Solvent Scales

	ε	α	β
Water	78	1.17	0.47
DMSO	47	0.00	0.76
DMF	37	0.00	0.76
Methanol	33	0.93	0.66
HMPA	29	0.00	1.05
Acetone	21	0.08	0.43
Methylene Chloride	9	0.13	0.10
THF	8	0.00	0.55
Ethyl acetate	6	0.00	0.45
Ether	4	0.00	0.47
Benzene	2	0.00	0.10
Hexane	2	0.00	0.00

α: solvent's ability to act as a hydrogen bond-donor to a solute

β: solvent's ability to act as a hydrogen bond acceptor from a solute

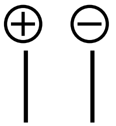
ε: Dielectric constant: correlates with solvent polarity (molecular dipoles, molecular polarizabilities hydrogen bonding capability, etc)

Hydrogen Bond Strengths

O–H •••O=C	formic acid-formic acid	-7.4 kcal/mol (gas phase)
O–H •••O–H	methanol-methanol	-7.6 kcal/mol (gas phase)
O–H •••OR_2	Phenol - dioxane	-5.0 kcal/mol (CCl_4)
O–H ••• SR_2	Phenol-butyl sulfide	-4.2 kcal/mol (CCl_4)
O–H ••• SeR_2	Phenol-butyl selenide	-3.7 kcal/mol (CCl_4)
O–H ••• sp^2N	Phenol-Pyridine	-6.5 kcal/mol (CCl_4)
O–H ••• sp^3N	Phenol-Triethylamine	-8.4 kcal/mol (CCl_4)
N–H ••• SR_2	thiocyanic acid-butyl sulfide	-3.6 kcal/mol (CCl_4)

Non-Covalent Interactions

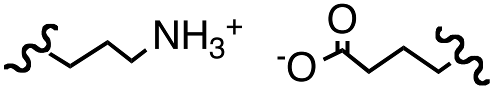
1. Ion-Pairing



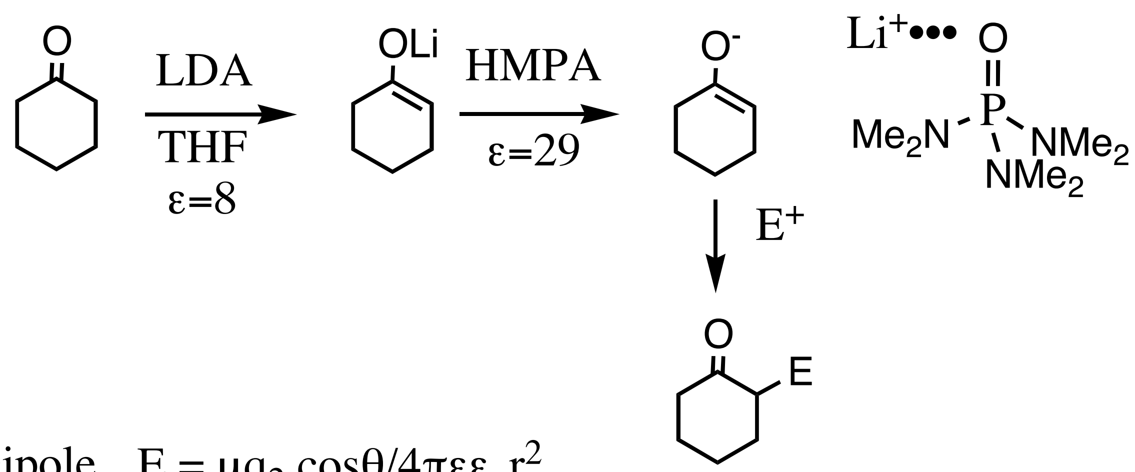
$E = q_1 q_2 / 4\pi\varepsilon\varepsilon_o r$

q=charge (in coulombs) of ion

Example: salt bridge in proteins



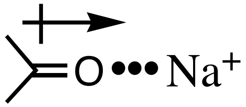
Strength of the interaction depends on context: dielectric constant in denominator, therefore high polarity solvents have weak interactions between charges



