6.1 S_N1 vs S_N2 reactions

A) Which reaction(s) happen(s) in one step:
- S_N1
- S_N2
- None
- Both

B) In an SN2 reaction, what is the stereochemical outcome at the carbon where substitution occurs?
- It stays the same
- It inverts
- It becomes racemic
- It depends on the reactants

C) Which reaction(s) involve an intermediate species?
- S_N1
- S_N2
- None
- Both

D) What is the rate determining step of an S_N1 reaction?
- Nucleophile attacking the electrophile
- Formation of a carbocation
- Loss of a proton
- Departure of the nucleophile

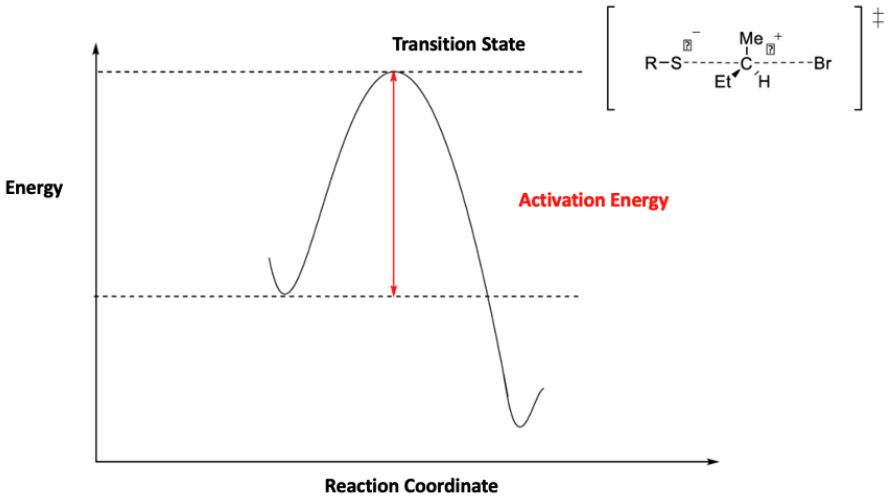
E) Which reaction(s) involve a transition state?
- S_N1
- S_N2
- None
- Both

6.2 S_N2 Reaction Mechanism

a) Thiophenolate reacts with 2-bromobutane in a substitution reaction. Draw the resulting products. Name the reactants (nucleophile, electrophile, leaving group) and draw the electron displacement arrows.

Nucleophile Electrophile

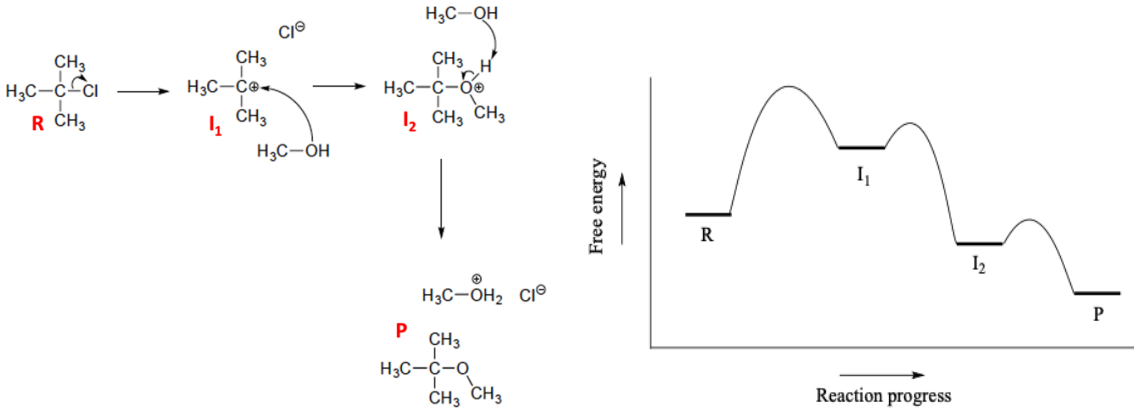
b) Draw the reaction profile in the diagram below. Also label the axes correctly and draw the structure of the transition state of the reaction.



