# Physical Organic Chemistry

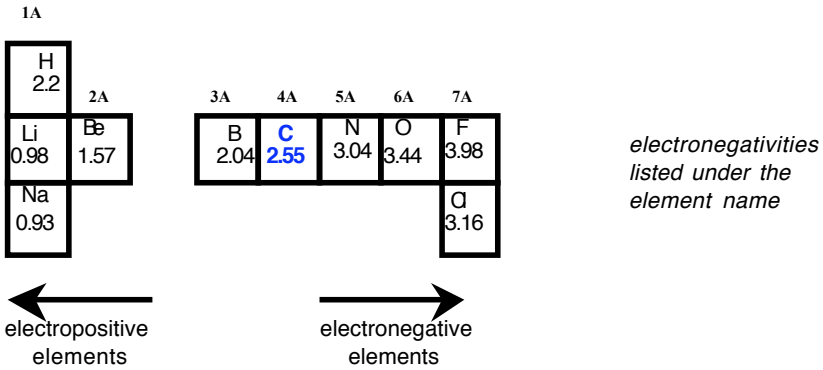
- The key to understanding organic reactions lies in gaining an understanding of:
  - the structure and bonding of stable organic compounds.
  - reactivity of organic compounds.
  - reactive intermediates and transition states.
  - mechanisms through which organic compounds transform into other organic compounds.
  - kinetics, thermodynamics and the relationship between the two.





# Revision: Structure and Bonding

- Electropositive elements tend to ***lose*** electrons to form an octet
- Electronegative elements tend to ***gain*** electrons to form an octet




*electronegativities listed under the element name*

Types of bonds:

- ionic bonds
- covalent bonds
- polar covalent bonds

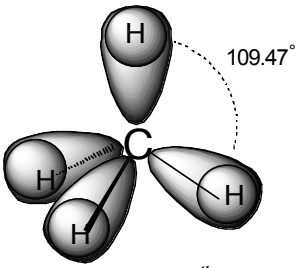
The type of bonding in a molecule affects:

- shape
- physical properties
- reactivity

# Models for Bonding

- Lewis structures: **valence bond theory**
  - Atoms interact to form discrete chemical bonds
- **Molecular orbital theory**
  - Nuclei interact, electrons are placed in molecular orbitals
  - Discrete bonds are not formed between atoms; electrons may "roam" over multiple nuclei.

Hybridization models: $sp^3$, $sp^2$, sp orbitals




*methane*

- **Valence shell electron pair repulsion (VSEPR) theory** rationalises the tetrhedral shape of methane without the use of atomic or molecular orbitals





# Models for Bonding

- Connection between hybridization of an atom and the arrangement in space of bonds around that atom:

  ***$sp^3$ hybridization*** *occurs for atoms having four groups in a tetrahedral arrangement (note: a "group" may be an electron pair)*

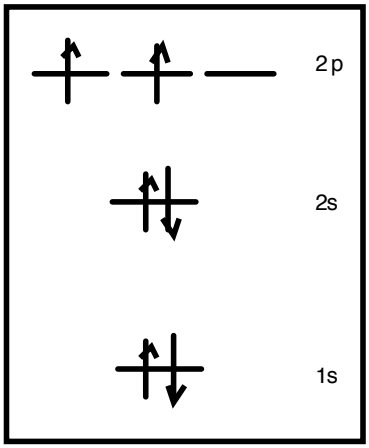
  ***$sp^2$ hybridization*** *occurs for atoms having three groups in a trigonal (planar) arrangement*

  ***sp hybridization*** *occurs for atoms having two groups in a linear arrangement*

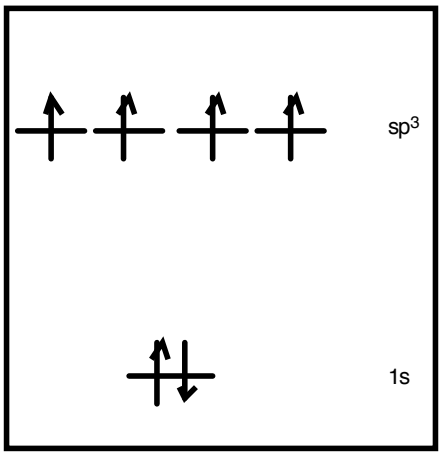
- ***Hybridization and molecular geometry are closely correlated***
- ***The covalent bond has a definite direction in space (compare to ionic bonds)***
- ***The directionality of covalent bonding is responsible for molecular shape***

