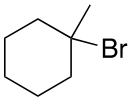
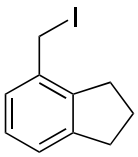
1. Draw all structural isomers of C_4H_9I, and then arrange them in order of increasing reactivity toward an S_N2 reaction. Assume the same nucleophile is used in the reactions involving each isomer.

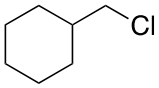
2. Classify each nucleophile as either good or weak nucleophile in a polar protic solvent. Determine if an S_N1 process involving each of the following nucleophile requires de-protonation step at the end of the mechanism. Assume the reaction involves the same alkyl halide for each nucleophile.

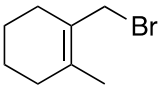
a)	NaSH	c)	H_2O	e)	NaCN	g)	$NaNH_2$
b)	H_2S	d)	EtOH	f)	NH_3		

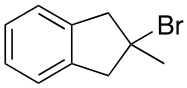
3. Identify whether each of the following substrates favours S_N2, S_N1, both, or neither.

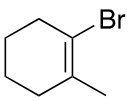
a) 

b) 

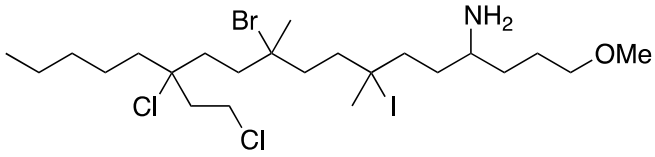
c) 

d) 

e) 

f. 

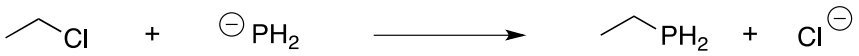
4. Consider the structure of the compound below.



a) identify each position where an S_N2 reaction is likely to occur, and why?

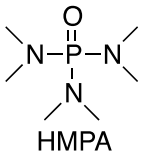
b) identify each position where an S_N1 reaction is likely to occur, and why?

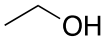
5. Determine if each of the following reactions predominantly undergoes S_N1 or S_N2. The, draw the species that is speculated to be generated in the transition state in each of the following reactions.

a) 

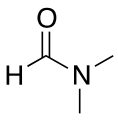
b) 

6. Does each of the following solvents favour an S_N2 reaction or S_N1 reaction?

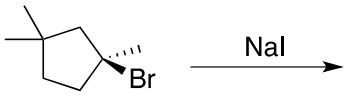
a) MeOH b) CH_3CN c) 

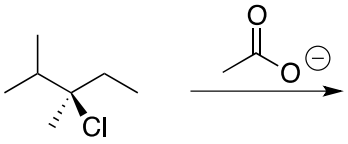
d) 

e) 

f. 

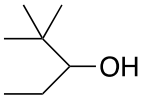
7. Determine if each alkyl halide is undergoing S_N1 or S_N2. Draw the products of each substitution reaction:

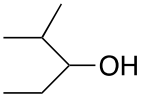
a) 

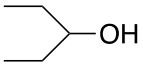
b) 

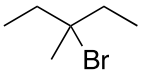
8. For each of the following substrates, determine whether an S_N1 process will involve a carbocation rearrangement or not. If the carbocation rearrangement is observed, is it via 1,2-hydride shift or 1,2-methyl shift?

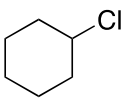
a) 

b) 

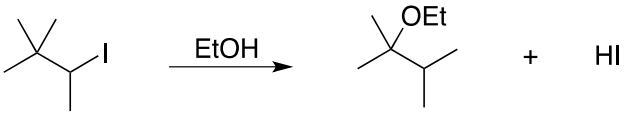
c) 

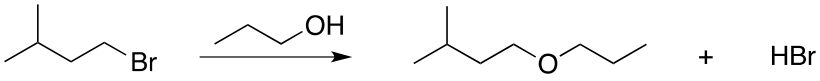
d) 

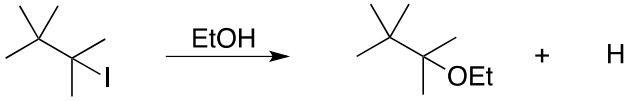
e) 

f. 

9. Determine if each reaction is an S_N2 or S_N1. Then draw the mechanism for the reaction.

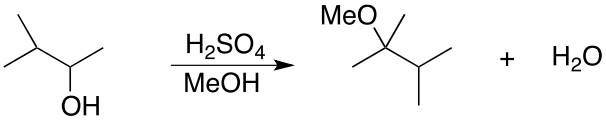
a) 

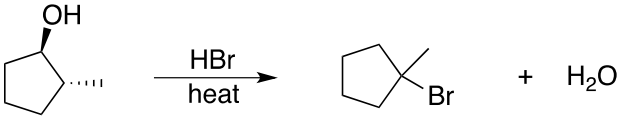
b) 

c) 

d) 

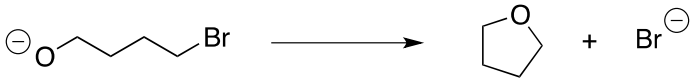
e) 

f) 

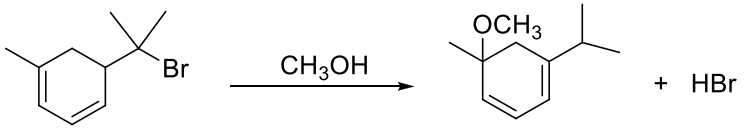
g) 

50 : 50 mixture
of R and S

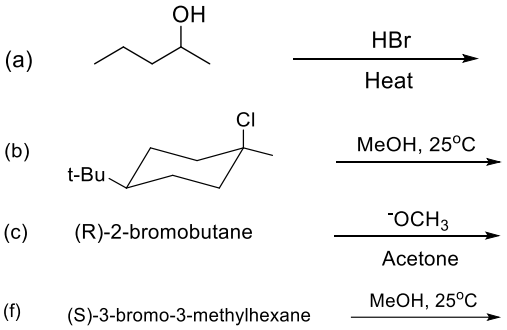
10. When a nucleophile and electrophile are tethered to each other (that is, both are present in the same compound), an intramolecular (within the molecule) substitution reaction can occur, as shown. Assume that this reaction occurs via a concerted process, and draw the mechanism of the reaction.



