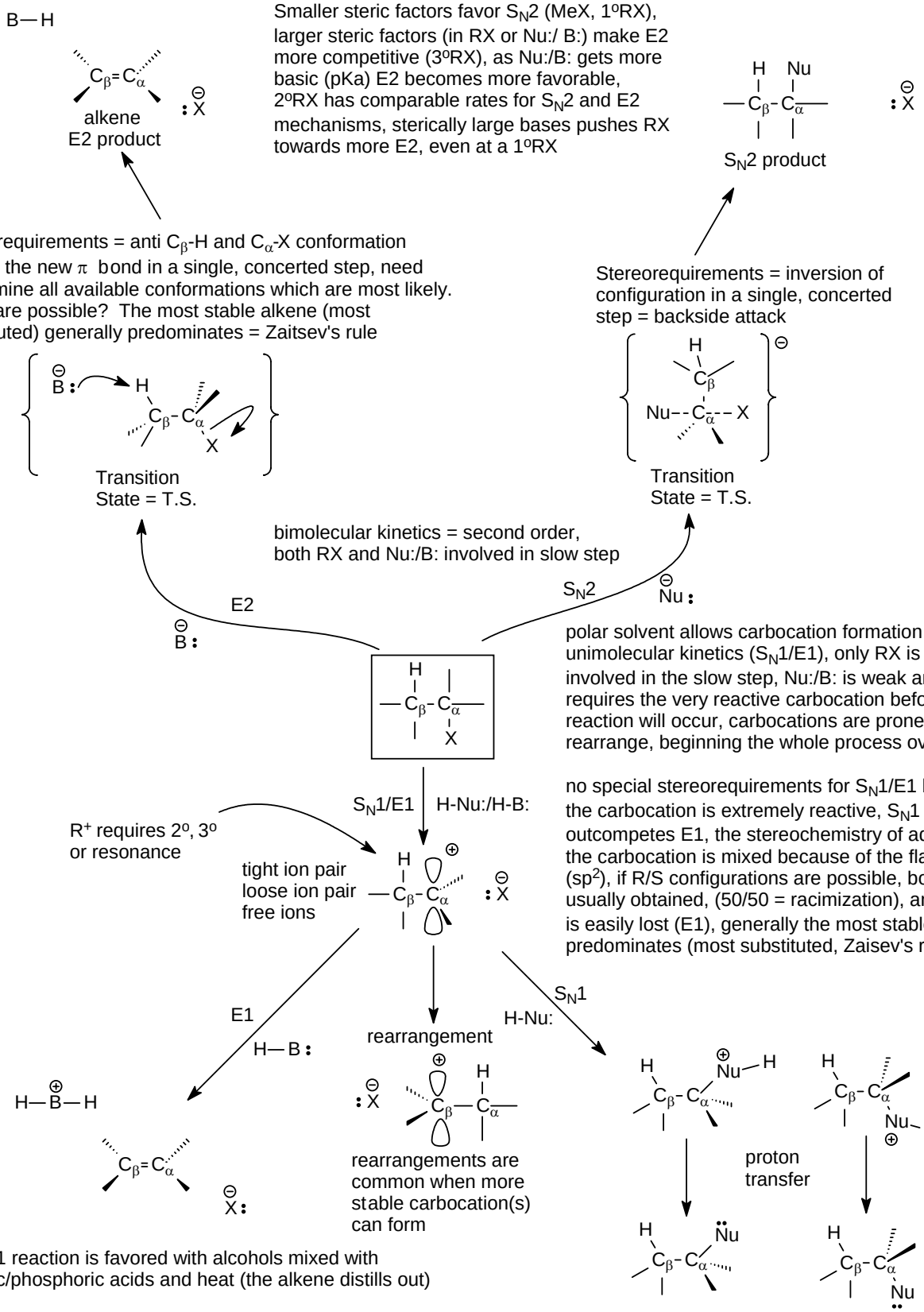
Four Classes of Reactions (Substitution vs. Elimination and Bimolecular vs. Unimolecular)



There are many details to keep track of. Need to organize these details to develop a "best guess". Generally some of each competing reaction occurs (e.g. S_N2 vs E2 or S_N1 vs E1). Our presentation is greatly simplified, but necessary as a first look at organic reactions.

General guidelines for S_N/E reactivity of RX compounds, usually true (but not always)

1. Nucleophiles (Nu:) and bases (B:) both have a donatable pair of elelctrons (lone pairs and pi bonds). When donated to a proton the electron pair donor is called a base and when donated to anything else (usually carbon for us) the donor is called a nucleophile.

2. In our course we will divide electron pair donors into two groups. Strong donors will be symbolized with a negative charge (S_N2 and E2 reactions) and weak donors will be symbolized with neutral charge (S_N1 and E1 reactions). Mostly this will lead us to correct choices, even though our assumptions are somewhat simplistic. Exceptions are neutral nitrogen (ammonia and amines) and neutral sulfur (thiols and sulfides) are considered good electron pair donors.

3. Leaving groups become very stable anions or neutral molecules (X = Cl^-, Br^-, I^-, TsO^-, H_2O, ROH, ROR, etc.) when they take their electron pair away from R.

4. Both S_N2 and E2 reactions are considered to be concerted, one-step reactions. They both require very specific orientations of the reactants for a successful reaction. S_N2 reactions always occur by backside attack of the nucleophile and E2 reactions usually (always for us) occur with an anti conformation of the C_β-H/C_α-X bonds.

5. Steric hindrance in either the RX electrophile or the electron pair donor slows S_N2 reactions by interfering with the backside approach. Complete substitution at the C_α-X carbon (tertiary RX) or complete substitution at any C_β carbon (4^o position) prevents S_N2 reaction (no reaction). By default E2 reactions will become the only possible choice if an anti C_β-H/C_α-X conformation can be attained.

6. All S_N2 reactions occur from the backside and produce inversion of configuration (R → S or S → R).

7. S_N2 reactions are generally run in polar, aprotic solvents like DMSO (dimethylsulfoxide) or DMF (dimethyl-formamide), which only weakly solvate the nucleophile, but strongly solvate the counter cation.

8. All E2 reactions require and anti C_β-H and C_α-X conformation and the major alkene is usually the most substituted alkene. Alkoxide/alcohol mixtures are often used for E2 reactions.

9. CH_3-X compounds only undergo S_N2 reactions with strong base/nucleophiles and "No reaction" with weak nucleophiles.

10. Tertiary RX compounds only undergo E2 reactions with strong base/nucleophiles (no S_N2 reaction).

11. The major product of primary RX with a strong base/nucleophile is usually S_N2 with minor E2 product. The only exceptions are when extreme steric hindrance is present in the base or the RX compound. If potassium t-butoxide is the base/nucleophile, then E2 is the major product even with 1^o RX compounds.

12. Secondary RX compounds have many choices. The major product of secondary RX with a strong base/nucleophile depends on the strength of the base. When two electron pair donors are similar (alkoxides vs carboxylates or cyanide vs terminal acetylides), the stronger base (higher pKa of conjugated acid) forms more E2 product and the weaker base (loser pKa) forms more S_N2 product. Examples from our course:

    a. HO^- [$pK_a(H_2O)$=16] and RO^- [pK_a(ROH)=16] are more basic (generally E2 > S_N2 at 2^o RX)
    b. RCO_2^- [$pK_a(RCO_2H)$=5] is less basic (generally S_N2 > E2 at 2^o RX).
    c. RCC^- [pK_a(RCC-H)=25] is more basic (generally E2 > S_N2 at 2^o RX)
    d. NC^- [pK_a(NC-H)=9] is less basic (generally S_N2 > E2 at 2^o RX).

13. S_N1 and E1 reactions always begin with the same first step: ionization of the R-X bond to form a carbocation, R+, and a stable leaving group (for us = Cl^-, Br^-, I^-, TsO^-, as anions or H_2O, ROH, RCO_2H as neutral molecules).

14. Methyl and primary RX compounds do not react under S_N1/E1 conditions (weak base/nucleophile) because they cannot form carbocations under usual reaction conditions (in our course).

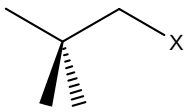
15. S_N1 usually out competes E1 reaction products and only occurs at 2^o, 3^o, allylic and benzilic RX compounds. Weak nucleophiles (H_2O, ROH, RCO_2H in our course) attack from both faces of the carbocation intermediate producing racemization of configuration, where observable, (in S_N1 reactions). E1 products can occur from loss of any C_β-H rotated up or down with the empty 2p orbital.

16. S_N1/E1 reactions require a very polar, ionizing solvent that allows formation of ions. Usually this is a protic, hydrogen bonding solvent that solvates both cations and anions. Often the solvent is also the nucleophile/base.

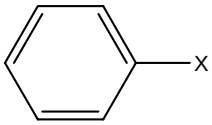
17. Carbocation rearrangements are competitive with S_N1 and E1 reactions when a similar or more stable carbocation can form ($3^o > 2^o >> 1^o >> CH_3$). We do not propose primary or methyl carbocations in our course.

