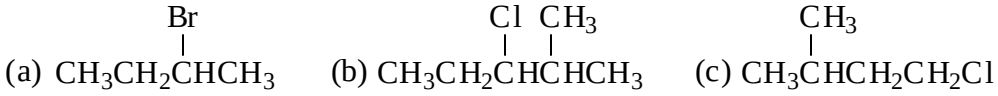
Chem 226 — Problem Set #7 —
"Fundamentals of Organic Chemistry," 4th edition, John McMurry.

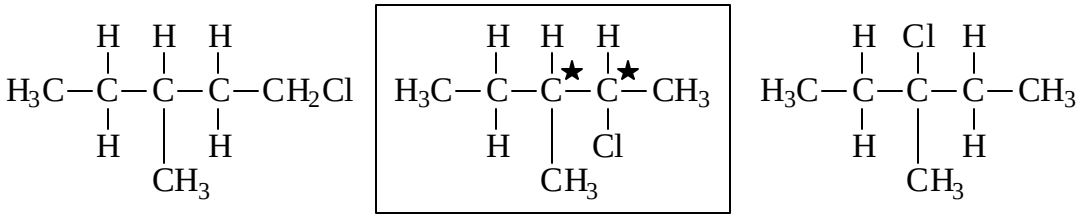
Chapter 7

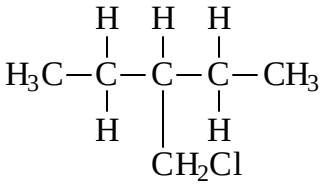
1. Give the IUPAC names of the following alkyl halides.



(a) 2-bromobutane, (b) 3-chloro-2-methylpentane, (c) 1-chloro-3-methylbutane

3. Draw and name all monochloro products you might obtain from radical chlorination of 3-methylpentane. Which, if any, are chiral?

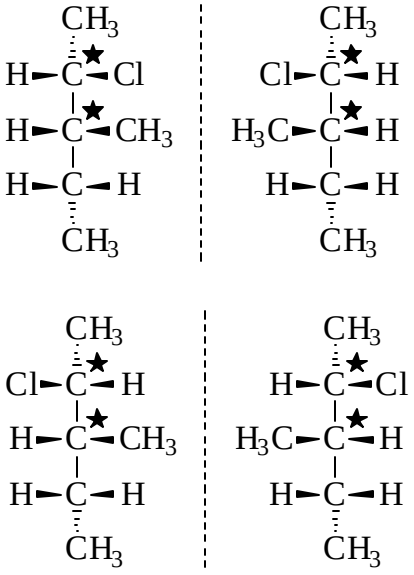




Each of the hydrogens in 3-methylpentane is replacable by chlorine. Four constitutional isomers can form.

The boxed structure has two stereocenters and is a chiral molecule. The maximum number of stereoisomers that is possible for a given structure, owing to stereocenters, is 2^n, where n is the number of stereocenters. If meso structures are possible, then the actual number of stereoisomers will be less than the calculated maximum number.

In this case the stereoisomers are shown to the right. There are two pairs of enantiomers. Each of the molecules in either pair of enantiomers is a diastereomer of either molecule in the other pair.



5. How would you prepare the following alkyl halides from the appropriate alcohols?

(a) 2-chloro-2-methylpropane,

(c) $BrCH_2CH_2CH_2CH_2CH(CH_3)CH_3$

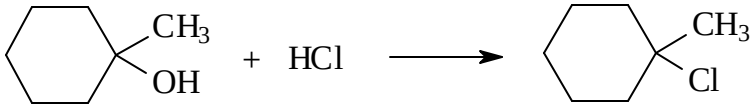
(a) $CH_3C(Cl)(CH_3)CH_3 \xleftarrow{HCl} CH_3C(OH)(CH_3)CH_3$

