

NUCLEOPHILIC SUBSTITUTION AND LUCAS TEST

Compounds containing carbon-halide bond could be classified as alkyl halides, aryl halide, allylic/benzylic/propargyl halides, vinylic or halogen-containing acetylene derivatives (Figure 1). The C-Hal σ -bond is formed by the overlap of an orbital of the halogen atom and the hybridized (sp^3 or sp^2 or sp). Alkyl halides (as well as allylic/benzylic halides) can be further organized into primary, secondary and tertiary halides, depending on how many carbon are located on the α -carbon (C-X).

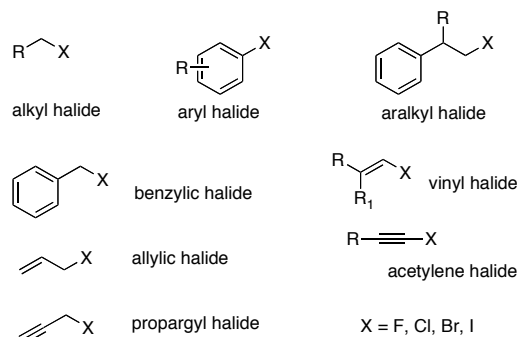
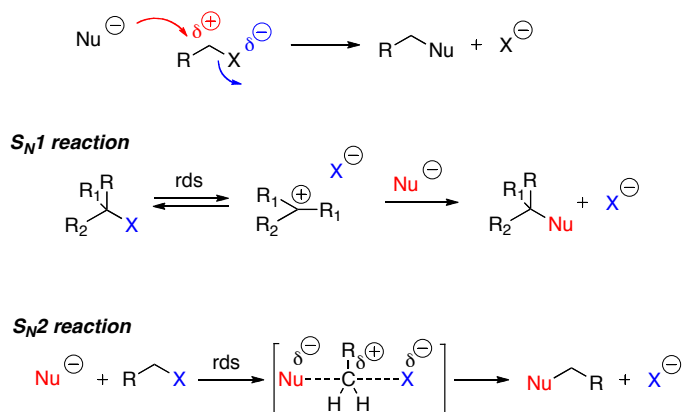


Figure 1

Substitution reactions

Electronegativity of halogen atoms is responsible for the polarity of the C-X bond, and due to this, the carbon atom has a partial positive charge. The electrophilicity of the α -carbon atom makes it a suitable reactive center for the attack by a nucleophile (Scheme 1). In this process, the halide atom is substituted with the incoming nucleophile, hence the name – nucleophilic substitution.



Scheme 1

The halide is the leaving group, *i.e.*, a group that is displaced from the carbon atom. Leaving groups can be divided into good and bad leaving groups, depending on how easy/difficult is to displace the leaving group. The rationale for deciding on the leaving group potential is similar to acid/conjugate base paradigm, including delocalization of the charge, basicity vs nucleophilicity, etc.

Depending on the nature of the substrates and the nucleophile as well as the reaction conditions, the substitution

reaction can proceed *via* several pathways (Scheme 1). Specifically unimolecular nucleophilic substitution (S_N1) and bimolecular nucleophilic substitution (S_N2) mechanisms operate. Obviously, the rate of the S_N2 reaction depends on the concentration of both nucleophile and the substrate (S_N2 rate = $k[\text{substrate}][\text{Nu}]$), whereas the rate of S_N1 reaction is nucleophile independent (S_N1 rate = $k[\text{substrate}]$). Hence, by varying the concentrations of the reactants and measuring the rates of the reactions, it is possible to suggest the mechanism of the substitution process. It should be noted that S_N2 is a concerted mechanism, whereas S_N1 proceeds in a step-wise fashion that involves a carbocationic intermediate.

Another way of discriminating between S_N1 and S_N2 mechanism, one could use an optically active substrate. S_N2 process proceeds with the inversion of stereochemistry, while an S_N1 reaction leads to a racemate (an equal mixture of enantiomers, resulting in optically inactive material). The carbon atom in the carbocation is sp^2 -hybridized, and therefore it is planar, hence the nucleophile can attack either from the bottom or from the top of, leading to a racemate.