18. E1 products are the major result when an alcohol (ROH) is mixed with sulfuric acid (H_2SO_4/Δ) and heated to high temperatures. The E1 alkene product is more volatile and distills from the reaction mixture, shifting the equilibrium towards E1. Any C_β-H can be lost from either anti or syn conformations relative to the original C_α-X group and the major alkene is usually the most substituted alkene.

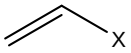
19. Neopentyl, vinyl and phenyl RX compounds generally do not react by any of these mechanisms. Vinylic and phenyl RX will undergo E2 reactions with very strong bases to form alkynes and benzyne, but do not react by S_N2, S_N1 or E1 reaction. We will not consider them reactive compounds in this topic.



1^o neopentyl RX



phenyl RX

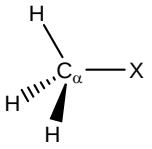
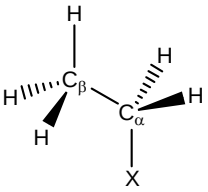
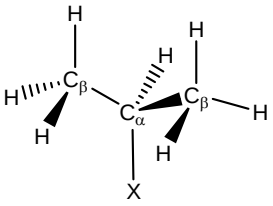
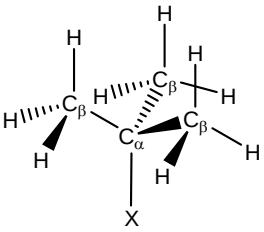
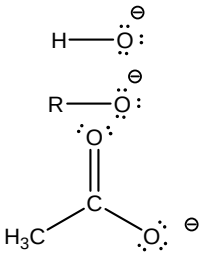
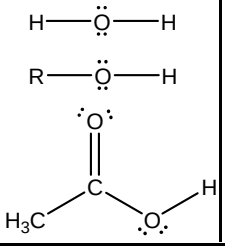
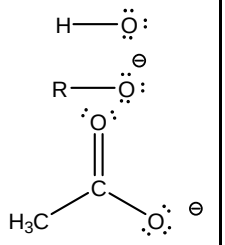
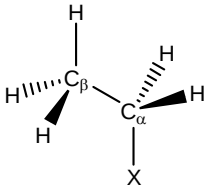
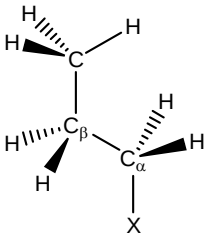
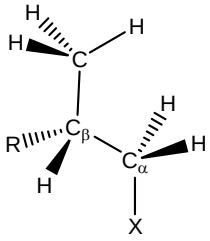
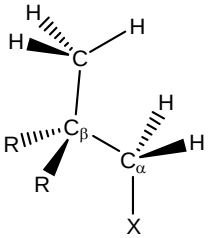


vinyl RX

These compounds are not usually reactive under S_N/E conditions.
In our course, we will consider them unreactive.

C_α and C_β substitution patterns

C_α substitution

typical RX patterns / typical RX electron pair donors	 methyl unsubstituted C_α	 primary 1 substituted C_α	 secondary 2 substituted C_α	 tertiary 3 substituted C_α
	S_N2 rel. rate ≈ 30	S_N2 rel. rate ≈ 1	S_N2 rel. rate ≈ 0.025 (1/40)	S_N2 rel. rate ≈ 0
	S_N1 rel. rate ≈ 0	S_N1 rel. rate ≈ 0	S_N1 rel. rate ≈ 1	S_N1 rel. rate ≈ 1,000,000
	C_β substitution (all 1° RX here)  0 substituted C_β S_N2 rel. rate ≈ 1	 1 substituted C_β S_N2 rel. rate ≈ 0.4	 2 substituted C_β S_N2 rel. rate ≈ 0.03	 3 substituted C_β S_N2 rel. rate ≈ 0

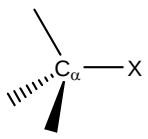
methyl = (1R)-bromodeuteriotritiomethane

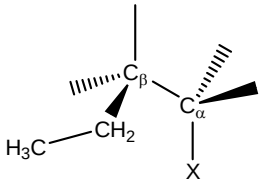
primary = (1R,2S)-1-bromo-1,2-dideuteriobutane

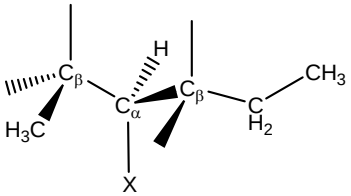
secondary = (2R,3S,4R)-3-bromo-4-deuterio-4-methylhexane

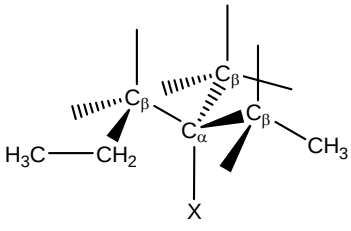
tertiary = (2S,3S)-3-bromo-2-deuterio-3-methylhexane

Fill in the necessary details from the names and predicte the expected products using the above electron pair donors.


methyl

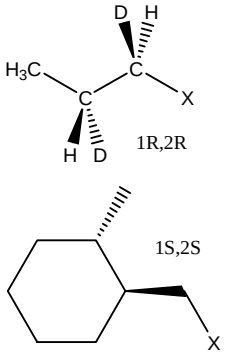
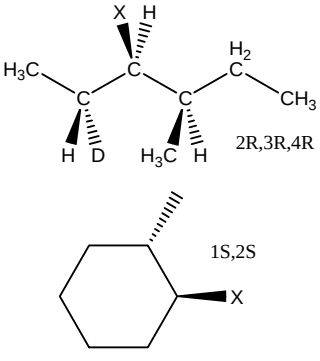
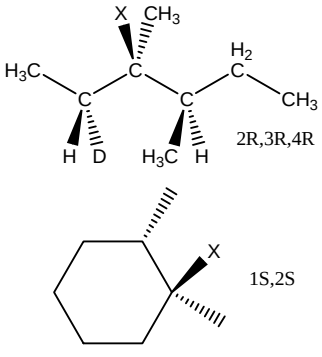
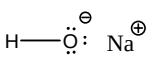
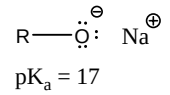
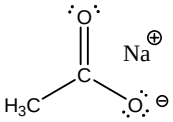
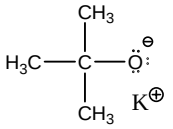
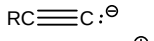
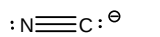
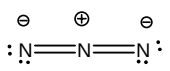
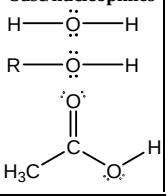

primary


secondary

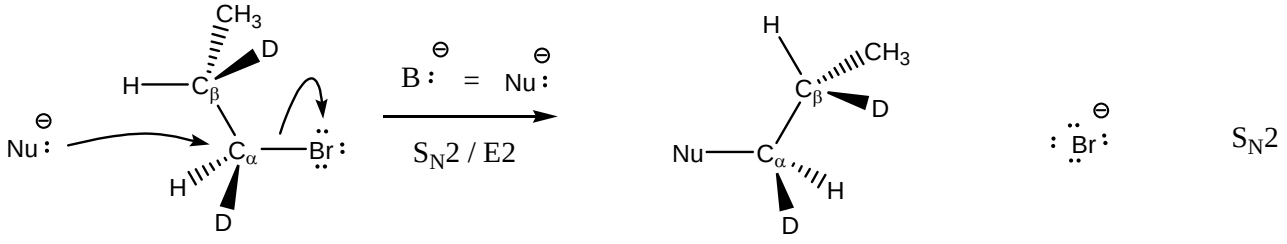

tertiary

S_N and E Reactions

Limited RX compounds for our course (open chains and cyclohexanes).

