

S_N1, S_N2, E¹ and E² Reactions

Whether an alkyl halide will undergo an S_N1, S_N2, E¹ or an E² reaction depends upon a number of factors. Some of the more common factors include the natures of the substrate carbon skeleton, the solvent, the leaving group, and the nature of the nucleophile.

S_N2: TERTIARY ALKYL HALIDES NEVER SHOW S_N2 REACTIONS

- The order of reactivity is as follows: Methyl > 1° > 2°
- Sterically less hindered substrates have faster rates in S_N2

Nucleophile: If the reacting atom is the same in a series, nucleophilicity* parallels basicity (i.e. -OH > -OCH₃ > -OCH₂CH₃ > H₂O)

- For the halogens in **GAS PHASE**: F⁻ > Cl⁻ > Br⁻ > I⁻
- For the halogens in **SOLUTION**: I⁻ > Br⁻ > Cl⁻ > F⁻ (due to solvation of nucleophile, rendering it inactive)
- Negatively charged nucleophiles give neutral products
- Neutral nucleophiles give cationic products

In **SOLUTION** nucleophilicity increases down a column in the periodic table (i.e. -OCH₃ > -SCH₃ > -SeCH₃)

- Anionic nucleophiles are usually stronger than neutral ones

Leaving Group: Best leaving groups are those that best accommodate a negative charge (large anions such as I⁻)

The best leaving groups are **WEAK BASES**

- the worst leaving groups are:

F⁻, OH⁻, OCH₃⁻, CN⁻, N₃⁻, NH₂⁻

- The best leaving groups are: **H₂O, CH₃OH, -OTs, -I**

Notes:

The S_N2 reaction is bimolecular - it depends on amounts of nucleophile and leaving group

S_N2 reaction goes with inversion about the stereogenic carbon.

Solvent: **Polar protic**¹ solvents are the **worst** for S_N2; they solvate the nucleophile so it cannot attack.

Polar aprotic solvents **stabilize the transition state** and speed SN^2 reactions up. Polar aprotic solvents are DMSO, DMF, CH_3CN , and Hexamethylphosphoramide, HMPA ($[(\text{CH}_3)_2\text{N}]_3\text{PO}$)

¹**Polar protic** solvent has a hydrogen atom attached to a strongly electronegative element (e.g. oxygen) that forms hydrogen bonds. On the other hand, **polar aprotic solvents** are those solvents whose molecules do not have a hydrogen atom that's attached to an atom of an electronegative element. **Polar protic** solvent solvate cations and anions effectively while **aprotic solvents** do not solvate anions to any appreciable extent.

SN^1 Reaction

Substrate: SN^1 reactions work best on a **TERTIARY!** THERE IS **NO SN^1 ON A PRIMARY!!**

Order of reactivity: $3 > 2$

Nucleophile: Has **NO** effect upon the rate of reaction!! Rate limiting step does not include the nucleophile!!

Leaving Group: Same as for SN^2 reactions!!

Solvent: **Polar aprotic** solvents work well. **Polar protic** solvents work even better because they stabilize the carbocation intermediate

Notes: SN^1 is unimolecular and depends only on amount of substrate. SN^1 goes through a carbocation intermediate. Stereochemistry is lost during an SN^1 reaction and the products usually display a small excess of inversion product
Watch out for CARBOCATION REARRANGEMENTS!

E^2 Reaction

Substrate: Requires anti-peri-planar geometry (two or more groups on the opposite side) between the halide and hydrogen

Relative rates of reaction: $3 > 2 > 1$

Stereochemistry: The stereochemistry of the starting material will determine whether you get the Z or E isomer when possible

Small strong bases always give the Zaitsev product

Bulky strong bases always give the Hoffman product

Notes: This is a bimolecular reaction whose rate depends on the base and substrate used. Whenever you have a basic nucleophile used on a 2° alkyl halide, you can expect a mixture of the E^2 and SN^2 reaction with the E^2 being the major product

Bases: The following bases give E^2 on 3° and 2° alkyl halides

OH^- , OCH_3^- , $\text{OCH}_2\text{CH}_3^-$, $\text{OC}(\text{CH}_3)_3^-$, CN^- . Remember that the secondary halides will also give SN^2 minor product

E¹ Reaction

Substrate: Works best on 3° (and 2°) substrates

Does not require the antiperiplanar geometry!

Stereochemistry: This reaction proceeds through a carbocation intermediate!
Typically favors the Zaitsev product

Watch out for CARBOCATION REARRANGEMENTS!

Notes: On 3 alkyl halides, this reaction competes with the SN^1

For a given SN^1 reaction, the minor product will always include the E^1 product

Nucleophiles

SN^2 nucleophiles (only on Methyl, 1 and 2 alkyl substrates):

N_3^- , I^- , NH_3 , Br^- , Cl^- , CN^- , HS^-

SN^1 nucleophiles with E^1 minor products (only on 3° alkyl substrates)

H_2O , CH_3OH , $\text{CH}_3\text{CH}_2\text{OH}$, HX (only on tertiary alcohols)

E^1 bases (only on 3° alkyl halides)

H_2SO_4 with H_2O and heat gives purely $\text{E}1$ elimination

$\text{SN}1$ nucleophiles also give minor $\text{E}1$ products

E^2 bases (only with 3 and 2 alkyl halides)

OH^- , OCH_3^- , $\text{OCH}_2\text{CH}_3^-$, $\text{OC}(\text{CH}_3)_3^-$, CN^- (only on 3 alkyl halide)

Substrates

Primary: SN^2 reaction with good nucleophiles

E^2 with **VERY** strong bases

NO E^1 or SN^1 !!

Secondary: With basic nucleophiles, get mixture of E^2 (major) and SN^2 (minor)

With pure nucleophiles (not basic) get only SN^2

With weak nucleophiles, get SN^1 with minor E^1

Tertiary: With strong bases, get E^2 exclusively

With weak nucleophiles, get SN^1 with minor E^1 product

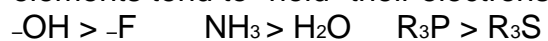
* Basicity is the ability of an atom or molecule to donate a lone pair of electrons to a proton (H^+). Nucleophilicity is the ability of an atom or molecule to donate a lone pair of electrons to carbon.

The following trends can be noted:

1. Species with negative charges are stronger nucleophiles than corresponding uncharged species

$\text{OH}^- > \text{H}_2\text{O}$ $\text{SH}^- > \text{H}_2\text{S}$ $\text{NH}_2^- > \text{NH}_3$

2. Nucleophilicity decreases going to the right in the periodic table. More electronegative elements tend to "hold" their electrons more tightly



3. Nucleophilicity increases going down the periodic table as polarizability increases.

