

Strengths of Brønsted acids and bases

Do you know the right answers to questions like:

- What base to use for a base-initiated reaction?
- What acid to use to remove a protecting group?
- Conditions to generate reactive carbanion intermediate?

How?

- pK_a values of common structures (all standard pK_a s are referenced to water!)
- The ability to predict relative acid or base strength!

Predicting relative acidities

Guiding principles for predicting relative acidities

- When the acids being compared are **neutral (HA)** and create negative conjugate bases (A^-), it is most convenient to predict the relative acidities by examining the relative stabilities of the anionic conjugate bases. The acid with the **most stable conjugate base A^-** will be **the strongest acid**.
- When the acids being compared are **cationic (HA^+)** and create neutral conjugate bases (A), it is most convenient to predict the relative acidities by examining the relative stabilities of the acids themselves. The **acid HA^+ that is the most stable** will be **the weakest acid**.

Predicting relative acidities

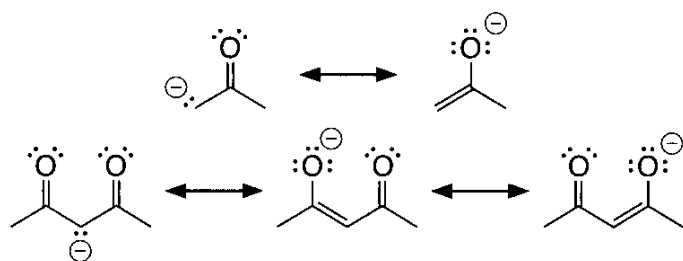
Important factors related to acidity

- Electronegativity effect
- Inductive effects
- Electrostatic effects
- Resonance
- Aromaticity/antiaromaticity
- Solvation
- Hybridization effects
- Polarizability
- Bond strengths
- Steric effects