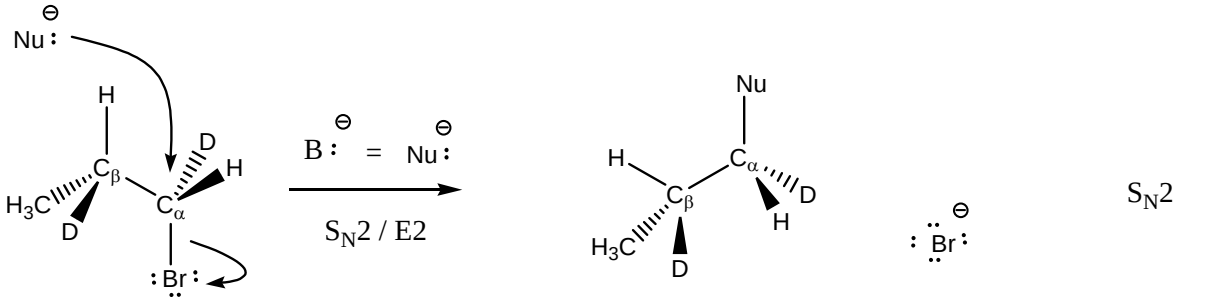
	X = Cl, Br, I $H_3C—X$ methyl RX	 1R,2R 1S,2S primary RX	 2R,3R,4R 1S,2S secondary RX	 2R,3R,4R 1S,2S tertiary RX
Strong base/nucleophiles				
 $pK_a = 16$	only S_N2 always inversion of configuration	$S_N2 > E2$	$E2 > S_N2$	only E2 requires anti $C_\beta H/C_\alpha X$ conformation
 $pK_a = 17$	only S_N2	$S_N2 > E2$	$E2 > S_N2$	only E2
 $pK_a = 5$	only S_N2	$S_N2 > E2$	$S_N2 > E2$	only E2
 sterically hindered and very basic $pK_a = 19$	only S_N2	$E2 > S_N2$	only E2	only E2
 $pK_a = 25$	only S_N2	$S_N2 > E2$	$E2 > S_N2$	only E2
 $pK_a = 9$	only S_N2	$S_N2 > E2$	$S_N2 > E2$	only E2
 azide	only S_N2	$S_N2 > E2$	$S_N2 > E2$	only E2
Weak base/nucleophiles 	No reaction (R^+ cannot form)	No reaction (R^+ cannot form)	$S_N1 > E1$ Major reactions of R^+ 1. add nucleophile from either face (S_N1) 2. lose any C_β-H (E1) from either side 3. rearrange to new R^+ and start over	$S_N1 > E1$ Major reactions of R^+ 1. add nucleophile from either face (S_N1) 2. lose any C_β-H (E1) from either side 3. rearrange to new R^+ and start over

Example 1 - two possible perspectives (deuterium is an isotope of hydrogen that can be distinguished)



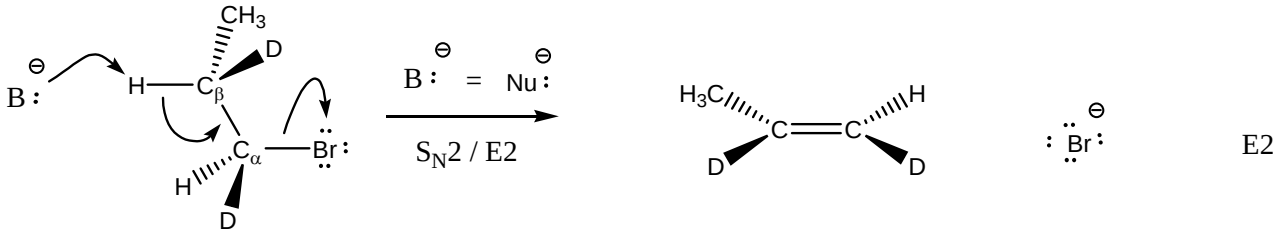
(1S,2S)- 1,2-dideuterio-1-bromopropane

C_α = R



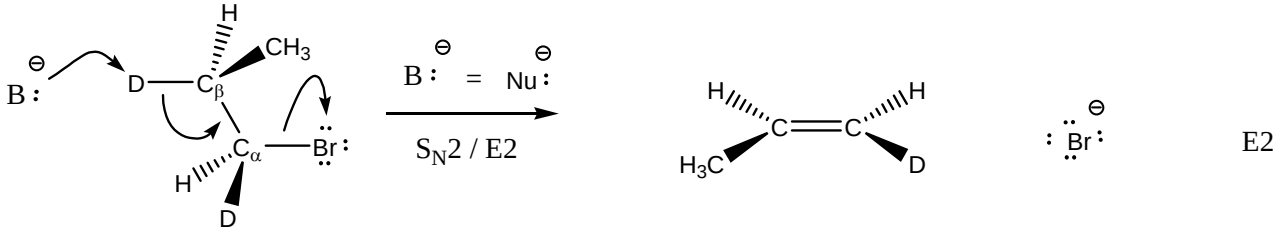
(1S,2R)- 1,2-dideuterio-1-bromopropane

C_α = R



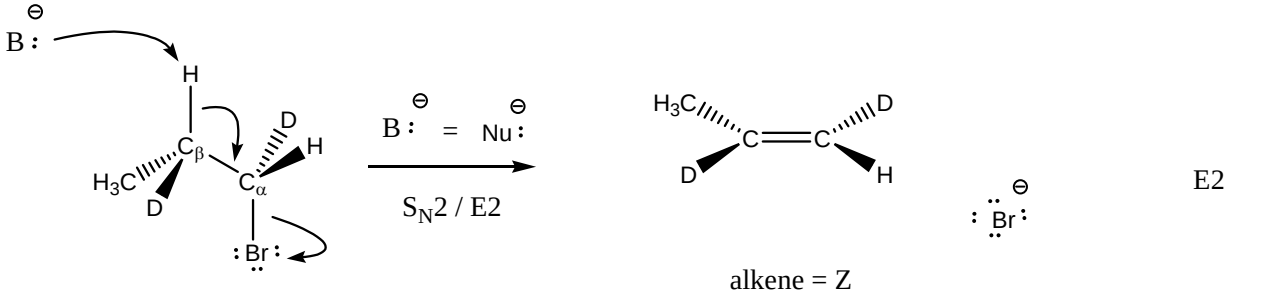
(1S,2S)- 1,2-dideuterio-1-bromopropane

alkene = E



(1S,2S)- 1,2-dideuterio-1-bromopropane

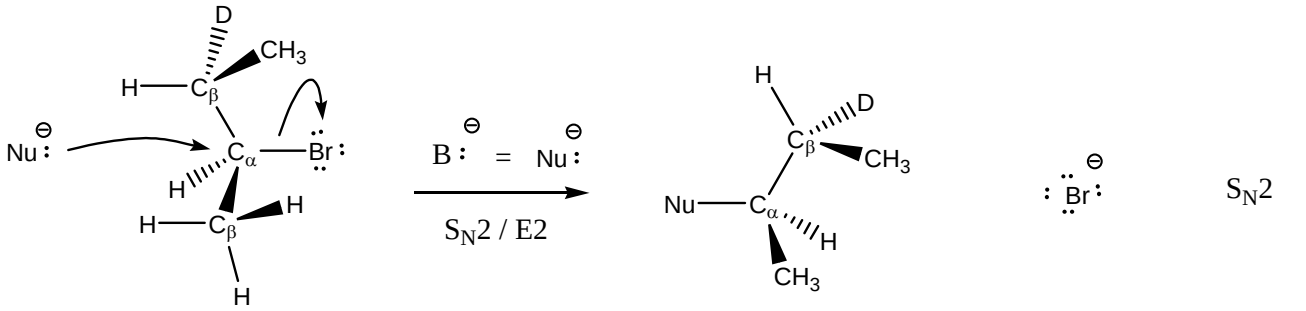
alkene = Z



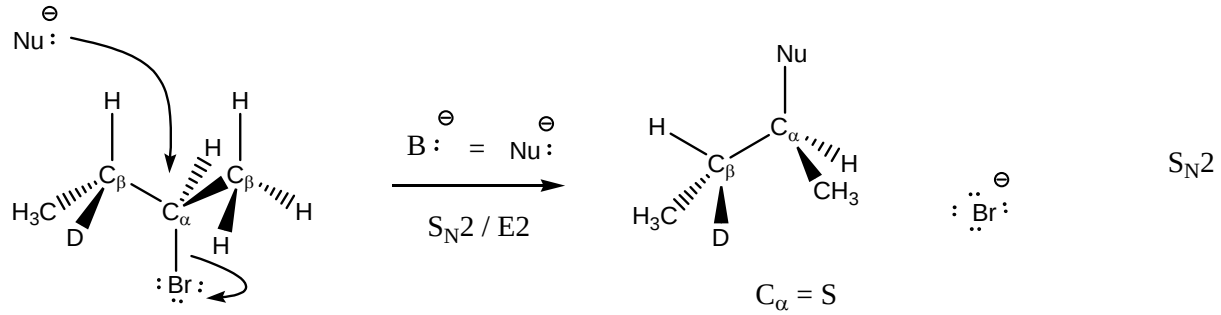
(1S,2R)- 1,2-dideuterio-1-bromopropane

alkene = Z

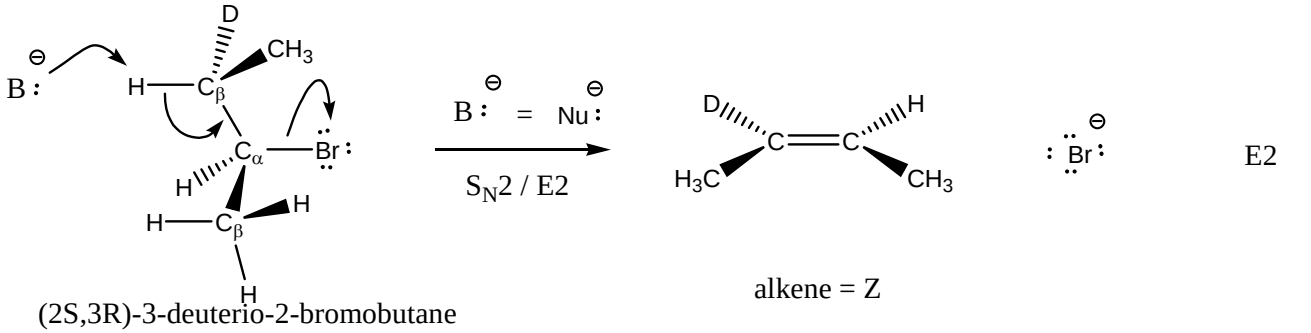
Example 2 - two possible perspectives (deuterium is an isotope of hydrogen that can be distinguished)



