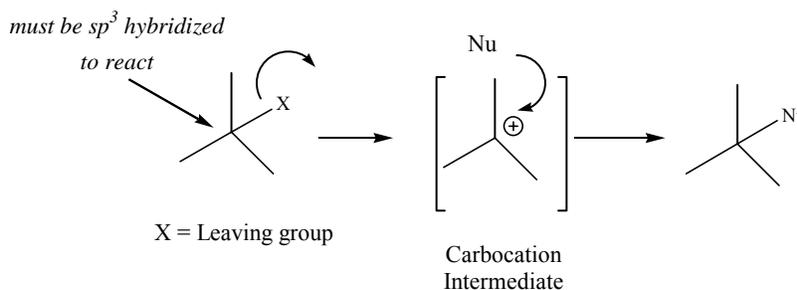


I. NUCLEOPHILIC SUBSTITUTIONS (sp^3 C)

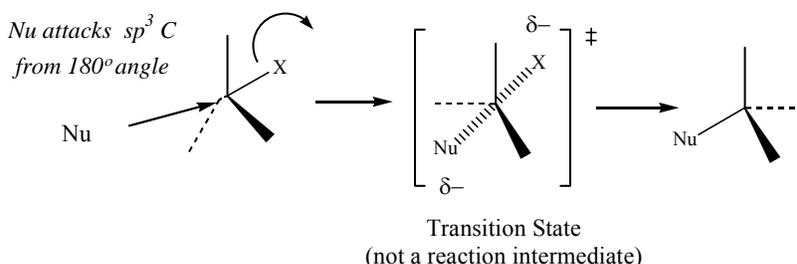
Nucleophilic substitutions occur with molecules that have an sp^3 carbon bonded to a leaving group (-halogen, $-OH_2^+$, $-OTs$). The reaction occurs when a nucleophile displaces the leaving group. The reaction can occur via two distinct mechanisms, SN_1 or SN_2 .

A. SN_1 NUCLEOPHILIC SUBSTITUTION



- SN_1 nucleophilic substitutions always involve a carbocation intermediate.
- The rate-determining step of an SN_1 reaction is formation of the carbocation.
- The rate at which an SN_1 reaction occurs will be determined by the stability of the carbocation generated in the reaction. More highly substituted alkyl halides react faster than less substituted alkyl halides because their corresponding carbocations are more stable. (Rate: $3^\circ > 2^\circ > 1^\circ$)
- Polar solvents enhance the rate of an SN_1 substitution.
- STEREOCHEMISTRY OF SN_1 NUCLEOPHILIC SUBSTITUTIONS
 - Attack of a nucleophile on a carbocation can occur from the top face or the bottom face
 - NO STEREOCHEMICAL BIAS IS OBSERVED when alkyl halides with no chiral centers or when the only chiral center in the molecule is the reacting carbon atom
 - STEREOCHEMICAL BIAS IS OBSERVED when an alkyl halide which contains a chiral center that is not the reacting carbon

B. SN_2 NUCLEOPHILIC SUBSTITUTION

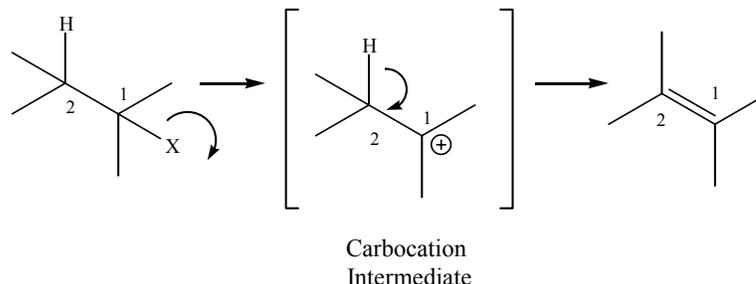


- SN_2 substitutions NEVER involve a carbocation intermediate.
- The rate-determining step of an SN_2 substitution involves bond formation between the attacking Nu and the reacting C atom, and bond cleavage between the leaving group and the reacting C atom.
- Less substituted alkyl halides react faster than bulky alkyl halides (Rate: $1^\circ > 2^\circ > 3^\circ$)
- Polar, aprotic solvents enhance the rate of an SN_2 substitution. Protic solvents slow down the rate of SN_2 substitutions.
- STEREOCHEMISTRY OF SN_2 NUCLEOPHILIC SUBSTITUTIONS
 - Attack of a nucleophile on an alkyl halide in an SN_2 substitution ALWAYS occurs at an angle of 180° to the carbon leaving group bond. This type of nucleophilic attack results in inversion of the configuration (i.e., R inverts to S and S inverts to R) of the reacting carbon atom IF THAT CARBON ATOM IS CHIRAL.

