Molecular Structure, Bonding, Properties, and Functionality*

Fall 2004, AMS-691 Section 2
Topics in Applied Mathematics

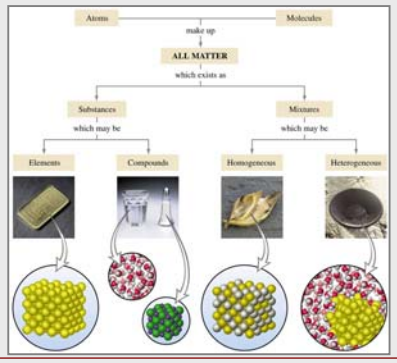
Introduction to Computational Structural Biology and Drug Design

Meeting 03, 09/08/04, Topics 1 and 2

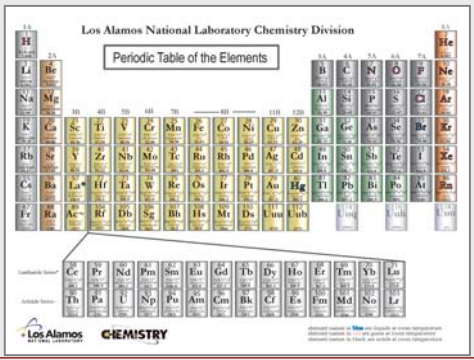
Robert C. Rizzo

*Adopted from http://web.uccs.edu/chemistry and other online sources

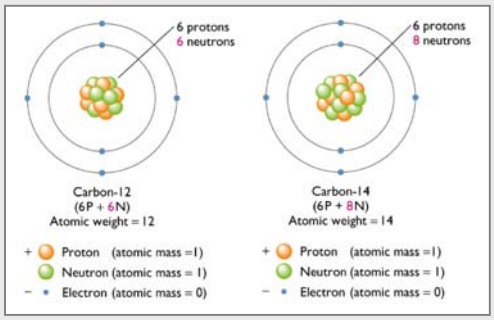
Matter



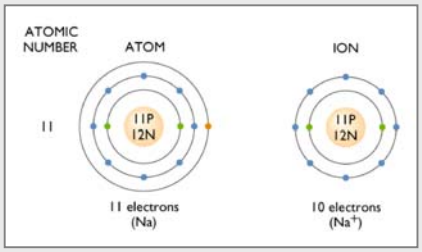
Elements



Planetary Model of the Atom: protons, neutrons, and electrons

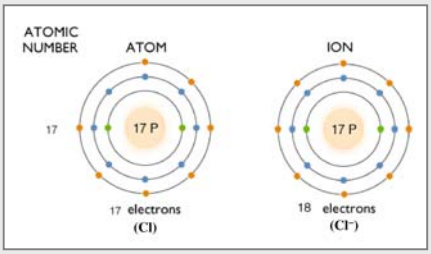


Ions: Atoms (or molecules) which have gained or lost electron e.g. Sodium (Na^+)



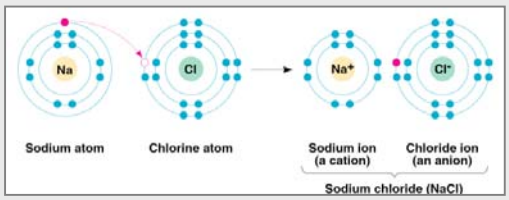
one electron lost
positive charge (cation)

Ions: Atoms (or molecules) which have gained or lost electron e.g. Chlorine (Cl^-)

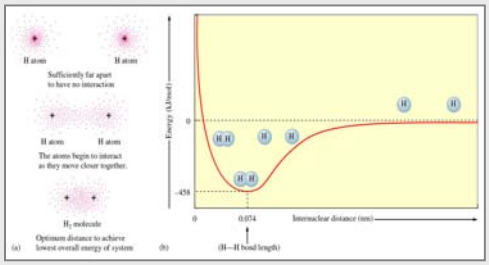


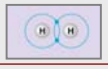
one electron gained
negative charge (anion)

Ionic bond: A favorable electrostatic interaction between oppositely charged species



