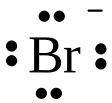
Nucleophiles, Electrophiles and Leaving Groups

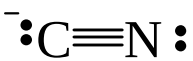
Nucleophiles

- Translation: Nucleus-loving
- Chemical meaning: Reacts with positively-charged (or partially positive) atoms (electrophiles: electron-loving)
- Characteristics: Nucleophilic atoms will have either lone pairs or pi bonds that can be used to form new bonds to electrophiles

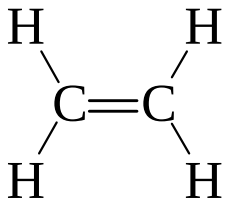
Nucleophile Examples

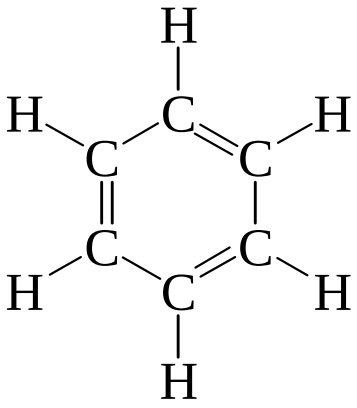
Anions



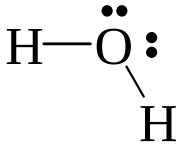


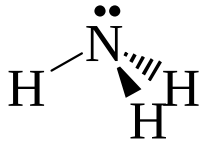
Pi bonds

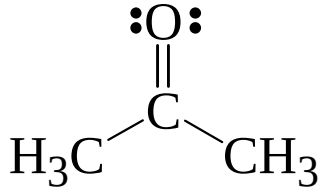




Atoms with lone pairs

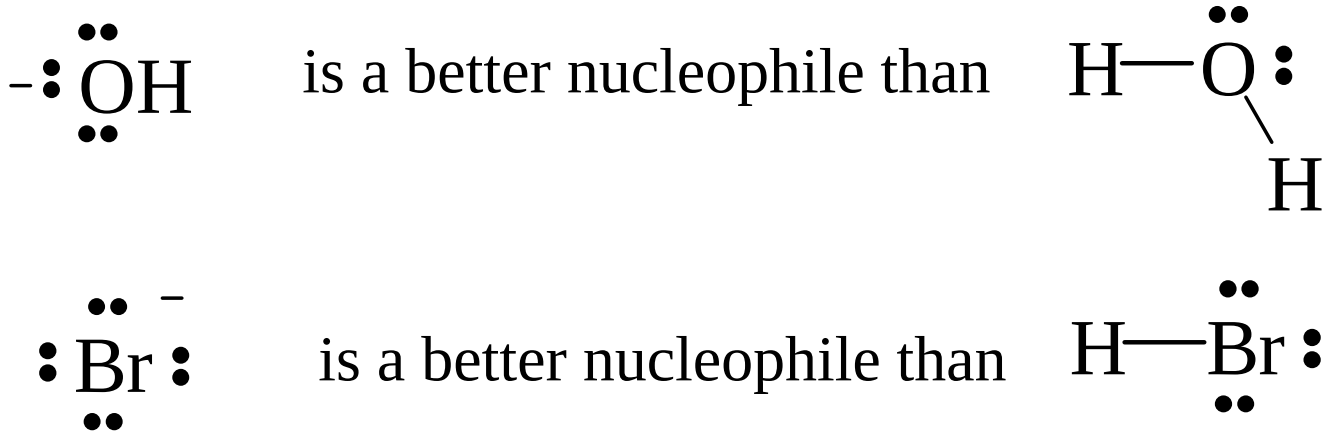






Relative Nucleophile Strength - Charge

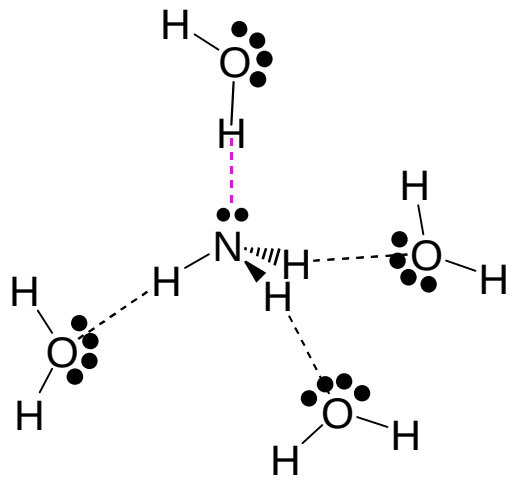
- Given two nucleophiles with the same nucleophilic atom, a negative charge makes the atom more reactive



- In more general terms, the stronger base is the stronger nucleophile (given the same nucleophilic atom)

