity of the dibenzofulvene is the driving force for this reaction

Nucleophilicity vs Basicity

Nucleophilicity *vs* basicity

Nucleophile?

Nucleophiles (nucleus-loving) are electron donor species

Base?

Species that can accept a proton by donating a pair of electrons

How do we measure basicity?

- Basicity, as expressed by pK_a, is measured by the position of an equilibrium involving an electron pair donor (base), a proton, the conjugate acid, and the conjugate base.
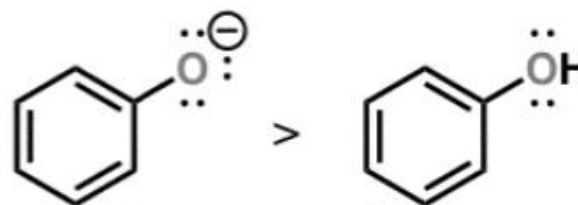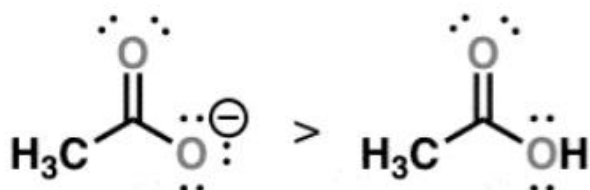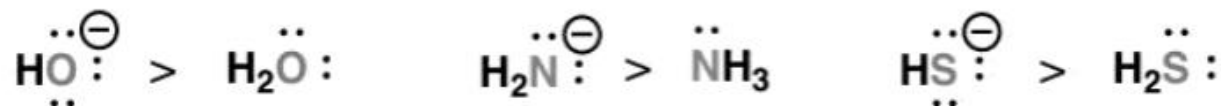
Factors that affect nucleophilicity

- Charge: The higher the electron density on a species, the more nucleophilic it is.

- Electronegativity: A highly electronegative atom is less willing to donate a pair of electrons

- Size or steric hindrance: Sterically bulky nucleophiles react more slowly

- Solvent: Solvation weakens the nucleophile; that is, solvation decreases nucleophilicity

- Resonance effect on nucleophilicity: If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive

Factors that affect nucleophilicity

Charge

- A nucleophile reacts by donating electrons.

- This means, that the higher the electron density on a species, the more nucleophilic it is

- A negatively charged species will be more nucleophilic than its neutral counterpart

- The conjugate base is always a better nucleophile because nucleophilicity increases with increasing electron density on the atom

Factors that affect nucleophilicity

Electronegativity

- A nucleophile reacts by donating electrons.

- A highly electronegative atom is less willing to donate a pair of electrons

- a less electronegative atom is more nucleophilic

- Across the periodic table, nucleophilicity increases with decreasing electronegativity

$$H_3C^{\ominus} \quad > \quad H_2N^{\ominus} \quad > \quad HO^{\ominus} \quad > \quad F^{\ominus} \quad \bigg| \quad H_3N \quad > \quad H_2O \quad > \quad HF$$
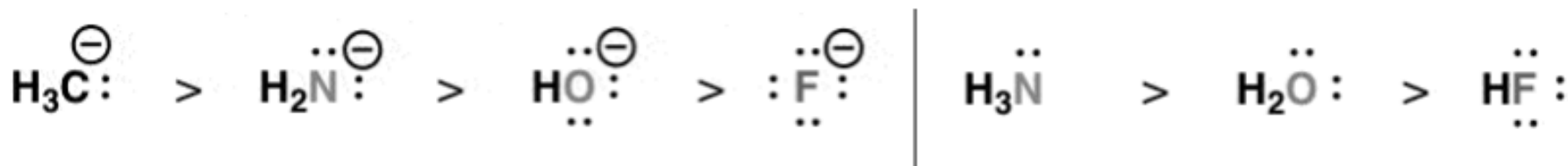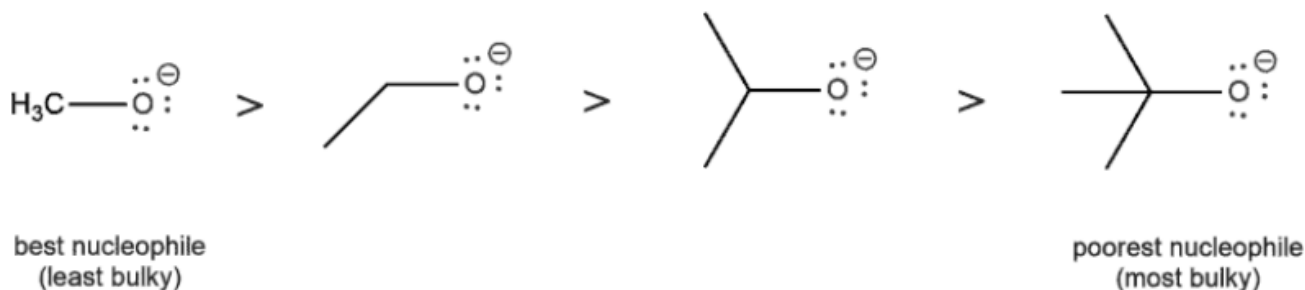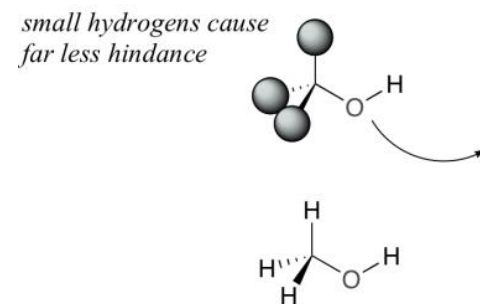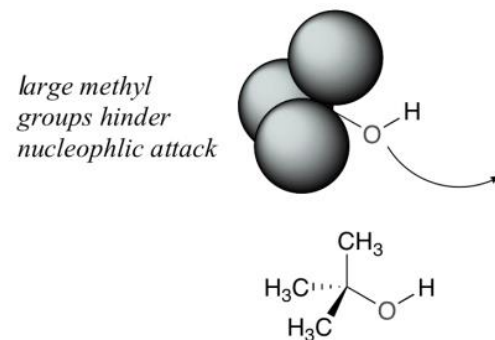
How about basicity?