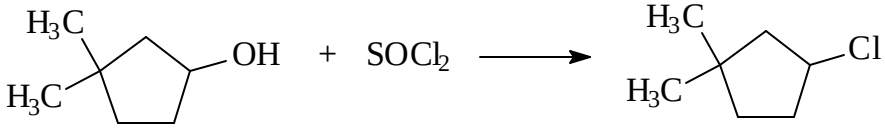
(c) $BrCH_2CH_2CH_2CH_2CH(CH_3)CH_3 \xleftarrow{PBr_3} HOCH_2CH_2CH_2CH_2CH(CH_3)CH_3$

Since the compound in (a) is a tertiary alkyl chloride it can be made from the corresponding tertiary alcohol using HCl. Since the compound in (c) is a primary alkyl bromide it can be made from the corresponding primary alcohol and phosphorous tribromide.

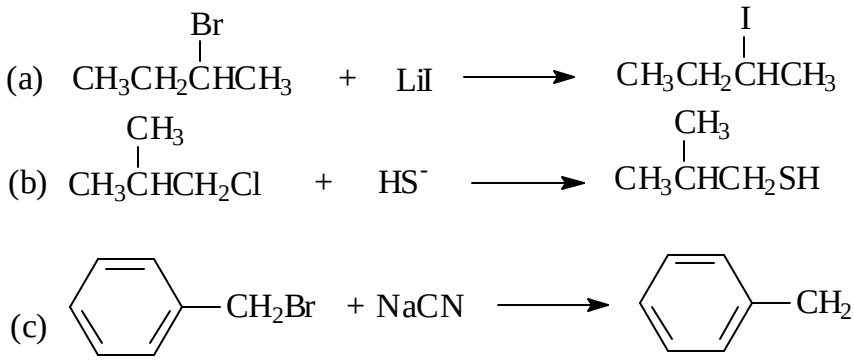
6. Predict the products of the following reactions.

(a) $CH_3CH_2CH(OH)CH_2CH(CH_3)CH_3 + PBr_3 \longrightarrow CH_3CH_2CH(Br)CH_2CH(CH_3)CH_3$

(b) 

(c) 

9. What substitution products would you expect to obtain from the following reactions?



10. How might you prepare the following substances by using nucleophilic substitution reactions?

You could also use 1-chlorobutane, but the bromine is a better leaving group. You could also use NaOH.

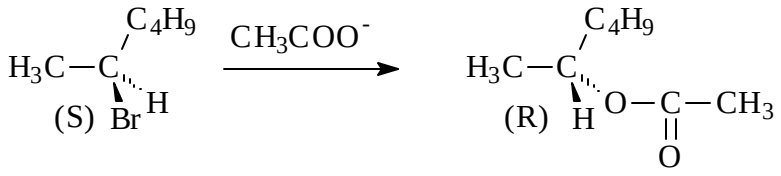
11. What effects would the following changes have on the rate of the S_N2 reaction between CH_3I and sodium acetate?

(a) The CH_3I concentration is tripled.
(b) Both CH_3I and CH_3CO_2Na concentrations are doubled.

The rate expression for S_N2 reactions is: rate = k[substrate][nucleophile].
In this case the substrate is iodomethane and the nucleophile is acetate ion.

(a) The rate would triple since the iodomethane concentration is tripled and the acetate concentration has not changed.
(b) If the concentration of both substrate and nucleophile are doubled, the rate will increase by a factor of 4, since 2x2 = 4.

12. What product would you expect to obtain from the S_N2 reaction of (S)-2-bromohexane with sodium acetate, CH_3CO_2Na? Show the stereochemistry of both product and reactant.



In S_N2 reactions the nucleophile, in this case acetate, attacks the carbon holding the leaving group, in this case bromine, from the side *opposite* the leaving group. This backside attack inverts the configuration of the carbon that is attacked.

In this reaction a bond to a stereocenter is broken. You may recall that when this happens the stereochemical outcome is dependent on the details of the mechanism. In S_N2 reactions the configuration is inverted.