The structure of the substrate sometimes is indicative of the mechanism of the substitution. Usually primary and secondary substrates undergo the nucleophilic substitution *via* an S_N2 process. The fact that a partial positive charge, instead of the full positive charge, is maintained on the primary or secondary α-carbon atom in the transition state is responsible for the S_N2 mechanism. Some secondary and especially tertiary substrates can undergo the nucleophilic substitution *via* an S_N1 mechanism. Obviously, tertiary carbon atom can fairly comfortably accommodate the positive charge. Also, the steric hindrance of the tertiary reactive center precludes an easy approach by the nucleophile, which also favors the S_N1 process.

Factors Influencing Reaction Pathways:

S_N2 versus S_N1:

Primary and secondary substrates (RX) generally undergo SN2
(At high solvent polarity, SN1 can become dominant for secondary)
Tertiary substrates proceed via SN1

SUBSTRATE TYPE	S _N 2	S _N 1
CH ₃ X (METHYL)	Very good	No
RCH ₂ X (PRIMARY)	Good	No
R ₂ CHX (SECONDARY)	Yes	Yes
R ₃ CX (TERTIARY)	No	Very good
ArCH ₂ X (BENZYLIC)	Good	Yes
C=C-CH ₂ X (ALLYLIC)	Good	Yes
O=C-CH ₂ X (α-CARBONYL)	Very good	No
ROCH ₂ X (α-ALKOXY)	Good	Very good
R ₂ NCH ₂ X (α-AMINO)	good	Very good

S_N2 versus E2:

Proportion of alkene by elimination increases if

- 1) strong base (hard, non-polarizable), negatively charged species
- 2) polar solvent (polar non-protic like DMF or DMSO, or polar-protic like RNH₂, ROH, H₂O)
- 3) increased reaction temperature (entropy: 2 molecules become 3)
- 4) increased steric bulk around the carbon bearing the leaving group (see table below)

Substrate reacted with EtONa	temperature	Alkene (elimination)
CH ₃ CH ₂ Br	55	1%
(CH ₃) ₂ CHBr	25	80%
(CH ₃) ₃ CBr	25	97%
CH ₃ CH ₂ CH ₂ Br	55	9%
(CH ₃) ₂ CHCH ₂ Br	55	60%

S_N1 versus E1:

In both cases, the rate does not depend on the concentration of nucleophile, not on the nature of the leaving group (the first ionization step is identical in both cases).

More elimination is observed if:

- 1) more basic (hard, non-polarizable) than nucleophilic
- 2) increased reaction temperature (entropy: 2 molecules become 3)

Substrate reacted with EtOH	temperature	Alkene (elimination)
$(\text{CH}_3)_3\text{CBr}$	25	19%

The classical case of E1 is the dehydration of tertiary alcohols under acidic conditions. The solvent is a poor nucleophile.