11. Write a detail mechanism using curved-arrows for the following transformation, clearly showing any intermediates formed during the reaction. (N.B. The reaction involves the **solvolysis**, the solvent acting as nucleophile)



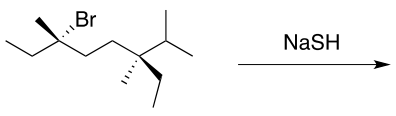
12. Determine if each reaction involves S_N2 or S_N1 mechanism and provide the structure of the final product. (*N.B.* if the stereochemical configuration is conveyed, make sure to include the correct stereochemistry in your drawing for the final product).



13. Draw the product for each of the following S_N2 reactions:

    a) (*S*)-2-chloropentane and NaSH
    b) (*R*)-3-iodohexane and NaCl

14. Draw the two products that you expect in the following reaction and describe their stereoisomeric relationship:

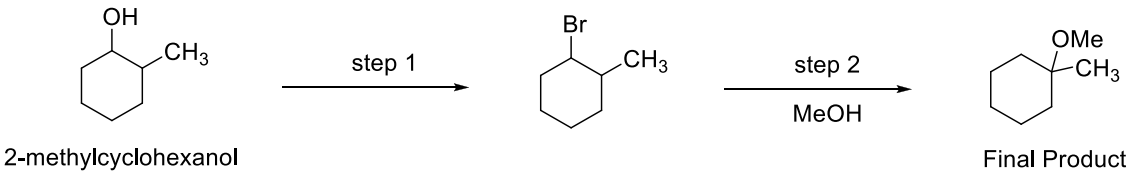


15. When (*S*)-1-bromo-1-fluoroethane reacts with sodium methoxide (NaOMe), an S_N2 reaction takes place in which the bromine atom is replaced by a methoxy group (OMe). The product of this reaction is (*S*)-1-fluoro-1-methoxyethane. How can it be that the starting material, and the product both have the S configuration? Shouldn't S_N2 involve a change in the configuration? Draw the starting material and the product of inversion, and then explain the anomaly.

16. Treatment of (2R, 3R)-3-methyl-2-pentanol with H_3O^+ affords a compound with no chirality centres. Predict the product of this reaction and draw the mechanism of its formation. Use mechanism to explain how both chirality centres are destroyed.

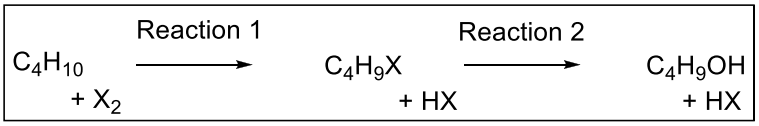
17. Hydrolysis (water as a nucleophile) of 2-bromo-3-methylbutane yields only 2-methyl-2-butanol. Provide the mechanism for this transformation.

18. **Multi-Step Synthesis** - i) Starting from the 2-methylcyclohexanol, propose the synthesis (using whatever reagents necessary) to generate 1-bromo-2-methylcyclohexane and provide the detail mechanism. ii) In the second step, 1-bromo-2-methylcyclohexane is reacted with high concentration of methanol, and the unexpected final product was resulted. Give mechanism to account for this product.



2-methylcyclohexanol Final Product

19. **Multi-Step Synthesis** - Look at the following functional group transformation, starting from a compound having a chemical formula, C_4H_{10}:



While carrying out the chemical reactions in sequence, the following observations were determined,

- Reaction 1 was carried out under highly vigorous condition and highly selective to yield the bulkiest (3^o) product having the formula, C_4H_9X, as the sole product.
- Reaction 2 proceeded fast when performed in H_2O, leading to the final alcohol product having the formula C_4H_9OH.

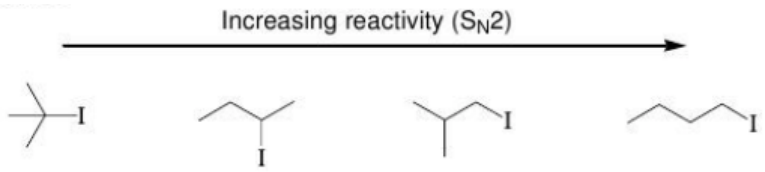
Referring to the information given above, answer the following questions:

a) Provide i) the structure of the reactant (C_4H_{10}), ii) a specific halogen reagent and iii) detail mechanism including the structure of the product using appropriate curved-arrows for reaction 1.

b) Provide i) the rate law for the expected mechanism in reaction 2, ii) justification for your answer in i) in no more than 4 sentences and iii) complete reaction mechanism, including the formation of all intermediates (if applicable), of this reaction using curved-arrows.

Solutions

1. Draw all structural isomers of C_4H_9I, and then arrange them in order of increasing reactivity toward an S_N2 reaction. Assume the same nucleophile is used in the reactions involving each isomer.



2. Classify each nucleophile as either good or weak nucleophile in a polar protic solvent. Determine if an S_N1 process involving each of the following nucleophile requires de-protonation step at the end of the mechanism. Assume the reaction involves the same alkyl halide for each nucleophile.

a) NaSH
Strong Nu and Deprotonation step not required since it is an anionic Nu

b) H_2S
Poor Nu and Deprotonation step required since it is a neutral Nu

c) H_2O
Poor Nu and Deprotonation step required since it is a neutral Nu

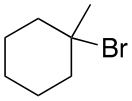
d) EtOH
Poor Nu and Deprotonation step required since it is a neutral Nu

e) NaCN
Poor Nu (check pka of HCN ~ 10), but deprotonation step not required since it is an anionic Nu

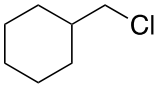
f) NH_3
Poor Nu and Deprotonation step required since it is a neutral Nu

g) $NaNH_2$
Strong Nu and Deprotonation step not required since it is an anionic Nu