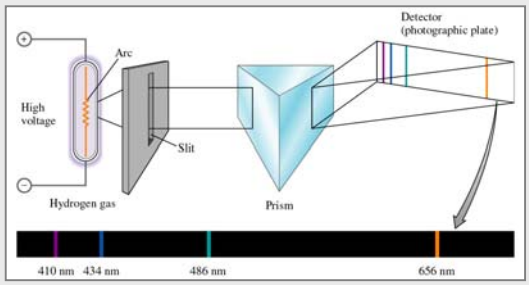
Covalent bond: Two valence electrons are shared





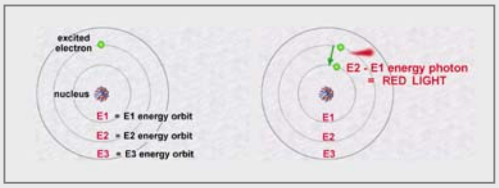
The bond is represented by a line, H—H

Hydrogen gas (H_2) emission spectrum is quantized



wave length λ (nm)

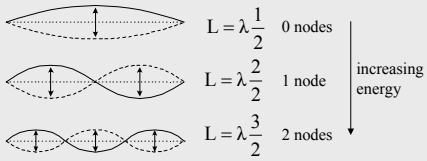
Bohr's planetary model of the atom: electrons orbit the nucleus only in specific quantized states (energy levels, orbitals)



$$\Delta E_{\text{Hydrogen atom}} = -Rhc\left(\frac{1}{n^2_{final}} - \frac{1}{n^2_{initial}}\right)$$

Standing waves: quantized energy levels

guitar string: ⟵ L ⟶



$L = \lambda\frac{1}{2}$ 0 nodes

$L = \lambda\frac{2}{2}$ 1 node

$L = \lambda\frac{3}{2}$ 2 nodes

increasing energy

general: $L = \lambda\frac{n}{2}$, only **integral** number of half-wavelengths allowed

Quantum mechanical model: Electrons behave like particle and waves

Heisenberg (1901-1976)

It is impossible to know simultaneously both the exact momentum and exact location of an electron.

Can only determine the **probability** of finding an electron within a given region of space.

Schrödinger (1887-1961)

Wave functions (Ψ) describe the standing wave for the electron around an atom.

Ψ^2 is the **probability** of finding an electron in a given region of space and describes the **orbital** within which an electron exists

Schrödinger's wave functions (orbitals) are described by 4 quantum numbers

(1) principle quantum number, n
determines: main energy level or shell and size of orbital
$n = 1, 2, 3, 4\ldots \infty$
second shell, etc.
first shell

(2) angular momentum quantum number, l
determines: shape (type) of orbital (subshell)

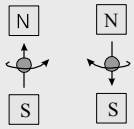
$l = 0$	1	2	3	4	5…
s	*p*	*d*	*f*	*g*	*h*…

fundamental
diffuse
principal
sharp

Schrödinger's wave functions (orbitals) are described by 4 quantum numbers

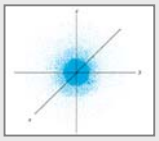
(3) magnetic quantum number, m_l
determines: orientation of orbital
$m_l = 0, \pm 1, \pm 2\ldots \pm l$

(4) spin quantum number, m_s
two spin states: up or down (quantized)
$m_s = +\frac{1}{2}, -\frac{1}{2}$

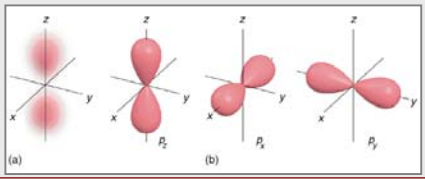


Atomic orbital representations (size, shape, orientation)

s orbitals

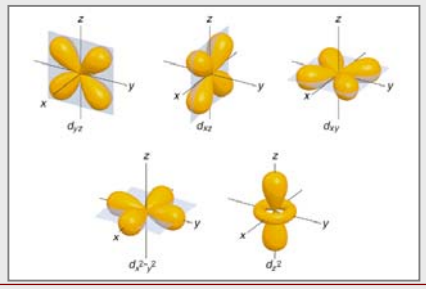


p orbitals



Atomic orbital representations (size, shape, orientation)