14. Which of the following S_N2 reactions would you expect to be faster?

(a) Reaction of CN^- (cyanide ion) with $CH_3CH(Br)CH_3$ or with $CH_3CH_2CH_2Br$?
(b) Reaction of I^- with $(CH_3)_2CHCH_2Cl$ or with $H_2C{=}CHCl$?

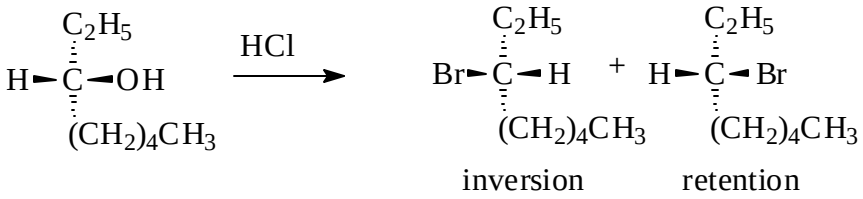
(a) In S_N2 reactions the order of reactivity of substrates is methyl > primary > secondary > tertiary owing to steric effects; alkyl groups attached to the carbon holding the leaving group block the nucleophile. In this case the primary 1-bromopropane would react faster than the secondary 2-bromopropane.

(b) Vinyl halides are unreactive toward S_N2 nucleophilic substitutions, so the primary halide wins.

15. Rank the following compounds in order of their expected reactivity toward S_N2 reaction:
CH_3I, CH_3F, CH_3Br.

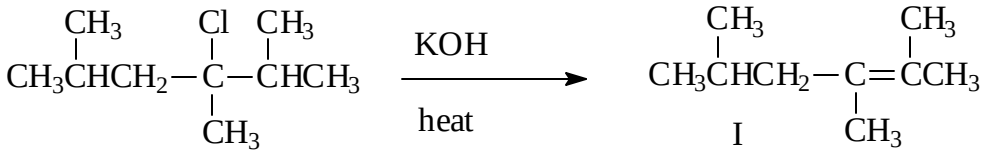
These substrates differ from each other only in terms of the leaving group. Since iodine is a better leaving group than bromine and bromine is better than fluorine, the most reactive compound is iodomethane and the least reactive is fluoromethane.

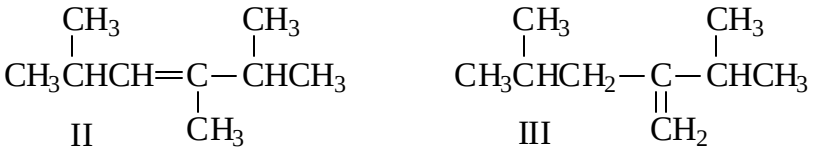
17. What product would you expect to obtain from the S_N1 reaction of (S)-3-methyl-3-octanol with HBr? Show the stereochemistry of both starting material and product.



McMurry says that S_N1 reactions proceed with complete racemization (pgs. 234-235). But this is not quite true. Typically, these reactions proceed with some racemization but net inversion of configuration. In the present example, this would mean that both products show above would be formed, but more product with inverted configuration would be produced. The reason for this is that as the protonated OH group (water molecule) departs from the newly formed carbocation it blocks attack by the nucleophile (Cl^-). Thus, attack is more likely on the side of the carbocation opposite the water molecule (the "backside"). This means that more product will have the inverted configuration. The more stable the carbocation the closer the product will be to racemic. Why?

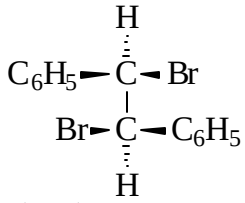
18. Ignoring double-bond stereochemistry, what elimination products would you expect from the following reactions? (Remember Zaitsev's rule.)



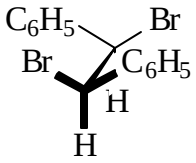


The more highly substituted an alkene is (with alkyl groups) the more stable it is and the more of it will form in elimination reactions. In this case that means that I > II > III.

19. What stereochemistry (E or Z) do you expect for the alkene obtained by E2 elimination of (1R,2R)-1,2-dibromo-1,2-diphenylethane? Draw a Newman projection of the reacting conformation.

