

Terms and Terminologies in Mechanistic Organic Chemistry

Key words: Acids, bases, nucleophiles, electrophiles,
Hardness-Softness (HSAB) concepts

Introduction

In this module, some very basic terms and terminologies are described. Historical perspectives and origin of some of the concepts are presented. Concepts such as electrophiles, nucleophiles, hardness and softness etc., are discussed.

These concepts are of high significance to the following modules under reaction Mechanisms.



The term *acid* was first used in the seventeenth century.

- It comes from the Latin root *ac*, meaning sharp, as in *acetum* i.e. vinegar.

Acids have long been recognized as a distinctive class of compounds whose **aqueous solutions** exhibit the following properties.

- a characteristic **sour** taste
- ability to change the color of **litmus** from **blue** to **red**
- **react with certain metals** to produce gaseous H_2
- **react with bases** to form a salt and water.

First definition of *acid* was given by Antoine Lavoisier, in 1787.

- According to his definition, *acids* are substances containing **common element** which gives that compound the acidic nature.
- And he postulated that element to be **oxygen**.



In 1811, Humphrey Davy showed that muriatic acid (HCl) does not contain oxygen.

- By 1830, dozens of oxygen free acids had been discovered.
- But it was only after 1840, the **hydrogen theory** of acid became generally accepted.

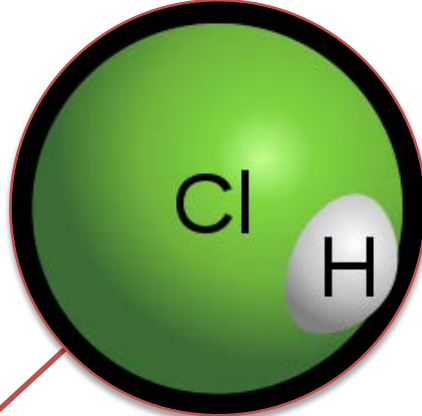
In 1890, the Swedish chemist Svante Arrhenius formulated the first important theory of acids.

- According to his theory, *acid* is a substance containing hydrogen atom that can dissociate or ionize when dissolved in water, producing hydrated hydrogen ion and an anion.

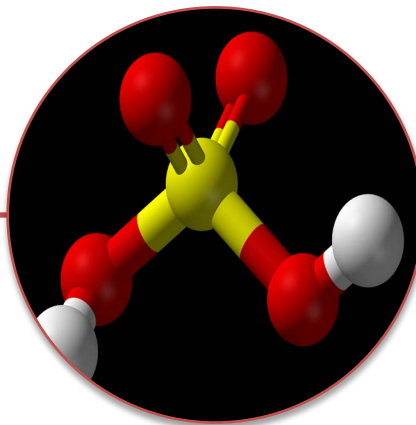
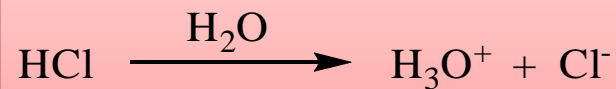
However, there are substances which do not contain H, but still yield H^+ ions when dissolved in water.

- Hence, definition of *acid* was modified to “a substance that yields an excess of hydrogen ions when dissolved in water.”

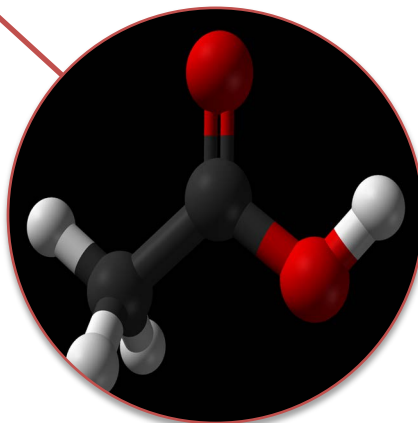
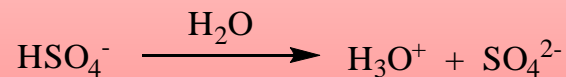
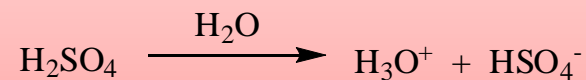
HCl



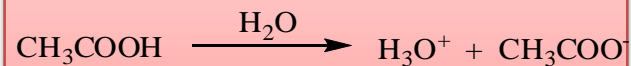
- HCl is a strong acid, it dissociates completely in water.



- H₂SO₄ is a polyprotic acid, it dissociates completely in water in two stages.



- Acetic acid is a weak acid, it does not dissociate completely in water.



'Base', as defined by Arrhenius, is substance that yields excess of OH^- ions when dissolved in water.

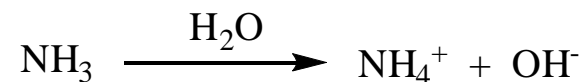
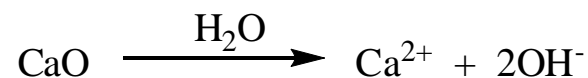
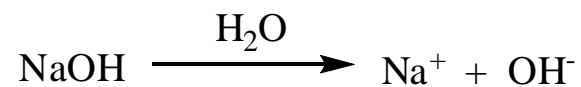
- The word **alkali** is synonymous with base. It is of Arabic origin, but the root word comes from the same Latin kalium i.e., potash
- Alkali more specifically used for those containing **OH^- ions**.