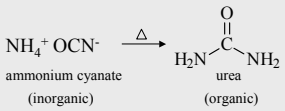
d orbitals



Organic chemistry

- originally: derived from living *organi*sms (not minerals)

- 1828 Wöhler:



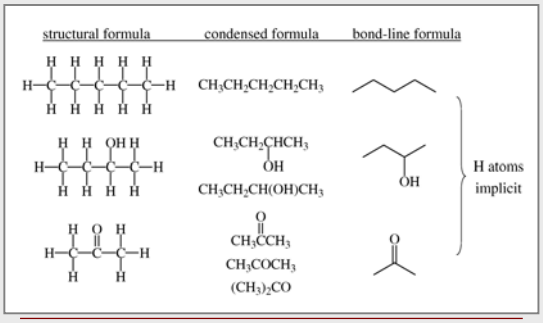
- compounds containing C, H, O, N, S, P, etc.

Organic molecules

- biological
  - –plants, animals
- fossil
  - –coal, oil, gas
- synthetic
  - –polymers
  - –pharmaceuticals
  - –flavors
  - –fragrances
  - –dyes
  - –food additives
  - –lots more

> 12,000,000 known
~ 100,000 added yearly

Organic molecule representations (each line is a covalent bond, 2 e⁻)



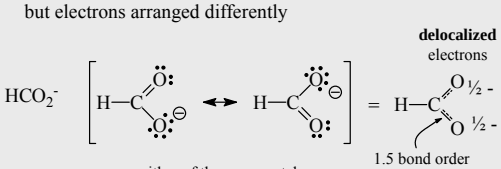
Lewis structures show molecular geometry

Formula	Lewis	Geometry
C_2H_2	H—C≡C—H	linear (180°)
CH_2O		trigonal planar (120°)
CH_4		tetrahedral (109.5°)
HCN	H—C≡N:	linear (180°)
NH_3		trigonal pyramidal (107°)
H_2O		bent (104.5°)

Resonance structures

-two or more **equivalent** Lewis structures

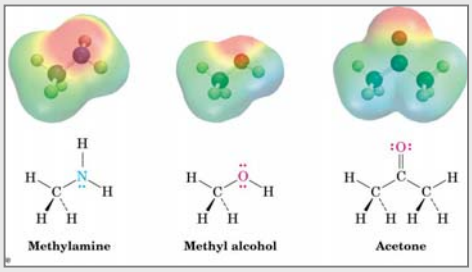
-nuclei remain in fixed positions, but electrons arranged differently



•neither of these accurately describes the formate ion

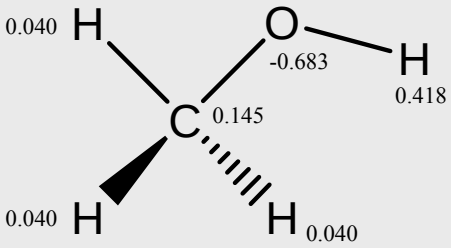
•actual species is an average of the two (**resonance hybrid**)

Molecules have uneven electron distributions



Colors indicate electron-rich (red) and electron-poor (blue) regions

Electron distributions can be modeled as a collection of "point charges" centered on the atomic nuclei

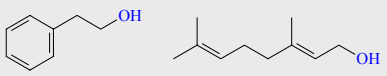


Functional groups: Alcohol (OH- group)

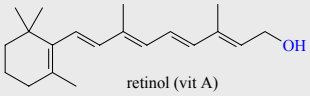
Definition: Groups of atoms that behave similarly, regardless of the structure to which they are attached.