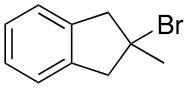
3. Identify whether each of the following substrates favours S_N2, S_N1, both, or neither.

a) 

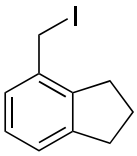
S_N1 favoured exclusively

c) 

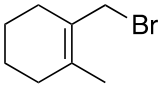
S_N2 favoured exclusively

e) 

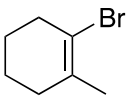
S_N1 favoured exclusively

b) 

S_N2 favoured predominantly* if Nu is strong. But this molecule can possibly undergo S_N1 if a poor Nu is applied due to resonance (benzylic position)

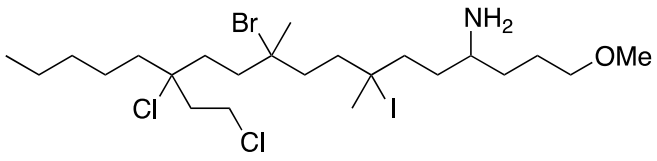
d) 

S_N2 favoured if Nu is strong. But this molecule can <u>equally</u> undergo S_N1 because of resonance effect if a poor Nu is applied (allylic position)

f) 

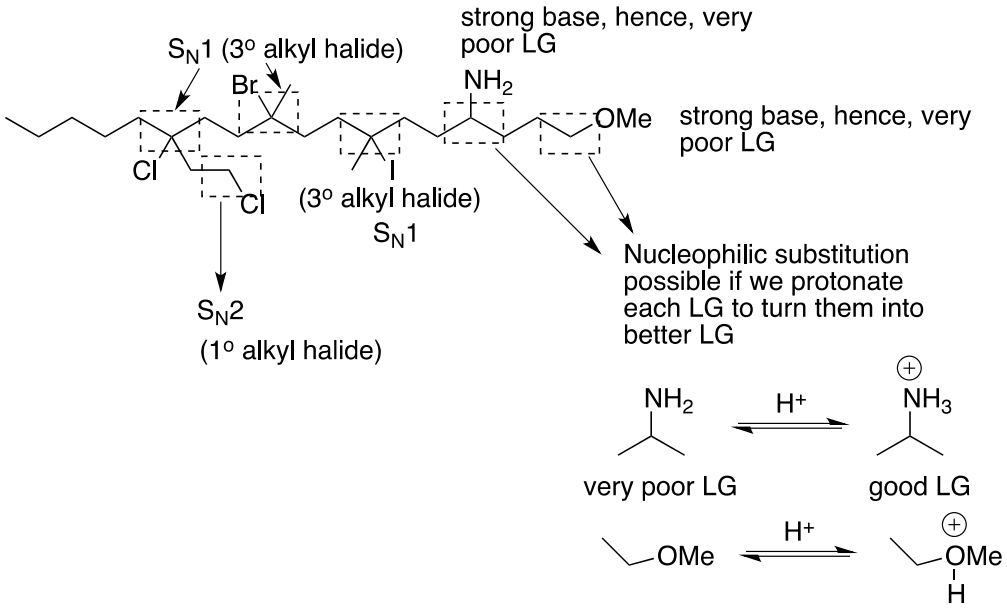
it is an alkenyl halide (bromine is bonded to a sp^2 carbon), not an alkyl halide. Neither S_N1 or S_N2 is possible.

4. Consider the structure of the compound below.



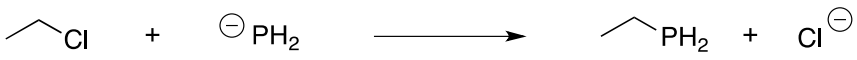
a) identify each position where an S_N2 reaction is likely to occur, and why?

b) identify each position where an S_N1 reaction is likely to occur, and why?



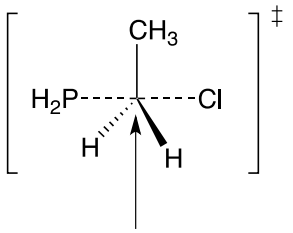
5. Determine if each of the following reactions predominantly undergoes S_N1 or S_N2. The, draw the species that is speculated to be generated in the transition state in each of the following reactions.

a)



The reaction undergoes S_N2 mechanism
(1° alkyl halide and strong Nu)

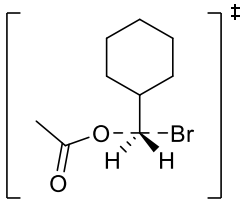
Because it is a concerted mechanism, the transition state species has 50% (reactant character) and 50% (product chracter).



The carbon atom in the transition state of S_N2 adapts trigonal planat grometry

b)

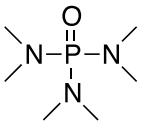
The reaction undergoes S_N2 mechanism
(1° alkyl halide even though nucleophile is weak)



6. Does each of the following solvents favour an S_N2 reaction or S_N1 reaction?

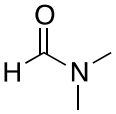
a) MeOH
Is a polar protic solvent, favours S_N1

b) CH_3CN
Is a polar aprotic solvent, favours S_N2

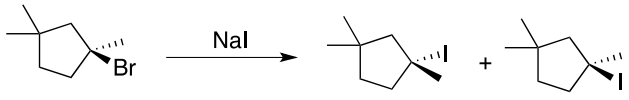
c) 
HMPA
Is a polar aprotic solvent, favours S_N2

d) 
Is a polar protic solvent, favours S_N1

e) 
Is a polar aprotic solvent, favours S_N2

f) 
Is a polar aprotic solvent, favours S_N2

7. Determine if each alkyl halide is undergoing S_N1 or S_N2. Draw the products of each substitution reaction:

a) 

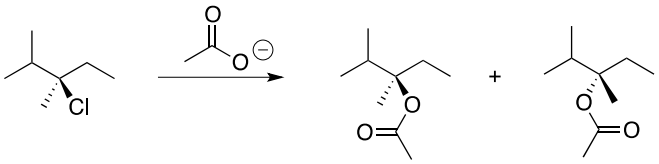
Pay attention to Stereochemistry when indicated