The name *base* has long been associated with a class of compounds whose **aqueous solutions** are characterized by

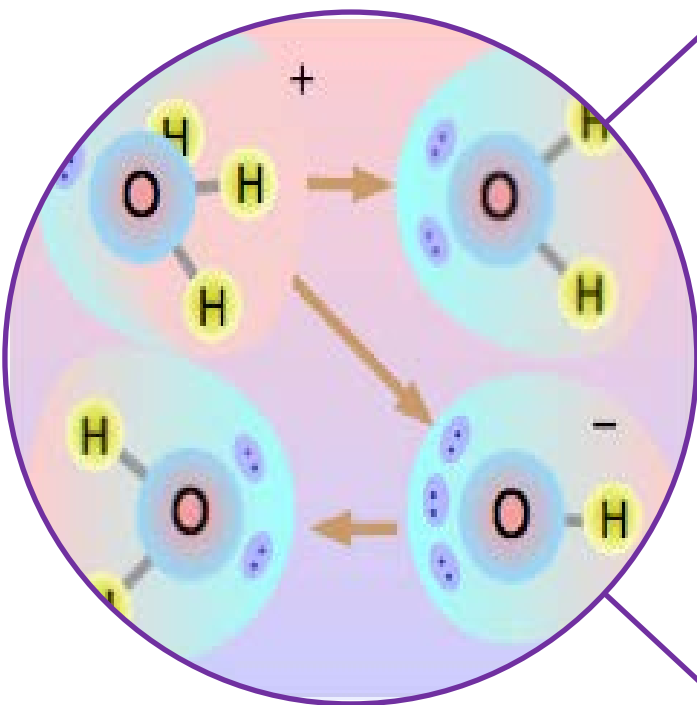
- a **bitter** taste
- a **soapy** feeling when applied to the skin
- ability to **restore the original blue color of litmus** that has been turned red by acids
- ability to **react with acids** to form salts.

NaOH , KOH , oxides of certain metal and hydrogen compound of certain nonmetals are classified as Arrhenius *bases*.



Although Arrhenius gave useful definition of acid and base, he could not justify nature of certain substances.

- *acidic* nature of FeCl_3
- *basic* nature of NH_3 , Na_2S

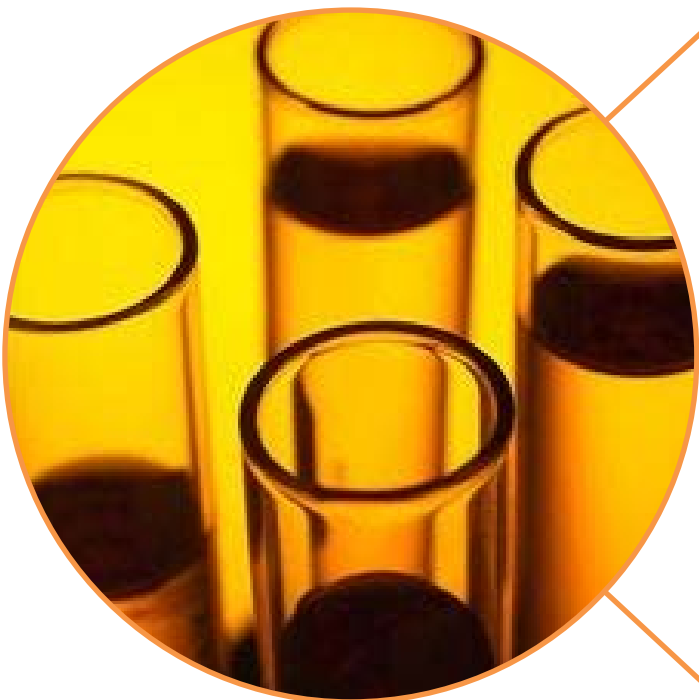


In 1923, a theory that is both simple and more general was proposed by two chemists.

- Danish chemist [J.N. Bronsted](#) and English Chemist [T.M.Lowry](#), put forward, independently, the **proton donor-acceptor concept**.

According to this concept, *acid* is a **proton donor** whereas *base* is a **proton acceptor**.

- Definition makes **no reference to the environment** in which proton transfer takes place, so that it applies to **all kinds of reaction**.



Reaction between acid and base is thus a **proton exchange reaction**.

- If the *acid* is denoted by **AH** and the *base* by **B**, then we can write a generalized acid-base reaction as



In this reaction, the **protonated base** formed is capable of losing H^+ ions in the solvent.

- It gives rise to a very important concept of **conjugate acid-base pair**.

- Conjugate pair **differ** by one proton.