Factors that affect nucleophilicity

Size or steric hindrance

- Steric hindrance is an important consideration when evaluating nucleophilicity

- Nucleophile needs to be in close proximity to the electrophile

- This can be hard if the nucleophile is a large and bulky molecule.

- In general, a smaller nucleophile is a stronger nucleophile.

How about basicity?
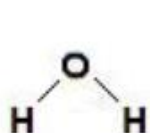
Factors that affect nucleophilicity: Solvent

- Solvents as being either polar or nonpolar. Polar solvents can be further subdivided into protic and aprotic solvents
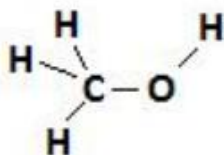
Protic Solvents

- A **protic solvent** is a solvent that has a hydrogen atom bound to an oxygen or nitrogen.
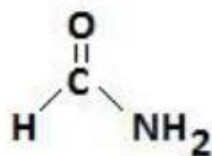
Polar Protic Solvents

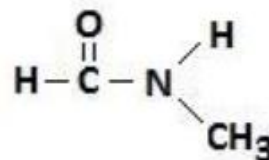H_2O, ROH, RNH_2, R_2NH

Water   Methanol   Formamide   N-Methylformamide

- the O-H and N-H bonds that are present in protic solvents result in a hydrogen that is positively polarized.

- the positively polarized hydrogen of the solvent molecule can interact with the negatively charged nucleophile

Factors that affect nucleophilicity: Solvent

- Hydrogen-bonding interactions can occur between a protic solvent and a negatively charged nucleophile

- Solvation weakens the nucleophile; that is, solvation decreases nucleophilicity.

- the solvent forms a "shell" around the nucleophile, impeding the nucleophile's ability to attack an electrophilic carbon.

- Because the charge on smaller anions is more concentrated, **small anions are more tightly solvated than large anions**.
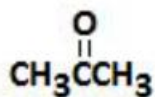
Protic Solvent
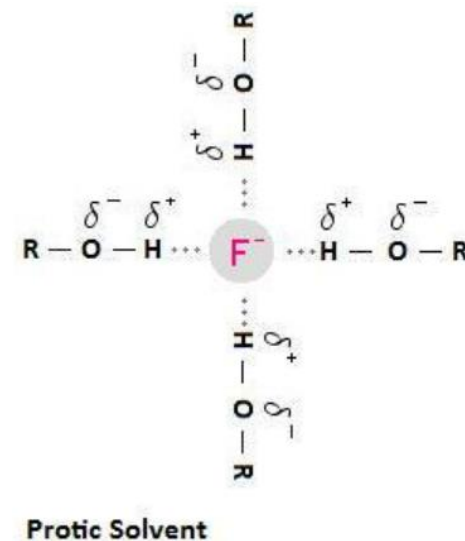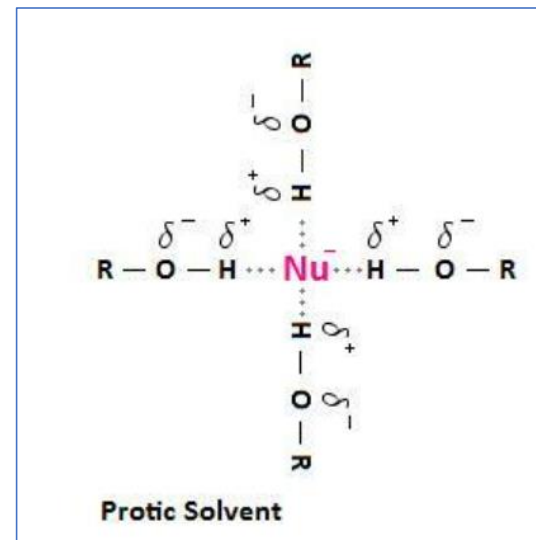
Protic Solvent