50 : 50 Racemic mixture

Hierarchical importance

1) **Alkyl halide type: tertiary**
2) Nucleophile: **I-** Strong
3) Solvent: not indicated

SN1 reaction

b) 

50 : 50 Racemic mixture

Hierarchical importance

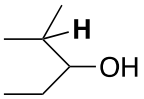
1) **Alkyl halide type: tertiary**
2) Nucleophile: acetate (weak)
3) Solvent: not indicated

SN1 reaction

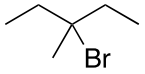
8. For each of the following substrates, determine whether an S_N1 process will involve a carbocation rearrangement or not. If the carbocation rearrangement is observed, is it via 1,2-hydride shift or 1,2-methyl shift?

a) 

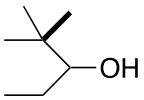
No carbocation rearrangement

c) 

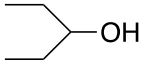
Rearrangement observed
1,2-hydride shift
(move the H in bold)

e) 

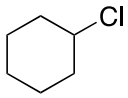
No carbocation rearrangement

b) 

Rearrangement observed
1,2-methyl shift (move the methyl in bold)

d) 

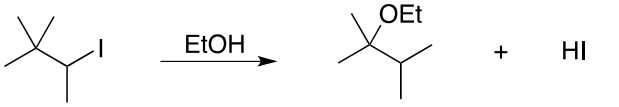
No carbocation rearrangement

f) 

No carbocation rearrangement

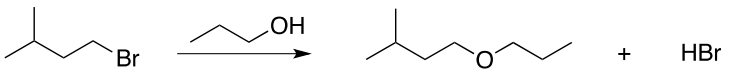
9. Determine if each reaction is an S_N2 or S_N1. Then draw the mechanism for the reaction.

The key factor leading to the decision of determining whether the reaction undergoes S_N2 or S_N1 is **in bold**

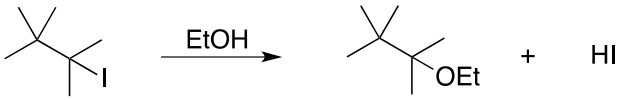
a) 

This reaction is an example of solvolysis (solvent acting as nucleophile)

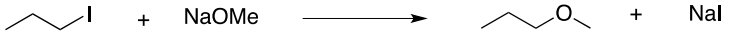
Hierarchical importance
1) Alkyl halide type: secondary
2) Nucleophile: ethanol (poor)
*also rearrangement has taken place!
↓
SN1 reaction

b) 

Hierarchical importance
1) Alkyl halide type: primary
2) Nucleophile: propanol (poor), solvolysis
↓
SN2 reaction

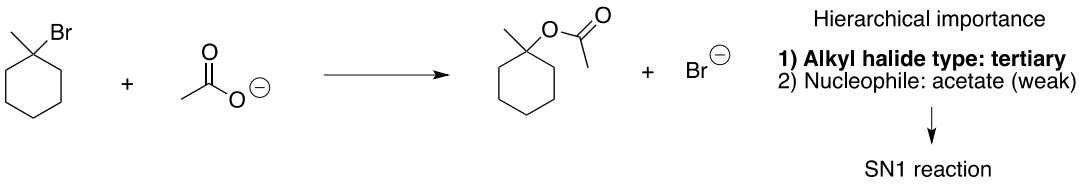
c) 

Hierarchical importance
1) Alkyl halide type: tertiary
2) Nucleophile: ethanol (poor)
↓
SN1 reaction

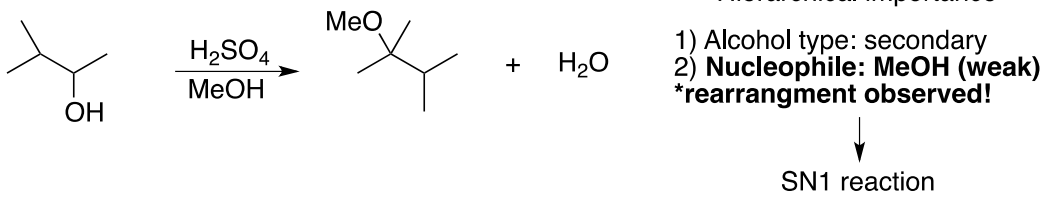
d) 

Hierarchical importance
1) Alkyl halide type: primary
2) Nucleophile: OMe (strong)
*OMe is the conjugate base of methanol (MeOH)
↓
SN2 reaction

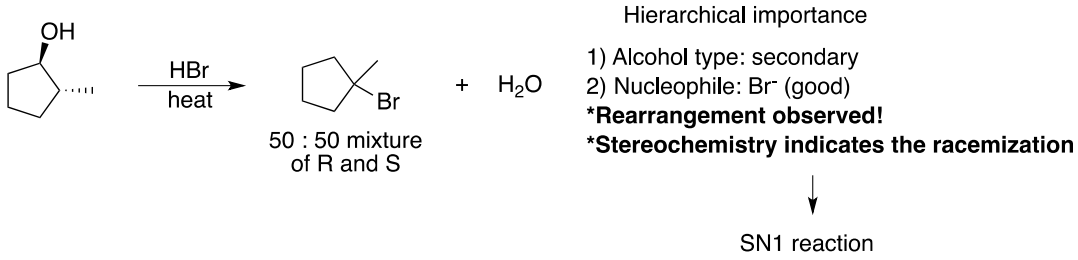
e)



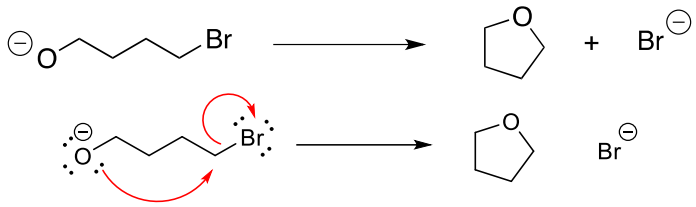
f)



