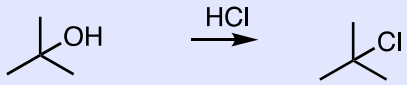
KEY TO CHAPTER 9 EXERCISES

(Susan Odom and Arthur Cammers, 2019)

Exercise 9.2.1 In Example 9.1.1, note that DMSO is not written into the rate equation, yet if we raise or lower the volume of DMSO, the rate of the reaction changes. Provide an explanation for this phenomenon.

Answer: DMSO is not involved in the rate determining step in that it is not part of the bond cleavage or formation involved, but the volume of DMSO affects the concentration of propanol and sodium hydroxide. So, if you keep the mass of reagents the same and decrease the volume of the solvent DMSO, the reaction rate will increase. Vice versa, increasing solvent volume will lower the concentration of the reagents and slow the reaction rate.

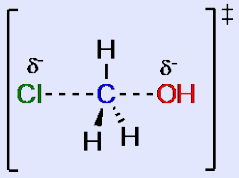
Exercise 9.2.2 In the reaction below, the reaction rate is dependent only on the concentration of *tert*-butanol and can be written as rate = k[*t*-BuOH]. What does this tell you about the involvement of HCl in the rate determining step?



Answer: By HCl not being involved in the rate determining step, this tells you only one species is involved. That said, HCl is involved in this reaction, as first an acid-base reaction with HCl occurs – it's just not the slow step, as acid-base reactions are quite fast compared to others.

Exercise 9.3.1 What is the measure in degrees) of the H-C-O angle in the S_N2 transition state illustrated above?

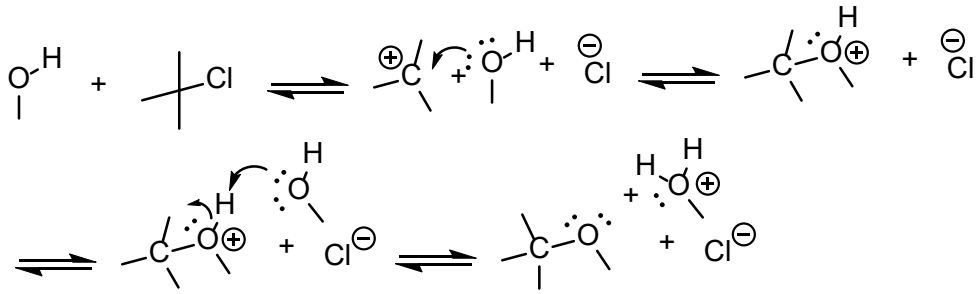
Reminder of transition state:



Answer: 90º The C–H bonds are hybridized sp^2. In the transition state the Cl—C—OH connection is composed of: 1) an sp hybrid orbital at Cl, 2) an sp hybrid orbital at OH, and 3) a pure p orbital at C.

Exercise 9.3.2 Draw a mechanism for the S_N1 solvolysis of *tert*-butyl chloride in methanol. What new functional group has been formed?

Answer:



The organic product is an ether, t-butyl methyl ether: $CH_3)_3COCH_3$

Exercise 9.3.3

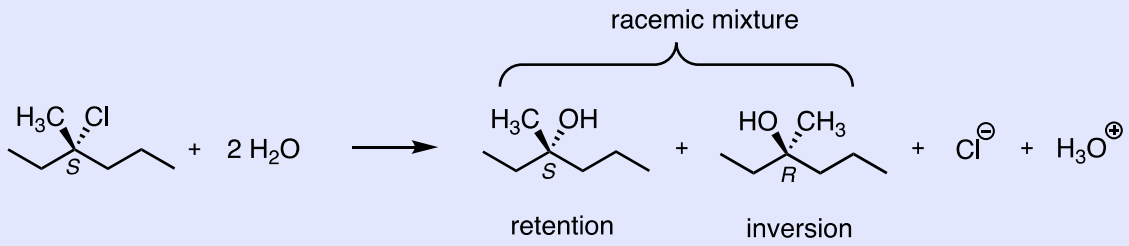
a) Draw a complete mechanism for the hydrolysis reaction in the previous figure, showing all bond-breaking and bond-forming steps, and all intermediate species.

b) Draw structures representing TS_1 and TS_2 in the reaction. Use the solid/dash wedge convention to show three dimensions.

c) What is the expected optical rotation of the product mixture?

