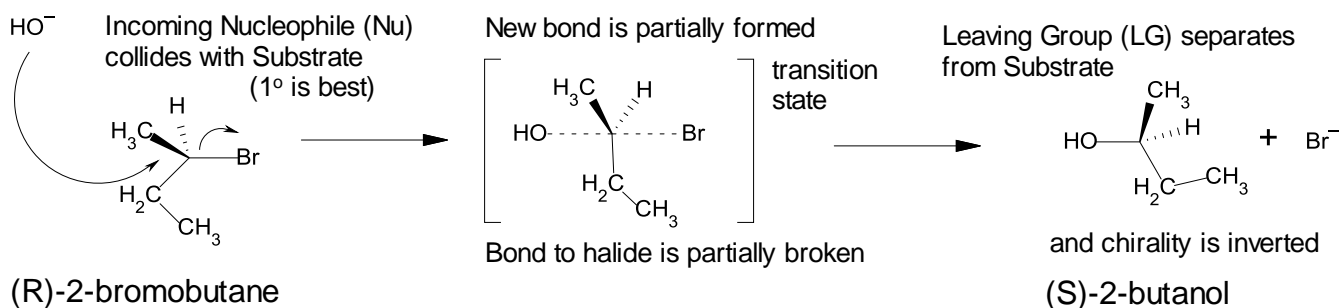


Ch 11 Reactions of Alkyl Halides

- Substitutions replace a leaving group (LG) with an incoming nucleophile (Nu).
- Eliminations create alkenes by removing H^{+1} from the C next to the C that loses the LG.

S_N2 Reaction

- Substitution (S), Nucleophilic (N), Bimolecular (2)
- The Nu collides with the Substrate molecule (such as CH_3X).
This results in bimolecular kinetics, so that reaction rate = $k[CH_3X][Nu]$.
The reaction rate is 2nd order overall.
- Reaction occurs in one single step.
- Transition State occurs when the lone pair on the Nu^{-1} partially bonds with the C, and the bond between C and X partially breaks.
- The lone pair forms the new bond between C and Nu^{-1} .
- X takes the $2e^{-1}$ from the old C-X bond to become X^{-1} .
- The Nu bonds on the opposite side of X.
So, an inversion of chirality results if C is a chiral center.

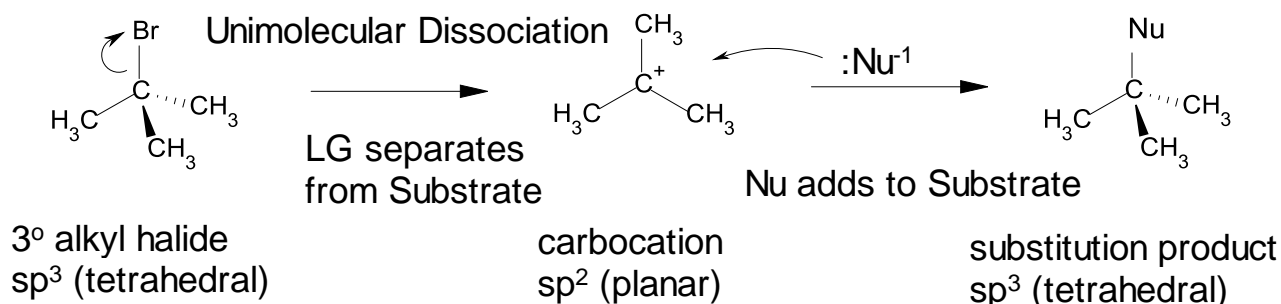


Optimizing S_N2

- **Substrate with least steric hindrance** is best $CH_3X > 1^\circ > 2^\circ > 3^\circ$
Methyl halides work best. 3° halides do not do S_N2 reactions at all.
- **Stronger Nu's** increase reaction rate.
Nucleophilicity is similar to basicity, both involve donating an e^{-1} pair.
Nucleophilicity increases down a column in the periodic table ($I^{-1} > Br^{-1} > Cl^{-1}$).
Nucleophilicity increases with charge ($OH^{-1} > H_2O$).
- Leaving Group (**LG**) is best if it becomes a **stable anion**, like I^{-1} , or a stable molecule, like H_2O .
For instance, OH^{-1} is very reactive (not stable), and is not a good LG.
- A polar solvent works best if it **does not have a $\delta+ H$** , so that it does not solvate the $\delta- Nu$.
That is, if the solvent destabilizes the Nu, then the Nu is more reactive towards the substrate.
A **polar aprotic solvent** is best. Example include acetonitrile (CH_3CN), dimethylformamide [$(CH_3)_2NCHO$, abbrev. as DMF] and dimethylsulfoxide [$(CH_3)_2SO$, abbrev. as DMSO].