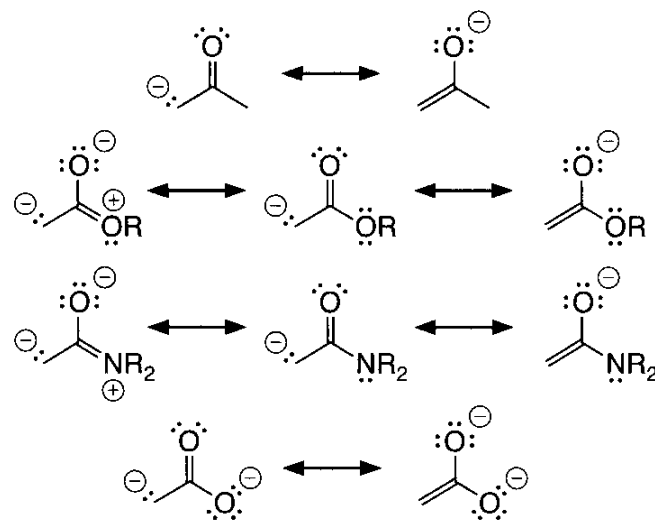
Electronegativity and Induction

Compound	pK _a	Compound	pK _a
A. Carbonyl derivatives		F. Phenyl stabilization	
CH ₃ COCH ₃	20.0	PhCH ₃	41.2
CH ₃ COCH ₂ Cl	16.0	Ph ₂ CH ₂	33.0
CH ₃ COCHCl ₂	14.9	Ph ₃ CH	31.5
CH ₃ COCH ₂ COCH ₃	8.84	G. Ylides and electrostatic effects	
CH ₃ CONH ₂	25	PH ₃ P ⁺ -CH ₃	22.4
2-Acetylcyclopentanone	8	(CH ₃) ₃ P ⁺ CH ₂ Ph	17.4
1-Ethylcarboxy-2-oxocyclopentane	10.5	(CH ₃) ₃ N ⁺ CH ₂ Ph	31.9
CF ₃ COCH ₂ COCF ₃	5.35	(CH ₃) ₃ As ⁺ CH ₂ Ph	22.3
CH ₃ CH ₂ O ₂ CCH ₂ CO ₂ CH ₂ CH ₃	13.3	(CH ₃) ₂ S ⁺ -CH ₂ COPh	8.3
NCCH ₂ CO ₂ CH ₂ CH ₃	9	Thiamin	17.6
CH ₃ CO ₂ ⁻	24	H. Hybridization effects	
B. Nitro derivatives		Ethane	50
CH ₃ NO ₂	10.2	Ethylene	44
NO ₂ CH ₂ NO ₂	3.63	Benzene	37
CH(NO ₂) ₃	0.14	Acetylene	24
C. Cyano derivatives		Phenylacetylene	19.9
CH ₃ CN	25.0	I. Aromaticity effects	
CH ₂ (CN) ₂	11.2	Cyclopentadiene	16.0
CH(CN) ₃	5.13	Cycloheptatriene	38.8
HCN	9.21	1,2,3-Triphenylcyclopropene	50
D. Sulfones and sulfoxides		J. Alkyl groups	
CH ₃ SOCH ₃	28.5	Cyclohexane	45
EtSO ₂ CH(CH ₃)SO ₂ Et	14.6	(CH ₃) ₃ CH	71
E. Cyclopentadienes		CH ₂ =CHCH ₃	43
Cyclopentadiene	16.0		
1-Cyanocyclopentadiene	9.78		
2,5-Dicyanocyclopentadiene	2.52		
Indene	20.2		
Fluorene	22.7		
9-Phenylfluorene	18.5		

Resonance related to acidity



Resonance structures for enolates



Resonance structures for enolates

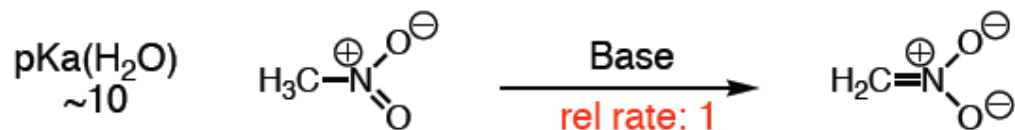
Other factors related to acidity

- Bond strengths
- Electrostatic effects
- Hybridization
- Aromaticity
- Solvation
- Cationic Organic Structure

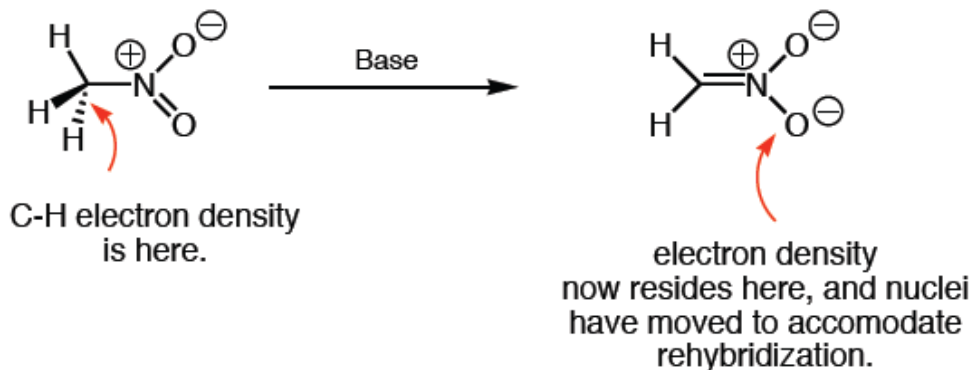
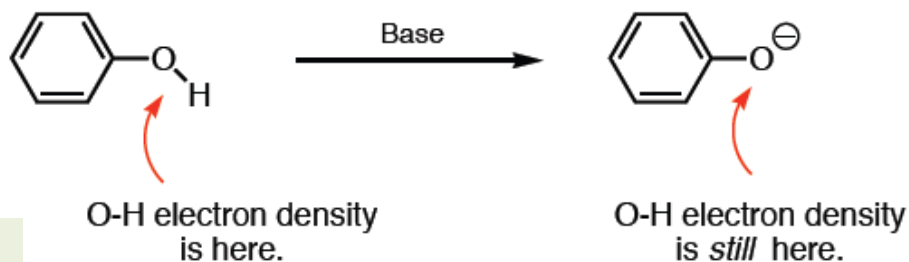
pKa values of cationic heteroatom acids