β=1.05: best acceptor of H-bond or M^+

2. Ion-Dipole $E = \mu q_2 \cos\theta / 4\pi\varepsilon\varepsilon_o r^2$

weaker:falls off more rapidly with distance



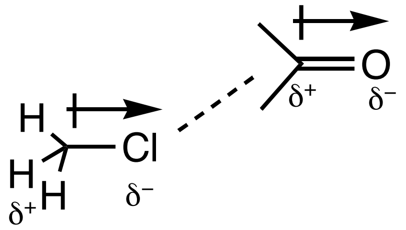
μ=dipole moment of polar molecule

The smaller the ion, the greater the solvation/hydration energy: $Li^+ > Na^+ > K^+ > Rb^+$ reason: more charge per unit area on smaller ion.

Non-Covalent Interactions

3. Dipole-Dipole $E = \mu_1\mu_2(3\cos^2\theta - 1)/4\pi\varepsilon\varepsilon_o r^3$

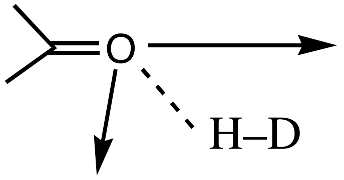
the force between two dipoles depends on their relative orientation



Hydrogen Bonding: a donor-acceptor interaction whose governed primarily by electrostatic considerations:

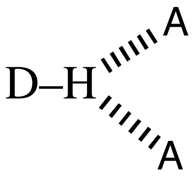
$\overset{\delta^-}{\text{Dn}}–\overset{\delta^+}{\text{H}} \bullet\bullet\bullet\bullet \overset{\delta^-}{:\text{Ac}} \leftarrow$ Any partial negative chage can accept H-bond

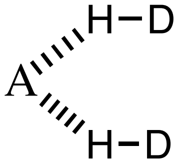
Optimal geometry is a colinear arrangement of three atoms, but geometry is not a major contributing factor to H-bond strength



lone pairs are diffuse and have weak directionality

Bifurcated H-bonds are possible:

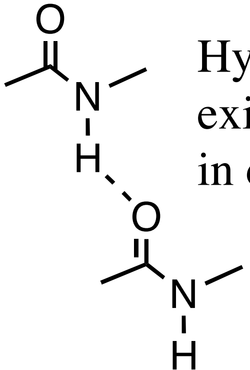




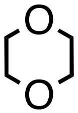
Hydrogen Bonding

Strength of H-Bonds:		
	Very Strong	15-40 kcal/mol
	Moderate	5-14 kcal/mol
	Weak	0-4 kcal/mol

Solvent influences the strength of Hydrogen Bonds:



Hydrogen bond exists in CCl_4, not in dioxane:



For competitive solvents:

$$D\text{–}H\bullet\bullet\bullet S \quad + \; A\bullet\bullet\bullet H\text{–}S \;\rightleftharpoons\; D\text{–}H\bullet\bullet\bullet A + \; S\bullet\bullet\bullet H\text{–}S$$

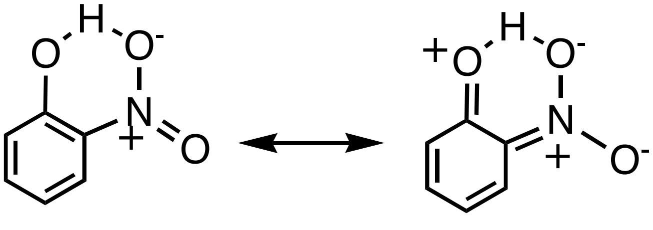
Electronegativity: donor ability: H–F > H–Cl > H–Br > H–I

acceptor ability: $H_3N > H_2O > H_2S > H_3P$

diffuse electron pairs of third row elements make them poor acceptors

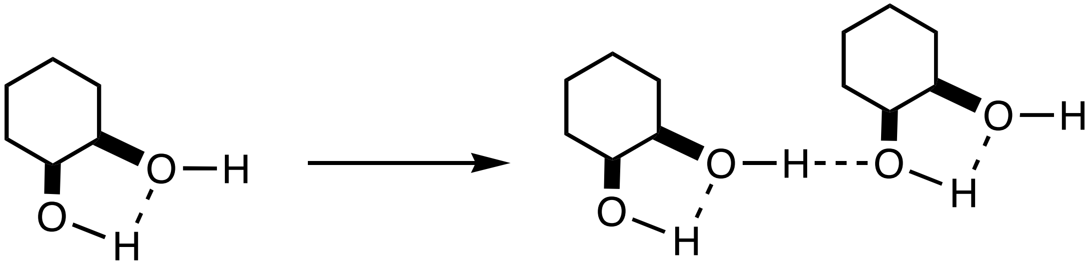
Strong hydrogen bonds occur when both partners are charged:

<u>Resonance-Assisted Hydrogen Bonding</u>

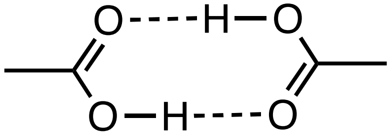


Hydrogen Bonding

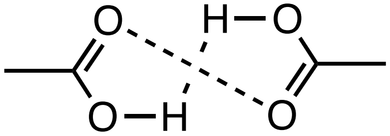
Cooperative Hydrogen bonding:
assisted polarization of Dn-H bond, making them better donors:



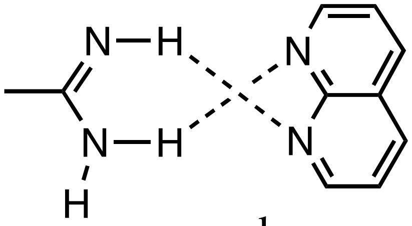
Secondary Interactions:



primary

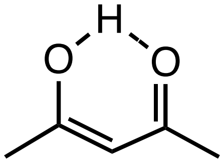


secondary
(repulsive)



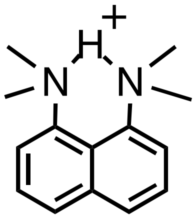
secondary
(stabilizing)

Short-Strong Hydrogen Bonds: low barrier/no barrier H-bonds arise when the distance between Dn and A is short (2.4-2.5Å)



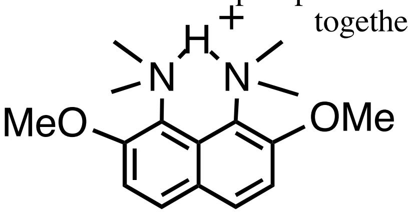
three center
four electron bond

proton sponges:



pKa=12.1

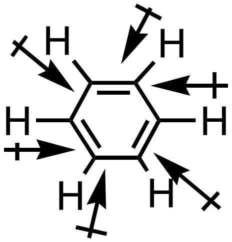
donor and acceptor pushed together



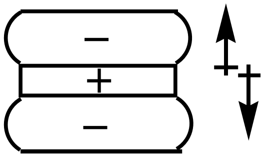
pKa=16.1

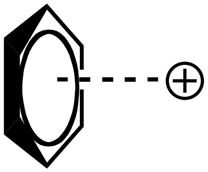
π–Effects

Cation-π Interaction: interaction between the face of a simple pi system (with negative electrostatic potential and a cation:



Csp^2 is more electronegative than H!



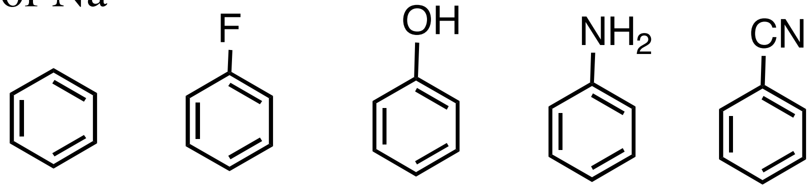


	−ΔG°(kcal/mol)
Li$^+$	38
Na$^+$	27
K$^+$	19
Rb	16

H_2O•••K^+ -18 kcal/mol

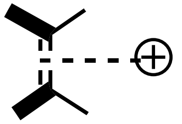
H_2O•••C_6H_6 -19 kcal/mol

binding of Na$^+$

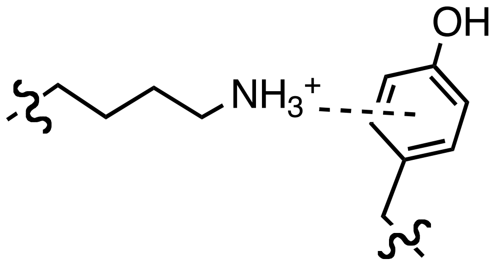


27.1 22.0 26.9 31.8 15.7 kcal/mol

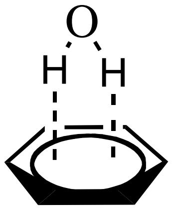
Also:



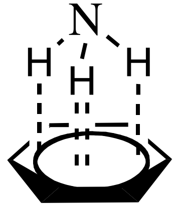
In Proteins:



Polar-π–Interactions

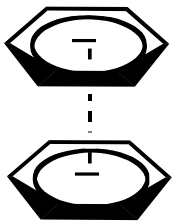


1.9 kcal/mol

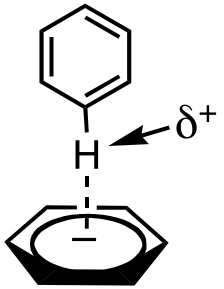


1.4 kcal/mol

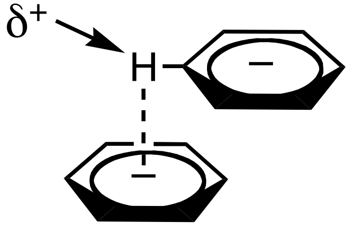
π-Stacking interactions:



face-to-face
is repulsive

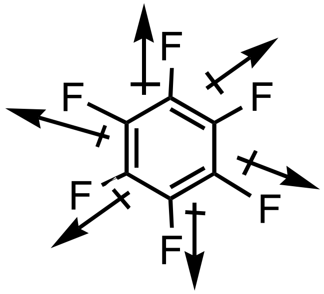


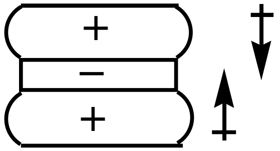
T-shaped
stabilizing

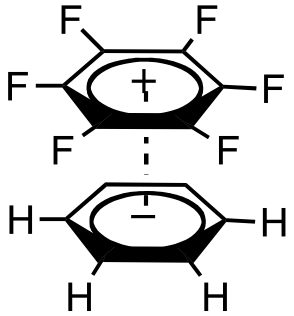


Slipped-Stack or
"Displaced" Stack-stabiliziang

Direct Face-to Face stack is favorable only
for Arene-Perfluoroarene interaction

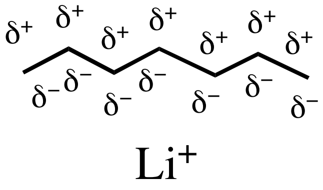






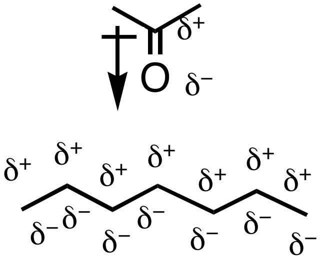
Non-Covalent Interactions

4. Ion-Induced Dipole $E = -q^2\alpha/(4\pi\varepsilon\varepsilon_o)^2r^4$



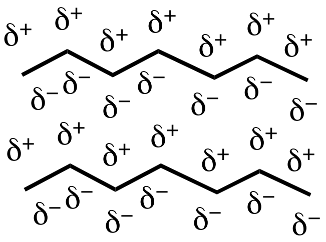
α=polarizaility of non-polar molecule
note: alkanes are quite polarizable, with many Csp^3-H bonds

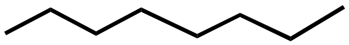
5. Dipole-Induced Dipole $E = -2\mu_1^2\alpha_2/(4\pi\varepsilon\varepsilon_o)^2r^6$



6. Induced Dipole-Induced Dipole $E \sim 1/r^6$

London forces, Van der Waals interactions: If there is a large enough surface area for two molecules to interact, these forces can become considerable





boiling point of octane =125°C, higher than H_2O!