S_N1 Reaction

- Substitution (S), Nucleophilic (N), Unimolecular (1)
- The reaction occurs in two steps, with a carbocation intermediate.
- In the first step, the substrate molecule (R₃CX) dissociates when LG⁻¹ leaves, producing a carbocation (R₃C⁺).
- Step 1 (forming carbocation) is the rate-determining (slow) step. So, reaction rate = k[R₃CX], and the rate is 1st order overall.
- In the second step, the carbocation reacts with Nu⁻¹ to form the product (R₃C-Nu).
- The Nu⁻¹ can add to either side of the planar carbocation, so the product will generally be a nearly racemic mixture if a chiral center is formed.

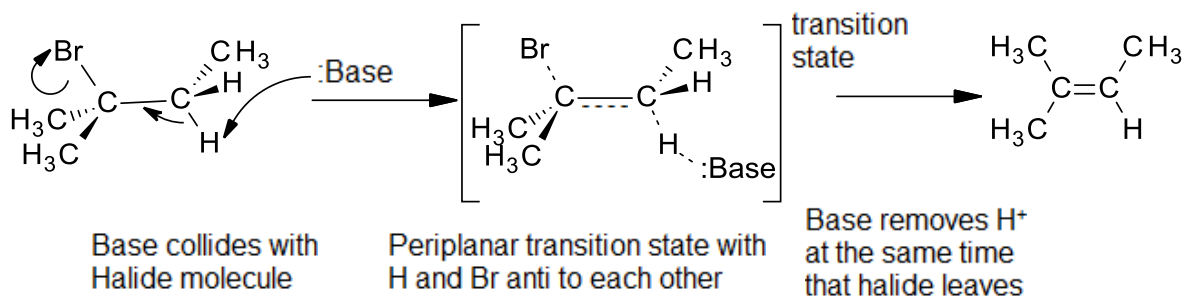


Optimizing S_N1

- Substrate needs to form a stable carbocation, so the **most substituted carbon** is best.
3° > 2° > 1° **3° halides** work best. 1° halides do not do S_N1 at all.
- Nu is not part of rate equation, so a weak Nu will work acceptably.
Also, a **weak Nu** will preclude S_N2.
- **LG** is best if it becomes a **stable anion or molecule**.
- The best solvent will stabilize (solvate) the transition state leading to the carbocation. The transition state has a dipole with a δ⁺ C and a δ⁻ halide atom. So, the **solvent** should be **polar** and **protic** (has δ⁺ H).
Water and alcohol work well. S_N1 may occur in some aqueous acid solutions as well, where either water or the acid's conjugate base anion functions as the Nu.

E2 Reaction

- Elimination (E), Bimolecular (2)
- Reaction occurs in one single step.
- B collides with Substrate molecule, which results in bimolecular kinetics.
So, reaction rate = $k[R_3CX][B]$, and the rate is 2nd order overall.
- Base (B) removes H^{+1} from C next to the C with the halide (X), and X^{-1} leaves simultaneously.
- Transition State for the reaction occurs when the lone pair on the B partially bonds with H, the C-H bond partially breaks, the C-C π bond partially forms, and the bond between C and X partially breaks. All of these changes in bonding occur simultaneously.
- For all these bonds to form and break simultaneously, the alkyl halide molecule needs to have the right geometric conformation. The best conformation will allow enough p orbital overlap to form the C-C π bond. These p orbitals are created from sp^3 orbitals as the two C's rehybridize from sp^3 to sp^2 .
- The H, C's, and X all must be in the same plane, with the H and X on opposite sides from each other. These conditions are called **periplanar** and **anti**. A Newman diagram with these atoms will show a staggered conformation with H and X 180° apart.