Compound	pK _{a1}	pK _{a2}	pK _{a3}
<i>A. Various effects on N acids (resonance, hybridization, sterics, and induction)</i>			
Guanidinium	13.5		
1,8-Bis(dimethylamino)naphthalene- H^+	12.37		
CH ₃ NH ₃ ⁺	10.6		
Imidazole- H^+	7.1		
Purine- H^+	2.39		
Pyridine- H^+	5.23		
Aniline- H^+	4.87		
Piperidine- H^+	11.1		
Pyrimidine- H^+	0.65		
Adenine	4.17	9.75	
Cytidine	4.08	12.24	
Guanine	3.3	9.2	12.3
NH ₄ ⁺	9.24		
CH ₃ NH ₃ ⁺	10.6		
(CH ₃) ₂ NH ₂ ⁺	10.8		
(CH ₃) ₃ NH ⁺	9.80		
RC≡NH ⁺	-12		
<i>B. Protonated cationic oxygen</i>			
RCO(H^+)X (X = H, R, OH, OR)	-2 to -8		
RCO(H^+)NR ₂	0 to -4		
PhOH ₂ ⁺	-7		
THF- H^+	-2.08		
H ₃ O ⁺	-1.74		
DMSO- H^+	-1.5		
NH ₂ CO(H^+)NH ₂	0.10		
PhO(H^+)CH ₃	-6.54		
CH ₃ CO(H^+)CH ₃	-7.5		
FCH ₂ CO(H^+)CH ₃	-10.8		
F ₃ CCO(H^+)CH ₃	-14.9		
RNO ₂ H ⁺	-12		

Kinetic Acidity



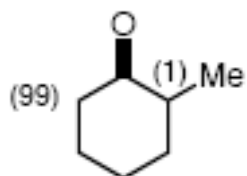
Why???



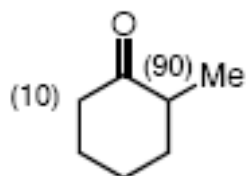
Carbon acids are stabilized by resonance. Significant structural reorganization must accompany deprotonation.

The greater the structural reorganization during deprotonation, the lower the kinetic acidity.

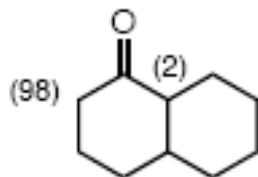
Comparison on kinetic and equilibrium ratios of enolates