CH_3OH CH_3CH_2OH

methanol ethanol

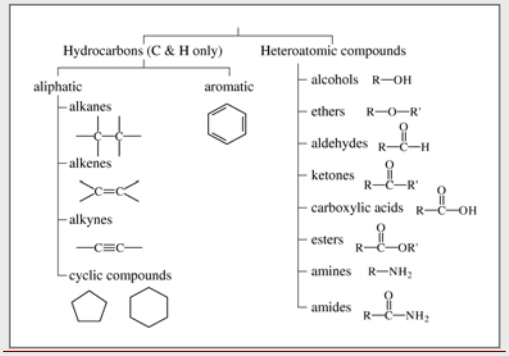


β-phenethyl alcohol (lilacs) geraniol



retinol (vit A)

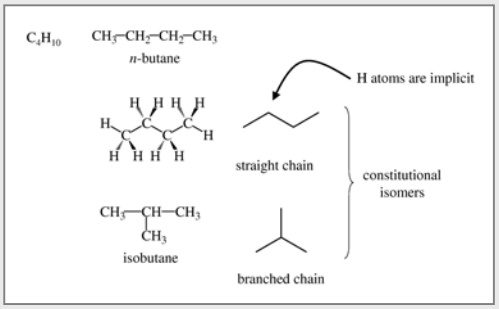
Common organic functional groups (R groups)



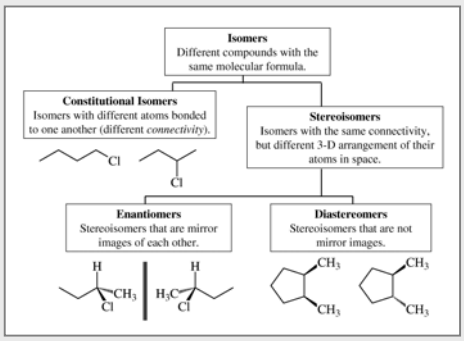
Alkanes

CH_4	(CH_4)	methane (natural gas, swamp gas)
CH_3–CH_3	(C_2H_6)	ethane
CH_3–CH_2–CH_3	(C_3H_8)	propane
$CH_3CH_2CH_2CH_3$	(C_4H_{10})	butane
$CH_3CH_2CH_2CH_2CH_3$	(C_5H_{12})	pentane

Alkanes: Constitutional isomers (different arrangements of alkyl units)



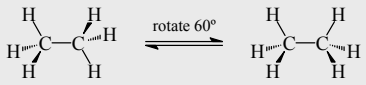
Stereoisomerism (molecules in 3D space)



Alkanes: Nomenclature, alkyl groups

CH_3—	methyl	CH_3–CH_2—	ethyl
CH_3–CH_2–CH_2—	propyl	CH_3–CH(—)–CH_3	isopropyl
$CH_3CH_2CH_2CH_2$—	butyl	$CH_3CH_2CH(—)CH_3$	*sec*-butyl

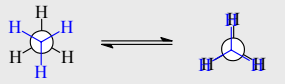
Conformations: 3D Newman projections



staggered conformation — in between: **skewed** — **eclipsed** conformation

Newman projections: sight along C-C bond

Conformations: 3D Newman projections

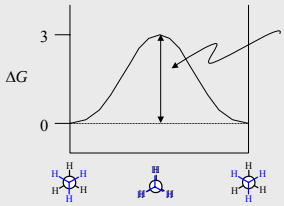


lower energy

higher energy

$\Delta G \sim 3$ kcal/mol

torsional strain
(eclipsing strain)



$E_a \sim 3$ kcal/mol

= barrier to free rotation

(but at RT most molecules have KE > E_a so rotation is essentially "free")

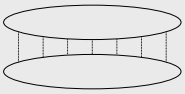
$k_{rot} \sim 10^6$ s^{-1}

Physical Properties (boiling point, b.p.)

Cmpd	b.p. (SAR property)
CH_4	-160ºC
C_2H_6	-89
C_3H_8	-42
n-C_4H_{10}	-0.4
n-C_5H_{10}	36

Intermolecular attractions

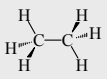
versus



greater surface area for attraction

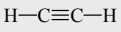
Bonding: Alkanes, Alkenes, Alkynes

Alkanes:	C_nH_{2n+2}	**saturated** hydrocarbons	(SINGLE)
Alkenes:	C_nH_{2n}	**unsaturated** hydrocarbons	(DOUBLE)
Alkynes:	C_nH_{2n-2}	**unsaturated** hydrocarbons	(TRIPLE)