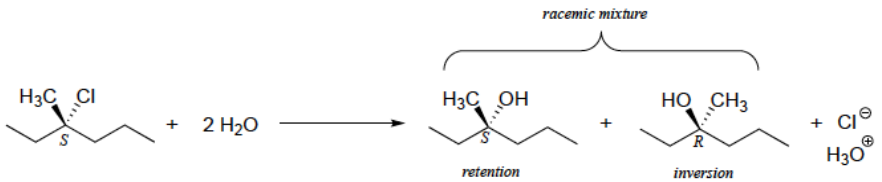
6.3 S_N1 Mechanism and Solvolysis

a) Draw a mechanism for the SN1 solvolysis of tert-butyl chloride in methanol. What new functional group has been formed? Also draw the reaction profile of the SN1 reaction in the diagram below and label the axes correctly.

An ether is formed



b) Now consider the solvolysis of (S)-3-chloro-3-methylhexane below:

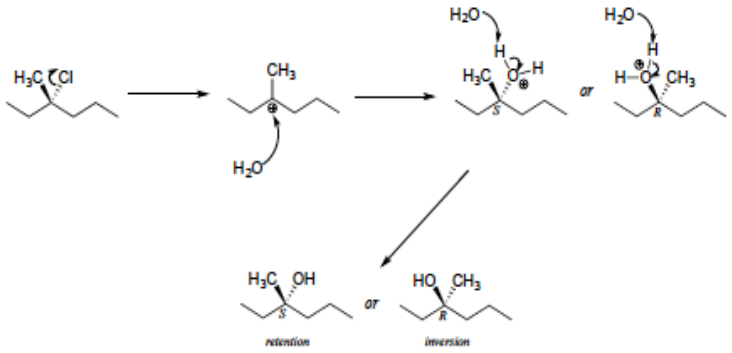


i) Draw a complete mechanism for this hydrolysis reaction, showing all bond-breaking and bond-forming steps, and all intermediate species.
ii) Draw structures representing TS1 and TS2 in the reaction. Use the solid/dash wedge convention to show three dimensions.
iii) What is the expected optical rotation of the product mixture?

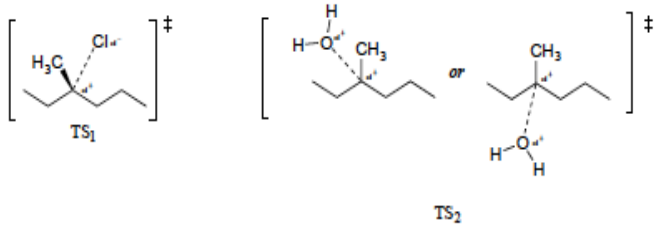
iv) Could the two organic products be separated on a silica column chromatography?

Solution

i)



ii)



iii) The product is expected to be a 50:50 racemic mixture (of R and S enantiomers), so there will be no observed optical rotation (0°).

iv) No - recall that enantiomers have the same physical properties and cannot be separated by silica, recrystallization, solubility, etc.

6.4 S_N1 vs S_N2 reactions

a) Tick the factors that clearly favor the S_N1 mechanism over the S_N2 mechanism, and explain why (give at least one example):

- good nucleophile
- presence of a strong base
- bulky groups at the reactive center

Bulky substrates (e.g., tertiary alkyl halides) hinder backside attack required for S_N2, making S_N1 more favorable as the reaction proceeds through a carbocation intermediate.

- strong electron-donor substituents at the reactive center

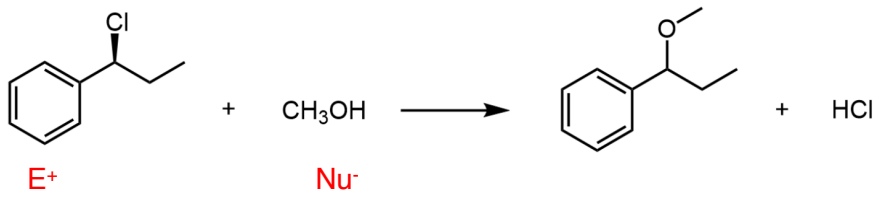
Electron-donating groups (e.g., alkyl groups, resonance-donating substituents) stabilize the carbocation formed in S_N1, making its formation easier.

- good leaving group

A good leaving group (e.g., Cl^-, Br^-, I^-, TsO^-) facilitates the departure of the leaving group in the rate-determining step of S_N1, allowing carbocation

- basic leaving group

b) In order to increase the rate of the following reaction, I should:



A) Add more electrophile (substrate)
B) Add more nucleophile
C) Increase the strength of the nucleophile
D) Decrease the polarity of the solvent

To answer this question, it is crucial to first define the type of the reaction, as S_N1 and S_N2 follow different reaction mechanisms. The presence of a bulky and aromatic ring on the electrophile, a good leaving group (Cl-), a weak nucleophile and the formation of a racemic product all indicate that this is an S_N1 reaction.