Non-Covalent Interactions

Summary: Distance dependence (indicative of strength) of the energy of interaction for various binding forces

	Monopole	**Dipole**	**Induced Dipole**
Monopole	**$1/r$**	**$1/r^2$**	**$1/r^4$**
Dipole	**$1/r^2$**	**$1/r^3$**	**$1/r^6$**
Induced Dipole	**$1/r^4$**	**$1/r^6$**	**$1/r^6$**

Hydrophobic Effect

The Association of Organics in Water: "Oil and water don't mix"

Attempt to quantify this tendency: ΔG° transfer of a hydrocarbon from the gas phase to water. This number generally scales with the surface area of the hydrocarbon.

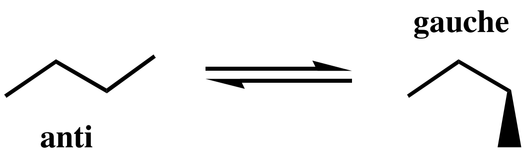
Hydrophobicity Constant π is defined for an R group based on its partitioning in octanol/water:

$$\pi = \log(P/P_o)$$

P_o = partitioning of an organic molecule with R between octanol and water
P = partitioning ofthe same structure without R between octanol and water

Hydrophobicity arises from the surface area of the group:

R	π	ΔG(kcal/mol)
CH_3	0.5	0.68
CH_2CH_3	1.0	1.36
$CH_2CH_2CH_3$	1.5	2.05
$CH(CH_3)_2$	1.3	1.77
CH_2Ph	2.63	3.59

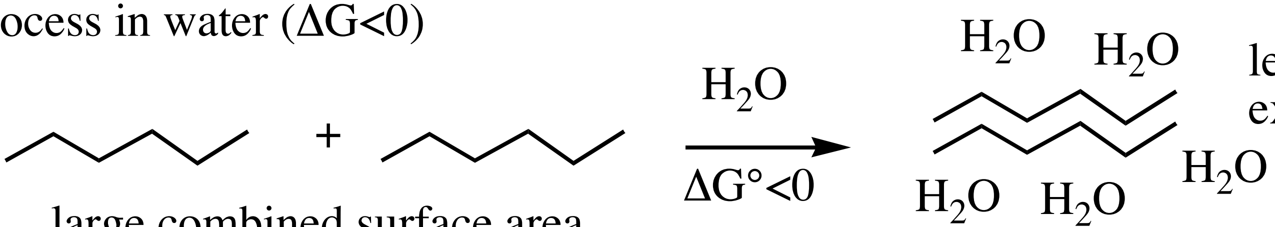


gauche form
minimizes
surface area

Gas Phase anti/gauche: 70/30
water anti/gauche: 55:45

Hydrophobic Effect: An Entropy Driven Process

Aggregation in water occurs because the exposed hydrocarbon surface area is minimized when two organics come together; aggregation is a spontaneous process in water (ΔG<0)