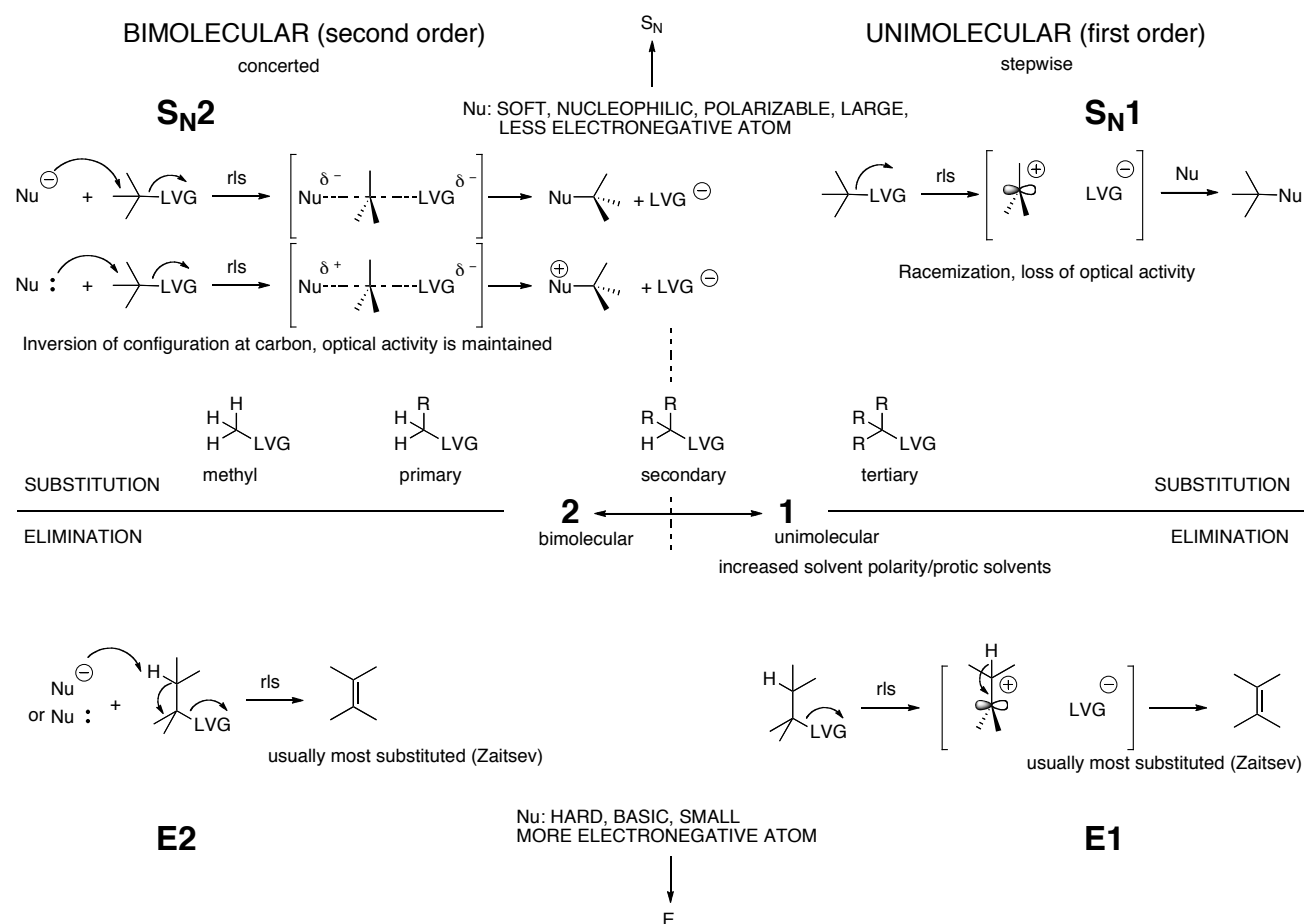
E2 versus E1:

Only E2 is affected by concentration of base. High base concentration means E2 is favored. Strong base favors E2, whereas weak base favors E1 (for E1, almost anything can serve as base: H_2O , ROH ...)