S_N1 reactions follow first-order kinetics (rate=k*[substrate]), meaning the rate depends only on the substrate (electrophile) and not on the nucleophile. → Correct answer: A)

Why not other options? B) Add more nucleophile → Incorrect, because the nucleophile does not affect the rate in an SN1 reaction. C) Use a stronger nucleophile → Incorrect, since in an SN1 reaction, the nucleophilic attack is not rate determining. D) Use a less polar solvent → Incorrect, because polar protic solvents (like water, alcohols) actually stabilize the carbocation and increase the reaction rate.

6.5 True or False ? (explain why)

a. S_N2 reactions are favored by strong nucleophiles. (True)
In S_N2 reactions, the nucleophile attacks the electrophilic carbon in a single step. A strong nucleophile increases the reaction rate by making the backside attack more efficient.
b. A serine side chain is a better nucleophile than a threonine side chain. (True)
Serine has a hydroxyl (-OH) group on a primary carbon, whereas threonine has an additional methyl group next to the hydroxyl. This extra methyl group in threonine introduces steric hindrance, making it slightly less nucleophilic than serine.
c. S_N1 reactions proceed faster with tertiary alkyl halides than with primary alkyl halides. (True)
Tertiary alkyl halides form more stable carbocations due to hyperconjugation and inductive effects, making the S_N1 reaction proceed faster.
d. Stronger nucleophiles increase the rate of S_N1 reactions. (False)
In S_N1 reactions, nucleophilicity doesn't affect the rate because the rate-determining step is carbocation formation, which occurs before the nucleophile attacks.
e. A weak nucleophile can still participate in an S_N1 reaction. (True)
Since the nucleophile attacks after carbocation formation (which is unstable), even weak nucleophiles (like water or alcohols) can react in S_N1 reactions.

f. Methanol (CH_3OH) is a better solvent for S_N2 reactions than DMSO. (False)
Methanol is a polar protic solvent, which stabilizes nucleophiles and slows S_N2 reactions. DMSO, a polar aprotic solvent, does not stabilize nucleophiles, making S_N2 reactions faster.

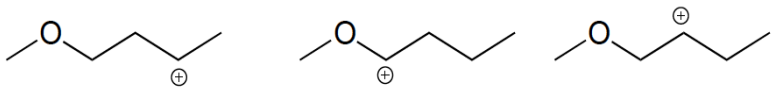
g. S_N2 reactions are favored in polar protic solvents. (False)
S_N2 reactions are favored in **polar aprotic solvents** (like DMSO, acetone, or acetonitrile) because protic solvents (like water or alcohols) stabilize the nucleophile, making it less reactive.

h. A cysteine side chain is a better nucleophile than a methionine side chain. (True)
Cysteine has a thiol (-SH) group, which is more nucleophilic than methionine's thioether (-S-CH_3) group. The thiol is more reactive because it can donate electrons more easily, while the thioether is less reactive due to steric hindrance and reduced availability of the sulfur lone pair.

6.6 Carbocation Stability

a) Rank the following carbocations from most to least stable and explain.

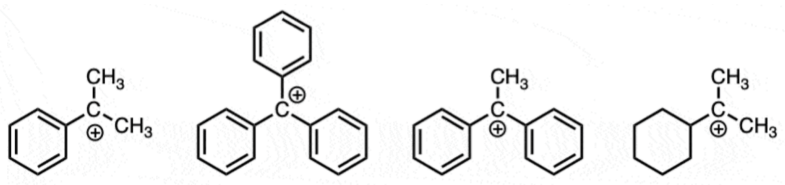
i)



A **B** **C**

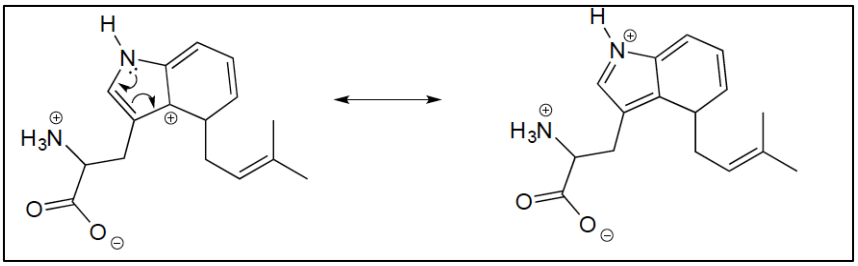
most stable B > A > C least stable. This is an example of resonance and inductive effects acting in opposite directions. Carbocation B is stabilized by resonance with the oxygen atom, which acts as an electron-donating group by resonance. In A and C, the oxygen atom cannot be an electron donating group by resonance due to the relative positions, but it does act as a (carbocation destabilizing) electron withdrawing group by induction, with a stronger effect seen for C due to closer proximity.

