

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.

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Revision: Structure and Bonding

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

| 1A | | | | | | | 7A | |
|------------|------------|-----------|-----------|-----------|-----------|------------|----|--|
| H 2.2 | | | | | | | | |
| | 2A | 3A | 4A | 5A | 6A | | | |
| Li 0.98 | Be 1.57 | B 2.04 | C 2.55 | N 3.04 | O 3.44 | F 3.98 | | |
| Na 0.93 | | | | | | Cl 3.16 | | |

← electropositive elements
→ electronegative elements

electronegativities listed under the element name

Types of bonds:

- ionic bonds
- covalent bonds
- polar covalent bonds

The type of bonding in a molecule affects:

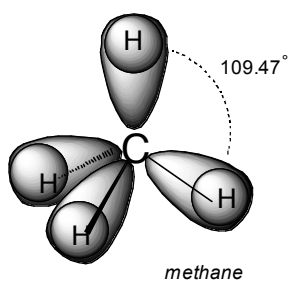
- shape
- physical properties
- reactivity

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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



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

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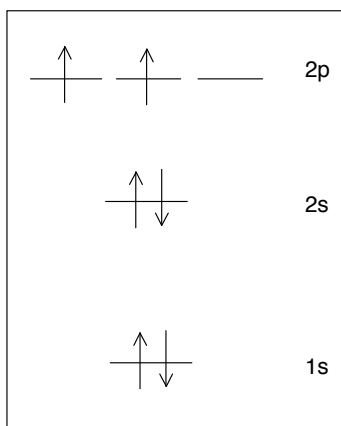
Models for Bonding

- 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**

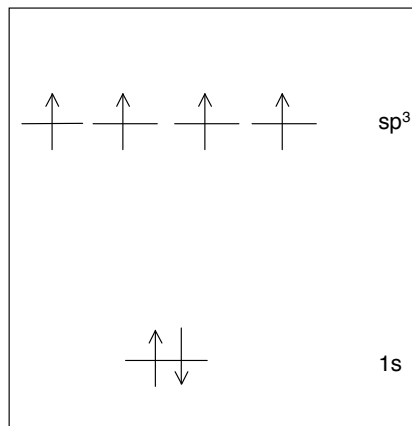
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Models for Bonding

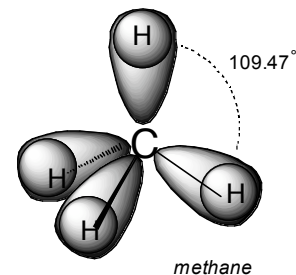
• Molecular orbital theory: methane



molecular orbitals of carbon



molecular orbitals of sp^3 hybridized carbon (as in methane)

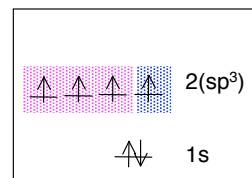
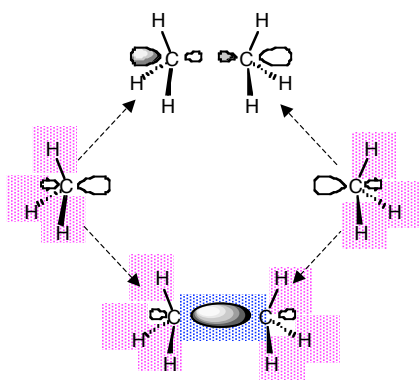


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Models for Bonding

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 ethane $sp^3 - sp^3 \sigma$ bond (shown shaded in blue below)



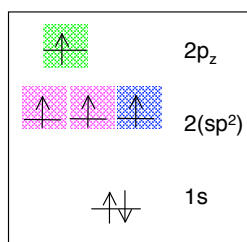
molecular orbitals of carbon in ethane

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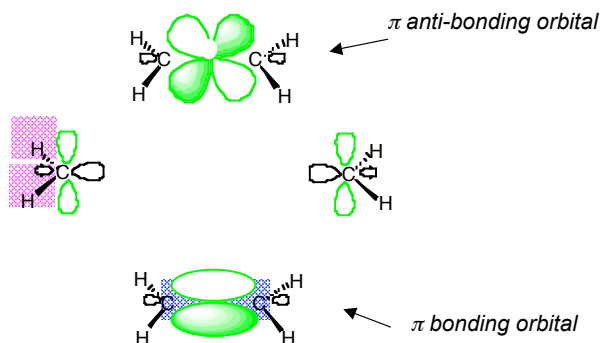
Models for Bonding