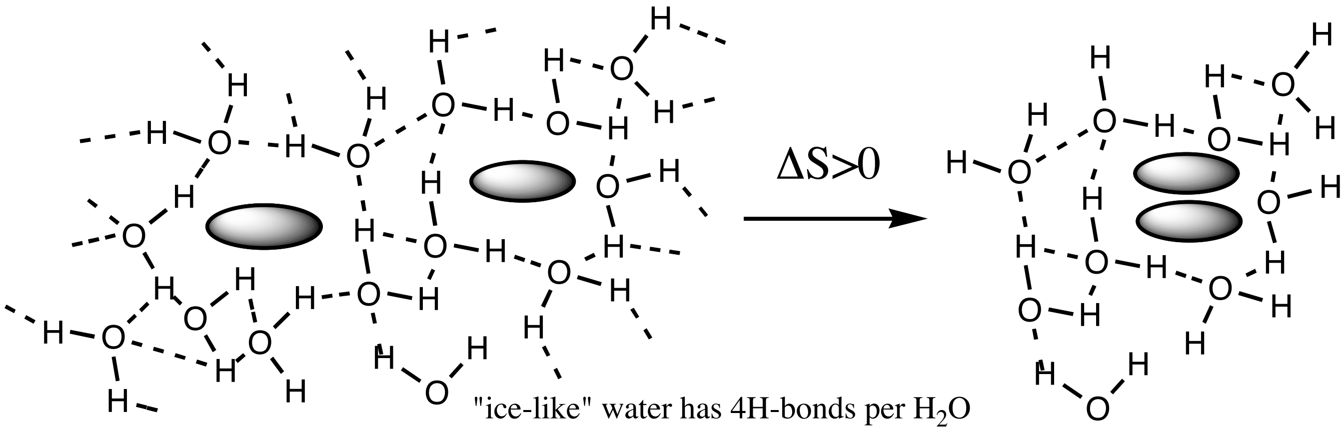
large combined surface area

less surface area exposed to water

Cohesive Energy of water- there is a strong penalty for creating a hole in water: break H_2O•••H_2O interactions, replaced with extremely weak H_2O•••hydrocarbon interactions.

ΔH (aggregation)~0, so ΔS (aggregation)>0

Water in contact with hydrocarbon becomes more ordered, "ice-like" to compensate for loss of H_2O•••H_2O interactions.



"ice-like" water has 4H-bonds per H_2O

less ice-like water

The release of ice-like water from around the organic molecule on dimerization leads to more normal water, with a concomitant entropy increase

Assessing the Strength of Non-Covalent Binding
The Binding Isotherm

Recall that $\Delta G° = -RT\ln K$, thus a determination of K will give ΔG

$$H + G \rightleftharpoons H{\bullet}G$$

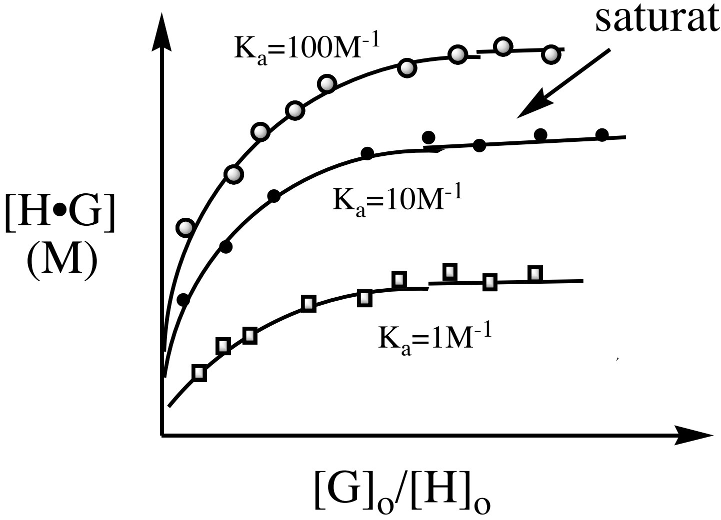
$K_a = [H{\bullet}G]/[H][G]$ $K_d = [H][G]/[H{\bullet}G]$ units: M^{-1}

H= Host
G=Guest
$H_o=[H{\bullet}G] + [H]$
$G_o=[H{\bullet}G] + [G]$

$$[H{\bullet}G] = [H]_o K_a[G]/1+K_a[G]$$

solve for K_a

Hold H constant, measure H•G as a function of free G in solution



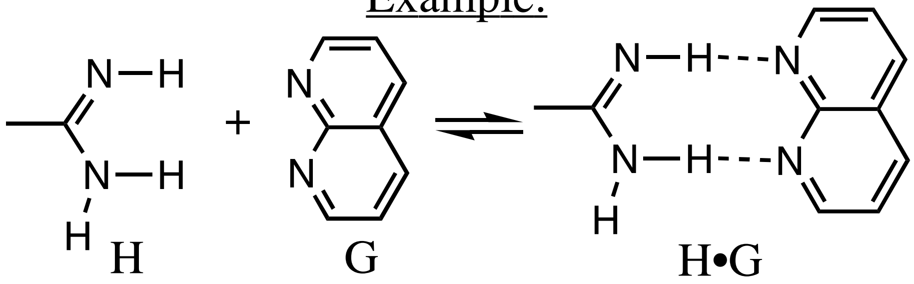
use best fit to the data to obtain K_a

saturation

at high concentrations of $[G]_o$, essentially all of [H] is converted to [H•G]

