Substitution and Elimination Reactions:

Substitution rxn - replacement of another atom/group

Elimination rxn - e- withdraw and 1 H from an adjacent C is eliminated, double bond forms

Leaving Group - atom or group that is replaced/eliminated

- The Halide is a good leaving group from an alkyl halide

Alkyl Halide Importance - Due to a polar bond in a C - X bond

S_N2:

https://www.youtube.com/watch?v=o7hnYlfwMMM

S_N2 Reactions: substitution, nucleophilic, bimolecular

nucleophile & alkyl halide

- nucleophile reacts with the alkyl halide from a direction opposite the group that is being displaced (the leaving group)
- as the nucleophile comes in on one side of the substrate and bonds to the carbon, the halide departs from the other side, thereby inverting the stereochemical configuration

ex. reaction of (S)- 2- bromobutane + OH^- --> (R) -2 - butanol

- the S_N2 reaction occurs in a single step that involves both the alkyl halide and the nucleophile

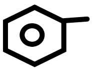
CHARACTERISTICS of Reactants in an SN2 reaction:

1) The Substrate: steric effects

- alkyl branching at the reacting center slows the reaction greatly

- normally useful only with - methyl halides
  primary halides
  few simple secondary halides

vinyl halides, $R_2C=CRX$

aryl halides,  X,

S_N2 reaction

2) The nucleophile:

- any species, either neutral or negatively charged, can act as a nucleophile as long as it has an unshared pair of electrons
  (Lewis Base)

- If the nucleophile is neutral, the product is positively charged

- If the nucleophile is negatively charged, the product is neutral

$$\mathrm{Nu}\!:^{-} \quad + \quad \mathrm{R-Y} \quad \text{-->} \quad \mathrm{R-Nu} \quad + \quad \dot{\mathrm{Y}}^{-}$$

$$\mathrm{Nu}\!: \quad + \quad \mathrm{R-Y} \quad \text{-->} \quad \mathrm{R-}\overset{+}{\mathrm{Nu}} \quad + \quad \dot{\mathrm{Y}}^{-}$$

ex. $\mathrm{R-C{\equiv}C}\!:^{-} \quad + \quad \mathrm{CH_3Br} \quad \text{-->}$

Nucleophile:

either neutral or negatively charged as long as it has an unshared pair of electrons (Lewis Base)

$H_2O < CH_3CO_2^{-1} < NH_3 < Cl^{-1} < OH^{-1} < CH_3O^{-1} < I^{-1} < CN^{-1} < HS^{-1}$

- Some trends can be detected:

a) nucleophilicity roughly parallel basicity: the more basic the species the more nucleophilic it is.

b) nucleophilicity usually increases going down a column of the periodic table.
thus, HS^- is more nucleophilic than $HO^{\ominus}$ and
$I^- > Br^- > Cl^-$

c) negatively charged nucleophiles are usually more reactive than neutral ones. As a result, S_N2 reactions are often carried out under basic conditions rather than neutral or acidic conditions

1) What product would you expect from S_N2 reaction of 1-bromobutane with each of the following?

a) NaI b) KOH c) $HC\equiv CLi$

2) Which substance in each of the following pairs is more reactive as a nucleophile?

a) $(CH_3)_2N^-$ or $(CH_3)_2NH$

b) $(CH_3)_3B$ or $(CH_3)_3N$

Leaving Group:

The greater the extent of charge stabilization by the leaving group, the lower the energy of the transition state and the more rapid the reaction

$OH^{-1} < NH_2 < OR^{-1} < F^{-1} < Cl^{-1} < Br^{-1} < I^{-1} < TosO^{-1}$

Nucleophilicity:

Nu: how easy is it to get into the alkyl halide (how fast it can attack an e- deficient atom)

- in a protic solvent: $I^- > OH^- > F^-$
- in an aprotic solvent
  - basicity and nucleophilicity correlate

$OH^- > F^- > I^-$

Factors that Affect Nucleophilicity:

1) Negative charge: anions are stronger than their corresponding conjugate acids

2) Basicity: a) within a family, it increases with polarizability not basicity

- $I^- > Br^- > Cl^- > F^-$

- $RSe^- > RS^- > OH^- > F^-$

b) within a row, it increases with basicity

- $NH_2^- > RO^- > OH^- > F^-$

3) Size: the bulkier the nucleophile, the lower its nucleophilicity

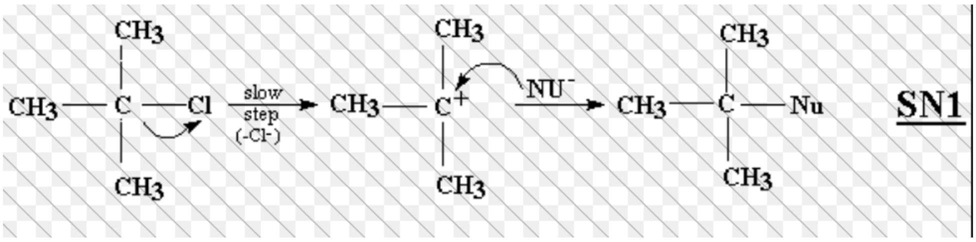
$CH_3CH_2O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$