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: **π bond** (shaded in green)



molecular orbitals of carbon in ethylene

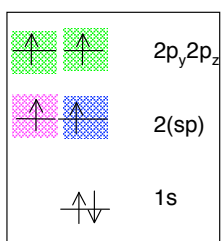


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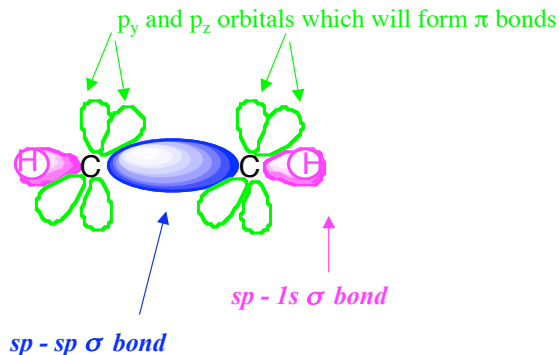
Models for Bonding

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 **π bonds** are formed from these orbitals.



molecular orbitals of carbon in acetylene



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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

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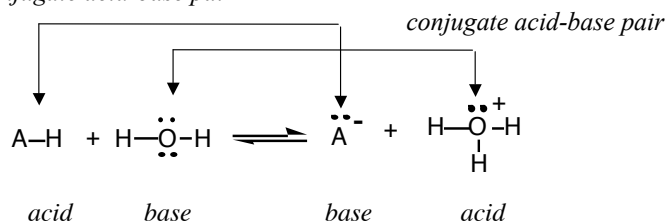
Relative Strengths of Bronsted Acids

- 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 H₂O 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



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

$$K_{eq} = \frac{a_{\text{A}^-} a_{\text{H}^+}}{a_{\text{AH}} a_{\text{H}_2\text{O}}}$$

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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 .

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

*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.

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

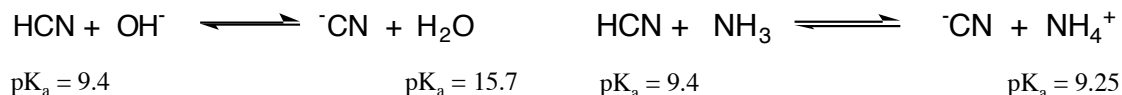
From this we see how the quantity used to measure acidity in Bronsted acids (pK_a) is related to aqueous acidity (pH)

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

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

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.



$$pK_a(\text{H}_2\text{O}) - pK_a(\text{HCN}) = 15.7 - 9.4 = 6.3$$

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

The equilibrium lies far to the right

$$pK_a(\text{NH}_4^+) - pK_a(\text{HCN}) = 9.25 - 9.4 = -0.15$$

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

The equilibrium is lies slightly to the left

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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 carried 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>i</i> -PrOH | <i>t</i> -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-diNO ₂ benzoic | 2.82 | 7.5 | | 8.3 | 10.6 | 16.9 | 7.4 | 8.9 |
| 2,4,6-triNO ₂ phenol | 0.3 | 3.7 | 4.1 | 3.7 | 4.8 | 11.0 | | |

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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^+

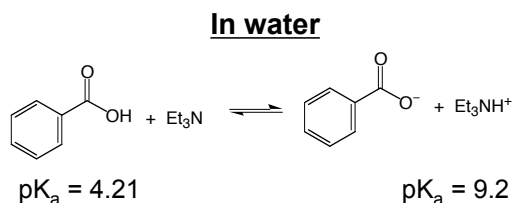
| Acid | pK_a | | | | |
|------------------------------|--------|------------------|------------------|------|-------------------|
| | W | MeOH | EtOH | DMSO | ACN |
| Ammonium | 9.2 | | | 10.5 | 16.5 |
| Ethylammonium | 10.6 | | | 11.0 | 18.4 |
| Diethylammonium | 11.0 | | | 10.5 | 18.8 |
| Triethylammonium | 10.7 | 10.9 | | 9.0 | 18.5 |
| <i>n</i> -Butylammonium | 10.6 | | | 11.1 | 18.3 |
| Di- <i>n</i> -butylammonium | 11.3 | | | 10.0 | 18.3 |
| Tri- <i>n</i> -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 |

