

V Nucleophilic Substitutions and Eliminations

5.1 Organic Halogen Compounds

- Rarely found in Nature
- Important in commercial applications

Examples:

Alkyl Halides: Alkane molecule in which a halogen has replaced a hydrogen

Primary Alkyl Halide: Secondary Alkyl Halides: Tertiary Alkyl Halides

Properties:

- Iodine containing molecules boil higher than bromine containing and so on
- Densities are higher than alkanes

Nomenclature:

IUPAC:

- halogens are designated by the prefixes fluoro, chloro, bromo, and iodo

Examples:

Common Nomenclature:

- Often alkyl halides are named in a 'salt like' way starting with the alkyl groups name, followed by the halide

Examples:

Trivial Names:

5.1.1 Synthesis of Haloalkanes

A) Free radical halogenation of alkanes

B) Addition of alkenes and alkynes

C) Electrophilic aromatic substitution

D) Conversion of alcohols to alkyl halides

5.1.2 Reactivity

Halogens are more electronegative than carbon. Carbon has a δ^+ while the halogen has a δ^- .

Two reactive sites:

- The carbon (electropositive) reacts with nucleophiles
- The hydrogen atom bonded to the carbon adjacent to the carbon atoms bonded to the halogen atoms. This hydrogen is very **ACIDIC**. The hydrogen is called the hydrogen in β position on the carbon.

Alkyl Halogens prefer to undergo two very specific reactions:

A) Attack of a nucleophile on the carbon atom that is bonded to the halogen

This results in a SUBSTITUTION of the halogen

B) Attack of a nucleophile on the hydrogen β to the halogen bonded carbon

This results in an ELIMINATION reaction

Both of these reactions take place at the same time

5.2 Nucleophilic Substitution

Nucleophilic Substitution: Substitution reaction in which a nucleophile replaces a leaving group such as a halide

Nucleophile: Species with electron availability that donates electrons to an electrophile in a chemical reaction. Nucleophiles are Lewis bases

Leaving Group: Group that is displaced by the nucleophile

Substrate: Compound on which the halogen is bonded

5.2.1 General Reaction

Nucleophilic Substitution:

Two types of nucleophiles can attach the carbon:

A) Negatively charged nucleophiles:

B) Neutral nucleophiles:

Examples:

5.2.2 Nucleophilicity versus Basicity

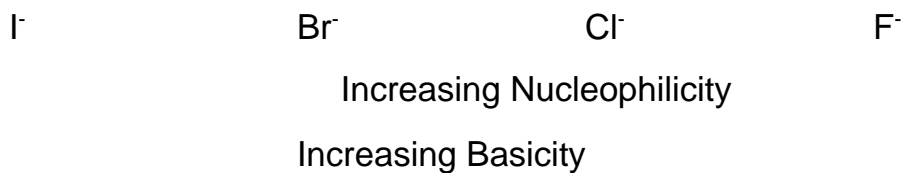
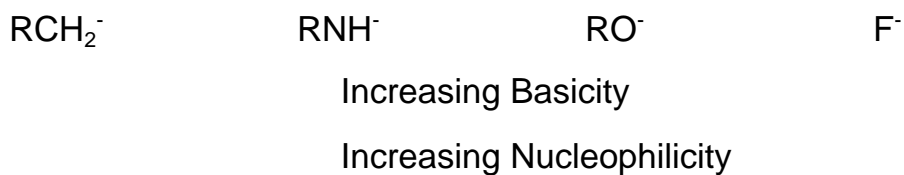
Nucleophilicity: Property of the nucleophile that gives it the ability to displace the leaving group

Remember: Nucleophiles are also bases Basicity

During a Substitution, the nucleophile acts as an attacking unit to the carbon

During an elimination, the nucleophile acts as a Brønsted base

Trend in nucleophilicity and basicity



Charges increase Nucleophilicity

Thiolate more nucleophilic but less basic than alkoxide ion

- Nucleophilic substitutions are based on two mechanisms: S_N1 and S_N2

5.2.3 The S_N2 Mechanism

S_N2 : Substitution nucleophilic bimolecular, the one-step nucleophilic substitution mechanism