S_N2:

- prefers 1° or 2°
- rate = k[substrate][Nu]
- 1 step
- requires good nucleophile
- inversion of configuration (R ---> S or S ---> R)
- good leaving group
- prefers polar aprotic solvent
- no possible rearrangement

https://www.youtube.com/watch?v=FuFpjx_ZeT0

S_N1 reaction:



Characteristics:

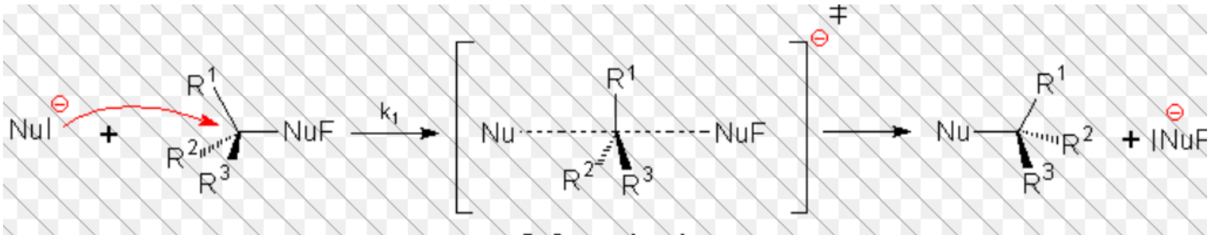
1) Substrate: the best substrate yield the most stable carbocations. As a result, S_N1 reactions are best for tertiary, allylic, and benzylic halides

2) Leaving group: good leaving groups increase the reaction rate by lowering the energy level of the transition state for carbocation formation.

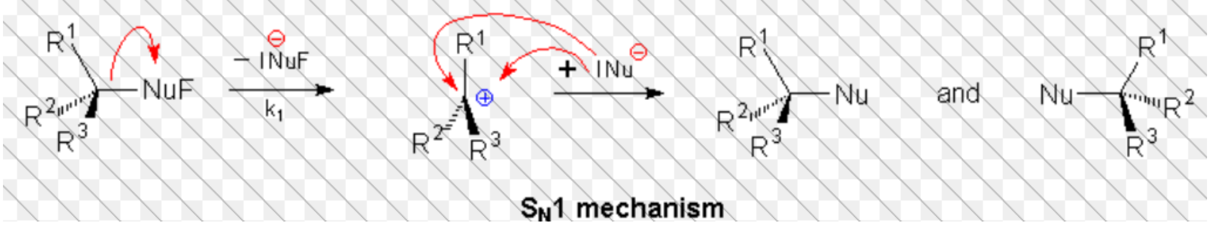
3) Nucleophile: the nucleophile must be nonbasic to prevent a competition elimination of HX, but otherwise does not affect the reaction rate. Neutral nucleophiles work well.

4) Solvent: Polar solvents stabilize the carbocation intermediate by solvation, thereby increasing the reaction rate

Mechanism difference of SN1 and SN2:



S_N2 mechanism



S_N1 mechanism

SN2	**vs**	**SN1**
1) Both alkyl halide and nucleophile conc affect rate		1) Only alkyl halide conc effects rate
2) Better nucleophile = faster rxn		2) Nucleophile strength DOES NOT MATTER
3) Product = asymmetric alkyl halide with opposite config.		3) Product = racemic alkyl halide

Elimination Reactions:

- give alkene products

- *Zaitsev's Rule*
  base induced elimination reactions generally give the more stable alkene product (the one with the more alkyl substituents on the double-bond carbons)