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

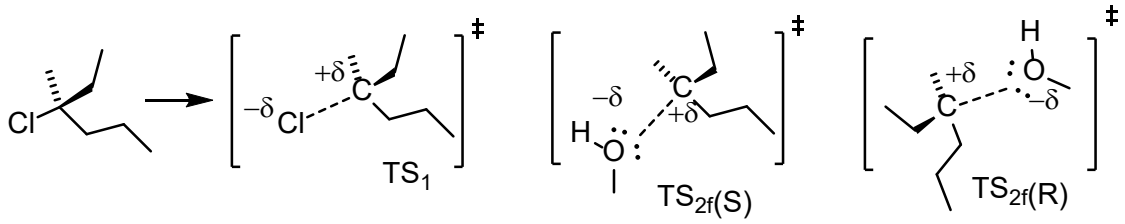
Reminder of the reaction:



Answer:

a) See the mechanism in the previous exercise. The carbocation is planar, meaning that the C—O bond formation in the next step can occur from both side equally because these two processes are enantiomers of one another. The rate and equilibria of enantiomeric processes are equivalent because due to the fact that enantiomers have identical physico-chemical properties. The S and R alcohols above must be produced in a 1: 1 ratio.

b) These TS_1 defines C—Cl bond breakage. TS_2 involves C—O bond formation (two enantiomers).



c) There will be no optical rotation.

d) No.

Exercise 9.3.4

a) Draw the product(s) of the hydrolysis of (R)-3-chloro-3-methylheptane.

b) What can you predict, if anything, about the optical rotation of the product(s)?

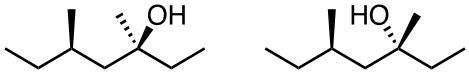
c) Draw the product(s) of the hydrolysis of (3R,5R)-3-chloro-3,5-dimethylheptane.

d) What can you predict, if anything, about the optical rotation of the product(s)?

Answer:

a) 

b) There will be no optical rotation.

c) 

d) There will be an optical rotation from the presence of two diastereomers.

Exercise 9.4.1 Which amino acid has the more nucleophilic side chain - serine or tyrosine? Explain.

Answer: Serine will have the more nucleophilic side chain because the alcohol is on an sp^3 hyridized O atom, which has higher energy lone pairs than the lone pairs in tyrosine – one of which is in a p orbital and delocalized into the pi system, the other being in a sp^2 orbital.

Exercise 9.4.2 In each pair, which is the better nucleophile: (a) A cysteine side chain or a methionine side chain? (b) A serine or a threonine? Explain.

Answer: (a) Cysteine, because the S in a thiol (RSH) is less hindered than the thioether (RSR') in methionine. (b) Serine will have the more nucleophilic side chain because the alcohol is on a 1º C atom and is less hindered than the alcohol on the 2º C atom in threonine.

Exercise 9.4.3 In each of the following pairs of molecules/ions, which is expected to react more rapidly with CH_3Cl in acetone solvent? Explain your choice.

a) phenolate (deprotonated phenol) or benzoate (deprotonated benzoic acid)?

b) water or hydronium ion?

c) trimethylamine or triethylamine?

d) chloride anion or iodide anion?

e) CH_3NH^- or $CH_3CH_2NH_2$?

f) acetate or trichloroacetate?

g) aniline or 4-methoxyaniline?

h) phenolate or 2,6-dimethylphenolate?

Answer:

a) Phenolate will react faster. The pKa of phenol is higher than benzoic acid. The O-atom as a nucleophile should be more reactive.

b) Water will react faster. The O-atom as a nucleophile should be more reactive in water hydronium ion is its conjugate acid. Hydronium ion IS the product of water and an electrophile: (H+).

c) The reactivity of trimethylamine and triethylamine will be determined by the steric difference between CH_3 and CH_2CH_3. While previous discussions of A-values showed us that there is not a large size difference between CH_3 and CH_2CH_3 here the net effect must be the sum of all three. Since the S_N2 mechanism requires approach to within bond distances, the effect is noteworthy.

d) Chloride anion or iodide anion? This is a complicated issue, but one you should be aware of in your study of organic chemistry. https://www.name-reaction.com/finkelstein-reaction

e) CH3NH– or CH3CH2NH2? See answer for b)

f) acetate or trichloroacetate? See answer for a). This is the inductive effect through σ bonds of electronegative Cl.

g) aniline or 4-methoxyaniline? The 4-methoxy is electron donating, which increases the pKa of its basicity (decreases the acidity of its conj. acid relative to the conj. acid of aniline. See answer for a). If you didn't know the structure of aniline you should have googled it and applied what you know about the reactivity of electrons to the structure.