ii)

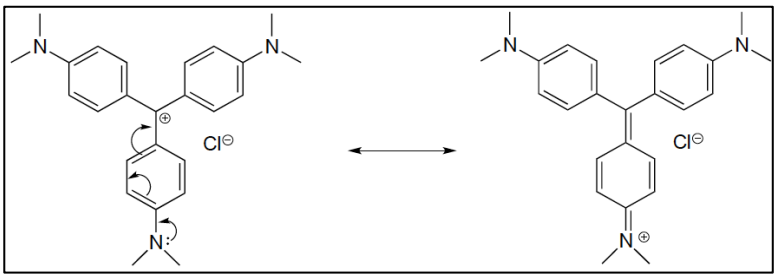


most stable B > C > A > D least stable. All carbocations are tertiary, but the aromatic rings can stabilize the charge through resonance. The more aromatic rings attached to the carbocation, the more stable it is.

b) The carbocation below is an intermediate species in a reaction that is part of the biosynthesis of a hallucinogenic compound in a fungus. Draw a resonance contributor that shows how it is stabilized by resonance with the nitrogen atom.

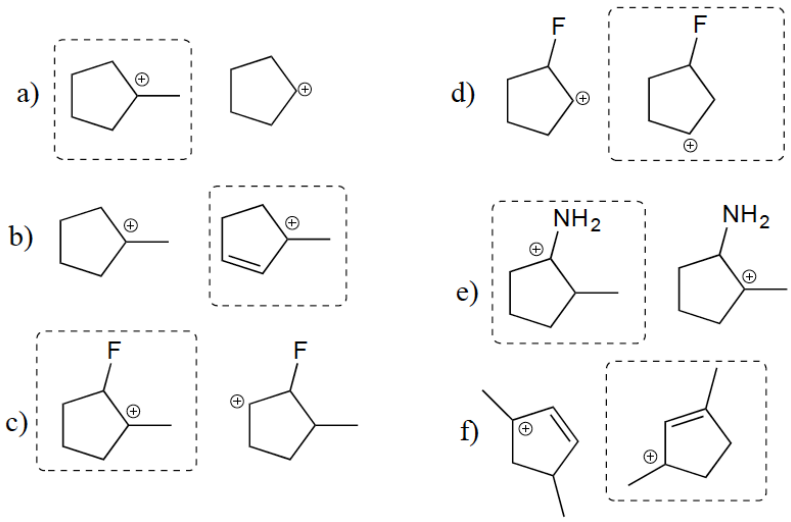


c) Consider the structure of crystal violet given below. Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.



d) State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.

The more stable carbocation is boxed.

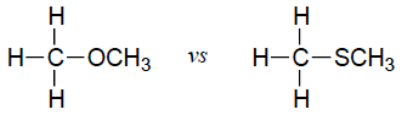


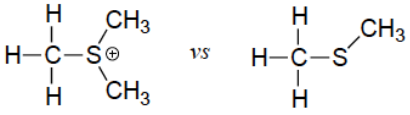
a) tertiary vs. secondary, b) tertiary vs. tertiary-allylic, c) tertiary vs. secondary, d) more

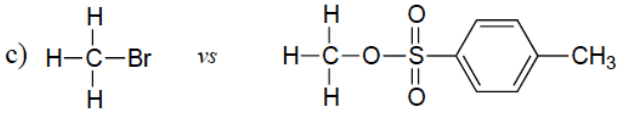
stable carbocation is further from electron-withdrawing fluorine, e) more stable carbocation can be delocalized by resonance with nitrogen, f) carbocation delocalized over two tertiary carbons vs. one tertiary and one secondary

6.7 Electrophilicity

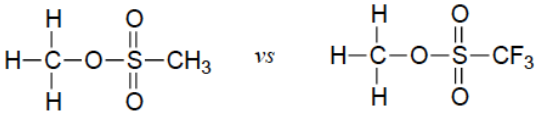
In each pair (A and B) below, which electrophile would be expected to react more rapidly with cyanide ion nucleophile in acetone solvent? Explain your reasoning.

a) 