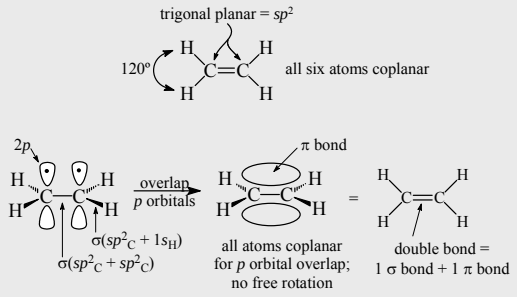
ethane

ethene
(ethylene)

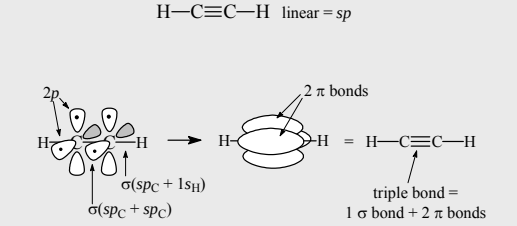


ethyne
(acetylene)

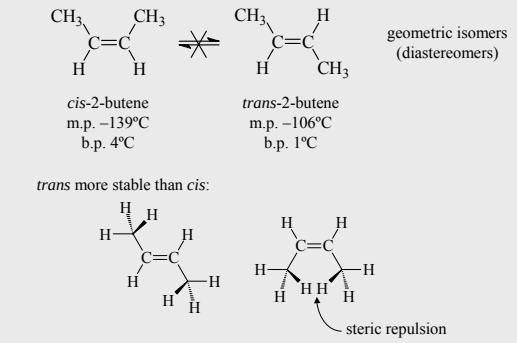
Double bonding



Triple bonding



Structure: Cis-trans isomers in alkenes

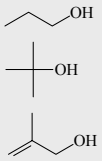


Functional groups: Examples

Alcohols

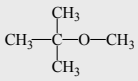
CH_3OH

CH_3CH_2OH

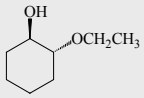


Ethers

$CH_3CH_2OCH_2CH_3$



$CH_3OCH_2CH_2OCH_3$



Functional groups: Examples

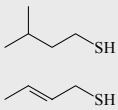
Cyclic Ethers

oxacyclopropane
oxirane
ethylene oxide
1,2-epoxyethane

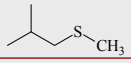
oxacyclobutane
oxetane
1,3-epoxypropane

oxacyclopentane
oxolane
1,2-epoxybutane
tetrahydrofuran

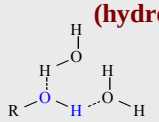
Thiols



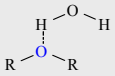
Sulfides (thioethers)



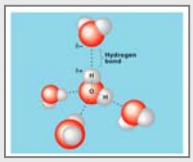
Physical Properties: Solubility in water (hydrogen bonding)



CH_3CH_2OH
H-bond donor and acceptor
(solubility: infinite)



CH_3OCH_3
H-bond acceptor only
(solubility: 7 g/100 g water)



Solubilities of short-chain alcohols in water

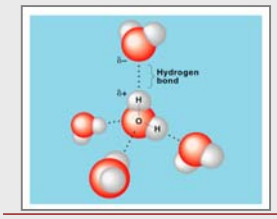
Alcohol	Structure	Solubility in water (mol/100 g 20°C)[a] H_2O at
Methanol	CH_3OH	∞
Ethanol	CH_3CH_2OH	∞
Propanol	$CH_3(CH_2)_2OH$	∞
Butanol	$CH_3(CH_2)_3OH$	0.11
Pentanol	$CH_3(CH_2)_4OH$	0.030
Hexanol	$CH_3(CH_2)_5OH$	0.0058
Heptanol	$CH_3(CH_2)_6OH$	0.0008

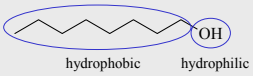
Physical Properties: Solubility in water As a function of R, (hydrophobic effect)