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

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Using pK_a

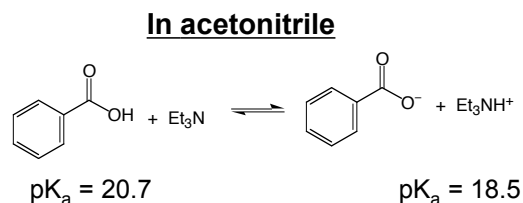
- Reaction is driven forward from the strong acid side to the weak acid side. This means that the equilibrium favors the side with the weaker acid and weaker base.
- This means that if we know the pK_a values of the acids on either side of the reaction equation, we can predict which direction will be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



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

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

The equilibrium lies far to the right



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

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

The equilibrium lies to the left

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



Water and methanol
have similar properties



MeCN, DMSO, and DMF
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 interactions:** 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 |

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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 as 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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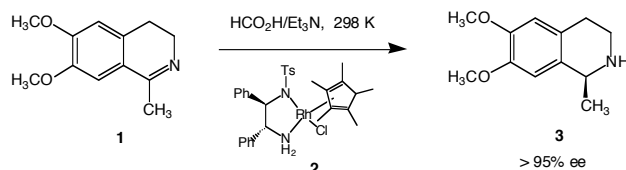
Example: Asymmetric Transfer Hydrogenation

- Imines can be reduced to amines using a transition metal catalyst and HCOOH as the hydrogen source.

(Avecia's CATHy catalyst process)

- When the reaction is carried out in MeOH as solvent, we need to think about what happens to the pK_a values of the reactants.

What state is the imine in during reaction?

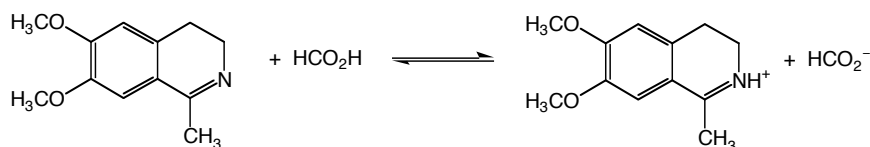


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Example: Asymmetric Transfer Hydrogenation

- The acidity of formic acid is drastically decreased in MeOH.
- We would expect this reaction to be driven towards the left.
- However, pK_a values are calculated for dilute solutions.

("thermodynamic" ionization constants vs. concentration pK_a values)

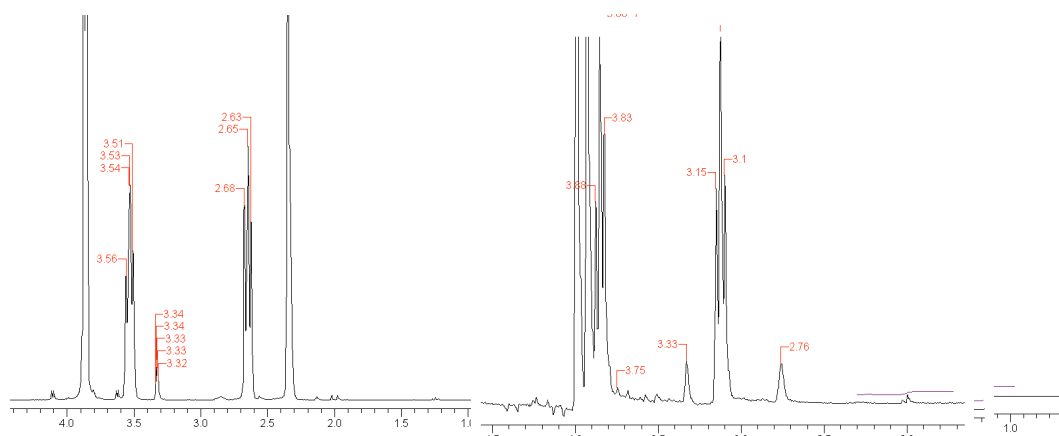


| | | |
|-----------------|------|-----|
| pK_a in water | 3.75 | 5.8 |
| pK_a in MeOH | 8.76 | 6.4 |

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Example: Asymmetric Transfer Hydrogenation

- Sometimes things are not what they seem....
- NMR spectra of pure imine in MeOH and imine mixed with HCOOH at 0.5, 1 and 2 equivalents.



Pure imine

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