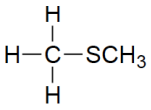
b) 

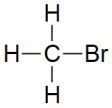
c) 

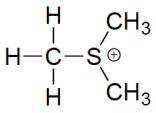
(hint - use a pKa table)

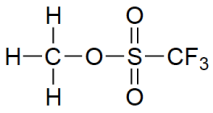
d) 

Solution

a) 

c) 

b) 

d) 

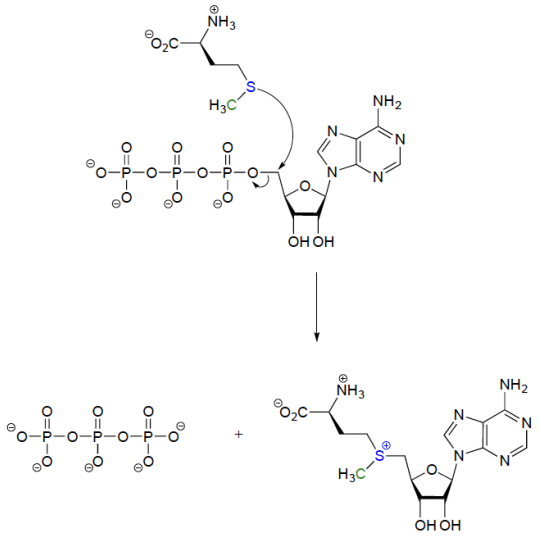
Reasoning:

a. thiolates are weaker bases and better leaving groups than alkoxide (pKa of thiol is ~10; pKa of alcohol is ~15+)
b. Leaving group is a sulfide vs thiolate. Sulfides are very weak bases, thus very good leaving groups.
c. HBr (pKa = -9) is a stronger acid than para-toluenesulfonic acid (pKa = -2.8), so bromide ion is a weaker base and better leaving group than para-toluenesulfonate.
d. Both are sulfonate leaving groups, but the inductive effect of fluorines stabilizes the negative charge on the fluorinated leaving group by inductive effects.

6.8 Nucleophilic Substitution in Biology

a) *S*-adenosyl methionine (SAM) is formed by a nucleophilic substitution reaction between methionine and adenosine triphosphate (ATP). Draw a mechanism for this reaction, and explain why you chose either an SN1 or and SN2 pathway.

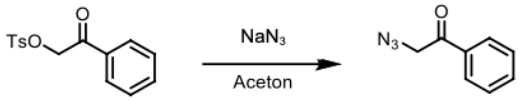
Solution



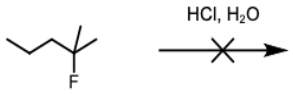
The electrophile is a primary carbon, so this reaction is expected to be SN2.

6.9 Nucleophilic Substitution Reactions

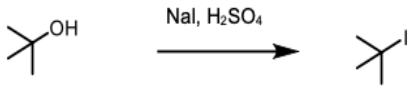
Indicate whether the reactions take place according to SN1, SN2 or not at all (extremely slow) and complete the reaction equations.



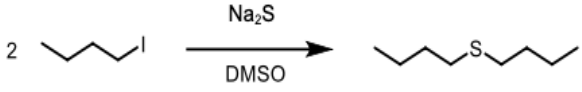
SN2 reaction, as the reaction takes place on a primary carbon atom. Furthermore, the carbonyl group stabilizes the negative charge in the transition state. In addition, an aprotic polar solvent is used.



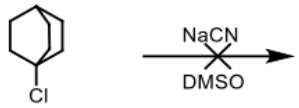
Since fluorine is not a leaving group, no SN1 reaction takes place.



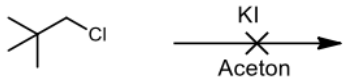
SN1 reaction, as the reaction takes place on the tertiary carbon atom.



SN2 reaction, as the reaction takes place on the primary carbon atom. A polar-aprotic solvent is also used. Note: The nucleophile can react twice.



The polar-aprotic solvent favors SN2 reactions. However, since the substrate (reactant) is sterically hindered, no backside attack takes place. In an SN1 reaction, the resulting carbocation could be non-planar (sp2-hybridized). Consequently, an SN1 mechanism is also unlikely.



SN2 reaction. The reaction would take place at the primary carbon atom, but as this is sterically hindered (neopentyl position), no reaction takes place.

SN2 reaction. DMF (N,N-dimethylformamide) is a polar-aprotic solvent that favors SN2 reactions. The configuration at the reaction center is inverted.