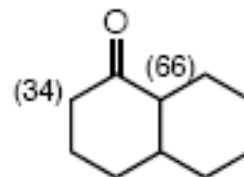
Kinetic Ratios



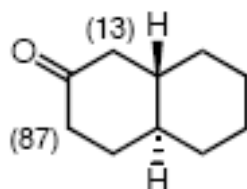
Equilibrium Ratios



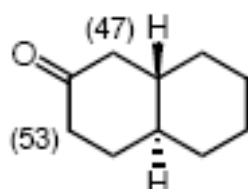
Kinetic Ratios



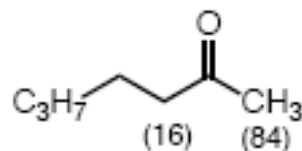
Equilibrium Ratios



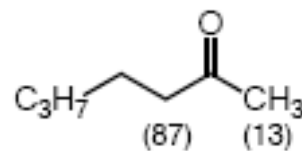
Kinetic Ratios



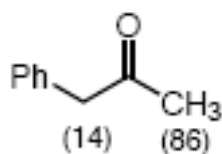
Equilibrium Ratios



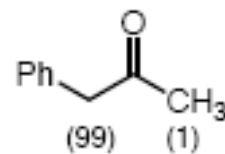
Kinetic Ratios



Equilibrium Ratios



Kinetic Ratios

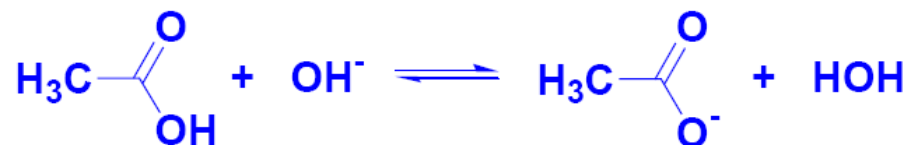
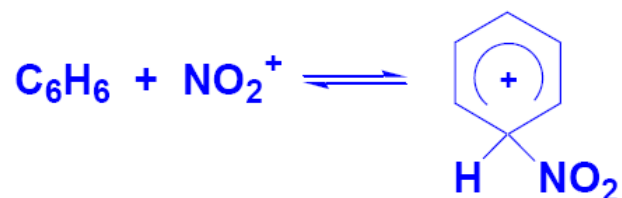
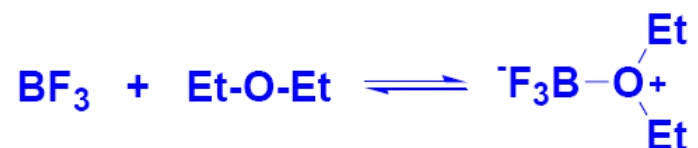


Equilibrium Ratios

Lewis acids/bases & electrophiles/nucleophiles

- Lewis acid: electron pair acceptor (electrophile)
- Lewis base: electron pair donor(nucleophile)
- Lewis acid/base terms --- thermodynamic discussions
- Electrophile/nucleophile --- reactivity and kinetics

Lewis acid-base reactions



Characteristics of Hard and soft acids and bases

1. *Hard acids* are characterized by small acceptor atoms that have outer electron not easily excited and that bear considerable positive charge.
2. *Soft acids* have acceptor atoms of lower, positive charge, large size, and with easily excited outer electrons.
3. *Hard bases* contain highly electronegative donor atoms of low polarizability, are typically difficult to oxidize, and have no empty low-energy orbitals available.
4. *Soft bases* are polarizable, have less electronegative donor atoms, and have empty orbitals of low energy and electron that are more easily removed by oxidizing agents.

Classification of Lewis Acids

Class (a)/Hard	Class (b)/Soft
H^+ , Li^+ , Na^+ , K^+ Be^{2+} , Mg^{2+} , Ca^{2+} , Sr^{2+} , Sn^{2+} Al^{3+} , Se^{3+} , Ga^{3+} , In^{3+} , La^{3+} Cr^{3+} , Co^{3+} , Fe^{3+} , As^{3+} , Ir^{3+} Si^{4+} , Ti^{4+} , Zr^{4+} , Th^{4+} , Pu^{4+} , VO^{2+} UO_2^{2+} , $(CH_3)_2Sn^{2+}$ $BeMe_2$, BF_3 , BCl_3 , $B(OR)_3$ $Al(CH_3)_3$, $Ga(CH_3)_3$, $In(CH_3)_3$ RPO_2^+ , $ROPO_2^+$ RSO_2^+ , $ROSO_2^+$, SO_3 I^{7+} , I^{5+} , Cl^{7+} R_3C^+ , RCO^+ , CO_2 , NC^+	Cu^+ , Ag^+ , Au^+ , Tl^+ , Hg^+ , Cs^+ Pd^{2+} , Cd^{2+} , Pt^{2+} , Hg^{2+} CH_3Hg^+ Tl^{3+} , $Tl(CH_3)_3$, RH_3 RS^+ , RSe^+ , RTe^+ I^+ , Br^+ , HO^+ , RO^+ I_2 , Br_2 , INC , etc. Trinitrobenzene, etc. Chloranil, quinones, etc. Tetracyanoethylene, etc. O , Cl , Br , I , R_3C M^0 (metal atoms) Bulk metals
<i>HX (hydrogen-bonding molecules)</i> <i>Borderline</i> Fe^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , Zn^{2+} , Pb^{2+} $B(CH_3)_3$, SO_2 , NO^+	

Classification of Bases

Hard

H_2O , OH^- , F^-
 CH_3CO_2^- , PO_4^{3-} , SO_4^{2-}
 Cl^- , CO_3^{2-} , ClO_4^- , NO_3^-
 ROH , RO^- , R_2O
 NH_3 , RNH_2 , N_2H_4