Relative Nucleophile Strength - Solvent

- Hydrogen-bonding solvents (protic solvents) reduce nucleophilicity by interacting with the free electrons in the nucleophile



- This effect is particularly strong for small atoms with concentrated charges, thus larger atoms are more nucleophilic in protic solvents (~opposite basicity)

  $HS^- > HO^-$

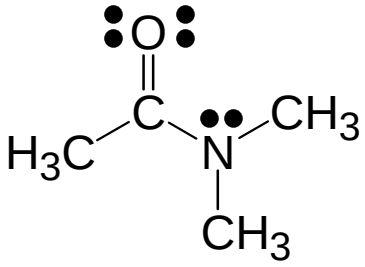
  $I^- > Br^- > Cl^- > F^-$

Relative Nucleophile Strength – Aprotic Solvents

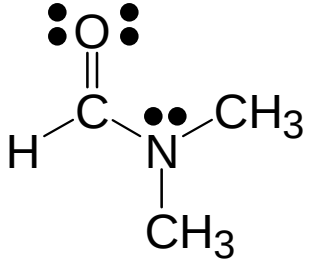
- In solvents that can accept, but not donate hydrogen bonds, nucleophiles are not solvated (but the cations providing countercharges are)
- Thus the nucleophilicity and basicity are more closely correlated:

$F^- > Cl^- > Br^- > I^-$

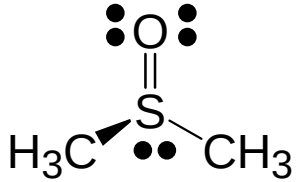
Aprotic Solvent Examples



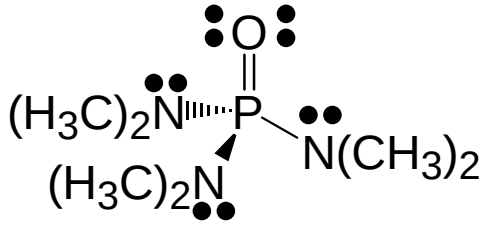
Dimethylacetamide (DMA)



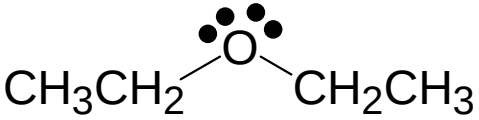
N,*N*-Dimethylformamide (DMF)



Dimethylsulfoxide



Hexamethylphosphoramide (HMPA)