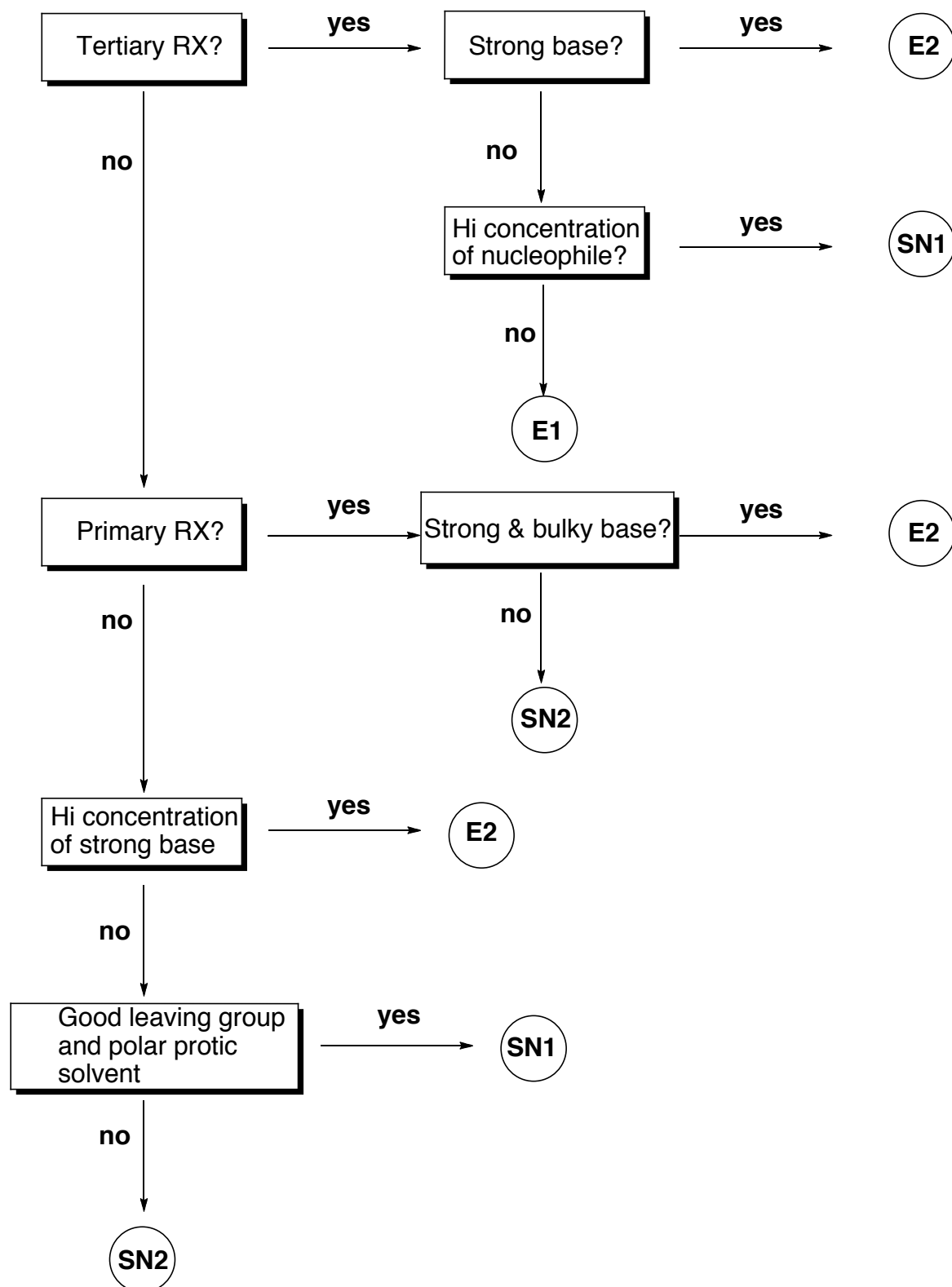
E1 can only occur when a relatively stable carbocation can form. More polar solvent favors E1. A better leaving group favors E1 (ionization is easier).

Leaving group which are next to an aryl or alkyl substituent (α -aryl, and α -alkyl) stabilize the carbocation and shift the mechanism towards E1 (for a given base).

Summary Scheme



DECISION TREE



PROBLEMS

A number of problems relate to nucleophilic substitution reactions covered in lecture

1. Alkyl bromides could be prepared by heating the corresponding alcohol in an aqueous solution of sodium bromide and excess of sulfuric acid. Provide the mechanism for this transformation, and indicate a rate-determining step.
2. Arrange the halide anions in the order of increasing: (a) basicity and (b) nucleophilicity.
3. Draw a two-step reaction sequence to convert (R)-2-hexanol to (S)-2-hexanol.
4. Explain, by drawing mechanism or intermediates, why tertiary alcohols take the shortest time to react in the Lucas test, while the primary is the longest, if any.
5. Why allylic and benzylic halides are more reactive in the substitution reactions than alkyl halides? Support your answer with resonance structures.
6. Benzylic halide could undergo a substitution reaction via either S_N1 or S_N2 mechanisms. Provide a structure of a benzylic halide that might indicate which mechanism is operating under a given set of conditions.