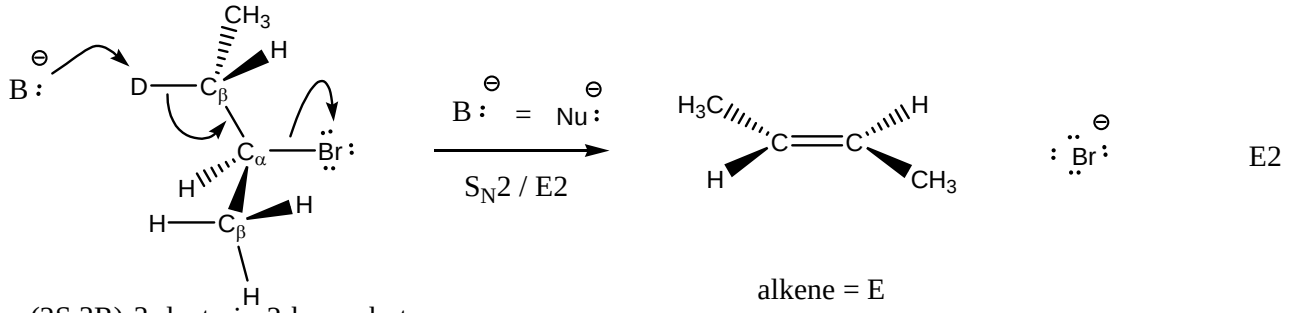
(2S,3R)-3-deuterio-2-bromobutane C_α = R



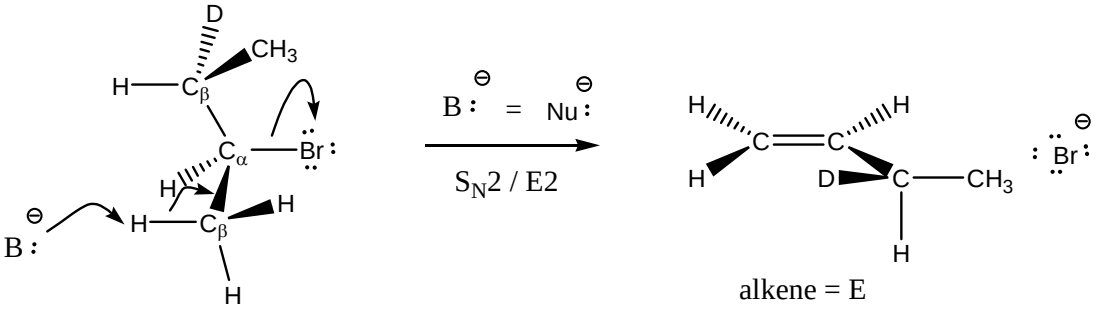
(2R,3R)-3-deuterio-2-bromobutane C_α = S



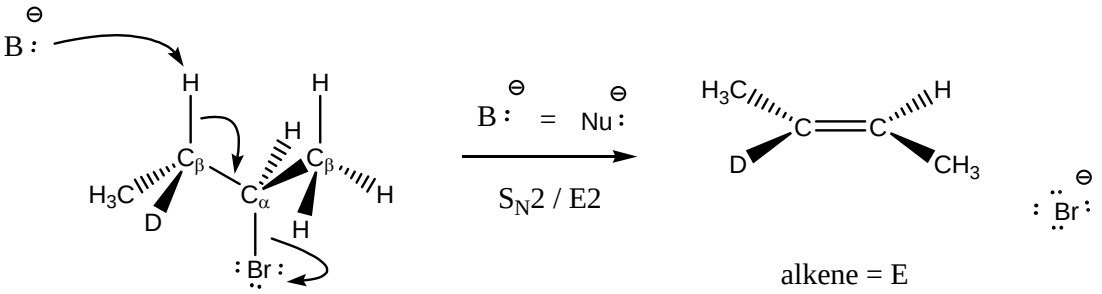
(2S,3R)-3-deuterio-2-bromobutane alkene = Z



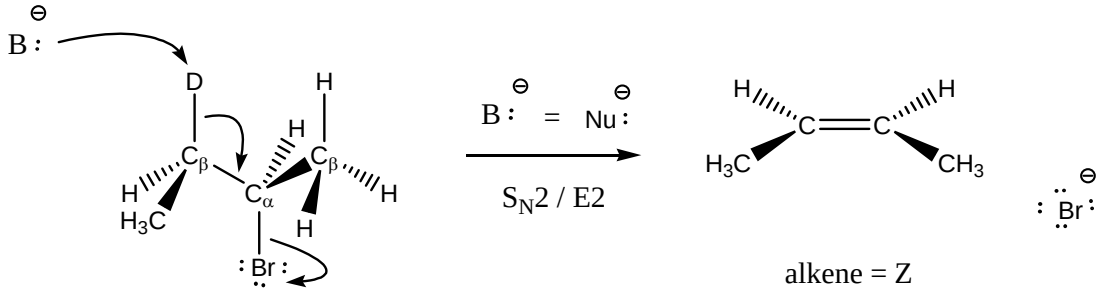
(2S,3R)-3-deuterio-2-bromobutane alkene = E



