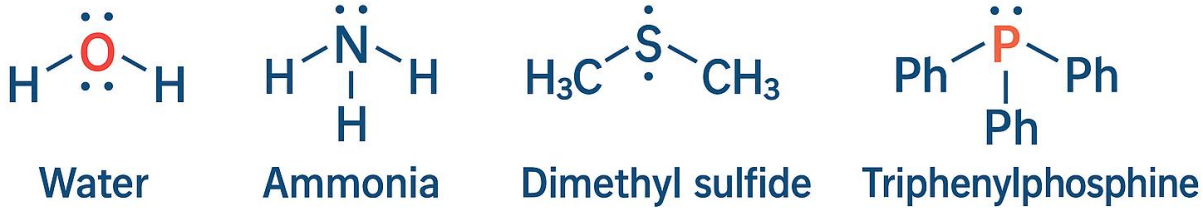
Nucleophilic Aliphatic Substitution Mechanism

Nucleophiles

Definition:

- A nucleophile (from Latin nucleus = nucleus and Greek philos = loving) is a chemical species that donates an electron pair to form a chemical bond in reaction.
- In organic chemistry, nucleophiles are electron-rich atoms or molecules that are attracted to electron-deficient centers—typically positively charged or partially positively charged atoms (often carbon atoms).
- In the context of nucleophilic aliphatic substitution, nucleophiles attack an electrophilic carbon atom in an alkyl group, displacing a leaving group and forming a new bond.





Characteristics of Nucleophiles:

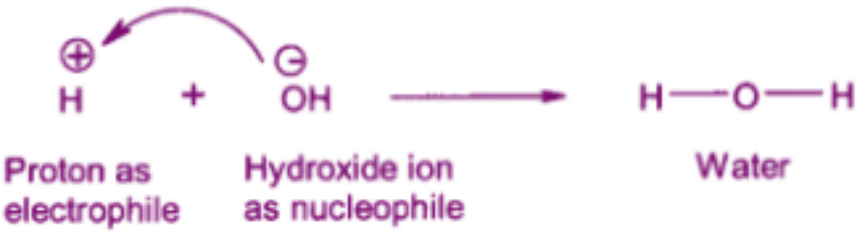
1. **Electron-rich nature:**
   - They must have lone pair(s) of electrons or π-electrons that can be donated.
   - This is often due to the presence of atoms such as oxygen, nitrogen, sulfur, or halogens.
2. **Negative charge or neutral with lone pairs:**
   - Nucleophiles can be **anions** (e.g., OH^-, CN^-, Cl^-) or neutral molecules with lone electron pairs (e.g., H_2O, NH_3, CH_3OH).
3. **Types of electron pairs used in bonding:**
   - Usually, non-bonding (lone) electron pairs.
   - Sometimes π electrons can be used, e.g., in alkenes and aromatic systems.
4. **Ability to form a bond with electrophilic center:**
   - The nucleophile must have an orbital containing the electron pair that can overlap with the empty orbital of the electrophile (usually the carbon undergoing substitution).

Common Examples of Nucleophiles:

Nucleophile	Charge	Type
OH^-	Negative	Strong
CN^-	Negative	Strong
NH_3	Neutral	Moderate
H_2O	Neutral	Weak
RO^-	Negative	Strong
RS^-	Negative	Strong
RNH_2	Neutral	Moderate
Cl^-, Br^-, I^-	Negative	Moderate

Electrophiles

- Electrophiles (electron-loving) are electron-deficient species and tend to attack the substrate at a site of high electron density.
- Electrophilic reagents are characterized by an atom with an incomplete outer electron shell and therefore, are very reactive.
- They may be neutral species as exemplified by Lewis acids (such as BF_3, $AlCl_3$, $ZnCl_2$, and carbenes (Cl_2C:)) or positively charged species as exemplified by proton (H^+), cations (such as Cl^+, NR_4^+) and carbocations.
- They have six valence electrons (except H^+) and can accept an electron pair from a nucleophile to acquire the stable octet.
- For example, hydroxide ion combines with a proton to give water.



Factors Affecting Nucleophilicity:

1. Charge:

- Negatively charged species are stronger nucleophiles than their neutral counterparts. Example: $OH^- > H_2O$

2. Electronegativity:

- Less electronegative atoms tend to be better nucleophiles since they are more willing to share their electrons.

- Example: $NH_2^- > OH^-$

3. Solvent Effects:

- **Polar protic solvents** (e.g., H_2O, alcohols): Hydrogen bonding stabilizes anions, reducing nucleophilicity.
- **Polar aprotic solvents** (e.g., DMSO, acetone): Do not hydrogen-bond to nucleophiles, hence enhance nucleophilicity of anions.
  - In aprotic solvents: $F^- > Cl^- > Br^- > I^-$
  - In protic solvents: $I^- > Br^- > Cl^- > F^-$ (opposite trend)

4. Steric Hindrance:

- Bulky nucleophiles are less effective due to difficulty in approaching the electrophilic center.
  Example: t-BuO^- is less nucleophilic than EtO^- due to steric bulk.