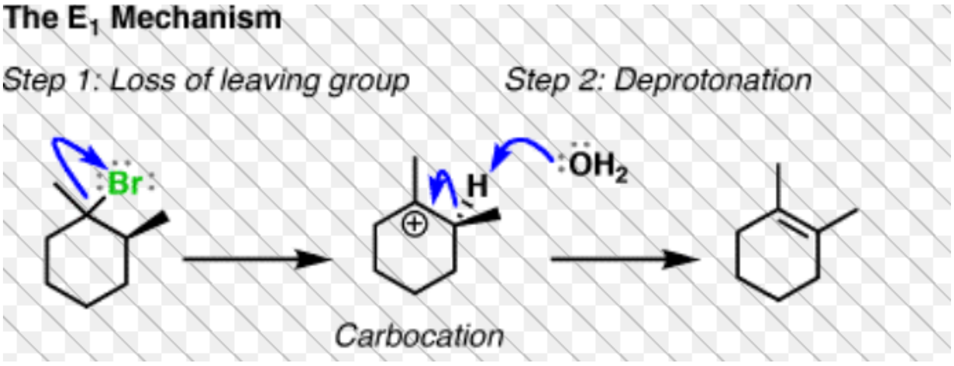
ex. 2-bromobutane $\xrightarrow[CH_3CH_2OH]{CH_3CH_2O^-Na^+}$ 2-butene + 1-butene

81% 19%

ex. 2-bromo-2-methylbutane ---> 70% + 30%

E1:

- the C-X bond breaks first to give a carbocation intermediate that undergoes subsequent base abstraction of H^+ to yield an alkene.



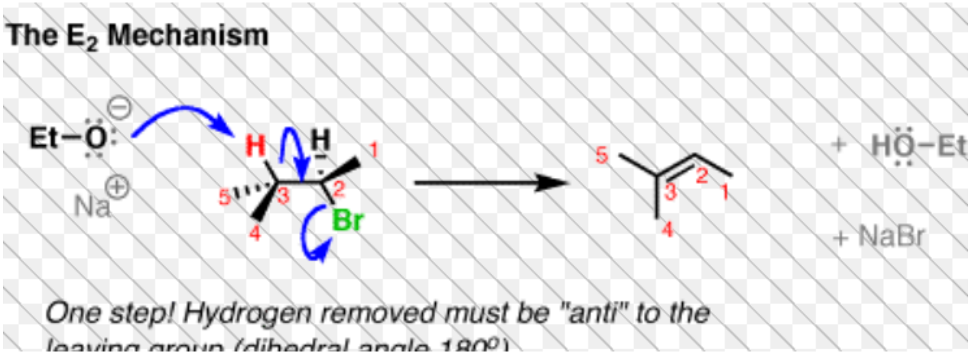
The E_1 Mechanism

Step 1: Loss of leaving group

Step 2: Deprotonation

E2:

- based induced C-H bond cleavage is simultaneous with C-X bond cleavage, giving the alkene in a single step.



The E_2 Mechanism

One step! Hydrogen removed must be "anti" to the leaving group (dihedral angle 180°)

ex. What product would you expect from the reaction of 1-chloro-1-methylcyclohexane with KOH in ethanol?

(Locate the hydrogen atoms on each carbon next to the leaving group - beta hydrogens) ex 2: Ignoring double-bond stereochemistry, what products would you expect from elimination reactions of the following alkyl halides? Which will be the major product in each case?

a) 3-bromo-2-methylpentane

b) 3-chloro-2,3,5-trimethylhexane

c) 1-bromoethylcyclohexane

ex. 3: What alkyl halides might the following alkenes have been made from?

a) 3,6-dimethyl-1-heptene

b) 3,4-dimethylcyclohexene

E2	E1
strong base	independent of strength of base
$3^o > 2^o$	$3^o > 2^o$
usually no rxn with 1^o	no rxn with 1^o
leaving group: $I^- > Br^- > Cl^- > F^-$	leaving group: $I^- > Br^- > Cl^- > F^-$
more stable alkene formed	more stable alkene formed
polar aprotic solvent best	polar protic solvent
higher temp favored (over S_N2)	higher temp favored (over S_N1)

S_N2:	S_N1
good nucleophile	independent of strength of nucleophile
methyl > $1^o > 2^O$	$3^o > 2^o$
no rxn with 3^o	no rxn with methyl or 1^o
inversion	racemic mixture
leaving group: $I^- > Br^- > Cl^- > F^-$	leaving group: $I^- > Br^- > Cl^- > F^-$

E1 reaction:

- Just as the E2 reaction is analogous to the S_N2 reaction, the S_N1 has a close analog called the E1 reaction

- unimolecular
- two steps are involved
  - the first is the rate determining step and a carbocation intermediate is present
  - the second step is the loss of H^+ from an adjacent carbon rather than by substitution.
  - E1 and S_N1 reactions normally occur together whenever an alkyl halide is treated in a protic solvent with a nonbasic nucleophile. Thus, the best E1 substrates are also the best S_N1 substrates, and mixtures of substitution and elimination products are usually obtained.

ex. 2-chloro-2-methylpropane $\xrightarrow{H_2O\text{, ethanol}}$ 2-methyl-2-propanol (64%)

Some Trends:

1) Primary alkyl halides:
   - S_N2 substitution occurs if a good nucleophile is used, E2 elimination occurs if a strong base is used.