# Models for Bonding

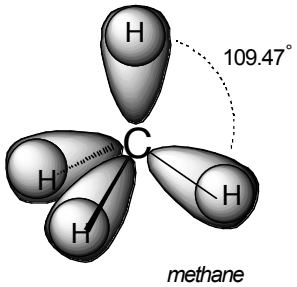
- **Molecular orbital theory: methane**




molecular orbitals of carbon




molecular orbitals of hybridized carbon
*(as in methane)*




*methane*



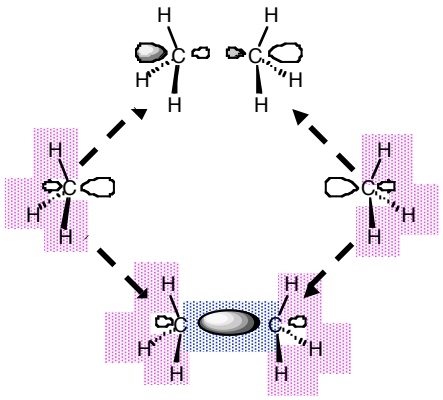


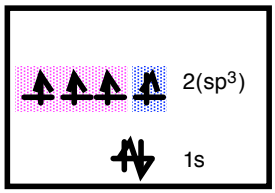
# Models for Bonding

**Molecular orbital theory: ethane**

- Three of the carbon $sp^3$ orbitals combine with one hydrogen 1s orbital each to form C-H bonds
  ***$sp^3$ - 1s $\sigma$ bonds*** (shown shaded in pink below)

- The remaining carbon $sp^3$ bonding orbital from each carbon is used to form the C-C- bond in ethylene
  ***$sp^3$ - $sp^3$ $\sigma$ bond*** (shown shaded in blue below)



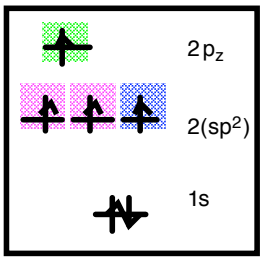



molecular orbitals of carbon in ethane

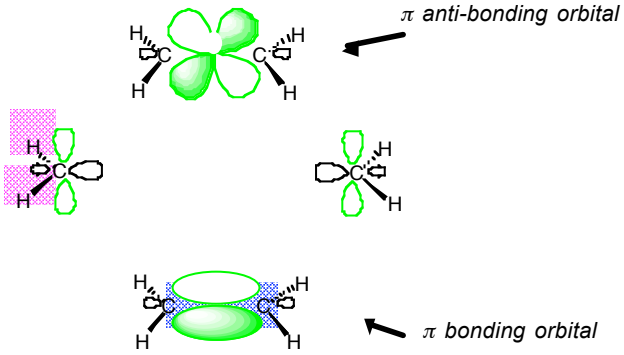
# Models for Bonding

## Molecular orbital theory: ethylene

- Two carbon $sp^2$ orbitals combine with one hydrogen 1s orbital each to form C-H bonds: ***$sp^2$ - 1s $\sigma$ bonds*** (shaded in pink)
- The remaining carbon $sp^2$ bonding orbital from each carbon is used to form the C-C- bond in ethylene: ***$sp^2$ - $sp^2\sigma$ bond*** (shaded in blue)
- One half-occupied, unhybridized $2p_z$ orbital left over on each carbon combine to form two new **p orbitals** ( one bonding and one antibonding orbital).
- Each carbon atom contributes one electron to occupy the bonding orbital to form a: ***pi bond*** (shaded in green)




molecular orbitals of carbon in ethylene



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# Models for Bonding

## Molecular orbital theory: acetylene

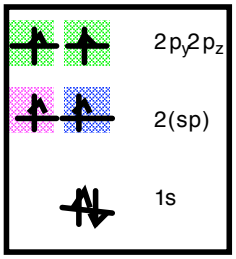
- One carbon sp orbital combines with one hydrogen 1s orbital to form one C-H bond