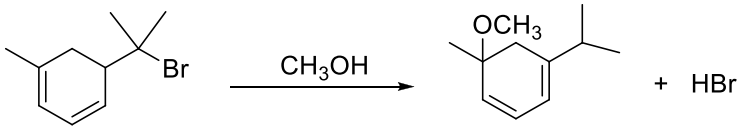
g)

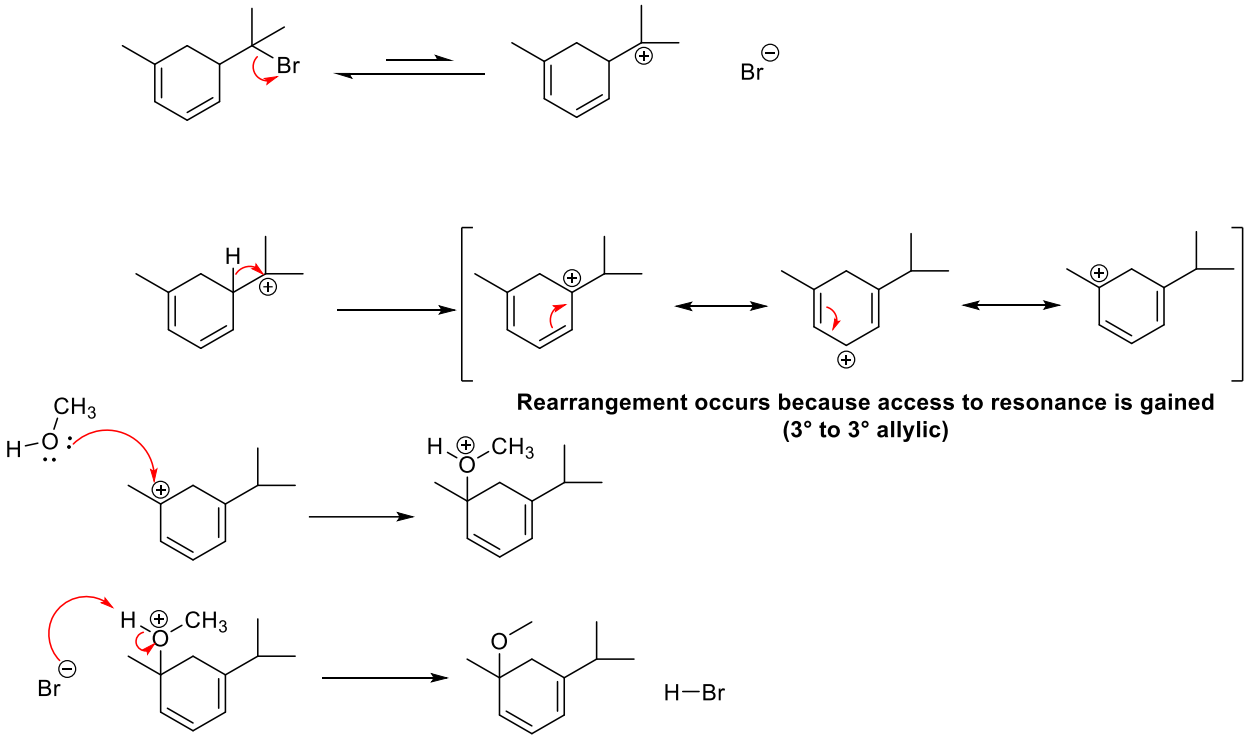


10. When a nucleophile and electrophile are tethered to each other (that is, both are present in the same compound), an intramolecular (within the molecule) substitution reaction can occur, as shown. Assume that this reaction occurs via a concerted process, and draw the mechanism of the reaction.

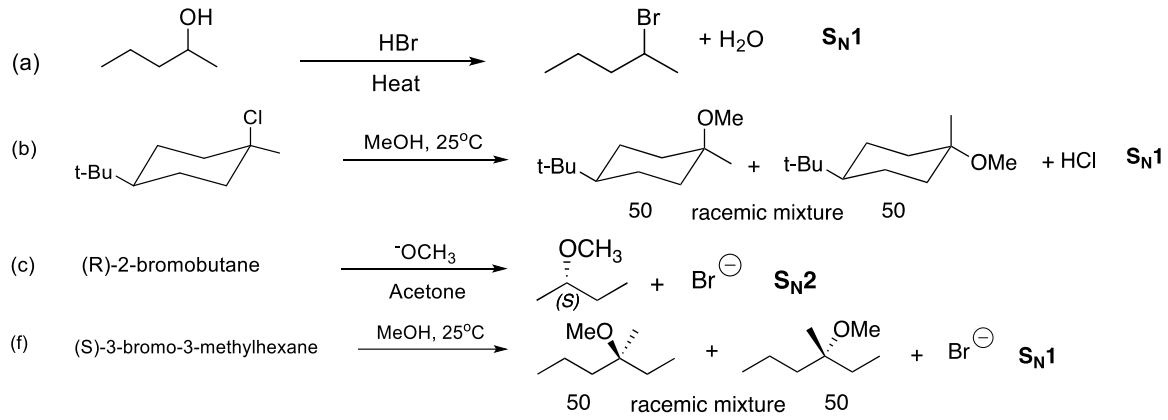


11. Write a detail mechanism using curved-arrows for the following transformation, clearly showing any intermediates formed during the reaction. (N.B. The reaction involves the **solvolysis**, the solvent acting as nucleophile)

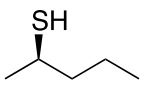


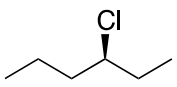


12. Determine if each reaction involves S_N2 or S_N1 mechanism and provide the structure of the final product. (*N.B.* if the stereochemical configuration is conveyed, make sure to include the correct stereochemistry in your drawing for the final product).

