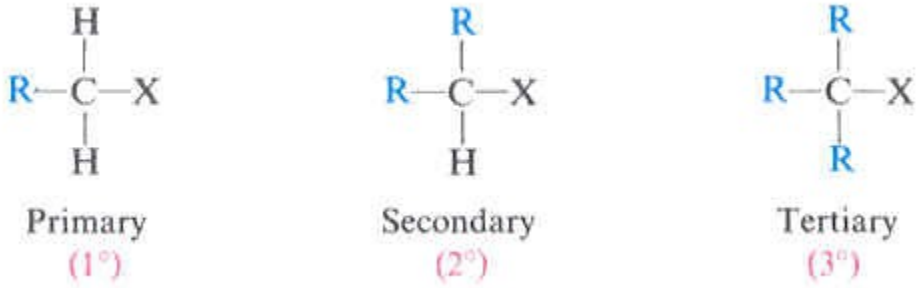
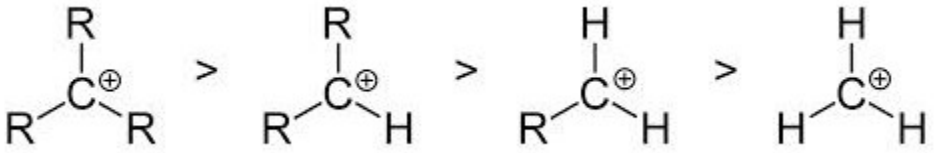
- Alkyl halides
  - An **alkyl halide** is an alkane with a halogen bonded to a carbon.
  - Types (X = halogen):
    - Methyl halide = CH_3X
    - Primary alkyl halide = RCH_2X
    - Seocndary alkyl halide = R_2CHX
    - Tertiary alkyl halide = R_3CX

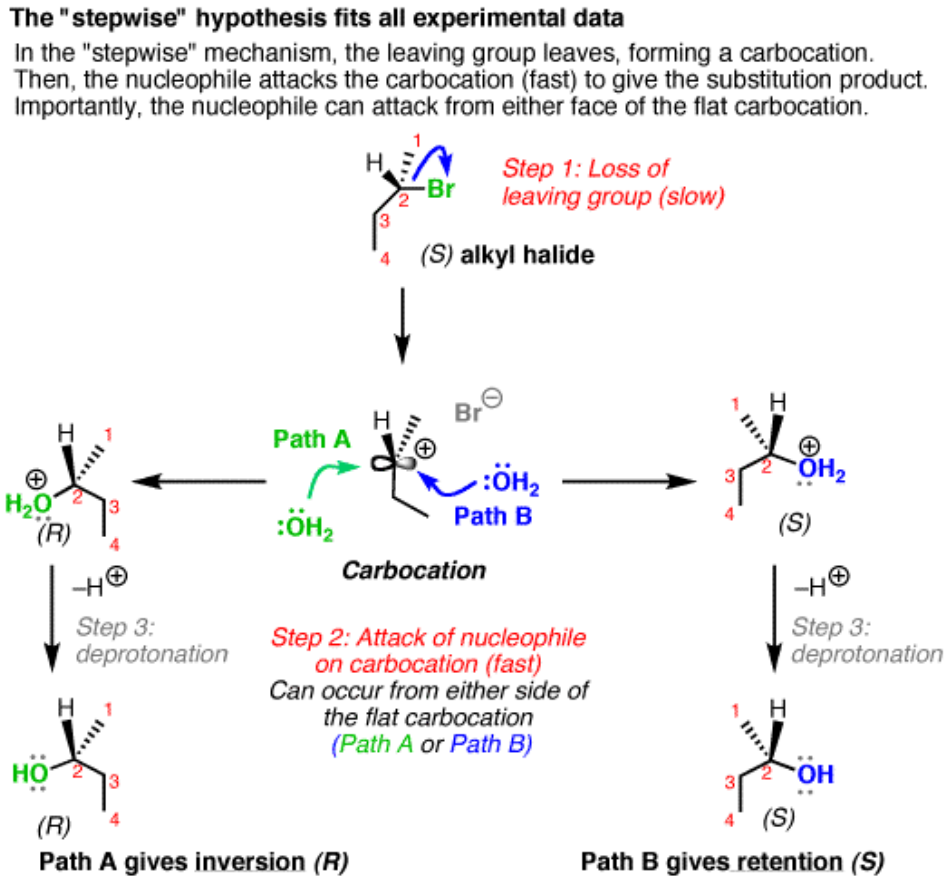


- Carbocations
  - **Carbocations** are positively charged carbon atoms.
    - Methyl carbocation = CH_3^+
    - Primary carbocation = RCH_2^+
    - Seocndary carbocation = R_2CH^+
    - Tertiary carbocation = R_3CX^+
    - Tertiary > Secondary > Primary > Methyl in terms of <u>stability</u>