  ***sp - 1s $\sigma$ bond***

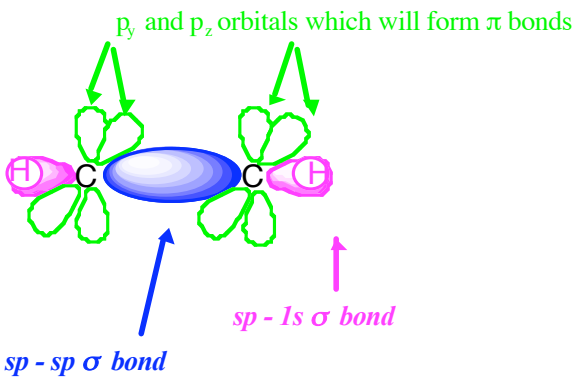
- The remaining carbon *sp* bonding orbital from each carbon is used to form the C-C- bond in ethylene

  ***sp - sp $\sigma$ bond***

- In acetylene, there are *two* left-over, half-occupied p orbitals: $p_y$ and $p_z$ These can form two sets of p orbitals. Two mutually perpendicular **$\pi$ bonds** are formed from these orbitals.




molecular orbitals of carbon in acetylene



# Acids and Bases

**Lewis acids and bases**

- A ***Lewis acid*** is an **electron acceptor**
- A ***Lewis base*** is an **electron donor**

**Bronsted acids and bases**

- A ***Bronsted acid*** is a **proton donor**
- A ***Bronsted base*** is a **proton acceptor**

**Electrophiles and Nucleophiles**

This terminology is used almost interchangeably with that of Lewis acids and Lewis bases

- Electrophile ("electron-loving") = Lewis acid
- Nucleophile ("nucleus-loving:") = Lewis base





# Relative Strengths of Bronsted Acids

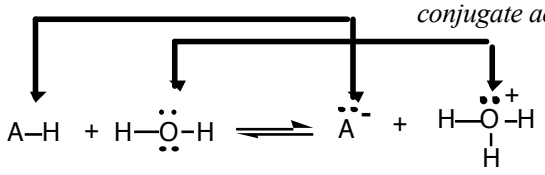
- The relative strengths of Bronsted acids are determined by how well they transfer a proton to a Bronsted base.
- In order to have a basis for comparison, reactions of different acids with the base are compared.

What base is used for comparison? | ***water***

The transfer of a proton from an acid, HA, to $H_2O$ is a reversible reaction. An acid and a base react to form a base and an acid. In general, these are called conjugate acid-base pairs.

*conjugate acid-base pair*

*conjugate acid-base pair*




the **equilibrium constant** of the reaction given in terms of ***activities*** ($a_i$):

$$K_{eq} = \frac{a_{A^-} a_{H^+}}{a_{AH} a_{H_2O}}$$

# Definition of $pK_a$

- The quantity "activity" may be thought of as an effective mole fraction. When reactions are carried out with very highly dilute acids in water, the activity of water approaches unity.
- We call this equilibrium constant for dissociation $K_a$.

$$K_{eq} = \frac{a_{A^-} a_{H^+}}{a_{AH} a_{H_2O}} \approx \frac{a_{A^-} a_{H^+}}{a_{AH}} \rightarrow \boxed{K_a = \frac{[A^-][H^+]}{[AH]}}$$

*In terms of concentrations and activity coefficients*

When we work in very dilute solutions, activity coefficients approach unity, and we can approximate the expression for $K_a$ using concentrations.





# Definition of $pK_a$

Bronsted acids exhibit a *huge* variation in strength, over many powers of 10. Therefore a log scale is used to describe acidity.

$$pK_a = -\log(K_a) = \left\{ -\log\left(\frac{[A^-]}{[HA]}\right) + \log([H^+]) \right\}$$

From this we see how the quantity used to measure acidity in Bronsted acids ($pK_a$) is related to aqueous acidity (pH)

$$pH = -\log([H^+])$$

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

# Using $pK_a$

- Reaction is driven forward from the strong acid side to the weak acid side. This means that the equilibrium favors the side with the weaker acid and weaker base.
- This means that if we know the $pK_a$ values of the acids on either side of the reaction equation, we can predict which direction will be favored.