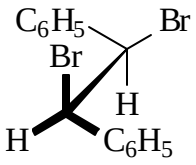


(R,R)

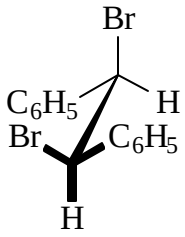


sawhorse projection, same conformation as shown to the left

Reactive conformations --
H and Br must be anti-periplanar.

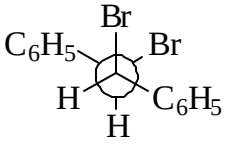


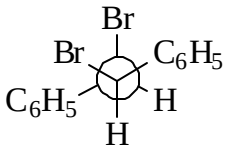
This one is formed by rotating the front 60 degrees clockwise.



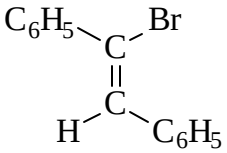
This one is formed by rotating the back 60 degrees counterclockwise.

Newman projections of above sawhorse projections.





As the anti-periplanar H and Br depart simultaneously (E2) the molecule flattens (sp^3 becomes sp^2) giving this alkene.



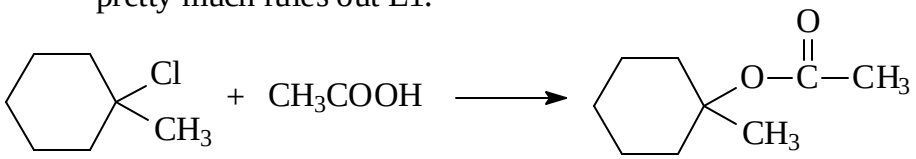
21. Tell whether the following reactions are S_N1, S_N2, E1, or E2.

(a) $CH_3CH_2CH_2CH_2Br + NaN_3 \longrightarrow CH_3CH_2CH_2CH_2N_3$

S_N2 -- This is clearly a substitution and the substrate is a primary alkyl halide.

(b) $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 + KOH \longrightarrow CH_3CH_2CH{=}CHCH_3$

E2 -- This is clearly an elimination. E1 would only happen in the absence of an aggressive base and usually only for tertiary substrates. Hydroxide ion, an aggressive base, pretty much rules out E1.

(c) 

S_N1 -- This is a tertiary substrate so S_N2 is out of the question. Also, acetic acid is not an aggressive nucleophile and is not basic. The lack of a strong base in the reaction mixture is important; a strong base would cause E2 elimination.

25. Describe the effects of the following variables on both S_N2 and S_N1 reactions.

(a) substrate structure, (b) leaving group

(a) The more bulky the substrate the less S_N2 is favored. This is a steric effect. Alkyl groups attached to the carbon holding the leaving group block backside attack by the nucleophile. S_N1 is favored by alkyl groups attached to the carbon holding the leaving group because the carbocation that needs to form will be more stable.

(b) A better leaving group will speed up both S_N1 and S_N2 mechanisms. In each of these mechanisms the leaving group leaves in the rate limiting step. The better the leaving group the faster this step.

29. Which alkyl halide in each of the following pairs will react faster in an S_N2 reaction with OH^-?

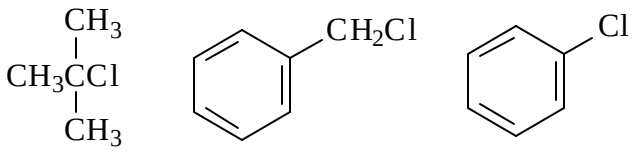
(a) bromobenzene or benzyl bromide?
(b) CH_3Cl or $(CH_3)_3CCl$
(c) $CH_3CH{=}CHBr$ or $H_2C{=}CHCH_2Br$

(a) Benzyl bromide. Benzyl bromide is a primary alkyl halide. Bromobenzene is an aryl halide. Aryl halides are unreactive to S_N2 conditions.

(b) Chloromethane. S_N2 backside attack is easy on the methyl group. It is impossible on the tertiary carbon of 2-chloro-2-methylpropane.