- Leaving group
  - A **leaving group** is the species that leaves in a substitution or elimination reaction.
    - The better the leaving group, the faster the reaction.
  - How to determine leaving group strength:
    - The less basic/more acidic, the better the LG
    - LG strength follows the periodic trend for acidity
- Protic vs. Aprotic solvent
  - A **solvent** is a liquid that serves as the medium for a reaction. It can serve two major purposes:
    - (<u>Non-participatory</u>) to dissolve the reactants. Polar solvents are best for dissolving polar reactants (such as ions); nonpolar solvents are best for dissolving nonpolar reactants (such as hydrocarbons).
    - <u>Participatory</u>: as a source of acid (proton), base (removing protons), or as a nucleophile (donating a lone pair of electrons). The only class of solvents for which this is something you generally need to worry about are polar protic solvents (see below).
  - **Protic solvents** have O-H or N-H bonds. These bonds serve as sources of protons.
    - We see that protic solvents favor Sn1 and E1 reactions.
  - **Aprotic solvents** may have hydrogens on them somewhere, but lack O-H or N-H bonds.
    - We see that aprotic solvents favor Sn2 and E2 reactions.

- Electrophiles vs. Nucleophiles
  - **Electrophiles** accept electrons whereas **nucleophiles** donate electrons.
    - For this chapter, the electrophile will always be an alkyl halide.
  - A stronger nucleophile will lead to a faster elimination or substitution reaction. How to determine nucleophile strength:
    - In polar, protic solvents:
      - Nucleophilicity **increases** as the attacking atom moves **down** a group of the periodic table.
      - Nucleophilicity **increases right to left** across a row of the periodic table.
    - In polar, aprotic solvents:
      - Nucleophilicity **increases** as the attacking atom moves **up** a group of the periodic table.
      - Nucleophilicity **increases right to left** across a row of the periodic table.
    - If comparing the same atom species, the more basic molecule = the better nucleophile.
- Sn1
  - rate = k[RX]
    - Rate law only depends on the alkyl halide concentration, not the nucleophile concentration.
    - The first step is rate determining step
  - Likes to happen in <u>protic</u> solvents
  - Favored by <u>weaker</u> nucleophiles
  - <u>Stereochemistry</u>: get both stereoisomers (retention and inversion), but slightly more retention than inversion occurs.
  - Alkyl halide that reacts the fastest forms the most stable carbocation. Tertiary > secondary > primary > methyl halide



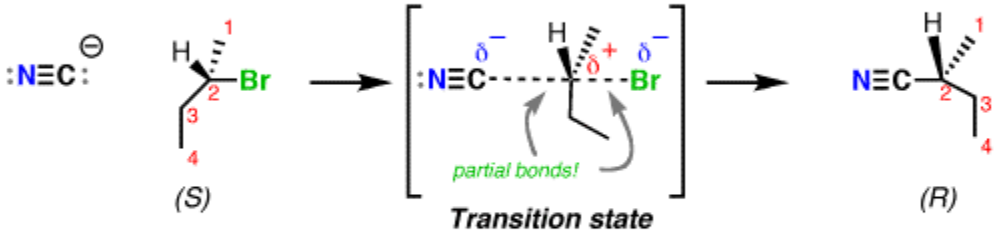
• Explains unimolecular rate law (depends only on concentration of substrate)
• Explains why a mixture of retention and inversion obtained (attack can occur from either face of the carbocation)
• Explains sensitivity to substitution pattern (3°>2°>>1° because tertiary carbocations are more stable).