diethyl ether

Problem

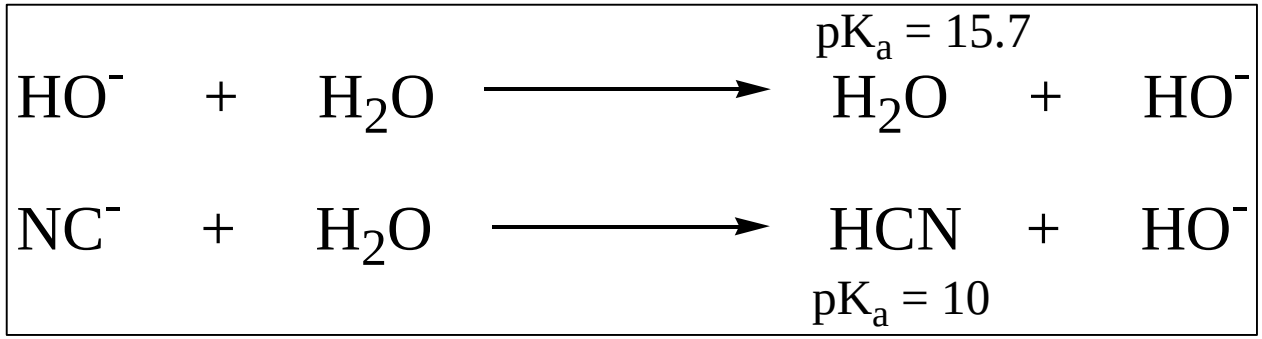
- Draw a sketch demonstrating how your assigned solvent from the previous slide can solvate a cation, and describe why it cannot solvate an anion

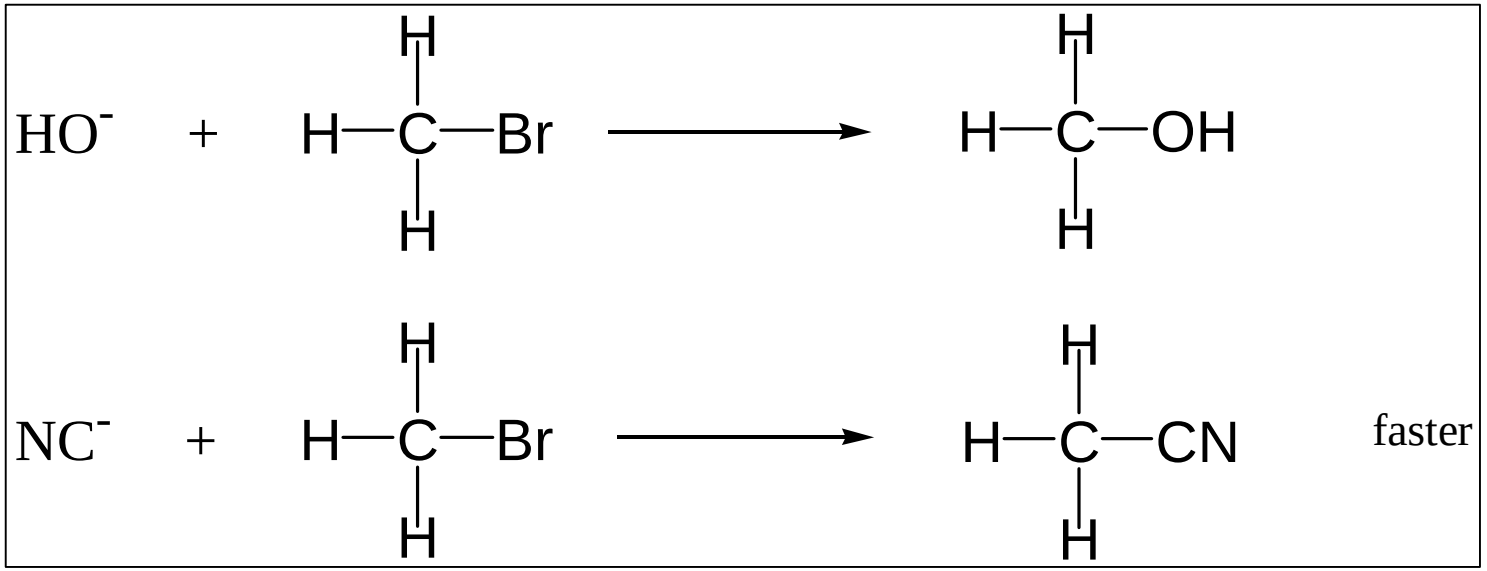
Nucleophilicity vs. Basicity

- Strong nucleophiles tend to be strong bases, but these properties are not measured the same way
  - Base strength is quantitated based on the position of the equilibrium for that base to accept a proton from water
  - Nucleophile strength is based on relative rates of reaction with a common electrophile
- Thus basicity is a thermodynamic property and nucleophilicity is a kinetic property