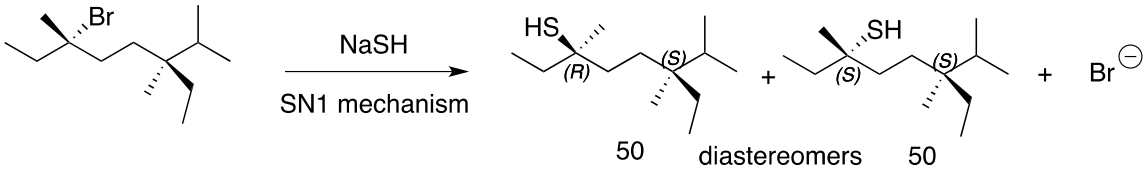


13. Draw the product for each of the following S_N2 reactions:

(a) 

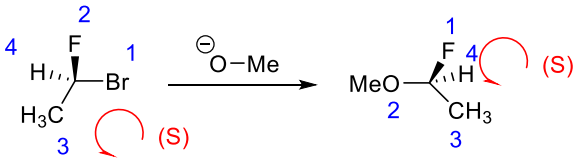
(b) 

14. Draw the two products that you expect in the following reaction and describe their stereoisomeric relationship:



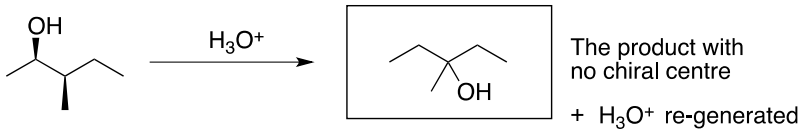
Forced to do Sn1 since it is a tertiary alkyl halide

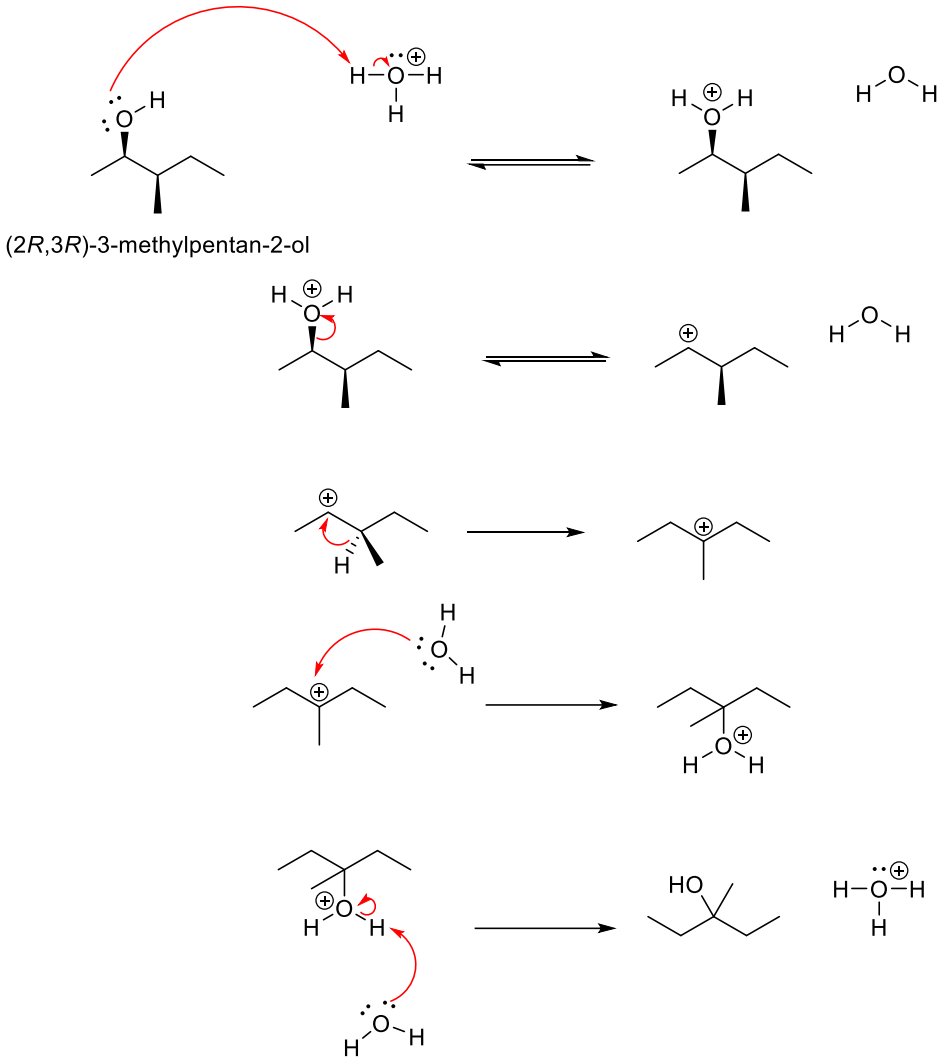
15. When (*S*)-1-bromo-1-fluoroethane reacts with sodium methoxide (NaOMe), an S_N2 reaction takes place in which the bromine atom is replaced by a methoxy group (OMe). The product of this reaction is (*S*)-1-fluoro-1-methoxyethane. How can it be that the starting material, and the product both have the S configuration? Shouldn't S_N2 involve a change in the configuration? Draw the starting material and the product of inversion, and then explain the anomaly.



The reaction <u>does</u> proceed with inversion of configuration. However, the Cahn-Ingold-Prelog system for assigning R or S is based on a prioritization scheme. In the reactant, the highest priority group is the leaving group (bromide), which is then replaced by a group that does not receive the highest priority. In the product, the fluorine atom has been promoted to the highest priority as a result of the reaction, and as such, the prioritization scheme has changed. In this way, stereodescriptor (s) remains unchanged, despite the fact that the chiral centre undergoes inversion.

16. Treatment of (2R, 3R)-3-methyl-2-pentanol with H_3O^+ affords a compound with no chirality centres. Predict the product of this reaction and draw the mechanism of its formation. Use mechanism to explain how both chirality centres are destroyed.