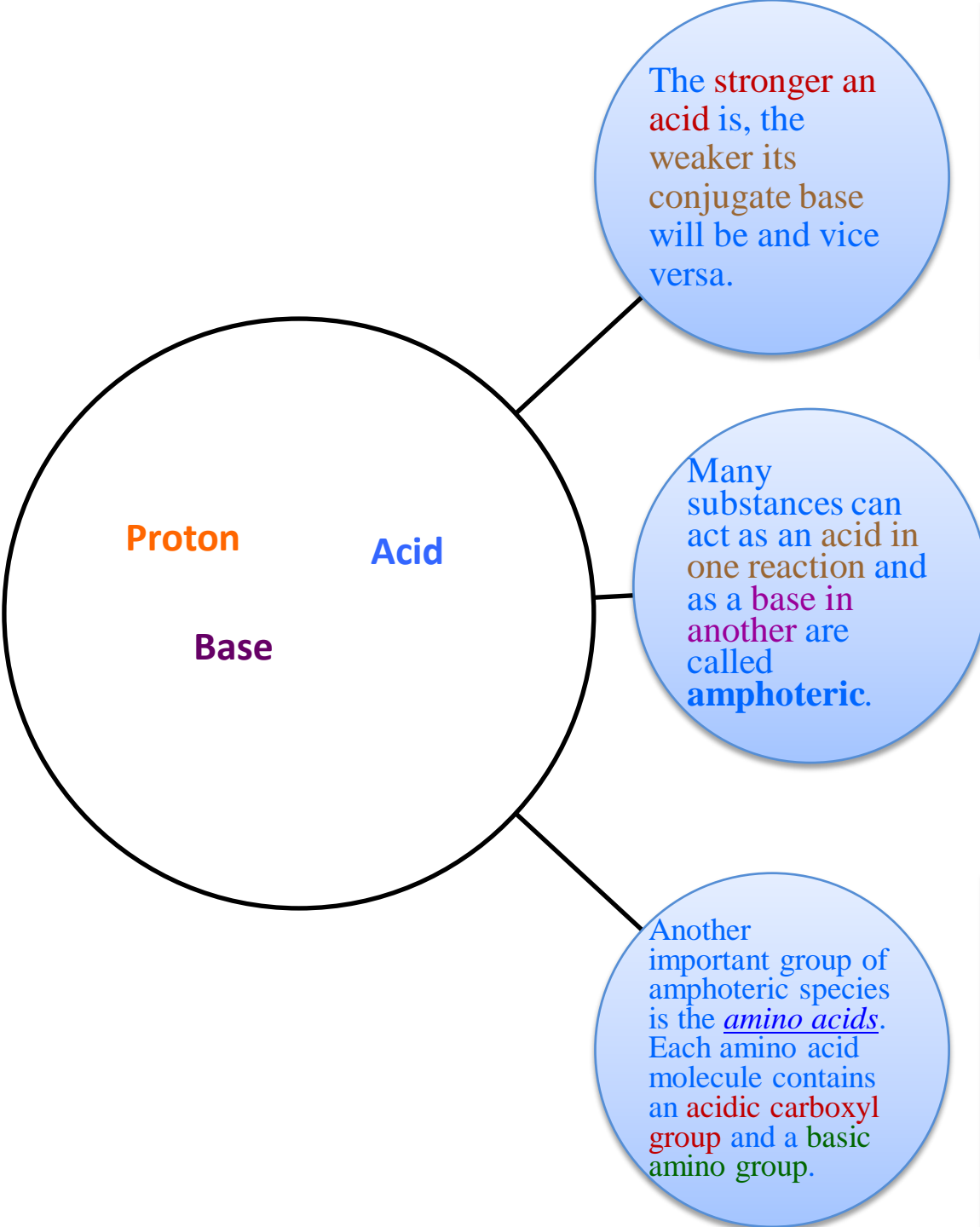
- Conjugate acid and base are in **equilibrium** in solution.



Thus, the **protonated base** is another potential acid and anion of first acid is another potential base.

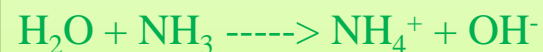
Some common conjugate acid-base pairs

Substance	Acid	Conjugate base
Hydrochloric acid	HCl	Cl^-
Acetic acid	CH_3COOH	CH_3COO^-
Nitric acid	HNO_3	NO_3^-
Ammonium chloride	NH_4^+	NH_3
Water	H_2O	OH^-
Hydronium ion	H_3O^+	H_2O

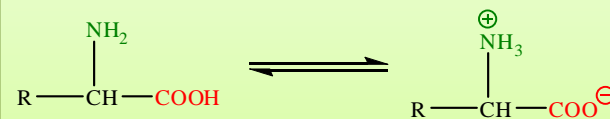


- Table showing examples of strong and weak conjugate acid base pairs.

- For example *water* is a Bronsted-Lowry base in its reaction with HCl and an acid in its reaction with NH₃.



- In fact the amino acids usually exist in zwitterion form, where the proton has transferred from the carboxyl to the amino group.





The Bronsted-Lowry theory is more general than any that preceded it.

- But still it fails to explain reactions between substances that show similar features but **no protons are transferred** in the reaction.