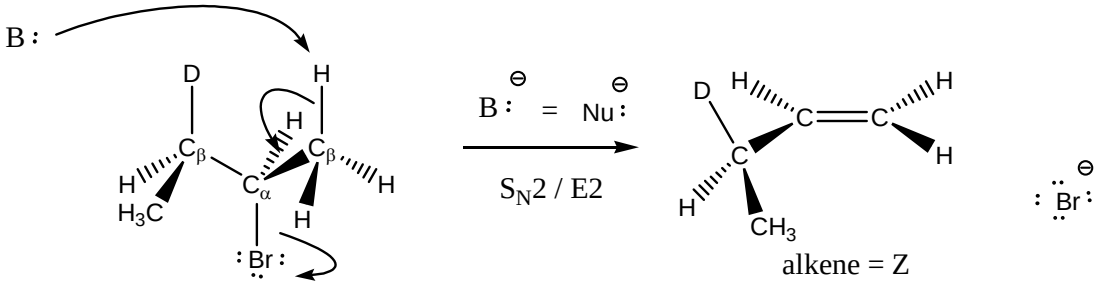
(2S,3R)-3-deuterio-2-bromobutane E2



(2R,3R)-3-deuterio-2-bromobutane E2

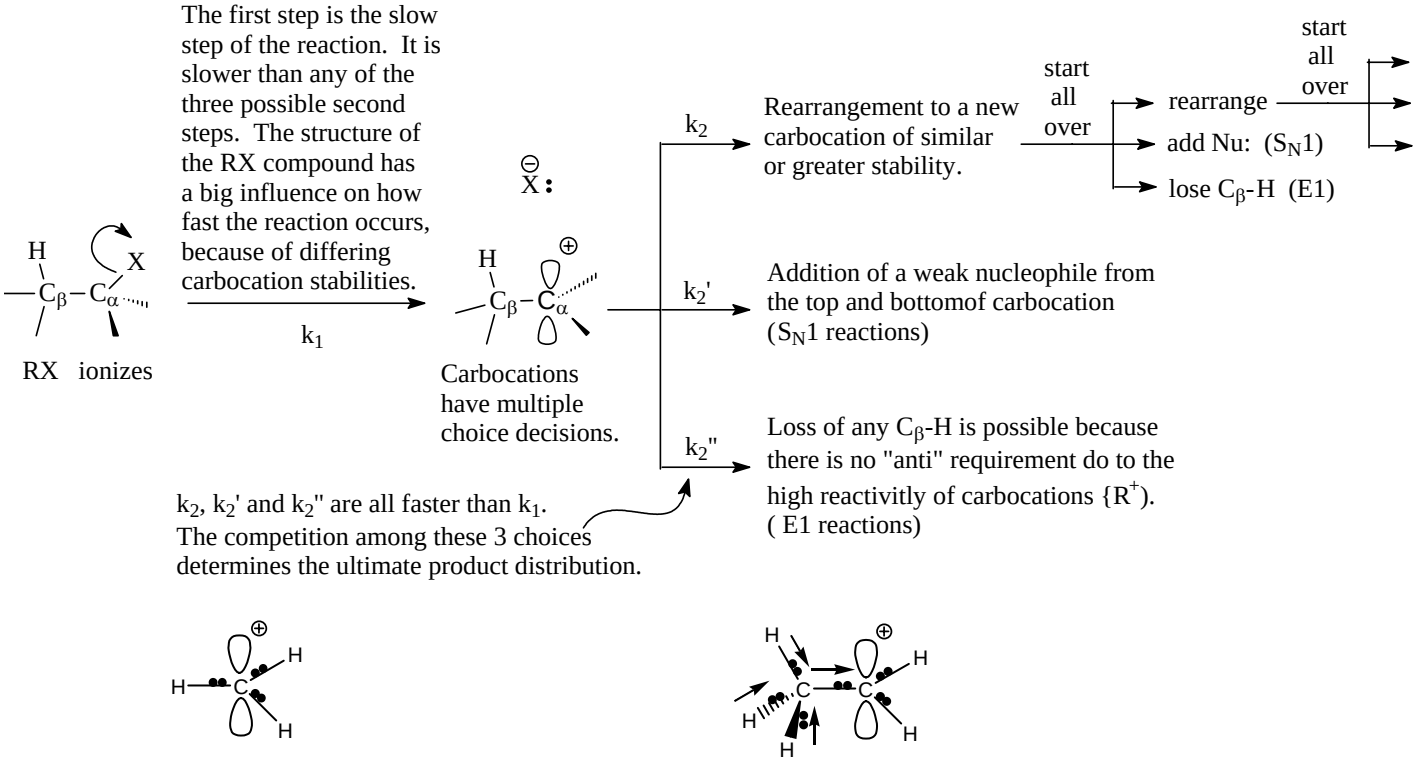


(2R,3R)-3-deuterio-2-bromobutane E2

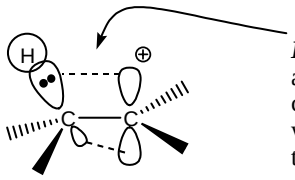


(2R,3R)-3-deuterio-2-bromobutane E2

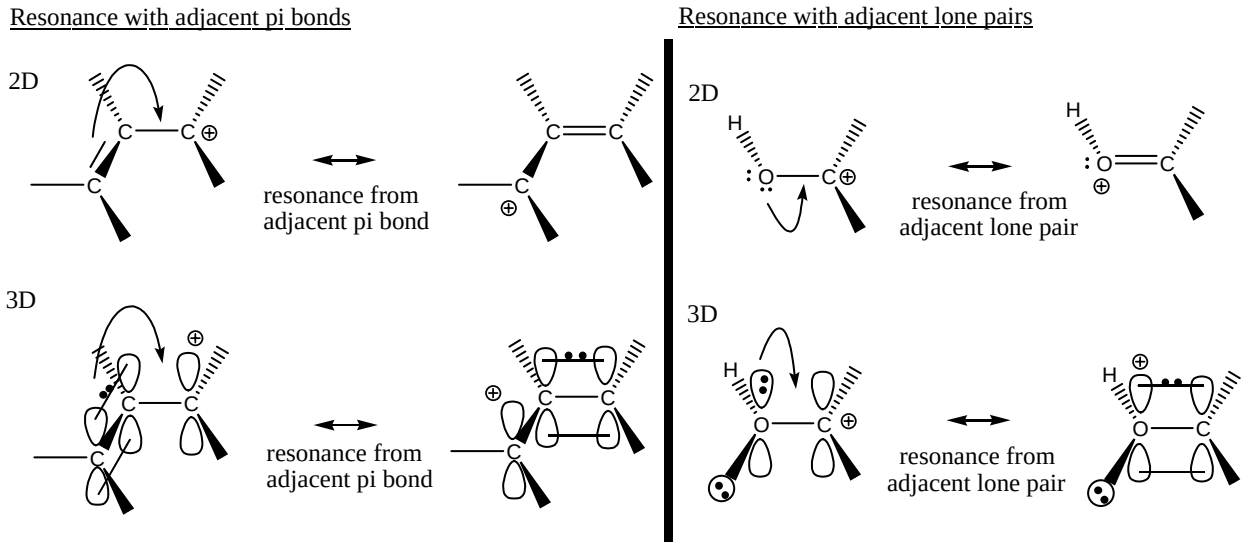
S_N1, E1 and Carbocations



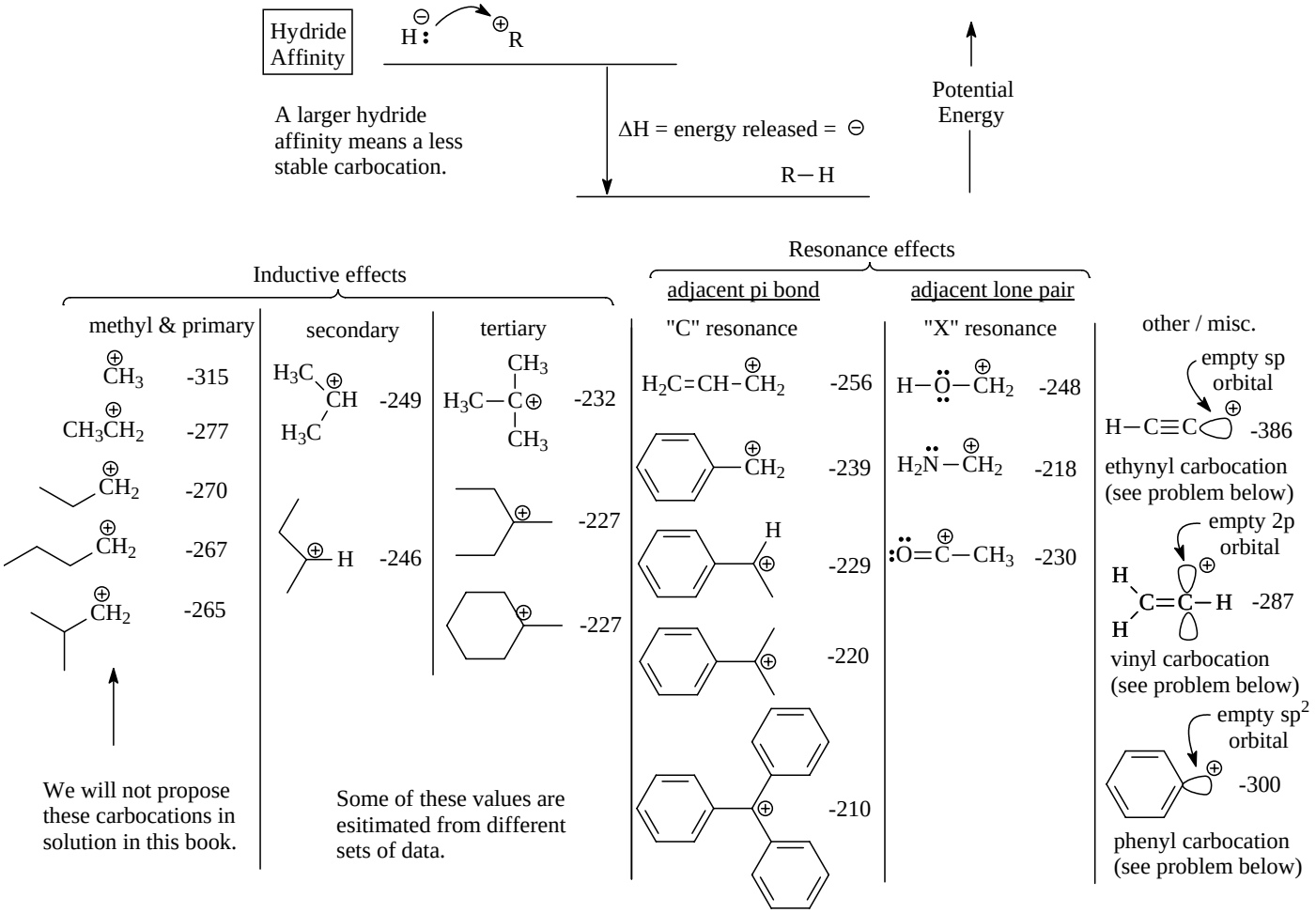
Inductive Effects are either electron withdrawing from a center of interest, due to the intrinsic tendency of a substituent to pull electrons to itself based on its greater relative electronegativity, or they are electron donating towards a center of interest due to the intrinsic tendency of a substituent to give up electrons based on its lower relative electronegativity. Electron donation can stabilize (a positive center) or destabilize (a negative center). Likewise, electron withdrawal can stabilize (a negative center) or destabilize (a positive center).