Bimolecular: Term that describes a reaction rate that depends on the concentration of TWO species

Concerted: The attack of the nucleophile and the removal of the leaving group take place in one step

- The formation of the new bond to the nucleophile and the breakage of the carbon halogen bond take place simultaneously
- There is only one transition state
- The leaving group leaves OPPOSITE of the attacking nucleophile due to steric reasons (back side attack)
- Inversion of the configuration takes ALWAYS place (Walden inversion)

General Mechanism:

Potential Energy Diagram:

Rate: The rate of the reaction (how fast it goes) depends on two components, the nucleophile and the substrate

Doubling the amount of nucleophile, doubles the rate

Doubling the amount of substrate, doubles the rate

Example and Rate Equation:

Example of Walden inversion:

5.2.4 The S_N1 Mechanism

S_N1: Substitution nucleophilic unimolecular, the two-step nucleophilic substitution mechanism

Unimolecular: Term that describes a reaction rate that depends on the concentration of ONE species

- In the first step the leaving groups (the negative halide ion) leaves, creating a carbocation
- In the second step, the nucleophile enters with the electron pair and bonds to the carbocation

General Mechanism:

Potential Energy Diagram:

- The first step (creation of the carbocation) is the slow or Rate-determining step
 - Reaction is only dependent on the alkyl halide and NOT the nucleophile
 - Reaction is unimolecular
- The second step is the fast step
- Carbocations are planar
 - Nucleophile can attack from both sides (no 100% inversion)
- The rate depends on the stability of the carbocation
 - Decrease in the order $3 > 2 > 1$
 - However, resonance stabilized carbocations (allylic, benzylic) are favored

S_N1 mechanism takes place mostly in neutral to acidic conditions with neutral nucleophiles such as water, alcohols, amines

- Often, if you have a neutral nucleophile you need a third step, loss of H^+

Reaction Rate:

- Rate depends on the slowest step
- Formation of carbocation is the slowest step
- Reaction Rate:

- Doubling or tripling the concentration of the alkyl halides results in twice or three times as fast reaction rates

Example of racemization of a pure compound because of an S_N1 reaction:

5.2.5 Factors Influencing the Reaction Mechanism: S_N2 versus S_N1

A) Carbocation stability:

- S_N1 needs a carbocation, S_N2 not
- The more stable the potential carbocation, the more likely S_N1

Alkyl halide series:

B) Steric Effects:

- For a brief period, the carbon has 5 groups coordinated to it during a S_N2 reaction

The more crowded the carbon center is (that means the bigger the groups around the carbon are) the more difficult it is to undergo five coordination

More likely S_N1

Alkyl halide series:

C) Strength of Nucleophile:

- The rate of an S_N2 reaction depends on the nucleophile and therefore on the strength of the nucleophile
- The rate of the S_N1 reaction is independent of the nucleophile and does not care about the strength of the nucleophile
- Charged nucleophiles are stronger than their uncharged counterparts
- More electronegative elements hold their electrons tighter to the nucleus and are therefore not as good nucleophiles as less electronegative atoms
HS⁻ better than HO⁻
- Stronger nucleophiles favor S_N2 over S_N1

D) Solvent:

- Polar solvents with unshared electron pairs such as water, amines, and alcohols can use these electrons to solvate and therefore stabilize a carbocation

Solvating Picture:

- These solvents promote the S_N1 mechanism

- Solvents also affect nucleophilicity

A solvent that has a proton that can form a hydrogen bond can interact with the nucleophile, thereby changing (decreasing) the strength of the nucleophile

These solvents include alcohols and amines and are called **PROTIC** solvents

These solvents again promote the S_N1 mechanism

Examples:

- Solvents that do NOT have protons available for hydrogen bonding are called **APROTIC** solvents

There are two types of aprotic solvents:

- Non polar aprotic (not a polar molecule) solvent

Example:

- Polar aprotic solvent (a polar but aprotic solvent molecule)

Example:

- Polar aprotic solvents have usually atoms that have non-bonded electron pairs
 - These free electron pairs can solvate cations but not anions
 - You never add a free, charged nucleophile but an anion-cation pair
 - Since polar aprotic solvents solvate the cation but NOT the anion (both would have electron pairs and this is repulsive), the anion can stay free and very active in solution
 - This increases the strength of the nucleophile
- Polar aprotic solvents promote the S_N2 mechanism

Summary of nucleophilic substitutions:

Two mechanisms

- *unimolecular (two steps)*
- *bimolecular (one step)*

Rate:

- S_N1 depends only on the substrate
- S_N2 depends on nucleophile and substrate

Stereochemistry:

- S_N1 racemic mixture
- S_N2 Walden inversion

Nucleophiles

- Stronger nucleophiles favor S_N2

Solvent:

- Protic solvents favor S_N1
- Polar aprotic solvents favor S_N2

Steric:

- Bulky side groups favor S_N1

5.3 Elimination Reaction

- The other major reaction nucleophiles can undergo is the elimination reaction
- Eliminations can occur by two mechanisms: The E₁ and E₂ mechanisms

5.3.1 The E₂ Mechanism

The E₂ mechanism is a concerted, one step reaction like the S_N2 mechanism

E₂: Elimination bimolecular, the one-step elimination mechanism

General Mechanism:

- The nucleophile abstracts an H⁺ from the molecule, the former C-H electron pair is moving towards the carbon that has the bonded halogen and simultaneously the leaving group (halogen) is getting kicked out

You generate a double bond

5.3.2 The E₁ Mechanism

The E₁ mechanism is a two-step reaction sequence

E₁: Elimination unimolecular, the two-step elimination mechanism

General Mechanism:

- In the first step, the Leaving Group leaves the substrate with the bonding electron pair creating a carbocation (the slow or rate determining step)
- In the second step, the nucleophile abstracts an H from the carbon next to the carbocation, the electron pair that bonded the hydrogen to the carbon flips toward the carbocation, creating a double bond

5.3.3 Comparison of E₁ versus E₂

A) Reaction Rates:

- The E₂ reaction depends on the alkyl halide and the nucleophile

Rate equation the same as the one for the S_N2 reaction

Rate Equation:

- The E_1 reaction depends only on the alkyl halide

Rate Equation:

B) Stereochemistry:

- The groups being eliminated must be in anti or syn relationship

The developing p orbitals must be parallel to each other for the overlap

Newman projection:

- The E_2 mechanism occurs from the anti position

This allows maximal distance between nucleophile and leaving group

- The E_1 mechanism proceeds through a carbocation

Does not care if syn or anti, the carbocation can form from either

Once the carbocation is formed, it can rotate freely thereby destroying any stereochemistry

Example:

5.4 Substitution versus Elimination

Schematic Representation of all mechanisms:

A) Tertiary Haloalkanes:

- only able to undergo S_N via S_N1
- can undergo elimination by either E_1 or E_2

Factors that influence the outcome:

- If the resulting alkene after elimination is very stable, elimination preferred
- If you have a strong nucleophile E_2 preferred since S_N2 not possible (sterics)
- If you have a weak nucleophile either E_1 or S_N1

Examples:

B) Primary Haloalkanes:

- Do not undergo S_N1 or E_1 because of unstable cation
- But do E_2 or S_N2
- Strong nucleophiles give only S_N2
- Weak nucleophile gives mixtures
- Use of tert-butoxide ion increases elimination

Examples:

C) Secondary Haloalkanes:

- Can react via all mechanisms
- Strong nucleophiles with low basicity give S_N2
- Weak nucleophile S_N1 with some E_1
- Good bases push it to E_2

Examples:

Summary of Chapter 5:

⇒ *Alkylhalides*

⇒ *Nucleophilic Substitutions*

→ S_N1

→ S_N2

→ *Similarities*

→ *Differences*

→ *Rates and Stereochemistry*

→ *When which mechanism*

⇒ *Elimination*

→ E_1

→ E_2

→ *Similarities*

→ *Differences*

→ *Rates and Stereochemistry*

→ *When which mechanism*

⇒ *Elimination versus Substitution*