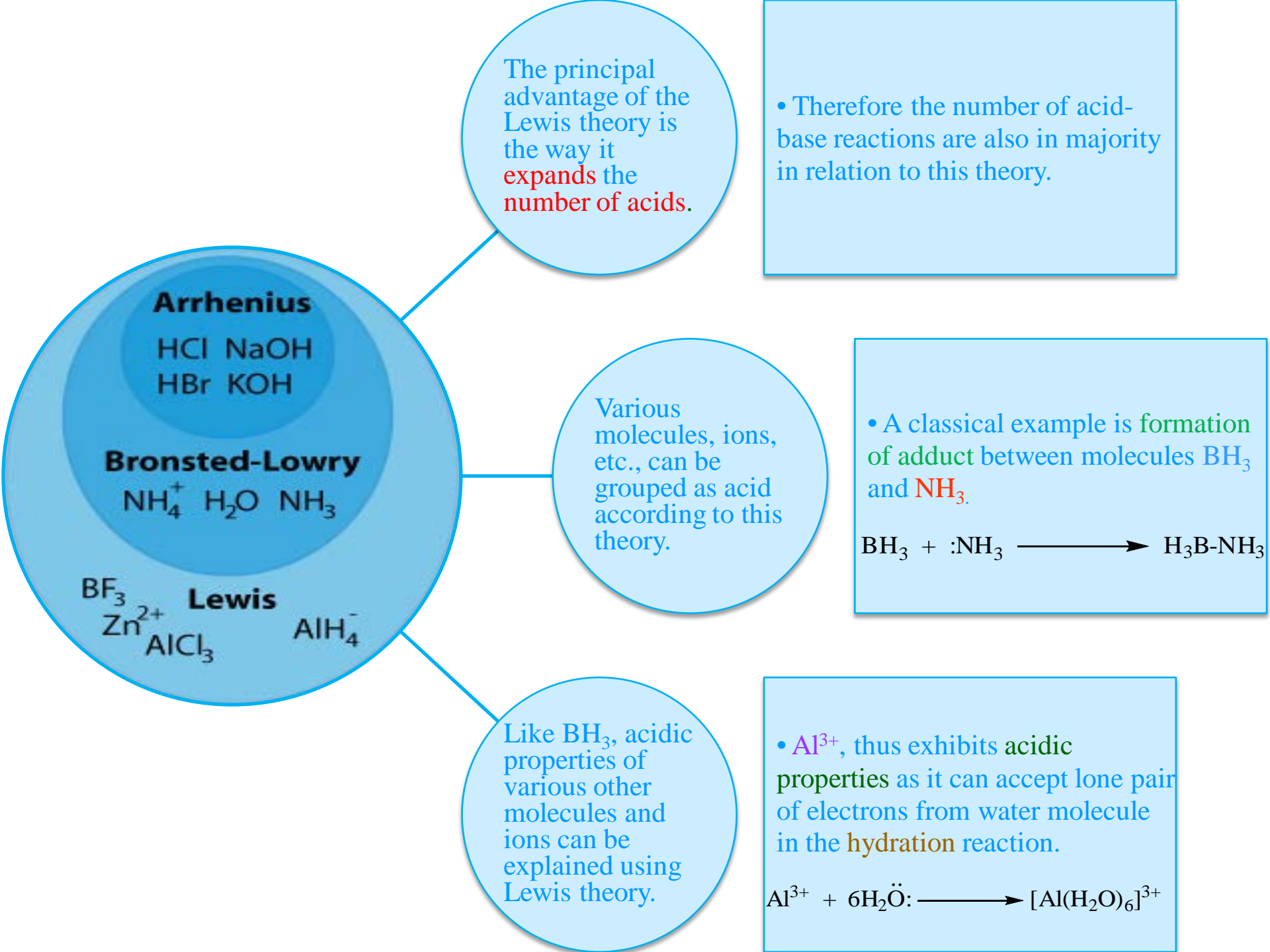
This deficiency was overcome by more general concept proposed by American chemist, **G N Lewis** in 1923.

- According to this concept, *acid* is an electron pair acceptor while *base* is an electron pair donor.

The acid-base reaction is **sharing of electrons** between the two.

- If *acid* is denoted by **A** and *base* by **B:**, then acid-base reaction between them is **formation of adduct A-B**.







The Lewis acid-base theory can also be used to explain why nonmetal oxides such as CO_2 dissolve in water to form acids.

- In the course of the reaction, water molecule acts as a base donating a pair of electrons to carbon in CO_2 molecule.



The **proton** (H^+) is one of the strongest but also one of the most complicated Lewis acids.

- Ignoring the fact that H^+ is solvated, acid-base reactions of H^+ can be viewed as formation of adduct.



Nearly all compounds of transition metals can be viewed as a collections of the Lewis bases.

- Many Lewis bases are **multidentate**, i.e., they can form several bonds to the Lewis acid. These multidentate Lewis bases are called chelating agents.

Molecular orbital interpretation

The acid-base nomenclature can create confusion with Bronsted nomenclature.

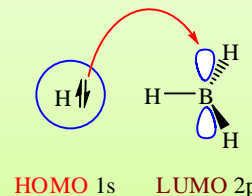
• Reactions like,
 $\text{FeCl}_3 + \text{Cl}^- \longrightarrow \text{FeCl}_4^-$
are a little confusing viewed as the acid (FeCl_3) being a species lacking an octet, (Fe^{3+}) is a neutral species.

The reactions can be viewed as involving the **interaction of molecular orbitals** on the base and the acid.

- a filled atomic or molecular orbital on the *base*
- an empty atomic or molecular orbital on the *acid*

The filled orbital would be the **highest energy occupied molecular orbital**, the **HOMO**, and the empty orbital will be the **lowest energy unoccupied molecular orbital**, the **LUMO**.

• Then we refer to the reaction simply as a **filled-empty interaction** or a **HOMO-LUMO interaction**.



ARRHENIUS THEORY

Substance that yields H^+ (H_3O^+) in solution is an **ACID**.

Substance that yields OH^- in solution is a **BASE**.



is actually

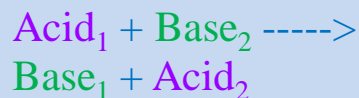


ACID	BASE
Hydrogen halides : HCl, HBr, HI	NaOH, KOH, LiOH
Halogen oxyacids : HClO, HClO ₂ , HClO ₃ , HClO ₄	Ba(OH) ₂ , Ca(OH) ₂ , Mg(OH) ₂
H ₂ SO ₄ , HSO ₃ F	Al(OH) ₃
HNO ₃ , H ₃ PO ₄	
Acetic acid, Benzenesulfonic acid, PTSA	
Oxalic acid	

BRONSTED-LOWRY THEORY

ACID is a proton donor.

BASE is a proton acceptor.