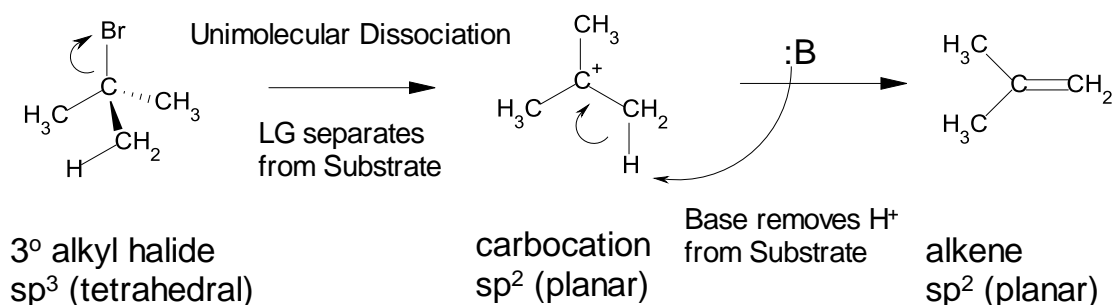


Optimizing E2

- **Zaitsev's rule** is that the **most substituted alkene will be the predominant product** of elimination reactions. This occurs because increasing the number of alkyl substituents on the π bonded C's increases the stability of the π bond.
- Because a more substituted alkene is more stable, the **more substituted** alkyl halide is best. $3^\circ > 2^\circ > 1^\circ$ **3° halides** work best. 2° and 1° halides need a strong base for E2.
- **LG** is best if it becomes a **stable anion or molecule**.
- A strong Nu causes competing reactions. A **non-nucleophilic base** is best. Typically, a basic anion that is too large to approach the halide C will be a poor Nu. $CH_3CH_2O^{-1}$ would be a good example, as it is a strong base, but it is a weak nucleophile due to the steric hindrance of the alkyl group.

E1 Reaction

- Elimination (E), Unimolecular (1)
- The reaction occurs in two steps, with a carbocation intermediate.
- The first step is identical to that of S_N1 . The substrate molecule (R_3CX) dissociates when LG^{-1} leaves, producing a carbocation (R_3C^{+1}).
- In the second step, the carbocation then reacts with a base (B) to form the alkene product. B removes H^{+1} from the C next to C^{+1} .
The $2e^{-1}$ from the broken C-H bond are used to create the new π bond.
- Step 1 (forming the carbocation) is the rate-determining step.
So, reaction rate = $k[R_3CX]$, and the rate is 1st order overall.



Optimizing E1

- E1 essentially needs the same conditions as S_N1 . The two reactions generally compete with each other and occur together, although S_N1 usually predominates.
- S_N1 requires a weak Nu. However, **E1 does not need a Nu.**
Non-nucleophilic weak bases may favor E1 over S_N1 , while strong bases and nucleophiles favor E2 and S_N2 .
- Neutral mixtures of water and alcohol alone are generally sufficient, although small amounts of base may be added to remove the proton from the substrate.
- Substrate needs to form a stable carbocation, so the **most substituted carbon** is best.
 $3^\circ > 2^\circ > 1^\circ$ **3° halides** work best. 1° halides do not do E1 at all.
- **LG** is best if it becomes a **stable anion or molecule.**
- As with S_N1 , the best solvent will stabilize (solvate) the first step's transition state (polar).
So, like S_N1 , the **solvent** should be **polar** and **protic** (has $\delta^+ H$).
Water and alcohol work well. E1 may occur in some aqueous acid solutions as well, if water or the acid's conjugate base anion can function as the base for the reaction.

1° Alkyl Halides

- **S_N2** almost always **predominates** whenever a Nu is present.
- **S_N1** and **E1** do **not** happen.
- **E2** can compete with S_N2 if a **strong base** is present.

2° Alkyl Halides

- **S_N2** predominates with a **nonbasic Nu** in a **polar aprotic solvent**.
- **S_N1** and **E1** predominate and compete with a **weak base or nucleophile** in a **protic solvent**.
The polar solvent should be neutral or acidic.
- **E2** predominates if a **strong base** is present.

3° Alkyl Halides

- **S_N2** does **not** happen.
- **S_N1** and **E1** predominate and compete in a **neutral** or **acidic** solvent.
- **E2** predominates if a **base** is present.