II. ELIMINATIONS

A. E₁ ELIMINATION

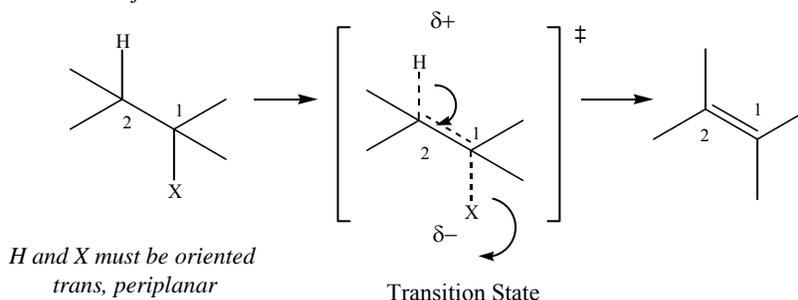
*H atom must be bonded
to an adjacent C*



1. E₁ eliminations always involve a carbocation intermediate.
2. The rate-determining step of an E₁ elimination is formation of the carbocation.
3. The rate of the reaction will be determined by the stability of the carbocation generated in the reaction. (3° > 2° > 1°).
4. The rate at which an E₁ reaction occurs is also determined by the ability of the leaving group to stabilize a negative charge.
5. E₁ reactions often compete with the S_N1 substitution to give mixtures of substitution and elimination products.
6. Under thermodynamic conditions, E₁ eliminations occur to give the MOST SUBSTITUTED ALKENE PRODUCT
7. Polar solvents enhance the rate of an E₁ elimination reaction.

B. E₂ ELIMINATION

*H atom must be bonded
to an adjacent C*



*H and X must be oriented
trans, periplanar*

1. E₂ substitutions NEVER involve a carbocation intermediate.
2. The rate-determining step of the E₂ mechanism involves simultaneously breaking the C-X bond and the C-H bond of an adjacent C, while forming the C-C pi bond.
3. E₂ reactions occur with 1°, 2° and 3° alkyl halides.
4. STEREOCHEMISTRY OF E₂ ELIMINATIONS: There are two stereochemical requirements for E₂ elimination reactions.
 - a. The four reacting atoms (H, LG and the two C atoms) must be in the same plane (i.e., periplanar).
 - b. The hydrogen atom and the leaving group must be trans.
 - c. The overall description of this required orientation of atoms is referred to as "antiperiplanar".

III. IDENTIFYING WHICH REACTION WILL OCCUR

Reaction conditions for the S_N1 and E_1 mechanisms are similar. Reactions are also similar for the S_N2 and E_2 reaction mechanisms. The following process can be used to help determine which reaction(s) is (are) favored under a given set of reaction conditions.

- A. Identify the reactive functional group(s) in the starting material and the reaction mechanism favored for that functional group.

Functional Group	Reaction(s) Favored
1° Alkyl Halide, Tosylate	E_2 , S_N2
2° Alkyl Halide, Alcohol, Tosylate	E_1 , E_2 , S_N1 , S_N2
3° Alkyl Halide, Alcohol	E_1 , S_N1

- B. Identify the reaction conditions. Consider both pH (acidic or basic) and the solvent.

Reaction Condition	Reaction(s) Favored
Acidic <i>Reagents:</i> H^+ , H_3O^+ , HX , H_3PO_4 , H_2SO_4 , CH_3CO_2H (acetic acid)	E_1 , S_N1
Basic <i>Reagents:</i> HO^- , $NaOH$, KOH , NH_3 , RNH_2 , RO^-Na^+ (alkoxides)	E_2 , S_N2
Solvents	
Polar, Protic	E_1 , S_N1
Polar Aprotic	E_2 , S_N2

- C. Other Factors

- Determine if elimination reactions can occur. Look for an sp^3 carbon adjacent to the sp^3 carbon bearing the leaving group (halogen or water). If the adjacent sp^3 carbon is bonded to at least one hydrogen, elimination may occur.
- Determine if substitution can occur. Look for the presence of a nucleophile. If a nucleophile is present, substitution can occur.