These are called
*conjugate acid-base
pairs.*

LEWIS THEORY

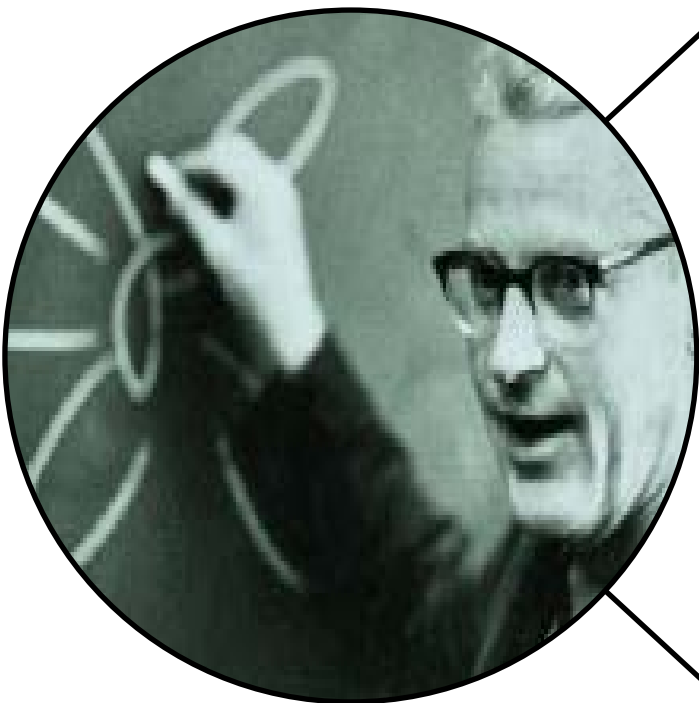
ACID is an electron pair acceptor.

BASE is an electron pair donor.



Acid: species *lacking an
octet*: BH_3 , CH_3^+ , etc.

Base: species with an
*unshared pair of
electrons*: H_2O , NH_3 , H^- ,
 Cl^- , etc.



In 1965, [Ralph Pearson](#) attempted to explain the differential affinity of *Lewis bases* towards *Lewis acids*.

- He introduced the *hard and soft acid-base* (HSAB) principle.
- He classified Lewis acids and bases as **hard**, **borderline** or soft.

According to him, *hard acids* prefer to coordinate to *hard bases* and soft acids to soft bases.

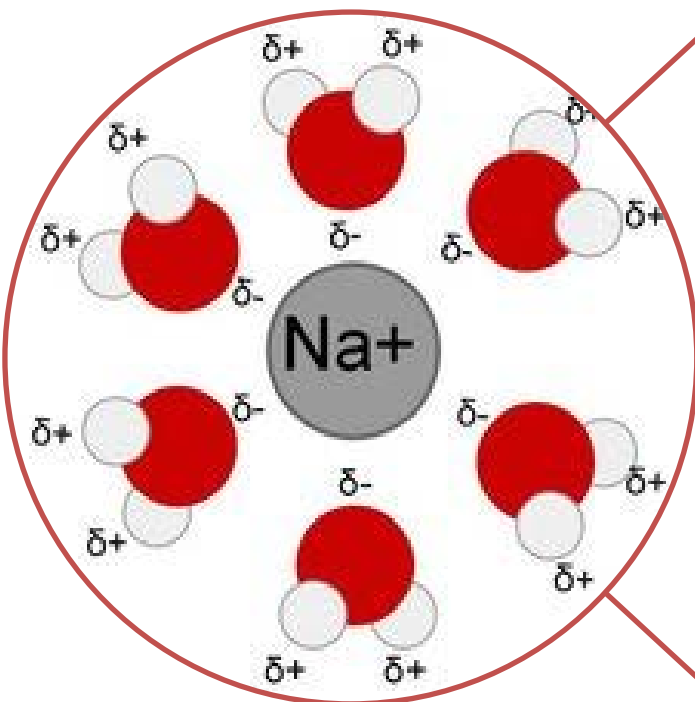
- This statement is neither an explanation or a theory. It is simply a guideline that helps one to qualitatively predict the **relative stability** of acid-base adducts.

Ralph G Pearson, [JACS](#), **85**, 3533(1963)

- The adjectives hard and soft doesn't mean strong and weak.
- Classification in the original work was mostly based on **equilibrium constants** for reaction of two Lewis bases competing for a Lewis acid.

In 1968, G. Klopman quantified Pearson's HSAB principle using *frontier molecular orbital theory*.

- Hard acids bind to hard bases to give **charge controlled ionic complexes**.
- Soft acids bind to soft bases to give FMO controlled covalent complexes.

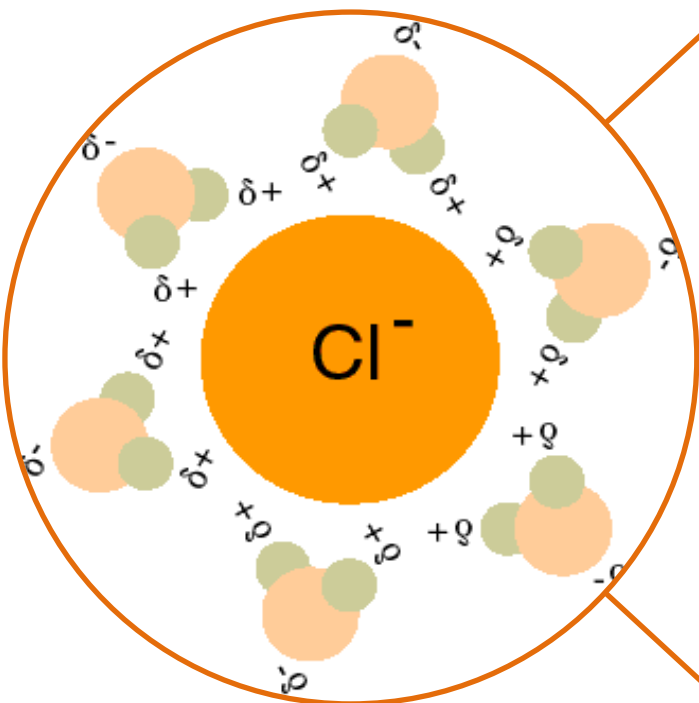


In 1983, the **qualitative** definition of HSAB was **converted to a quantitative** one by using the idea of **polarizability**.