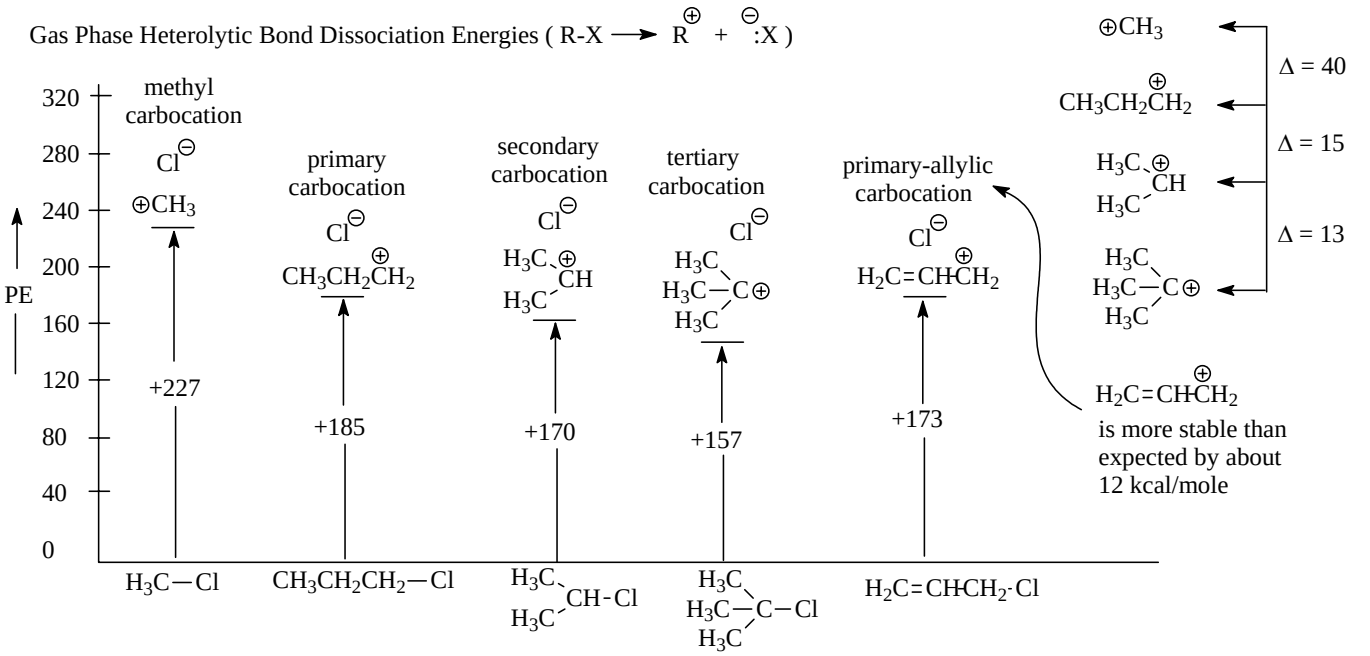
Hyperconjugation = Weak pi-like interaction from adjacent parallel sigma bond helps to stablize the carbocation carbon atom. It can also be described with HOMO/LUMO interactions of molecular orbital theory.

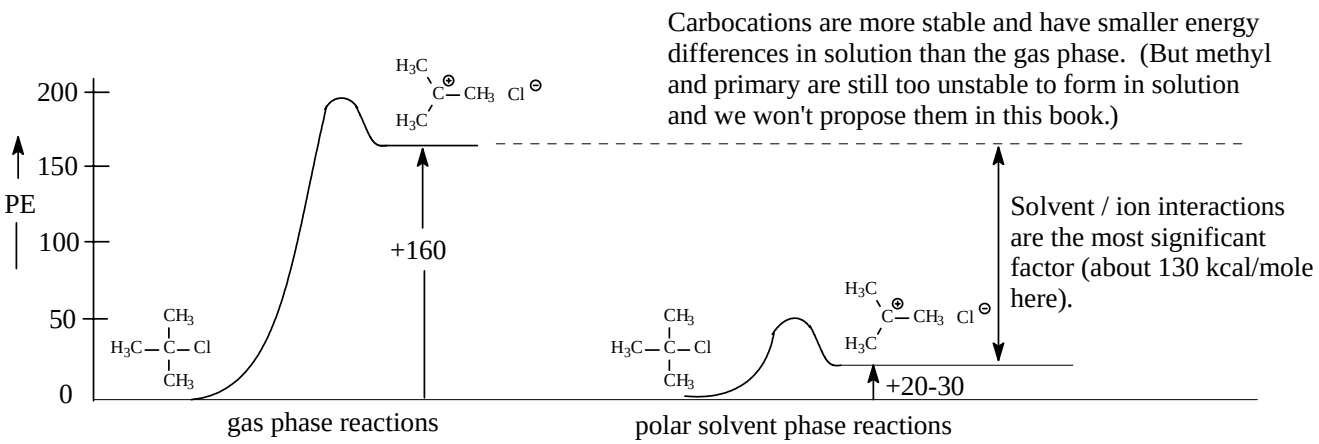


Resonance effects help stabilize carbocations and makes them easier to form.



Gas Phase Ionization Energies for R-Cl Bonds **(kcal/mole, 1 kcal = 4.184 kJoule)**

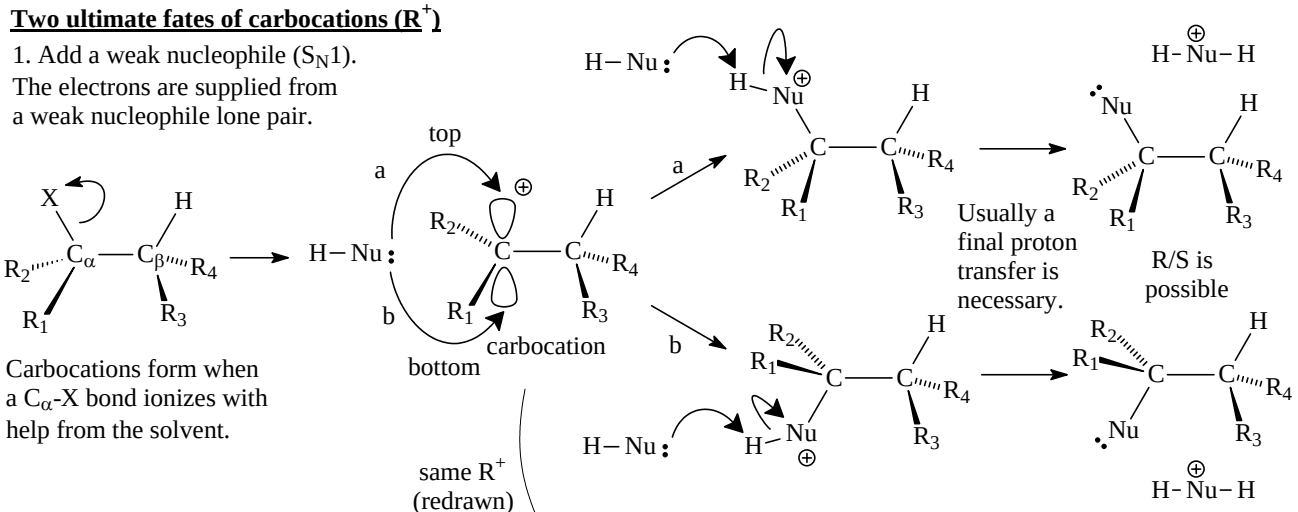




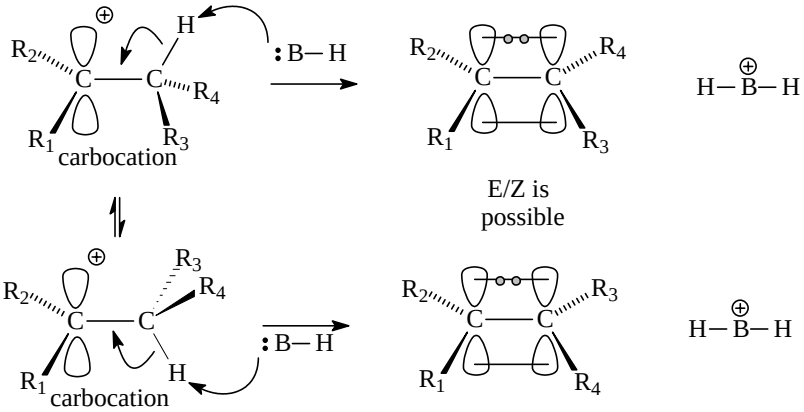
Two ultimate fates of carbocations (R^+)

1. Add a weak nucleophile (S_N1). The electrons are supplied from a weak nucleophile lone pair.

Carbocations form when a C_α-X bond ionizes with help from the solvent.