This is called the S_N1 mechanism (Substitution, Nucleophilic, unimolecular)

- Sn2
  - rate = k[RX][nucleophile]
    - Rate law depends on the concentration of the alkyl halide and the nucleophile
  - Likes to happen in aprotic solvents
  - Favored by stronger nucleophiles
  - Transition state is triagonal bipyramidal. Leaving group has a negative charge and the nucleophile has a positive charge. The carbon involved changes from an sp^3 to an sp^2 hybridization.
  - Stereochemistry: inversion of stereocenter (called this backside attack)
  - **Beta branching** (branching at the beta carbon) slows down the reaction
  - Favored by unhindered alkyl halides: methyl halide > primary > secondary > tertiary
  - The mechanism occurs in a single, **concerted** step.

The "backside attack" hypothesis fits all experimental data

In the "backside attack", the nucleophile attacks the substrate from the backside in a single step, resulting in inversion of configuration.



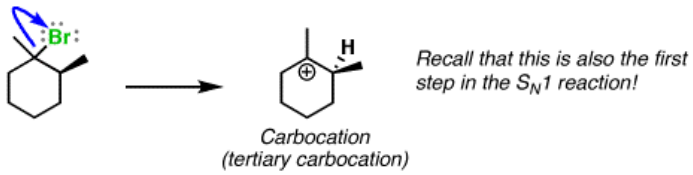
- Explains bimolecular rate law (depends on conc. of nucleophile and substrate)
- Explains inversion of stereochemistry
- Explains sensitivity to steric hindrance (bulky groups slow down backside attack)

This is called the S_N2 mechanism (Substitution, Nucleophilic, bimolecular)

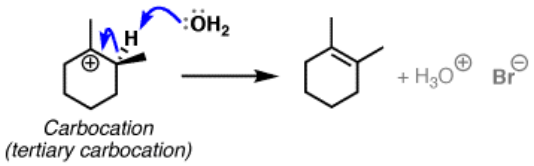
- E1
  - rate = k[RX]
    - Rate law only depends on the alkyl halide concentration, not the nucleophile concentration.
    - The first step is rate determining step
  - Likes to happen in protic solvents
  - Favored by weaker bases
  - More substituted alkene is favored (**zaitev's rule**)

How to explain these results?

The best theory we have is that the reaction proceeds through two steps.
First, the leaving group leaves to form a carbocation



Second, a proton is removed by base to give the alkene

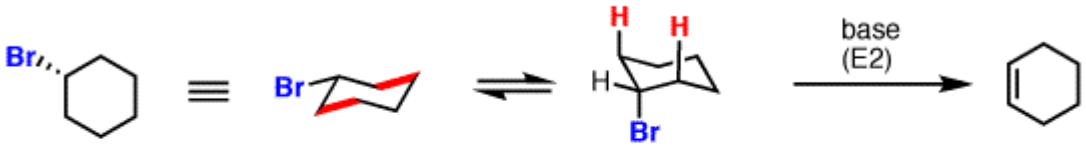


This explains several key facts:
1) the rate determining step (slow step) is loss of leaving group to form the carbocation
2) the rate is proportional to carbocation stability (tertiary > secondary >> primary)
3) Recall that loss of the leaving group is also the first step in the S_N1 reaction. This is why S_N1 byproducts can also be observed

This is called the E_1 mechanism [Elimination, unimolecular]

- E2
  - rate = k[RX][nucleophile]
    - Rate law depends on the concentration of the alkyl halide and the nucleophile
  - Likes to happen in aprotic solvents
  - Favored by stronger bases
  - more substituted alkene is favored (zaitev's rule)
  - There must be an **antiperiplanar arrangement** of H and X, meaning they must be 180 degrees apart.
    - If H and X are not antiperiplanar, rotate the bond until it is. If you cannot rotate the bond to make H and X antiperiplanar, no reaction will occur.
      - How can I tell if H and X are antiperiplanar? Draw a newman projection!
    - If you are doing an elimination of a cyclohexane ring, draw the chair and see if H and X are 180 degrees apart. Note that you may even need to flip the chair in order to see the antiperiplanar relationship (as shown below)

In a cyclohexane, the E2 can only occur when the leaving group is axial:



Equatorial

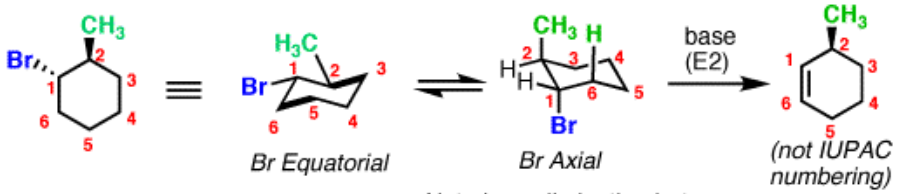
No *hydrogens anti-periplanar to the Br (only carbons are)*

Axial

Two *hydrogens are anti-periplanar to the Br. The double bond can form through removal of either hydrogen*

- Sometimes, you will only see that one anti-periplanar relationship is possible and that may be the less substituted double bond. For more information, visit http://www.masterorganicchemistry.com/2012/10/18/the-e2-reaction-and-cyclohexane-rings/

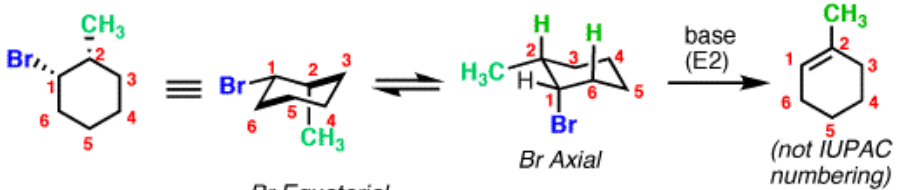
How Cyclohexane Stereochemistry Affects Elimination



Br Equatorial *Br Axial* *(not IUPAC numbering)*

Note how elimination between C_1 and C_2 is **not possible**, since there is no H at C_2 that is axial to the leaving group

Elimination can only occur between C_1 and C_6 here



Br Equatorial *Br Axial* *(not IUPAC numbering)*

Note how elimination between C_1 and C_2 **is possible**, since there is now an H at C_2 that is axial to the leaving group

Elimination can occur between C_1 and C_2 here (favored due to Zaitsev's rule)

Bottom line: elimination can't occur when there is no H "anti" to the leaving group

- The mechanism occurs in a single, **concerted** step.

We have enough evidence to propose a mechanism!
A proposal for how this reaction works:

The reaction is concerted (explaining the rate law)

Secondly, this mechanism explains the *stereochemistry* of this reaction

Note that the H and the Br are oriented at 180° to each other ("anti")

Imagine the pair of electrons from C_3–H doing a "backside attack" on the C_2–Br bond, forming the new π bond.

This is called the E_2 mechanism

- Choosing between E1, E2, Sn1, and Sn2
  - NOTE: bicyclo compounds, halides attached to aromatic rings or to carbon that participates in a double/triple bond do not react in these schemes.
  - Step 1: determine if you have primary, secondary, or tertiary alkyl halide.
    - If I have a primary alkyl halide:
      - Step 2: determine if the base is bulky
        - If it is, then do E2
        - If it is not, then do Sn2
      - NOTE: if the base is a bad nucleophile, then there will be no reaction
    - If I have a secondary alkyl halide:
      - Step 2: determine if the base is bulky
        - If it is, then do E2
        - If it is not, proceed to step 3
      - Step 3: determine if the base is strong
        - If it is, then E2 and Sn2 will occur, but E2 will be favored
        - If it is not, proceed to step 4
      - Step 4: determine if the species is a good nucleophile
        - If it is, then E2 and Sn2 will occur, but Sn2 will be favored
        - If it is not, then Sn1 and E1 will be favored
    - If I have a tertiary alkyl halide:
      - Step 2: determine if the base is strong
        - If it is, then do E2
        - If it is not, then do Sn1 and E1
  - What does "strong base" mean?
    - For our purposes, look for anions (e.g. RO-) that are not sulfur-based.
    - Weak bases will be protonated (e.g. ROH)
  - What is a bad base but a good nucleophile?
    - For DAT, think of sulfur-based nucleophiles and cyanide nucleophiles.
  - Benzylic and allylic halides do Sn1 and Sn2 depending on the solvent.
  - Note that if you can create a conjugated double bond system via elimination, do elimination!

- A special note on bulky bases:
  - $(CH_3)_3CO^- K^+$ is **hoffman elimination**. Form the less substituted double bond!
  - $C_2H_5O^- Na^+$ is **standard E2 elimination** (zaitev's rule)