- Fluoride will not function as a nucleophile at all in protic solvents

Factors that affect nucleophilicity: Solvent
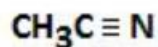
Aprotic Solvents

An **aprotic solvent** is a solvent that lacks a positively polarized hydrogen.
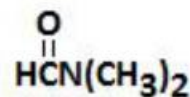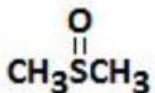
Polar Aprotic Solvents

$$CH_3\overset{O}{\overset{\|}{C}}CH_3$$
Acetone

$$CH_3C \equiv N$$
Ethanenitrile (Acetonitrile)

$$H\overset{O}{\overset{\|}{C}}N(CH_3)_2$$
N,N-Dimethylformamide (DMF)

$$CH_3\overset{O}{\overset{\|}{S}}CH_3$$
Dimethyl sulfoxide (DMSO)

$$CH_3\overset{+}{N}\overset{O}{\underset{O^-}{\diagup}}$$
Nitromethane
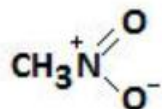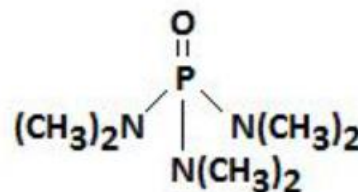
$$(CH_3)_2N\overset{O}{\overset{\|}{\underset{N(CH_3)_2}{P}}}N(CH_3)_2$$
Hexamethylphosphoric triamide (HMPA)

- Nucleophilicity of halides can be enhanced significantly with the aid of aprotic polar solvents

Solvents and Nucleophilicity

Example - Protic Solvent

$$KI \;+\; CH_3CH_2-Br \;\xrightarrow{\text{Methanol}}\; CH_3CH_2-I \;+\; Br^-$$

Example - Aprotic Solvent

$$KI \;+\; CH_3CH_2-Br \;\xrightarrow{\text{Acetone}}\; CH_3CH_2-I \;+\; Br^- \qquad \text{500 times faster!}$$
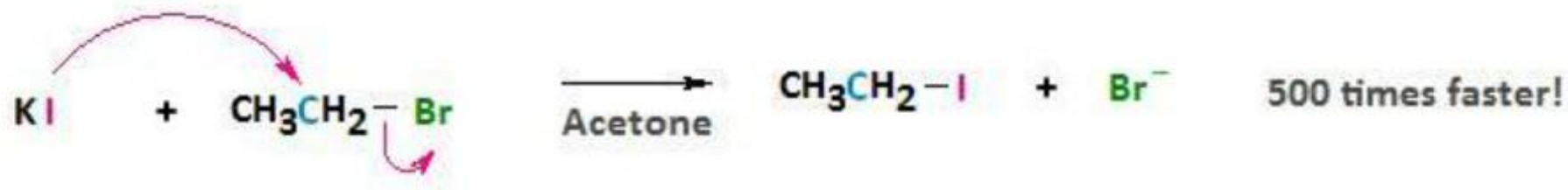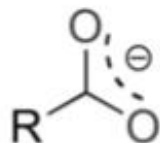
Factors that affect nucleophilicity

Resonance effect on nucleophilicity

- Resonance also affects the strength of the nucleophile.

- If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive – meaning less nucleophilic, and also less basic.
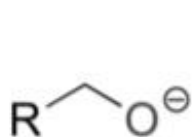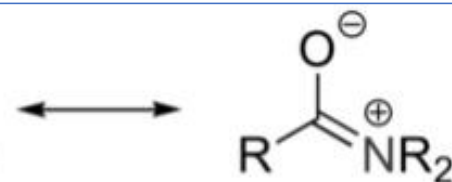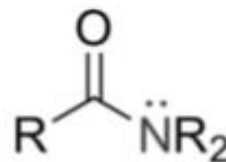

alkoxide ion:
charge is localized
more nucleophilic

carboxylate ion:
charge is spread over both oxygens
less nucleophilic

amine
more nucleophilic

amide
less nucleophilic

Factors that affect nucleophilicity

- Charge: The higher the electron density on a species, the more nucleophilic it is.

- Electronegativity: A highly electronegative atom is less willing to donate a pair of electrons

- Size or steric hindrance: Sterically bulky nucleophiles react more slowly

- Solvent: Solvation weakens the nucleophile; that is, solvation decreases nucleophilicity

- Resonance effect on nucleophilicity: If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive

Rank the following species from best nucleophile to poorest nucleophile in an aqueous solution:

$$\text{C}_6\text{H}_5\text{—O}^- \quad \text{CH}_3\text{OH} \quad \text{HO}^- \quad \text{CH}_3\overset{\overset{\displaystyle O}{\|}}{\text{C}}\text{O}^- \quad \text{CH}_3\text{S}^-$$