$HCN + OH^- \rightleftharpoons {}^-CN + H_2O$

$pK_a = 9.4$ $\qquad$ $pK_a = 15.7$

$HCN + NH_3 \rightleftharpoons {}^-CN + NH_4^+$

$pK_a = 9.4$ $\qquad$ $pK_a = 9.25$

$pK_a((H_2O) - pK_a(HCN) = 15.7 - 9.4 = 6.3$

$K_{eq} = 10^{6.3} = 2 \times 10^6$

*The equilibrium lies **far to the right***

$pK_a((NH_4^+) - pK_a(HCN) = 9.25 - 9.4 = -0.15$

$K_{eq} = 10^{-0.15} = 0.71$

*The equilibrium is lies **slightly to the left***





# The influence of Organic Solvents on $pK_a$

- $pK_a$ values are defined and compiled for aqueous solutions.
- Most of our reactions in organic chemistry are carrried out in organic solvents!
- We must adjust our thinking about $pK_a$

Table 3
Ionization constants of neutral acids of type HA in water, amphiprotic and dipolar aprotic solvents, respectively

| Acid | $pK_a$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | W | MeOH | EtOH | *i*-PrOH | *t*-BuOH | ACN | DMSO | DMF |
| Acetic | 4.73 | 9.7 | 10.3 | 11.3 | 14.2 | 22.3 | | 13.3 |
| Chloroacetic | 2.81 | 7.8 | 8.3 | 9.2 | 12.2. | 18.8 | | 10.1 |
| Dichloroacetic | 1.30 | 6.3 | 7.3 | 7.8 | 10.2 | 15.8 | | |
| Benzoic | 4.21 | 9.4 | 10.1 | | 15.1 | 20.7 | 11.0 | 12.3 |
| 3,4-diMe benzoic | 4.4 | 9.7 | | 11.7 | 15.4 | 21.2 | 11.4 | 13.0 |
| 3-Br benzoic | 3.81 | 8.8 | 9.4 | 10.1 | 13.5 | 20.3 | 9.7 | 11.3 |
| 3,4-diCl benzoic | 3.6 | 8.5 | | 9.8 | 13.0 | 19.0 | 9.2 | 11.0 |
| 4-$NO_2$ benzoic | 3.45 | 8.3 | 8.9 | 9.6 | 12.0 | 18.7 | 9.0 | 10.6 |
| 3,5-di$NO_2$ benzoic | 2.82 | 7.5 | | 8.3 | 10.6 | 16.9 | 7.4 | 8.9 |
| 2,4,6-tri$NO_2$ phenol | 0.3 | 3.7 | 4.1 | 3.7 | 4.8 | 11.0 | | |

*K. Sarmini, E. Kenndler / J. Biochem. Biophys. Methods 38 (1999) 123–137*

# The influence of Organic Solvents on $pK_a$

- Acid $pK_a$ values are affected more than weak bases are by organic solvents.

Table 4
Ionization constants of cation acids (monoprotonated bases) of type $HB^+$

| Acid | $pK_a$ | | | | |
|---|---|---|---|---|---|
| | W | MeOH | EtOH | DMSO | ACN |
| Ammonium | 9.2 | | | 10.5 | 16.5 |
| Ethylammonium | 10.6 | | | 11.0 | 18.4 |
| Diethylammonium | 11.0 | | | 10.5 | 18.8 |
| Triethylammonium | 10.7 | 10.9 | | 9.0 | 18.5 |
| *n*-Butylammonium | 10.6 | | | 11.1 | 18.3 |
| Di-*n*-butylammonium | 11.3 | | | 10.0 | 18.3 |
| Tri-*n*-butylammonium | 10.9 | | | 8.4 | 18.1 |
| Anilinium | 4.6 | | 5.7[a] | 3.6 | 10.6 |
| Pyridinium | 5.2 | 5.2[b] | | 3.4 | 12.3 |
| 4-Ethylpyridinium | | 6.1[c] | | | 13.6[c] |