- A **less polarizable** atom or ion is **hard**.
- A **more easily polarized** atom or ion is **soft**.

With these modifications, *hard acid* is supposed to be associated with **properties** such as

- **High positive charge**
- **Small size**
- **Not easily polarizable**
- **High energy LUMO**
- **No electron pairs in their valence shells**
- **Low electron affinity**
- **Strongly solvated**



On the other hand *soft acids* have *properties* such as

- Low or partial positive charge
- Large size
- Easily oxidized
- Highly polarizable
- Low energy LUMO and large LUMO coefficients
- Electron pairs in their valence shells

Hard bases have *properties* such as

- Low polarizability
- High electronegativity
- Not easily oxidized
- Low energy HOMO
- Highly solvated

Soft bases have *properties* as

- High polarizability
- Diffuse donor orbital
- Low electronegativity
- Easily oxidized
- High energy HOMO and large HOMO coefficients

Characteristic Properties of Hard and Soft acids and bases

Properties	Hard Acids	Soft Acids	Soft Bases	Hard Bases
Electronegativity	0.7 – 1.6	1.9 – 2.5	2.1 – 3.0	3.4 – 4.0
Ionic radius (pm)	< 90	> 90	> 170	~ 120
Ionic charges	$\geq +3$	$\leq +2$		

Borderline species have intermediate properties. It is not necessary for species to possess all properties.

HARD

H^+ , Na^+ , K^+ , Li^+

Bi^{2+} , Mg^{2+} , Ca^{2+} , Mn^{2+} , Sr^{2+}

Al^{3+} , Se^{3+} , Ga^{3+} , Gd^{3+} , In^{3+} ,
 La^{3+}

Cr^{3+} , Co^{3+} , Fe^{3+} , As^{3+} , Ir^{3+}

Si^{4+} , Ti^{4+} , Zr^{4+} , Tb^{4+} , Pu^{4+} ,
 VO^{2+}

UO_2^{2+} , $(\text{CH}_3)_2\text{Sn}^{2+}$

BeMe_2 , BF_3 , BCl_3 , B(OR)_3

$\text{Al}(\text{CH}_3)_3$, $\text{Ga}(\text{CH}_3)_3$,
 $\text{In}(\text{CH}_3)_3$

RPO_2^+ , ROPO_2^+

RSO_2^+ , ROSO_2^+ , SO_3

I^{7+} , I^{5+} , Cl^{7+}

R_3C^+ , RCO^+ , CO_2 , NC^+

HX (Hydrogen bonding
molecules)

BORDERLINE

Fe^{2+} , Co^{2+} , Ni^{2+} , Sn^{2+} ,
 Ru^{2+} , Rh^{3+} , Cu^{2+} , Zn^{2+} ,
 Pb^{2+} , $\text{B}(\text{CH}_3)_3$, SO_2 ,
 NO^+ , C_6H_5^+

SOFT

Cu^+ , Ag^+ , Au^+ , Tl^+ , Hg^+ , Cs^+ ,
 Co^+

Pd^{2+} , Cd^{2+} , Pt^{2+} , Hg^{2+}

CH_3Hg^+

Ti^{3+} , $\text{Ti}(\text{CH}_3)_3$, RH_3 , InCl_3

RS^+ , RSe^+ , RTe^+ , BH_3

I^+ , Br^+ , HO^+ , RO^+

I_2 , Br_2 , INC , etc.

Trinitrochlorobenzene, etc.

Chloranil, Quinones, etc.

Tetracyanoethylene

Carbenes

M^0 (Metal atoms)

Bulk Metals

ACID

HARD

H_2O , HO^- , 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

BORDERLINE

Aniline, Pyridine, N_3^- ,
 Br^- , NO_2^- , SO_3^{2-} , N_2

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

Ethylene, Benzene

H^- , R^-

BASE



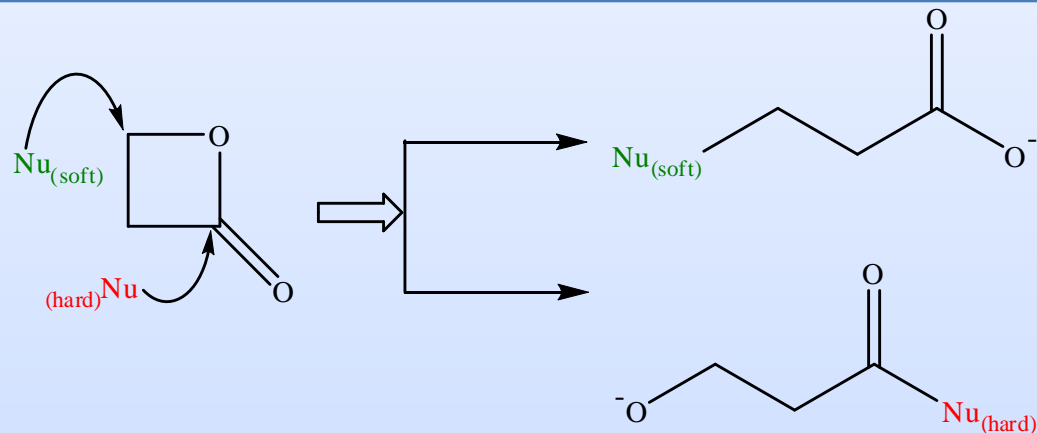
The HSAB Principle for Organic and Main Group Chemists

For our purposes main group and organic reaction chemistry the Pearson approach is very successful when comparing pairs of species:

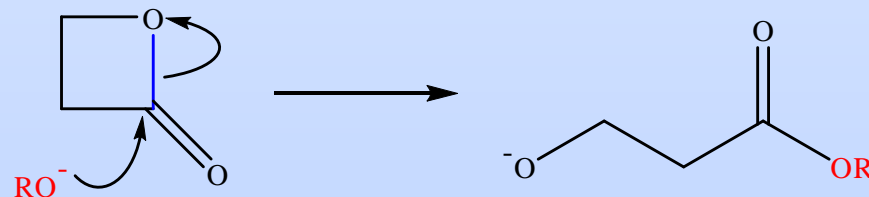
- Sodium ion, Na^+ , is harder than the silver ion Ag^+
- Copper(II) ion is harder than copper(I) ion
- Alkoxide ions, RO^- , are harder than thioanions, RS^-
- The nitrogen anion end of the ambidentate cyanide ion, CN^- , is harder than the carbon anion end, NC^-
- The ambidentate enolate ion, has a hard oxyanion centre while the carbanion centre is softer and more nucleophilic

This type of analysis can be very useful in explaining reaction selectivity.

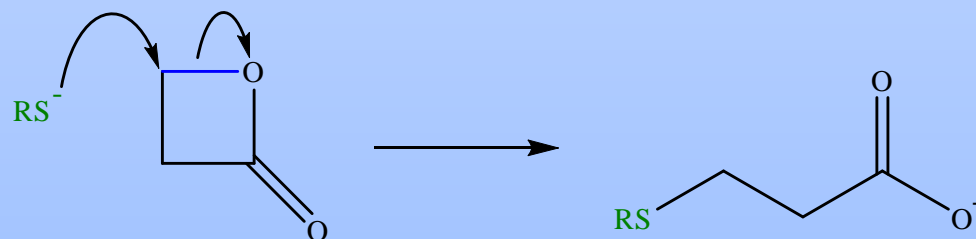
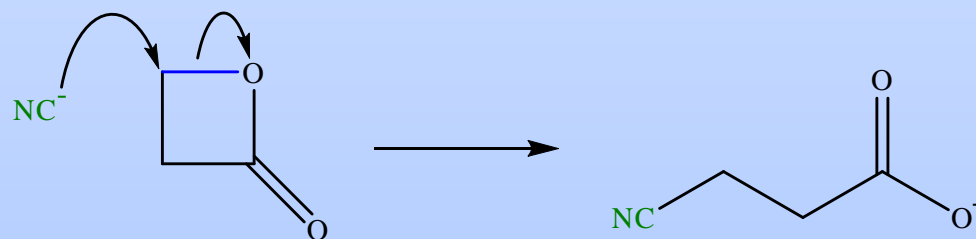
For example, in ring opening reaction of β -propiolactone by nucleophilic Lewis bases, attack can occur at two positions and nucleophiles exhibit regioselectivity.



Harder nucleophiles like alkoxide ion (RO^-) attack the carbonyl carbon.



Softer nucleophiles like a cyanide ion (NC^-) or a thiolate (RS^-), attack the β -alkyl carbon.



In a nucleophilic substitution reaction in which one Lewis base replaces another, for example, if the acid site is hard, then soft nucleophile will not provide a high rate of reaction. If the acid is soft, then a soft nucleophile will react more quickly. [Pearson R. G. and Songstad J, *JACS*, **1967**, 89, 1827.]

Although, it certainly does not say that soft acids do not ever complex with hard bases, or that hard acids do not form stable complexes with any soft bases.

ELECTROPHILES AND NUCLEOPHILES

- History
- Terminology
- Examples
- Types
- Key Facts

HISTORY

- The terms *nucleophile* and *electrophile* were introduced by [Christopher Kelk Ingold](#) in **1929**, replacing the terms *cationoid* and *anionoid* proposed earlier by [A. J. Lapworth](#) in **1925**.
- The word nucleophile is derived from nucleus and the Greek word *phile* for affinity, while electrophile is derived from electros meaning electron.

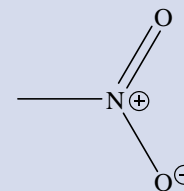
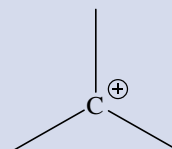
Electrophile (E / E⁺)

- **Electron loving**
- **electron deficient** molecules
- **attracted to negative charge** i.e. **high electron density**
- **bear partial** or **full positive charge** or an **open octet**
- accepts pair of electrons
- **similar to Lewis acid**

Examples

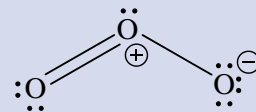
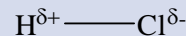
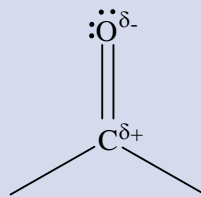
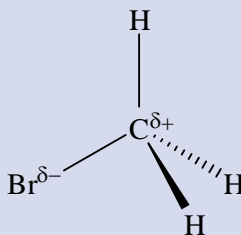
Positively charged ions

- **deficiency** in **valence electron shell**



Polar molecules

valence saturated but contain an **atom** from which **bonding electron pair** can be **removed as leaving group**