R-OH

C_1 ↔ C_4 ↔ C_6 ↔ C_{20}

very soluble — slightly soluble — not soluble



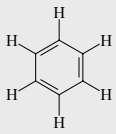


hydrophobic hydrophilic

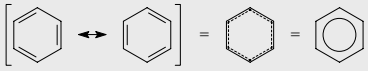
R = length of hydrocarbon chain

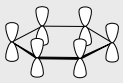
Benzene and Aromaticity: sharing of electrons in a contiguous (conjugated) π system

C_6H_6



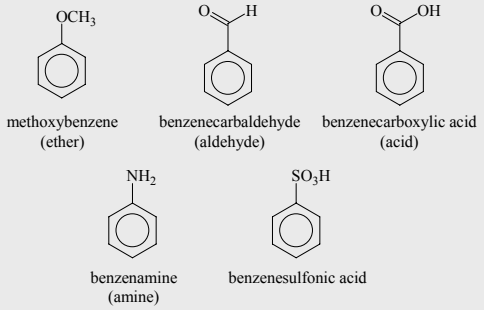
- planar hexagon, all angle 120º
- all C-C bonds = 140 pm
- all sp^2 hybridized





6 e^- in 6 *p* orbitals

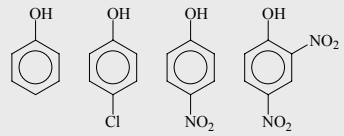
Nomenclature: Rings (single group)



methoxybenzene (ether) | benzenecarbaldehyde (aldehyde) | benzenecarboxylic acid (acid)

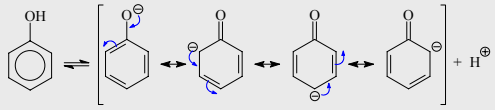
benzenamine (amine) | benzenesulfonic acid

Phenols and pKa's (ability to lose a hydrogen)



pK_a 9.95 9.18 7.15 3.96

increasing e^- withdrawal further stabilizes anion

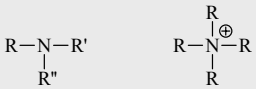


Functional groups: Amines

NH_3 ammonia

$R-NH_2$ primary amine

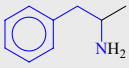
$R-NH-R'$ secondary amine



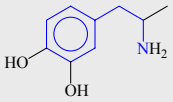
tertiary amine

quaternary ammonium ion

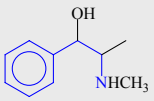
Alkaloids contain amines



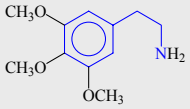
amphetamine ("speed")



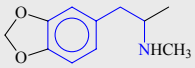
dopamine (nerve conduction)



ephedrine (adrenaline)

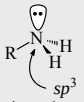


mescaline (mescal cactus)



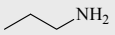
methylenedioxymethamphetamine (MDMA, "ecstasy")

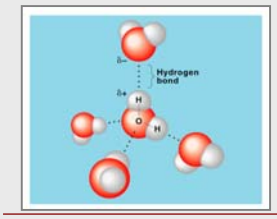
Amines: Physical Properties



sp^3

trigonal pyramidal

	b.p.	sol.
	48	sol.
	34	sol.
	3	s. sol.



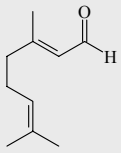
Functional groups: Aldehydes and ketones