[H•G] usually obtained by UV-Vis or NMR methods

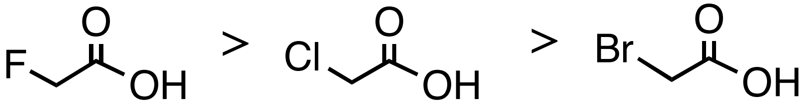
Example:



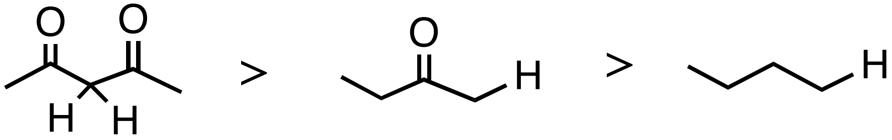
Factors Affecting Acidity

Stability of A^- $\quad$ $HA + H_2O \rightleftharpoons A^- + H_3O^+$

1. Electronegativity / Induction



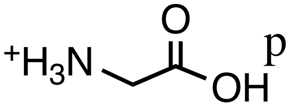
2. Resonance



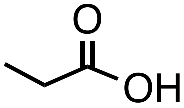
3. Bond Strength $\quad$ $H_2Te > H_2Se > H_2S > H_2O$;

$H{-}I > H{-}Br > H{-}Cl > H{-}F$

4. Electrostatic Effects



pKa=2.31 vs.

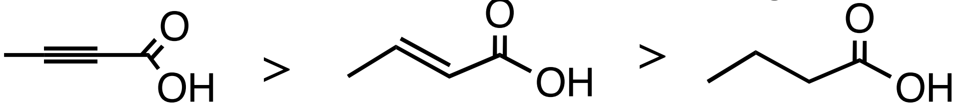


pKa=4.82

$Ph_3P^+CH_3$

pKa=22.4

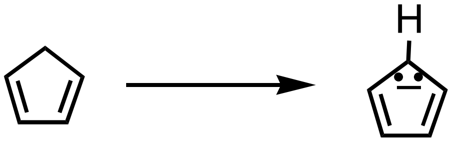
5. Hybridization



6. Solvation

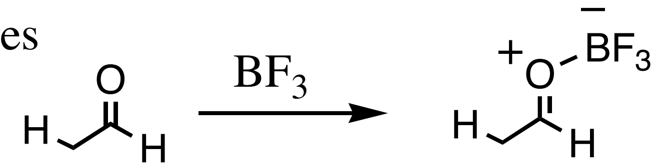
$H_3C{-}OH > CH_3CH_2{-}OH > (CH_3)_2CH{-}OH > (CH_3)_3C{-}OH$

7. Aromaticity



pKa=16

8. Cationic Structures



pKa=17 $\quad$ pKa=-7

A very
strong
acid:

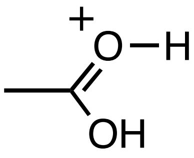


Table of pKa's

	pKa		pKa		pKa
$\mathrm{(CH_3)_3C\mathit{H}}$	71	$\mathrm{RO\mathit{H}}$	16-18	$\mathrm{H_2Te}$	3
$\mathrm{CH_3CH_3}$	50	cyclopentadiene	16	$\mathrm{NO_2CH_2NO_2}$	3.63
$\mathrm{C_6H_{12}}$	45	$\mathrm{CH_3COC\mathit{H}_2Cl}$	16	HF	3.18
$\mathrm{CH_2{=}C\mathit{H}_2}$	44	$\mathrm{CH_3COC\mathit{H}_2Cl_2}$	15	$\mathrm{HNO_2}$	3.29
$\mathrm{CH_2{=}CHC\mathit{H}_3}$	43	$\mathrm{RCO_2C\mathit{H}_2CO_2R}$	13	$\mathrm{H_3PO_4}$	2.12
$\mathrm{PhC\mathit{H}_3}$	41	$\mathrm{C\mathit{H}_2(CN)_2}$	11	$\mathrm{HO_2CCO_2H}$	1.27
$\mathrm{R_2N\mathit{H}}$	38-42	$\mathrm{C\mathit{H}_3NO_2}$	10	$\mathrm{Cl_3CCO_2H}$	0.64
Cycloheptatriene	39	$\mathrm{PhO\mathit{H}}$	10	$\mathrm{F_3CCO_2H}$	0.52
Benzene	37	$\mathrm{CH_3S\mathit{H}}$	10	piciric acid	0.4
$\mathrm{Ph_2C\mathit{H}_2}$	33	$\mathrm{(CH_3)_3N\mathit{H}^+}$	10	$\mathrm{C\mathit{H}(NO_2)_3}$	0.14
$\mathrm{CH_3SOC\mathit{H}_3}$	29	$\mathrm{CNC\mathit{H}_2CO_2R}$	9	$\mathrm{HNO_3}$	-1.44
$\mathrm{C\mathit{H}_3CN}$	25	$\mathrm{N\mathit{H}_4{}^+}$	9	$\mathrm{DMSO\text{-}H^+}$	-1.5
$\mathrm{CH_3CON\mathit{H}_2}$	25	$\mathrm{\mathit{H}CN}$	9	$\mathrm{H_3O^+}$	-1.74
$\mathrm{C\mathit{H}_3CO_2CH_3}$	25	$\mathrm{RCOC\mathit{H}_2COR}$	9	$\mathrm{THF\text{-}H^+}$	-2.08
acetylene	24	$\mathrm{H_2S}$	7	HCl	-6.1
$\mathrm{Ph_3P^+\text{-}C\mathit{H}_3}$	22	imidazole-$\mathrm{H^+}$	7	HBr	-8
$\mathrm{CH_3COC\mathit{H}_3}$	20	Pyridine-$\mathrm{H^+}$	5	HI	-9
$\mathrm{PhCC\mathit{H}}$	20	RCOOH	2.21-5.69	$\mathrm{H_2SO_4}$	-9
$\mathrm{C\mathit{H}_3COH}$	17	$\mathrm{H_2Se}$	4	$\mathrm{HClO_4}$	-10

Lewis Acids and Bases

	Bases	Acids
Hard	H_2O, HO^-, F^-, RCO_2^-, Cl^- ROH, RO^-, R_2O, NH_3, RNH_2 N_2H_4	H^+, Li^+, Na^+, K^+, Al^{3+}, Mg^{2+}, Ca^{2+}, BF_3, $B(OR)_3$, $Al(CH_3)_3$, $AlCl_3$, RCO^+
Moderate	$PhNH_2$, C_5H_5N, N_3^-, Br^-	Fe^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, $B(CH_3)_3$, R_3C^+ $C_6H_5^+$
Soft	R_2S, RSH, RS^-, I^-, SCN^-, R_3P, $(RO)_3P$, NC^-, C_2H_4, C_6H_6, R^-	Cu^+, Ag^+, Hg^+, Pd^{2+}, I_2, Br_2, carbenes, radicals

$$E_I = E_{core} + E_{ES} + E_{overlap}$$

electrostatic effects (E_{ES}) dominate the interaction of hard acids and bases
orbital overlap effects ($E_{overlap}$) dominate the interaction of soft acids and bases

Additional References

Hydrogen Bonding

1. *JACS*, 99, *1316* (1977)
2. *Acc. Chem. Res.* 20, *39,* (1987)
3. *J. Chem. Soc., Chem Commun., 1295* (1991)

π-Effects

1. *Chem. Rev.*, 97, *1303* (1997)
2. *Angew. Chem. Int. Ed.* 42, *1210* (2003)

Hydrophobic Effect

1. *Angew. Chem. Int. Ed.* 32,*1545* (1993)
2. *Acc. Chem. Res.* 23, *23,* (1990)

Solvent Scales

Reichardt, C (1979) *Solvent Effects in Organic Chemistry*, Verlag Chemie, Weinheim

Ion Pairing

1. Szwarc, M. (ed.) (1972) *Ions and Ion Pairs in Organic Reactions* Wiley, New York, Vol. 2 .
2. *Acc. Chem. Res.* 2, *87,* (1969)

Acid Dissociation Constants

***Acc. Chem. Res.* 21, *456, 463* (1988)**