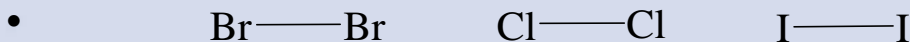


Polarizable molecules

easily polarizable bond

generates electrophilic end

Neutral molecules with incomplete octet



Key Facts

- for same electrophilic atom, **greater degree of positive charge** gives **stronger electrophile**

e.g. $\text{H}_3\text{C}^+ > \text{H}_3\text{C}^{\delta+} - \text{Br}^{\delta-}$

Nucleophile

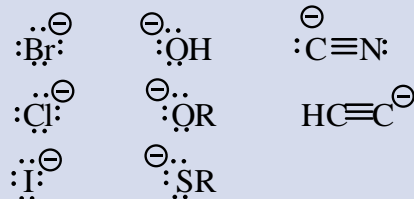
(Nu: / Nuc)

- Nucleus loving
- abundance of electrons i.e. electron rich molecules
- attracted to positive charge i.e. low electron density
- bear partial or full negative charge or pi bond or lone pair of electrons
- donates pair of electrons
- similar to Lewis base

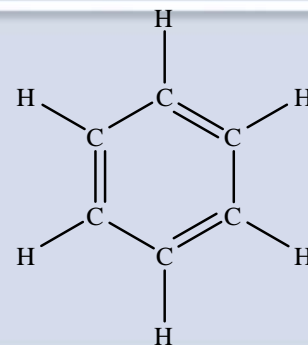
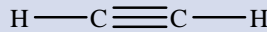
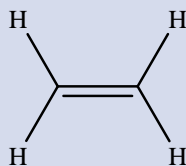
Examples

Anions

- easily available non-bonding electron pair



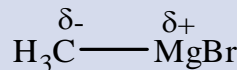
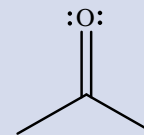
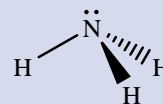
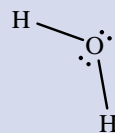
pi bonds



Molecules with lone pairs

bonding electron pair that can be
donated from bond involved

Polar molecules



Types of nucleophiles

- **Carbon nucleophiles**: alkyl metal halides such as [Grignard reagent](#), organolithium, [organozinc reagents](#), and anions of a terminal alkyne. Enolates are also carbon nucleophiles. [Enolates](#) are commonly used in condensation reactions such as [Claisen condensation](#), [Aldol condensation](#) reactions, etc.
- **Nitrogen nucleophile**: NH_3 , RNH_2 , RCN , H_2N^- , etc.

Types of nucleophiles

- **Oxygen nucleophiles**: H_2O , HO^- , ROH , RO^- , H_2O_2 , COO^- , etc.
- **Sulfur nucleophiles**: hydrogen sulfide and its salts (HS^-), thiols (RSH), thiolate anion (RS^-), thiocarboxylic acids (RCOSH), dithiocarbonates (ROCSS^-), dithiocarbamates (R_2NCSS^-), etc.
In general, sulfur is very nucleophilic. Due to its **large size**, it is **polarizable** and its **lone pair of electrons** are **easily accessible**.

Key Facts

- all nucleophiles are bases but not all bases can act as nucleophiles
e.g. lithium diisopropylamide is a very strong base but a very poor nucleophile
- stronger base is stronger nucleophile (same nucleophilic atom)
e.g. HO^- is better nucleophile than H_2O
 $\text{RO}^- > \text{HO}^- > \text{phenoxide} > \text{carboxylate} \gg \text{alcohol}, \text{H}_2\text{O} \gg \text{RSO}_3^-$

Key Facts

- nucleophile with negative charge is more powerful than its conjugate acid
e.g. $\text{H}_2\text{N}^- > \text{NH}_3$, $\text{HO}^- > \text{H}_2\text{O}$
- nucleophilicity decreases with increasing electronegativity of the attacking atom (within same period)
e.g. $\text{R}_3\text{C}^- > \text{R}_2\text{N}^- > \text{RO}^- > \text{F}^-$
 $\text{H}_2\text{N}^- > \text{RO}^- > \text{R}_2\text{HN}^- > \text{ArO}^- > \text{NH}_3 > \text{Py} > \text{F}^- > \text{H}_2\text{O} > \text{ClO}_4^-$

Key Facts

- going down in a group nucleophilicity increases
e.g. $\text{I}^- > \text{Br}^- > \text{Cl}^- \gg \text{F}^-$
 $\text{RS}^- > \text{RO}^-$
- more free nucleophile, more nucleophilicity
e.g. $\text{NaOH}_{\text{DMSO}} > \text{NaOH}_{\text{water}}$
In water Na^+ and HO^- both are solvated while in DMSO Na^+ is solvated preferably than HO^- , leaving HO^- as free nucleophile.

Key Facts

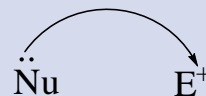
- Steric effect is also important in deciding strength of nucleophile. **Less basic but sterically unhindered** nucleophiles have **higher nucleophilicity**.
e.g. $\text{RCH}_2\text{O}^- > \text{R}_2\text{CHO}^- > \text{R}_3\text{CO}^-$
- Nucleophilicity is increased by attached heteroatom that possess free electron pair (**α -effect**).
e.g. $\text{HO-O}^- > \text{H-O}^-$, $\text{H}_2\text{N-NH}_2 > \text{H-NH}_2$

Key Facts

- Sometimes **not whole molecule**, but **small region** on large molecules **can function** as **nucleophile** or **electrophile**.
- Some molecules have both electrophilic and nucleophilic regions within them. They often go hand-by-hand.
- **More electronegative atom** functions as **nucleophilic region**. It may be partially negatively charged.

Key Facts

- Similarly, **less electronegative atom** functions as **electrophilic region**. It may be partially positively charged.
e.g. C=O bond
- **Flow of electrons**, in a reaction, is always from **nucleophile** to **electrophile**.



Electrophilic moiety

Nucleophilic moiety