carbonyl group

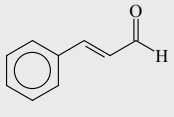
formaldehyde

aldehydes

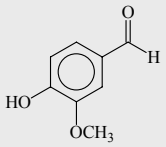
ketones



geranial

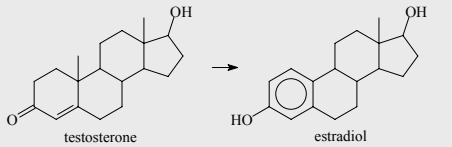


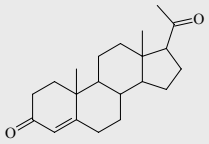
cinnamaldehyde



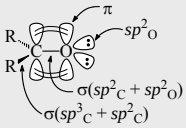
vanillin

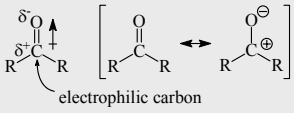
Ketone examples





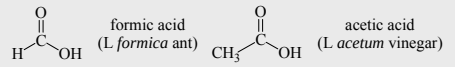
Physical Properties: ketones

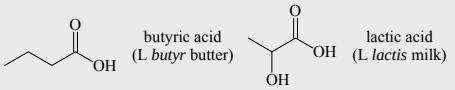


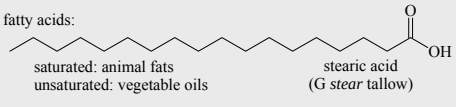


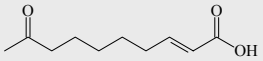
- more polar than ethers or alcohols
- more soluble than ethers
- less soluble than alcohols (H-bond acceptor only)

Functional groups: Carboxylic acids

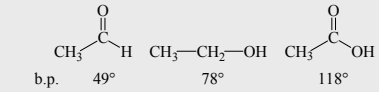






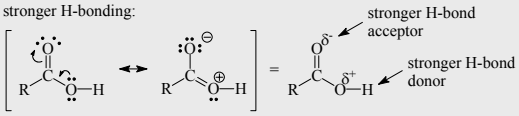


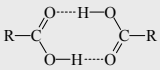
Physical Properties: Carboxylic acids



b.p. 49° 78° 118°

stronger H-bonding:





H-bonded **dimer** in neat acids

RCO_2H

R = C_1-C_3 miscible with H_2O

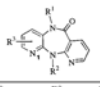
C_4-C_{10} increasingly less soluble

>C_{10} insoluble

Experimentally observed properties are a function of molecular makeup and structure

- Func. groups can be:
  - –polar/nonpolar
  - –hydrophobic
  - –hydrophilic
  - –Hydrogen bonding
  - –aromatic
  - –acidic (lose H)
  - –basic (gain H)
- Pure liquids properties
  - –boiling point
  - –density
  - –heat of vaporization
- Solutes (molecule) in solvent (water)
  - –solubility
  - –free energy of solvation/hydration
  - –octanol/water partition coeff.
- Drugs (chemotherapeutics)
  - –affinity
  - –potency
  - –specificity
  - –binding energy
  - –ADME

Small changes in organic functional groups affect a drugs properties (potency example)



no.	R^1	R^2	R^3	IC_{50}*	ca. ΔG_{bind}
N01	Me	Et	H	0.125	−9.42
N02	Me	Et	2-Me	0.17	−9.24
N03	Me	Et	2-Cl	0.15	−9.31
N04	Me	Et	3-Me	0.76	−8.35
N05	Me	Et	3-Cl	>1.0	>−8.19
N06	Me	Et	4-Me	1.9	−7.81
N07	H	Et	H	0.44	−8.67
N08	H	Et	4-Me	0.035	−10.17
N09	H	Et	4-Cl	0.095	−9.58
N10	H	c-Pr	4-Me	0.084	−9.65
N11	Me	c-Pr	4-Me	>1.0	>−8.19
N12	Me	Pr	H	0.45	−8.66
N13	Me	t-Bu	H	11.0	−6.77
N14	Me	$COCH_3$	H	15.3	−6.57
N15	Me	Et	4-Et	0.11	−9.49
N16	Me	CH_2SCH_3	H	0.85	−8.28
N17	H	c-Pr	4-CH_2OH	3.0	−7.54
N18	H	c-Pr	4-CN	1.25	−8.05
N19	Me	CH_2CH_2F	H	2.9	−7.56
N20	H	c-Pr	H	0.45	−8.66

Conclusions

- The atomic world behaves quantum mechanically. For our purposes we represent molecules classically.
- Atoms may gain or lose electrons and can "share" electrons to create a bond. Chemists represent a covalent bond by drawing a line between the two atoms (H, C, O, N, S, P, etc.) and double, triple bonds are possible
- 3D arrangement of atoms (functional groups) have known properties.
- Many experimental measurements can be understood in terms of the presence or absence of specific types of functionality (solubility, b.p.).
- Hydrogen bonds are critically important (a competing process).