Example

- Example: Hydroxide ion is a stronger base than cyanide ion, but cyanide ion is a stronger nucleophile (regardless of solvent)





Problem

- Rank the following nucleophiles from strongest to weakest when dissolved in diethyl ether:

Group I: H_2O HO^- H_2N^- H_3N

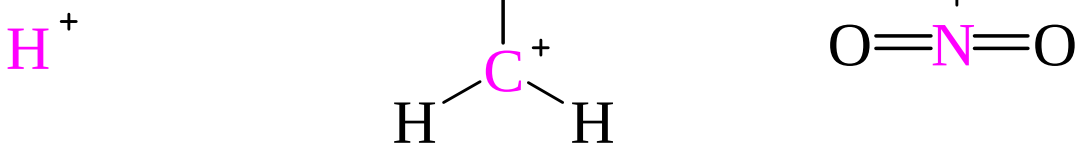
Group II: CH_3Li NaCN $CH_2=CH_2$

Electrophiles

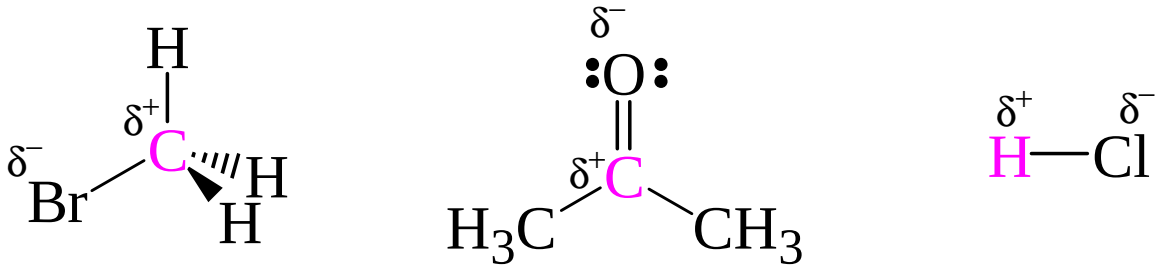
- Translation: Electron-loving
- Chemical meaning: Reacts with sources of electrons (nucleophiles: nucleus-loving)
- Characteristics: Electrophilic atoms will have
  - Positive charge, a partial positive charge, or be very polarizable
  - An empty orbital or a heterolytically breakable bond (to a leaving group)

Electrophile Examples

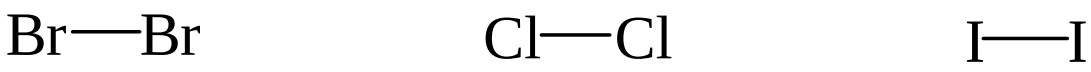
- Charged:



- Polar:

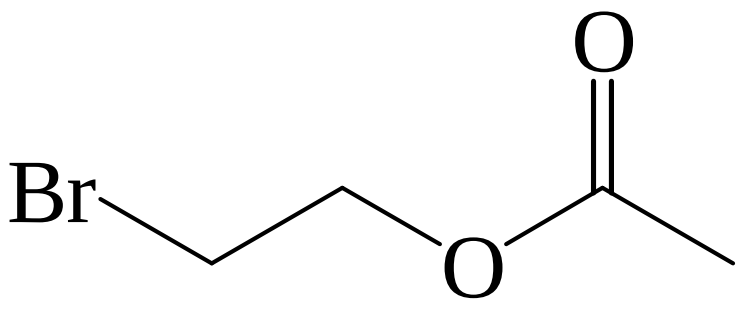


- Polarizable:



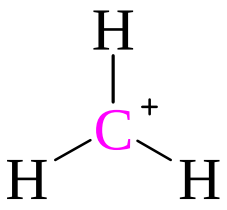
Problem

- Identify all electrophilic or nucleophilic atoms in the following structure:

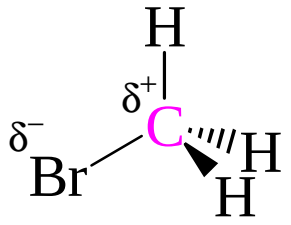


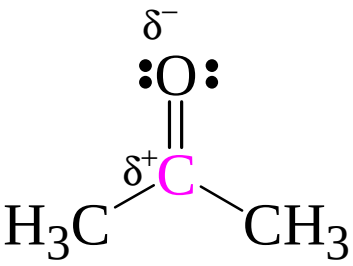
Electrophile Strength - I

- Given the same electrophilic atom, a greater degree of positive charge gives a stronger electrophile

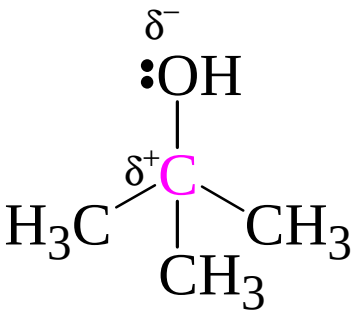


is a better electrophile than





is a better electrophile than

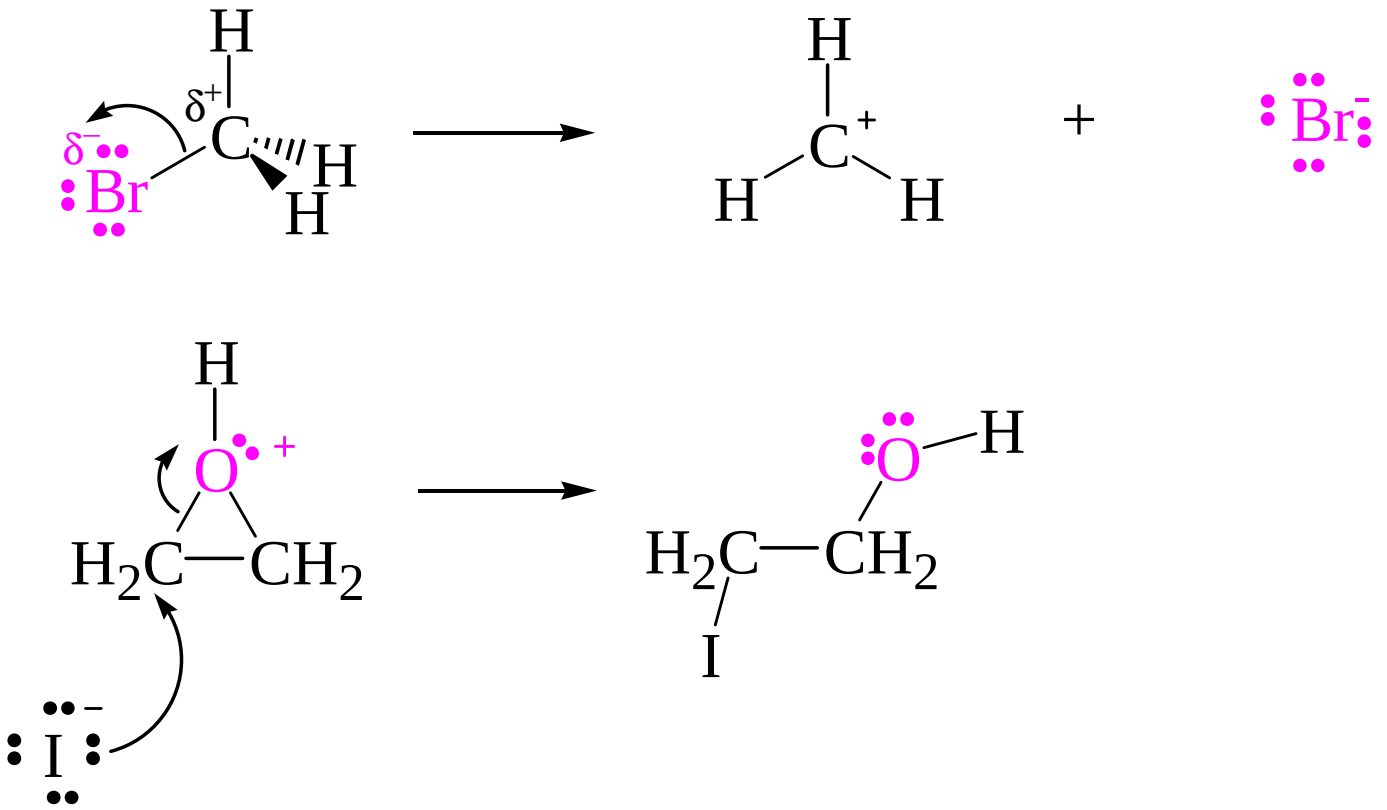


Electrophile Strength - II

- The strength of electrophiles without empty orbitals (to which a bond must be broken before another can form) is also influenced by the nature of the group to which the bond will be broken (leaving group)

Leaving Groups