2) Secondary alkyl halides:
   - S_N2 substitution occurs if a weakly basic nucleophile is used in a polar a protic solvent, E2 elimination predominates if a strong base is used. Secondary allylic and benzylic alkyl halides can also undergo S_N1 and E1 reactions if a weakly basic nucleophile is used in a protic solvent.

3) Tertiary alkyl halides:
   - E2 elimination occurs when a base is used, but S_N1 substitution and E1 elimination occur together under neutral conditions, such as in pure ethanol or water.

Substitution vs Elimination

1) Strong bases/nucleophiles force the reaction into second-order reactions. Thus, with strong bases and nucleophiles (such as OH^-), you get S_N2 or E2 reactions or both. With weak bases/nucleophiles, you more often get first-order products (those produced by either S_N1 or E1 reactions).

2) Reactions of primary substrates generally proceed via S_N2 reactions (methyl substrates always proceed by S_N2). When very strong bases/nucleophiles are used with primary substrates, you get a mixture of both S_N2 and E2 reactions.

3) Reactions of tertiary substrates produce E1 and S_N1 reactions with weak bases/nucleophiles plus a protic solvent; with strong bases, reactions of tertiary substrate produce E2 reactions.

4) The reactions of secondary substrates are the hardest to predict. Under the right conditions, secondary substrates can undergo reactions by all four mechanisms. Weak bases/nucleophiles plus a protic solvent will typically give you a mixture of E1 and S_N1 products; strong bases/strong nucleophiles will typically give you a mixture of E2 and S_N2 products.

5) Spotting nucleophiles that are not basic will help you distinguish substitution from elimination reactions. For example, the halides (I^-, Cl^-, Br^-) and thiols (R-SH) are nucleophiles but not terribly basic. The reactions of these molecules typically proceed exclusively by substitution. T-butoxide ($(CH_3)_3CO^-$), on the other hand, is a poor nucleophile but a powerful base, and almost exclusively force the reaction to go via an E2 elimination.

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E2 and predict the product for each:

1) chlorocyclopentane with sodium methoxide and methanol

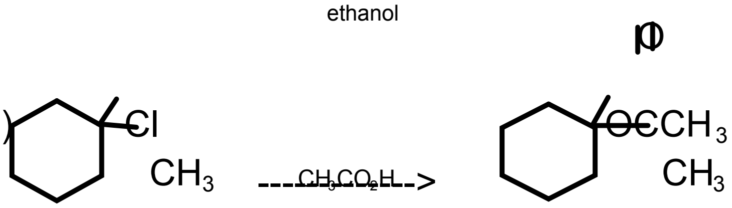
2) 1-bromo-1-phenylethane with methanoic acid and water

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E2 :

1) $CH_3CH_2CH_2CH_2Br \xrightarrow[THF]{NaN_3} CH_3CH_2CH_2CH_2N{=}N{=}N$

2) $CH_3CH_2CHClCH_2CH_3 \xrightarrow[ethanol]{KOH} CH_3CH_2CH{=}CHCH_3$

3)



Synthesizing Ethers:

$R\text{-}Br + RO^- \rightarrow R - O - R + Br^-$

$2ROH + 2Na \rightarrow 2Na^+ + H_2$

Williamson Ether synthesis
- nucleophilic substitution
- need high conc. of good nucleophile
- S_N2 rxn (1 step)

ex. butyl propyl ether

a) $CH_3CH_2CH_2Br + CH_3CH_2CH_2CH_2O^- \rightarrow$

b) $CH_3CH_2CH_2CH_2Br + CH_3CH_2CH_2O^- \rightarrow$

ex. t-butyl ethyl ether

a) $\mathbf{CH_3CH_2Br + (CH_3)_3CO^- \rightarrow}$

b) $(CH_3)_3CBr + CH_3CH_2O^- \rightarrow$

(E2 would predominate)

- The less hindered alkyl group is provided by the alkyl halide and the more hindered alkyl group comes from the alkoxide ion.

1) What product would you expect from S_N2 reaction of 1-bromobutane with each of the following?

a) NaI b) KOH c) $HC\equiv CLi$ d) NH_3

2) Which substance in each of the following pairs is more reactive as a nucleophile?

a) $(CH_3)_2N^-$ or $(CH_3)_2NH$

b) $(CH_3)_3B$ or $(CH_3)_3N$

c) H_2O or H_2S

3) Rank the following compounds in order of their expected reactivity toward S_N2 reaction

CH_3Br, CH_3OTos, $(CH_3)_3CCl$, $(CH_3)_2CHCl$