(c) $H_2C{=}CHCH_2Br$. This is primary halide. Backside attack is easy. $CH_3CH{=}CHBr$ is a vinyl halide and is unreactive to S_N2.

32. Order the following compounds with respect to both S_N1 and S_N2 reactivity.

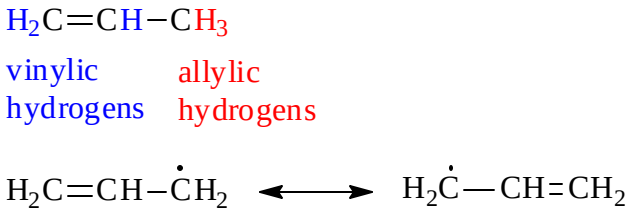


S_N1 – The stability of carbocation that is formed is the issue here. [Actually, it is the stability of the transition state leading to the carbocation that is important, but, as we have seen, this usually parallels the stability of the carbocation.] Chlorobenzene would need to form a phenyl carbocation; these species are very unstable. Benzyl chloride will form a carbocation that is primary but also benzylic; these guys are about as stable as ordinary secondary carbocations owing to resonance stabilization. 2-Chloro-2-methylpropane would form a tertiary carbocation. So, in decreasing order of reactivity: 2-chloro-2-methylpropane > benzyl chloride > chlorobenzene.

S_N2 – Steric interactions are key here. Alkyl groups attached to the carbon bearing the leaving group block attack by the nucleophile. Also, aryl halides are unreactive for this reason. In the instant case chlorobenzene and 2-chloro-2-methylpropane are unreactive. Benzyl chloride is a primary halide and would react quickly.

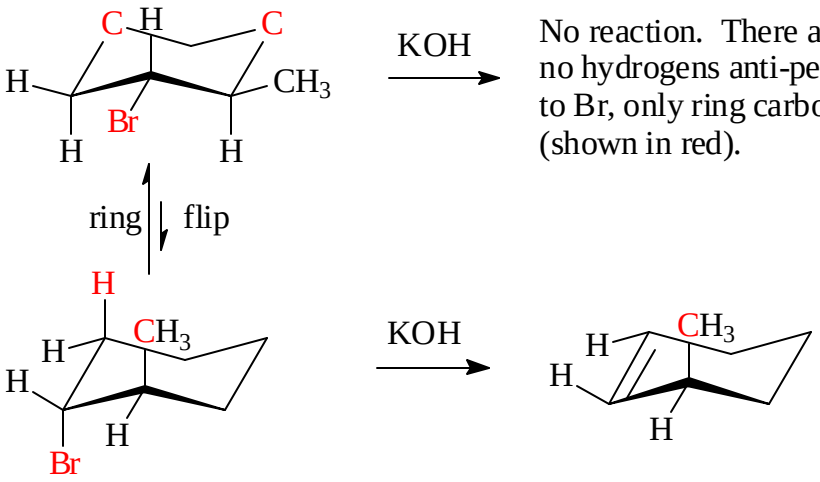
37. Although radical chlorination of alkanes is usually unselective, chlorination of propene, $CH_3CH{=}CH_2$, occurs almost exclusively on the methyl group rather than on the double bond. Draw resonance structures of the allyl radical, $CH_2{=}CHC^{\bullet}H_2$, to account for this result.

Well, OK, here they are. The allyl radical is stabilized by resonance. The vinyl radical that would have to form to replace one of the vinylic hydrogens is not resonance stabilized and is, in fact, quite unstable.



49. How can you explain the fact that *trans*-1-bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with base?

In the presence of a strong base we would expect an E2 elimination. The E2 requires that the halogen and a hydrogen on a carbon adjacent to the one holding the halogen be in an anti-periplanar conformation.



In this case the carbon of the methyl group and the hydrogen in red are anti-periplanar to the Br. In an E2 elimination the red hydrogen and Br would be eliminated giving the anti-Zaitsev product.