Ambident Nucleophiles and Regioselectivity

1. Definition

Ambident nucleophiles are nucleophiles that have two or more reactive sites, either of which can attack an electrophilic center. Depending on reaction conditions and electrophile, they attack through one site or the other.

2. Examples

Ambident Nucleophile	Two Reactive Sites	Example of Product
Cyanide ion (CN^-)	C and N atoms	R–CN (nitrile) or R–NC (isocyanide)
Nitrite ion (NO_2^-)	N and O atoms	R–ONO (alkyl nitrite) or R–NO_2 (nitro compound)
Thiocyanate ion (SCN^-)	S and N atoms	R–SCN (alkyl thiocyanate) or R–NCS (alkyl isothiocyanate)
Enolate ion	α-carbon and oxygen	C-alkylation or O-alkylation

3. Regioselectivity

Regioselectivity refers to the preference for attack at one site over another in an ambident nucleophile or in a substrate that has multiple reactive centers.

Factors affecting regioselectivity:

1. Nature of electrophile: Hard electrophiles prefer hard centers; soft electrophiles prefer soft centers (HSAB principle).

2. Reaction conditions: Solvent and temperature affect the attacking site.

3. Steric effects: Bulky electrophiles hinder approach of certain reactive sites.

4. Nucleophilic Substitution at Different Carbon Centers

(a) Aliphatic Carbon (sp^3 hybridized)

SN1 or SN2 mechanism occurs. SN2 gives inversion of configuration, while SN1 proceeds via carbocation formation leading to racemization.

(b) Allylic Carbon (sp^3 adjacent to C=C)

Allylic carbocations are stabilized by resonance. Both SN1 and SN2 can occur easily. SN2′ mechanism (allylic rearrangement) may also occur due to delocalization.

(c) Trigonal Carbon (sp^2 hybridized, e.g., carbonyl carbon)

Nucleophilic addition occurs at the carbonyl carbon due to polarization of the C=O bond. A tetrahedral intermediate is formed.

(d) Vinylic Carbon (sp^2 hybridized in C=C)

Vinylic carbons resist nucleophilic substitution due to partial double bond character and planar geometry. SNV reactions may occur only in activated vinyl systems with electron-withdrawing groups.

5. Summary Table

Carbon Type	Hybridization	Typical Mechanism	Reactivity Toward Nu	Notes
Aliphatic	sp^3	SN1 / SN2	Moderate	Most common substitution
Allylic	sp^3 (adj. to C=C)	SN1 / SN2′	High	Resonance-stabilized intermediates
Trigonal (Carbonyl)	sp^2	Addition / Acyl Substitution	High	Polarized C=O bond
Vinylic	sp^2 (C=C)	Rare / SNV	Very Low	Double bond prevents SN1/SN2

6. Key Concepts to Remember

• Ambident nucleophiles have more than one attacking site.

• Regioselectivity depends on HSAB principle, solvent, and steric effects.

• Allylic centers show resonance stabilization; trigonal undergo addition; vinylic are resistant to substitution.

• SN1, SN2, and SN2′ mechanisms dominate depending on substrate and reaction medium.