- Leaving groups are the fragments that retain the electrons in a heterolytic bond cleavage:



Leaving Group Ability

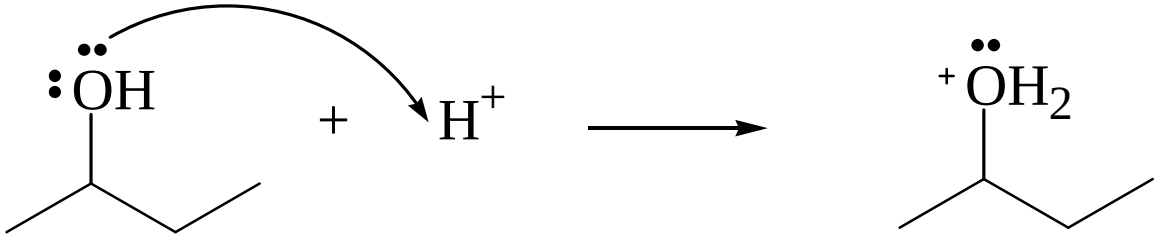
- Weaker bases are more stable with the extra pair of electrons and therefore make better leaving groups

H_2O > HO^-

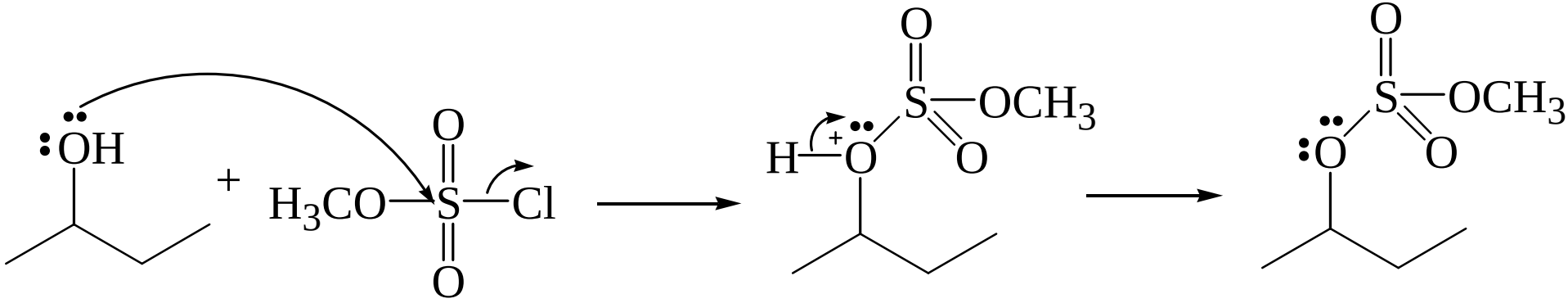
I^- > Br^- > Cl^- > F^-

Strategies to Improve Reactivity

- Alcohols do not react easily with nucleophiles due to the poor leaving ability of hydroxide
- Means to improve reactivity:
  - Let oxygen act as base first:



  - Let oxygen act as nucleophile first:



Problem

- Why is the group below a good leaving group?