5. Solvation:

- Strong solvation of anions (especially in protic solvents) makes them less available for reaction.
- Aprotic solvents allow "naked" anions, making them stronger nucleophiles.

6. Resonance:

- Delocalization of lone pair through resonance reduces nucleophilicity.
  Example: Acetate ion (CH_3COO^-) is less nucleophilic due to resonance delocalization.

Nucleophiles in Aliphatic Substitution (SN1/SN2):

- In SN2 reactions, the nucleophile directly attacks the electrophilic carbon and displaces the leaving group in one concerted step.
  - The strength and steric accessibility of the nucleophile greatly influence the reaction rate.
- In SN1 reactions, the nucleophile attacks after the formation of the carbocation intermediate.
  - Here, the nucleophile does not affect the rate of the reaction directly but influences the product distribution.

Leaving Groups

Definition:

- A leaving group (LG) is an atom or group of atoms that detaches from the substrate molecule during a chemical reaction, taking with it the electron pair that was used to bond it to the molecule.
- In nucleophilic aliphatic substitution reactions (SN1 and SN2), the leaving group is displaced by a nucleophile.

- For a substitution to be successful, the leaving group must be able to stabilize the negative charge (or lone pair) it acquires upon departure.

General Reaction Context:

$$R\text{–}LG + Nu^- \rightarrow R\text{–}Nu + LG^-$$

Where:

- **R–LG** = substrate with a leaving group attached to an electrophilic carbon.
- **Nu^-** = nucleophile.
- **LG^-** = leaving group (often negatively charged or neutral).

Key Characteristics of a Good Leaving Group:

- **A good leaving group should:**
  1. Stabilize negative charge effectively.
  2. Be a weak base, so it does not re-attack the product.
  3. Be electronegative enough to hold the electron pair after bond cleavage.
  4. Be polarizable to help in bond breaking.
  5. Be non-nucleophilic or non-basic in certain contexts (especially in SN1 to avoid side reactions).

Common Leaving Groups in Organic Chemistry:

Good Leaving Groups:

➢ These groups form stable anions or neutral molecules upon departure.

Leaving Group	Nature	Comments
I^-	Halide anion	Very stable, excellent LG
Br^-	Halide anion	Excellent LG
Cl^-	Halide anion	Good LG
TsO^- (Tosylate)	Sulfonate ester	Excellent LG, resonance-stabilized
MsO^- (Mesylate)	Sulfonate ester	Excellent LG
H_2O (from ROH_2^+)	Neutral	Excellent LG in acidic medium
NO_3^-, SO_4^{2-}	Conjugate bases of strong acids	Good LGs

Moderate or Poor Leaving Groups:

Leaving Group	Nature	Comments
F^-	Halide anion	Poor LG due to high basicity
HO^-	Hydroxide	Poor LG in neutral/basic media
RO^-	Alkoxide	Poor LG, strong base
NH_2^-	Amide	Very poor LG
H^-	Hydride	Extremely poor LG
R^-	Carbanion	Extremely poor LG

Trends in Leaving Group Ability:

1. Conjugate base of strong acid = good leaving group:

- The lower the **pKa** of the conjugate acid, the better the leaving group.
- Example: HCl (pKa ~ -7) → Cl^- is a great LG.
- Compare: H_2O (pKa ~ 15.7) → OH^- is a poor LG.

2. Halogen Trend:

- $I^- > Br^- > Cl^- >> F^-$
- This trend follows basicity and size/polarizability:
  - I^- is large and polarizable → stable anion → excellent LG
  - F^- is small, less polarizable, and more basic → poor LG

3. Stabilization via Resonance:

- Groups like $TosO^-$ (tosylate) are stabilized by resonance over multiple atoms.
- This delocalization makes them excellent leaving groups.

4. Solvation and Stabilization:

- In polar solvents, good leaving groups are better solvated and stabilized.
- This favors dissociation, especially in SN1 reactions.

Why OH^- is a Poor Leaving Group (in neutral/basic media):

- Hydroxide (OH^-) is a strong base and a poor LG.
- In neutral or basic conditions, it resists leaving because:
  - It cannot stabilize the negative charge well.
  - The backward reaction is often more favorable.
- However, in acidic conditions, OH can be protonated to form H_2O, which is a much better LG.
  - Protonation: OH^- → OH_2^+ → leaves as H_2O (neutral, stable)

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