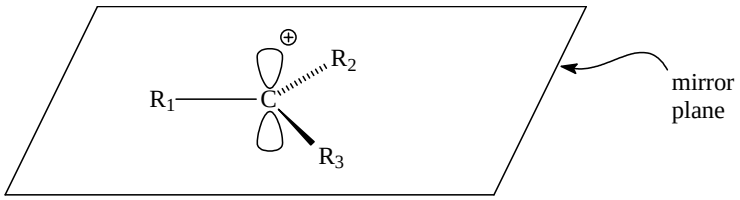


2. Lose an adjacent beta hydrogen atom to form pi bond (E1). The electrons are supplied from an adjacent C_β-H sigma bond

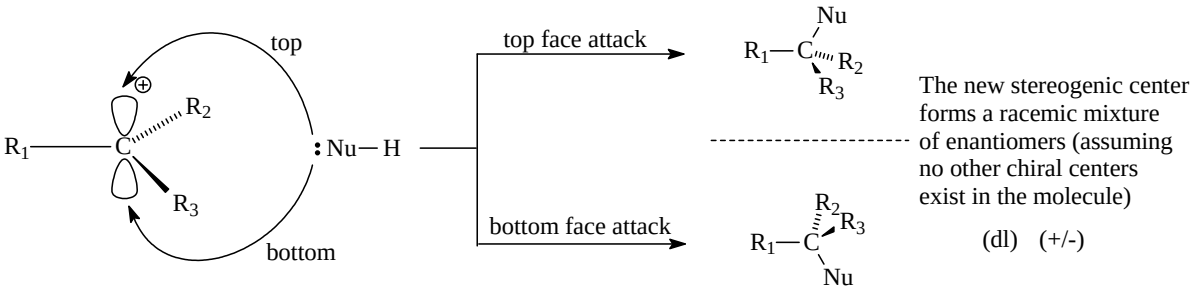


usually H-Nu: = H-B: = a protic solvent H-S: such as H_2O, ROH, RCO_2H.

usually H-Nu-H^+ = H-B-H^+ = a protonated solvent molecule H-S-H^+ such as H_3O^+, ROH_2^+, $RC(OH)_2^+$

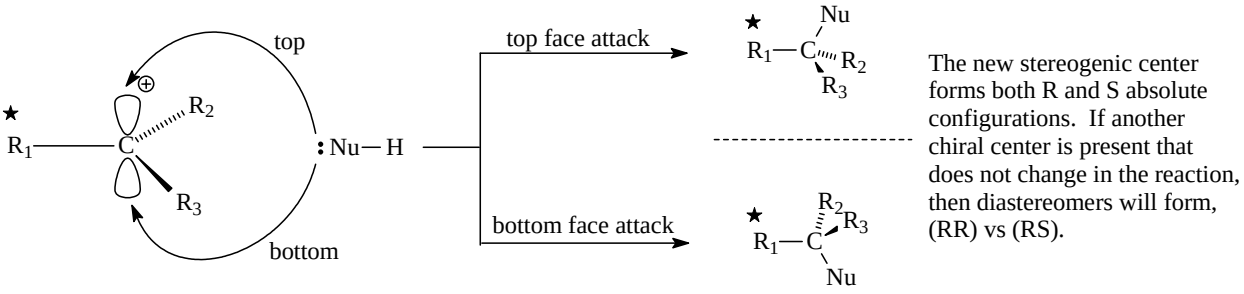


achiral carbocation carbon



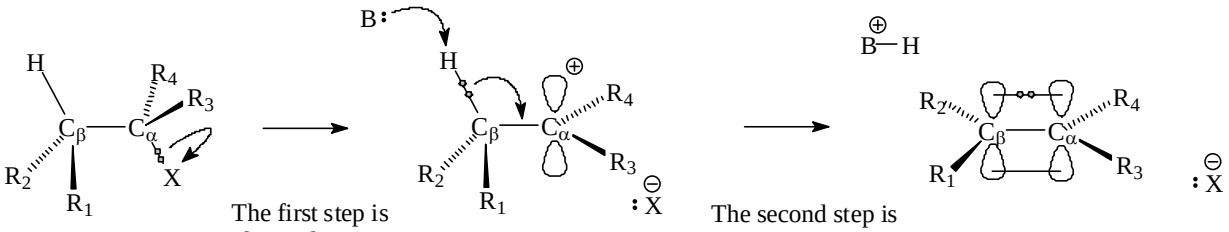
achiral carbocation carbon with no other chiral centers in R_1, R_2 or R_3

If all three attached groups at a carbocation carbon are different from one another and the attacking nucleophile, then a racemic mixture of enantiomers will form.

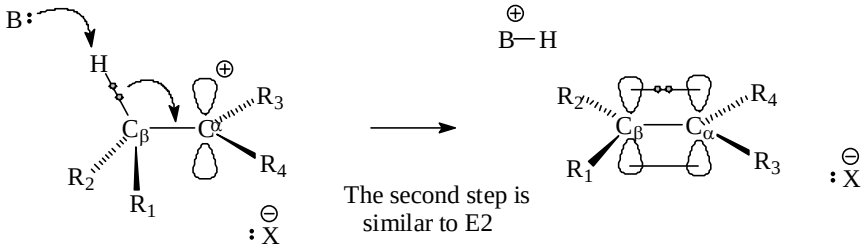


chiral branch in carbocation = ★

If one or more chiral centers were present in the carbocation, the top and bottom attack at the carbocation center would lead to diastereomers formed in unequal amounts.

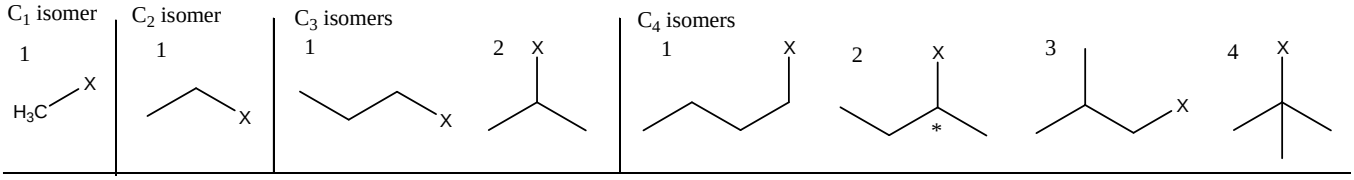


Rotate about the C_α-C_β bond.

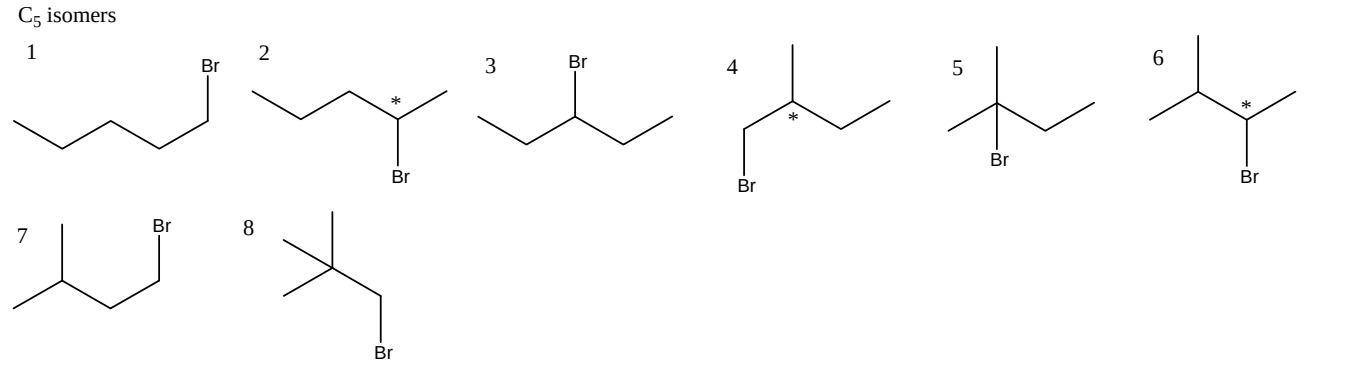


S_N / E possibilities

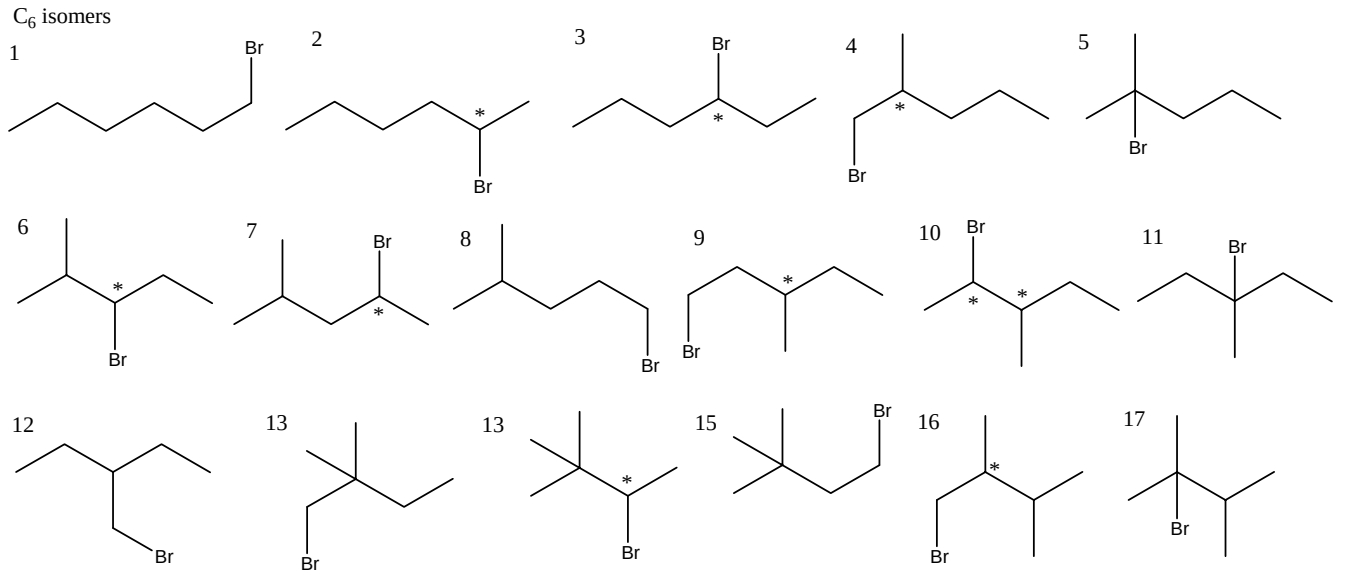
$C_1 – C_4$ RX isomers (* denotes a chiral center)