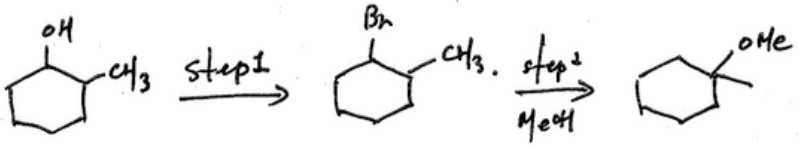


(2*R*,3*R*)-3-methylpentan-2-ol

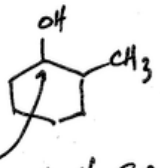
17. Hydrolysis (water as a nucleophile) of 2-bromo-3-methylbutane yields only 2-methyl-2-butanol. Provide the mechanism for this transformation.

See solution to question 16, consider that rearrangement is observed between the reactant and product

18. **Multi-Step Synthesis** - i) Starting from the 2-methylcyclohexanol, propose the synthesis (using whatever reagents necessary) to generate 1-bromo-2-methylcyclohexane and provide the detail mechanism. ii) In the second step, 1-bromo-2-methylcyclohexane is reacted with high concentration of methanol, and the unexpected final product was resulted. Give mechanism to account for this product.

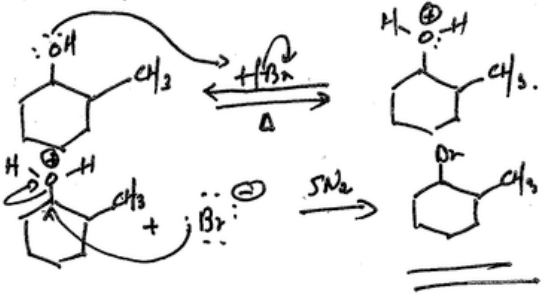


step 1



2° alcohol. both $SN1/SN2$ possible, but we need SN_2! (b/c if SN_1 happens, the rearrangement will take place).

mechanism:

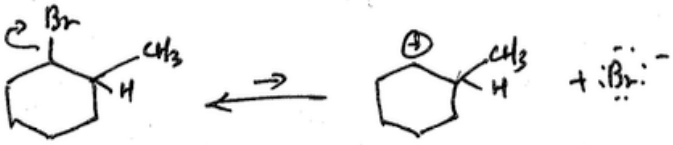


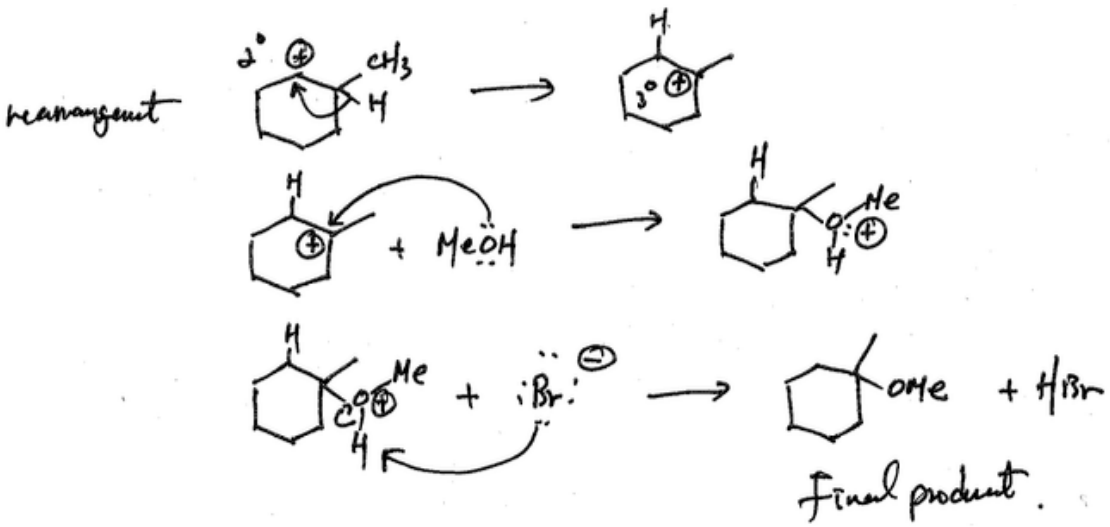
step 2

Based on where the substitution takes place, it requires rearrangement! (SN_1)

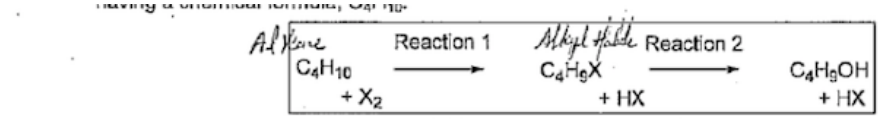
HINT: MeOH → weak Nu.

mechanism. (SN_1)




rearrangement
2°
CH3
H
3°
+ MeOH
Me
Br
OMe
+ HBr
Final product.

19. **Multi-Step Synthesis** - Look at the following functional group transformation, starting from a compound having a chemical formula, C_4H_{10}:



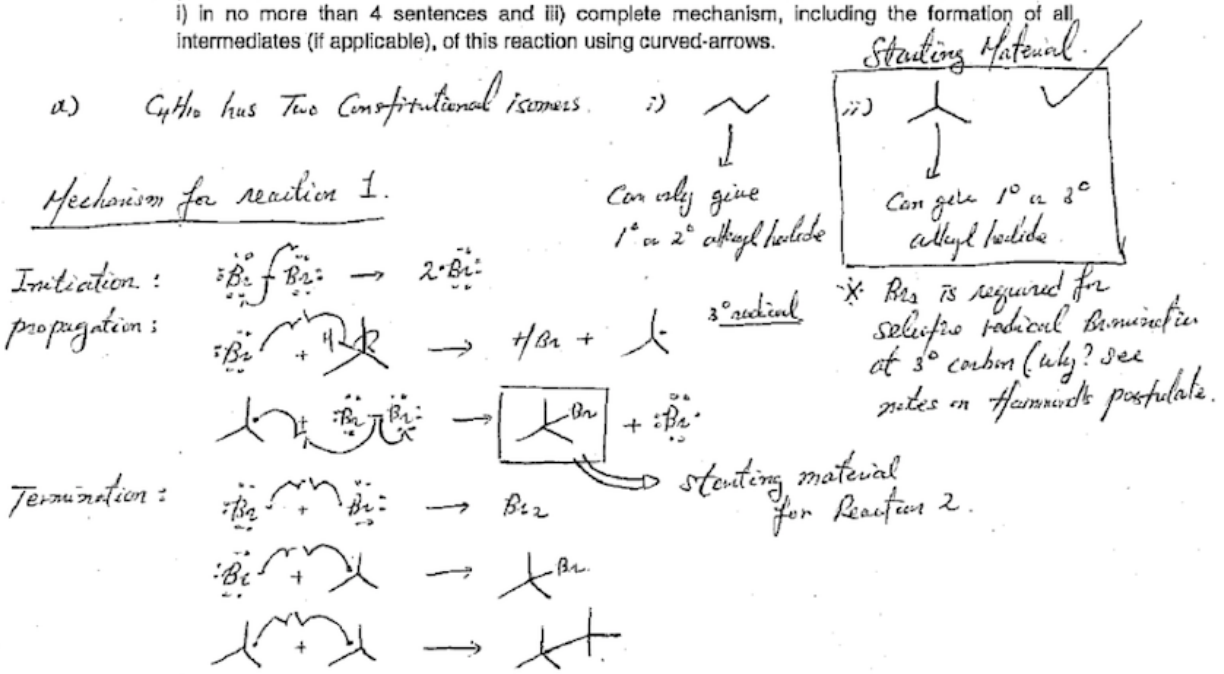
While carrying out the chemical reactions in sequence, the following observations were determined:

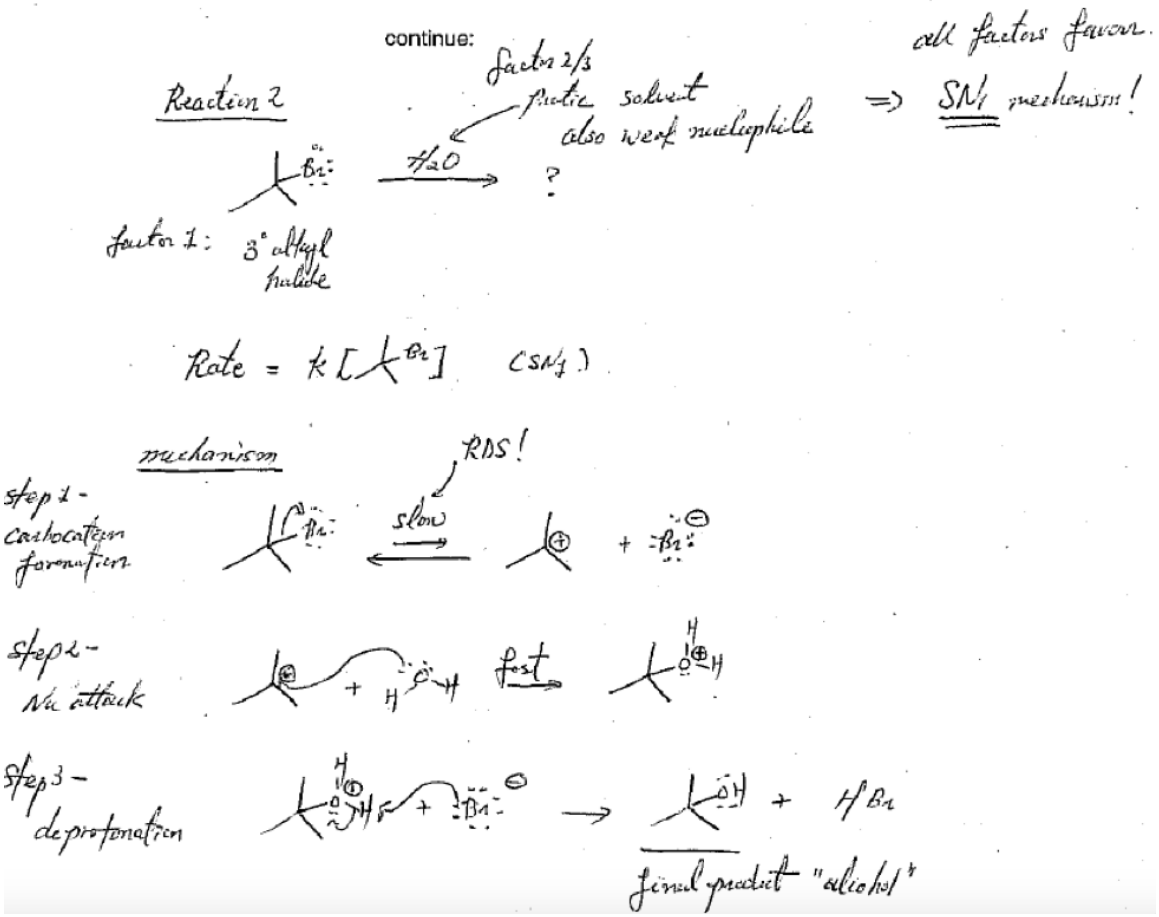
- Reaction 1 was carried out under highly vigorous condition and highly selective to yield the bulkiest (3°) product having the formula, C_4H_9X, as the sole product.
- Reaction 2 proceeded fast when performed in H_2O, leading to the final alcohol product having the formula C_4H_9OH.

Referring to the information given above, answer the following questions **(N.B. All structures must be drawn in bond-line representation):**

a) Provide i) the structure of the reactant (C_4H_{10}), ii) a specific halogen reagent and iii) detail mechanism including the structure of the product using appropriate curved-arrows for reaction 1.

b) Provide i) the rate law for the expected mechanism in reaction 2, ii) justification for your answer in i) in no more than 4 sentences and iii) complete mechanism, including the formation of all intermediates (if applicable), of this reaction using curved-arrows.




continue:
all factors favor.
Reaction 2
factor 2/3
protic solvent
also weak nucleophile
=> SN1 mechanism!
H2O
?
factor 1: 3° alkyl halide
Rate = k[ ]
(SN1)
mechanism
RDS!
slow
step 1 - carbocation formation
fast
step 2 - Nu attack
step 3 - deprotonation
+ HBr
final product "alcohol"