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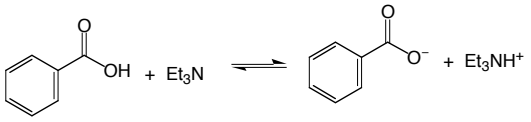
# Using $pK_a$

- Reaction is driven forward from the strong acid side to the weak acid side. This means that the equilibrium favors the side with the weaker acid and weaker base.
- This means that if we know the $pK_a$ values of the acids on either side of the reaction equation, we can predict which direction will be favored.

**In water**



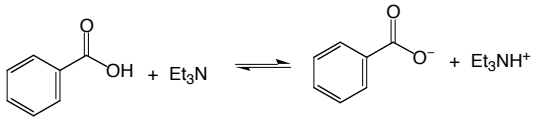

$pK_a = 4.21$ $pK_a = 9.2$

$pK_a((Et_3NH^+) - pK_a(PhCOOH) = 9.2 - 4.21$

$\log K_{eq} = 5$ $K_{eq} = 10^5$

*The equilibrium lies **far to the right***

**In acetonitrile**




$pK_a = 20.7$ $pK_a = 18.5$

$pK_a((Et_3NH^+) - pK_a(PhCOOH) = 18.5 - 20.7$

$\log K_{eq} = -2.2$ $K_{eq} = 10^{-2.2}$

*The equilibrium lies **to the left***

# Factors Affecting $pK_a$ in Organic Solvents

- Dielectric constant: this parameter takes into account electrostatic interactions of the ions in solution.

Table 1
Classification of solvents for potential use in CE, according to Ref. [21]

| High $\epsilon$ | | Low $\epsilon$ | |
|---|---|---|---|
| H-bonded | Non-H-bonded | H-bonded | Non-H-bonded |
| Water (W) | Acetonitrile (ACN) | Ethanol (EtOH) | Acetone |
| Methanol (MeOH) | *N*,*N*-Dimethylformamide (DMF) | *n*-Propanol (*n*-PrOH) | Dioxane |
| Ethylene glycol | *N*,*N*-dimethylacetamide (DMA) | *i*-Propanol (*i*-PrOH) | Tetrahydrofuran |
| Formamide | Dimethylsulfoxide (DMSO) | *n*-Butanol (*n*-BuOH) | |
| Acetamide | | *tert*-Butanol (*t*-BuOH) | |
| *N*-Methylformamide | | | |
| *N*-Methylacetamide | | | |

MeCN, DMSO, and DMF have similar properties

Water and methanol have similar properties

$pK_a$ of benzoic acid in:

| | |
|---|---|
| DMF | 12.3 |
| DMSO | 11.0 |
| MeCN | 20.7 |

***Clearly, dielectric constant is not telling the whole story!***



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# Factors Affecting $pK_a$ in Organic Solvents

- **Solute-solvent iinteractions:** looking at dielectric constant alone neglects the effects of interactions between solute and solvent (sometimes called "medium effects" as opposed to the "solvent effect" described by ε).
- An important characteristic is the ability of the medium to solvate ions.
- Solvation ability in a given solvent can be significantly different for cations compared to anions.

Table 8
Ability of solvents to solvate anions and cations

| Solvation ability | Solvent | | | |
|---|---|---|---|---|
| | Water | MeOH | DMSO | ACN |
| Anion | Very high | Medium | Low | Very low |
| Cation | Very high | Very high | Very high | Very low |

# Factors Affecting $pK_a$ in Organic Solvents

- Organic solvents are generally worse as solvators of anions than they are of cations.
- This helps explain why the $pK_a$ values for bases such at $Et_3N$ are less affected by solvent than are neutral acids.
- $pK_a$ is affected more in MeCN because it is much less basic than the other non-H-bonding solvents of similar dielectric constant.
- Medium effects must also consider the role of the other charged species present ($A^-$ and $HB^+$).

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