$C_5H_{11}X$ isomers

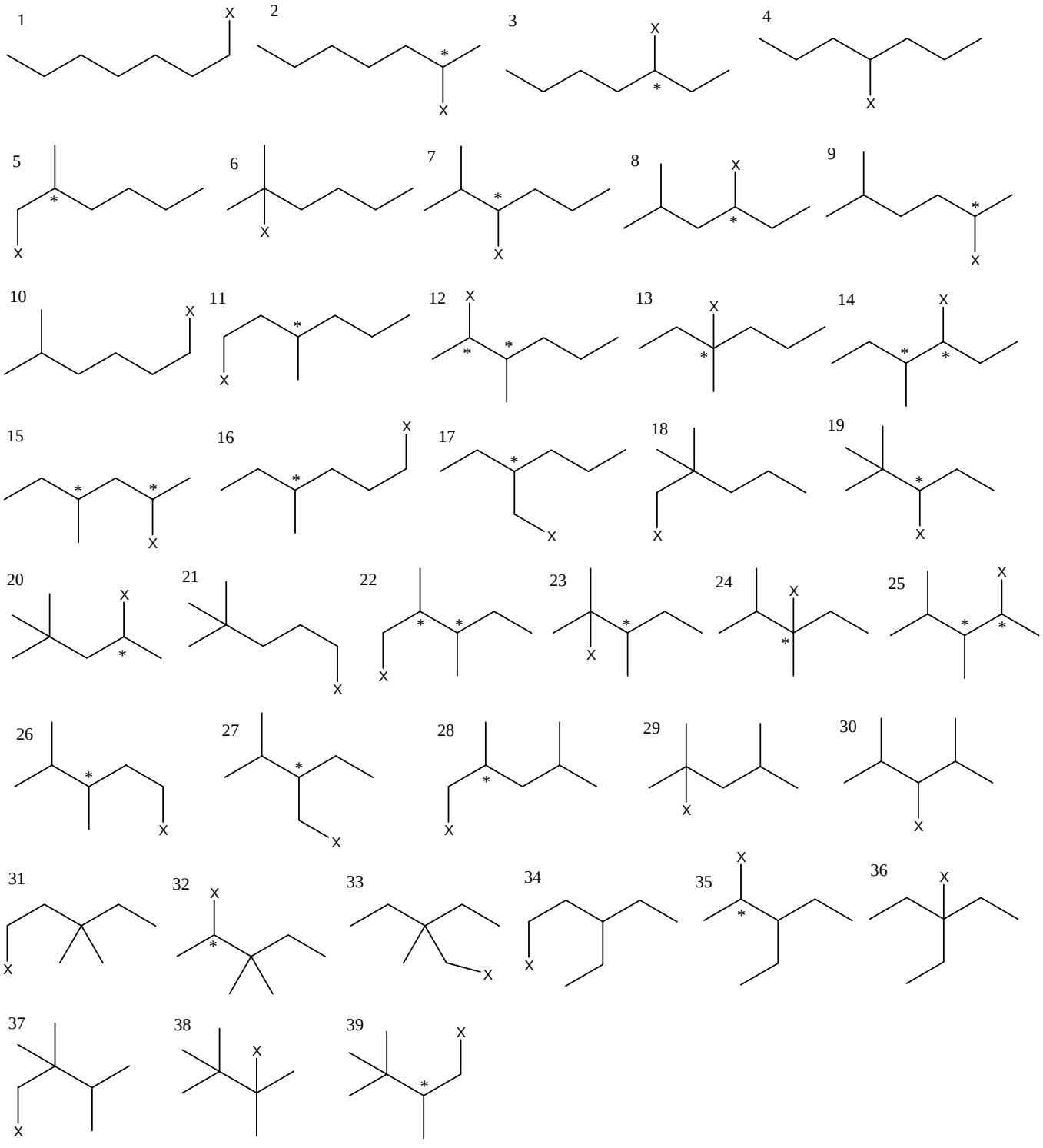


$C_6H_{13}X$ isomers

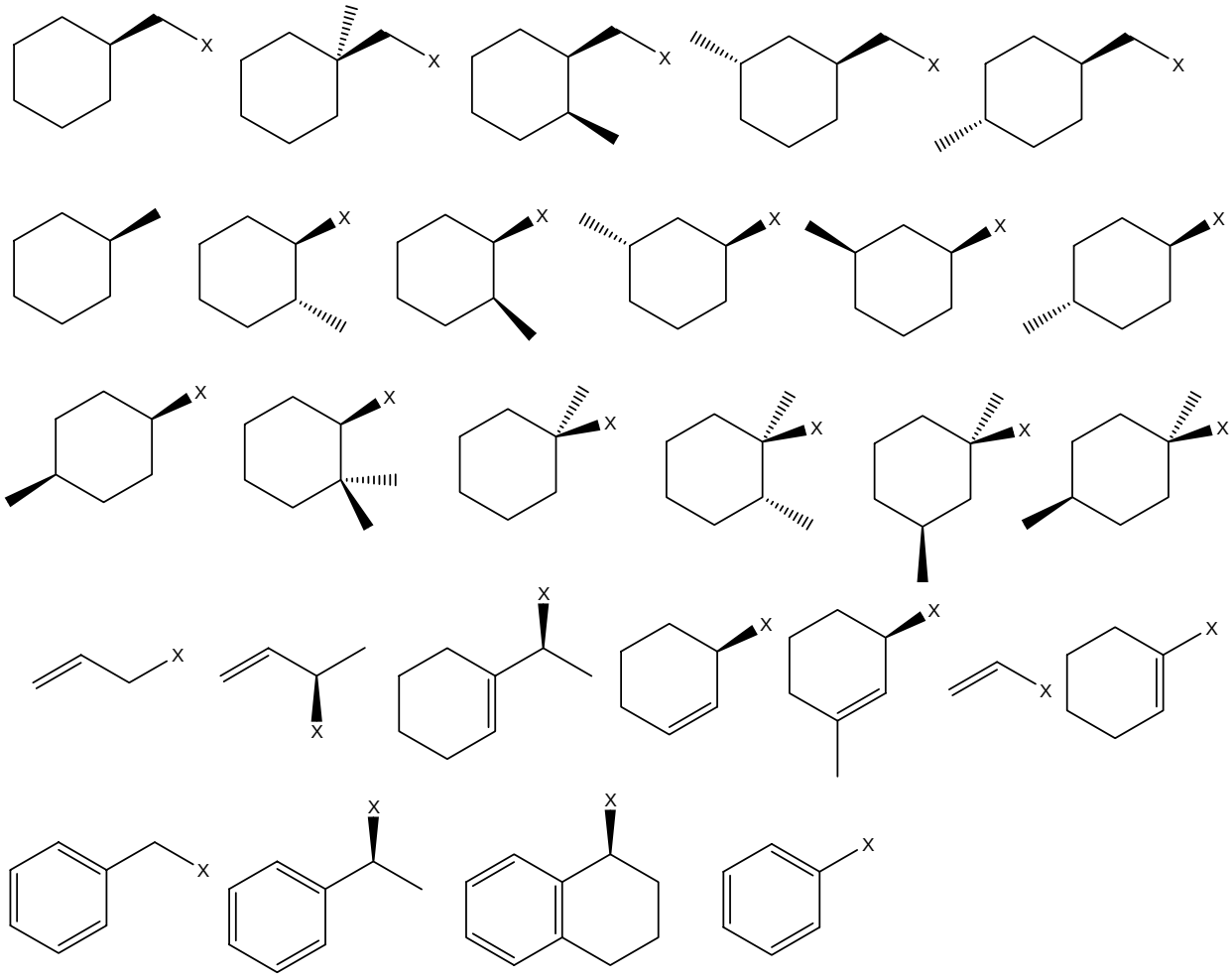


$C_7H_{15}X$ isomers

C_7 isomers



Other patterns – cyclohexyl, allyl, benzyl, vinyl, phenyl



Common reaction conditions (for S_N2, E2, S_N1, E1)