Soft

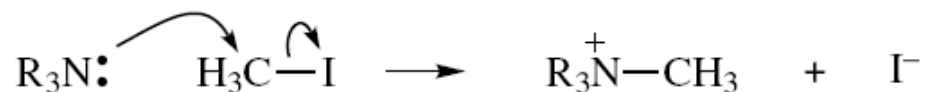
R_2S , RSH , RS^-
 I^- , SCN^- , $\text{S}_2\text{O}_3^{2-}$
 R_3P , R_3As , $(\text{RO})_3\text{P}$
 CN^- , RNC , CO
 C_2H_4 , C_6H_6
 H^- , R^-

Borderline

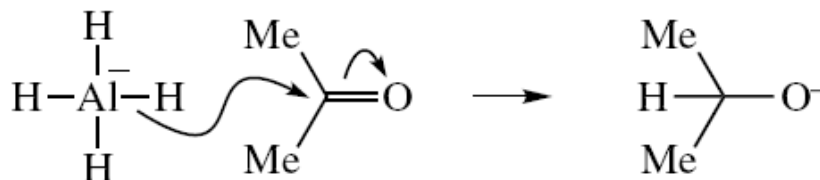
$\text{C}_6\text{H}_5\text{NH}_2$, $\text{C}_5\text{H}_5\text{N}$, N_3^- , Br^- , NO_2^- , SO_3^{2-} , N_2

Nucleophiles

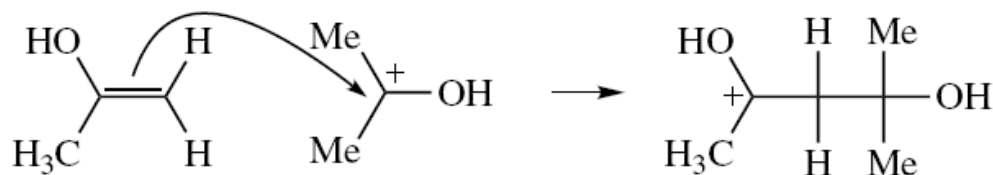
- Lone-pair nucleophiles:** alcohols (ROH), alkoxides (RO^-), amines (R_3N), metal amides (R_2N^-), halides (X^-), thiols (RSH), sulfides (R_2S), phosphines (R_3P)



- δ -Bond nucleophiles:** the bond between a nonmetal and a metal: NaNH_2 , KOH ; RMgBr , RLi , R_2CuLi ; NaBH_4 , LiAlH_4



- π -Bond nucleophiles:** π -Bonds directly attached to heteroatoms such as in enolates ($\text{C}=\text{C}-\text{O}^-$), enols ($\text{C}=\text{C}-\text{OH}$), enol ethers ($\text{C}=\text{C}-\text{OR}$) and enamines ($\text{C}=\text{C}-\text{NR}_2$)



Nucleophilicity and basicity

- **Nucleophilicity** of a compound is measured by determining how reactive it is toward CH_3Br in water at 25°C ; **Basicity** measures reactivity toward H^+
- **Nucleophilicity** is a kinetic property, whereas **basicity** is a thermodynamic property
- Increases in basicity generally parallel increases in nucleophilicity, except in the following ways:
 1. Going down the periodic table, nucleophilicity increases while basicity decreases
 2. Nucleophilicity decreases dramatically with increased crowding around the nucleophilic atom, while basicity increases slightly
 3. Delocalization of charge decreases basicity a lot and nucleophilicity somewhat.
 4. The absence of hydrogen-bonding in polar aprotic solvents (DMSO, HMPA, DMF, DMA, NMP, DMPU) increases both the basicity and nucleophilicity of anions, but nucleophilicity increases more.

Widely used nonnucleophilic bases: t-BuOK , $\text{LiN}(\text{i-Pr})_2$ (LDA), $\text{LiN}(\text{SiMe}_3)_2$ (LiHMDS), $\text{KN}(\text{SiMe}_3)_3$ (KHMDS), NaH , KH , $\text{EtN}(\text{i-Pr})_2$

Hard and soft acids and bases

- hard reactants --- non-polarizable
- soft reactants --- polarizable
- Principle of hard and soft acids and bases:
interactions are most facile between hard acids and hard bases and between soft acids and soft bases