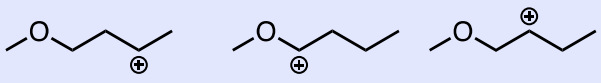
h) See answer for g) The 2,6-dimethylphenolate will be more reactive due to the electron donation of the methoxy groups.

Exercise 9.5.1 Which would be expected to react more rapidly in an S_N2 reaction with an azide ion (N_3^-) nucleophile in acetone solvent: 1-bromo-2,2-dimethylbutane or 1-bromo-3-methylbutane?

Answer: Since the S_N2 mechanism requires approach to within bond distances the steric effect of the more proximal dimethyl substituents in 1-bromo-2,2-dimethylbutane will decelerate the reaction at the 2° C atom more than the methyl groups in 1-bromo-3-methylbutane decelerates the S_N2 reaction at the 2° C atom.

Exercise 9.5.2 Fill in the missing numbers in this statement: The conjugated *π* system in the benzylic carbocation above is composed of ___7___ *p* orbitals overlapping to share __6____ π electrons.

Exercise 9.5.3 rank the following carbocations from most to least stable:

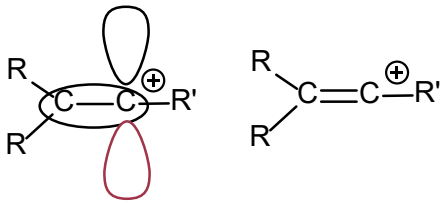


A B C

Answer: B is most stable due to π bonding, C is probably least stable due to bond-number proximity to the O atom which draws electron density due to its electronegativity.

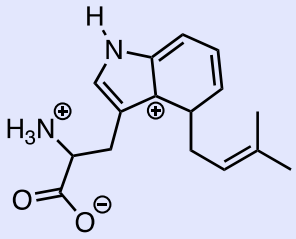
Exercise 9.5.4 Explain why vinylic carbocations are unstable. (Hint: think about hybridization and electronegativity)

Answer: The p orbital of the linear vinylic carbocation is not very stabilized by hyperconjugation.

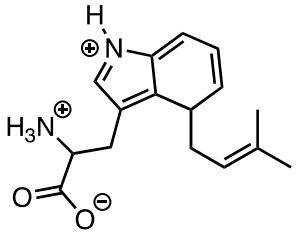


There is only one group that can stabilize the C center: R' in the figure above. Bond formation at the C atom should be highly enthalpically favored because an sp^2 bond at the C atom forms straight away from the poorly stabilized p orbital of the cation.

Exercise 9.5.5 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.

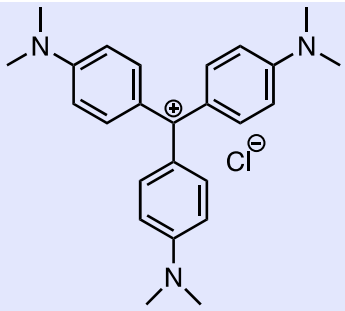


Answer:



Exercise 9.5.6

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



crystal violet

b) Notice that crystal violet is deeply colored. Explain why you could have predicted this from looking at its chemical structure.

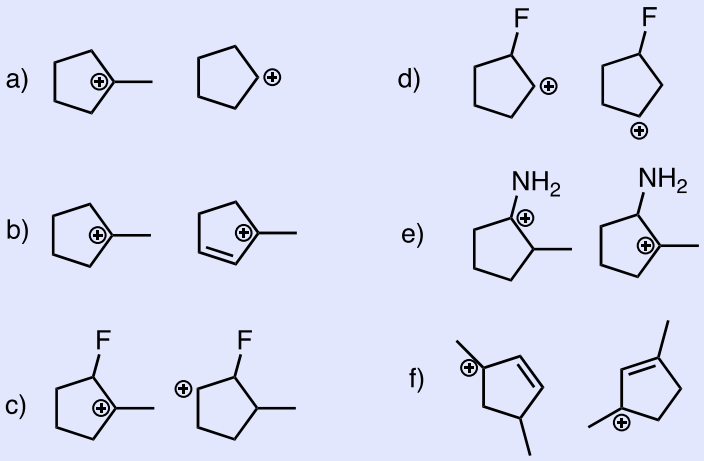
c) The conjugated system of crystal violet consists of how many overlapping *p* orbitals sharing how many π electrons?

Answer: a) See previous answer

b) The cation is composed of 22 conjugated p orbitals. The effect of conjugation decreases the difference in energy between the HOMO and LUMO. See sections on UV-Vis spectroscopy.

c) … see b)

Exercise 9.5.7 State which carbocation in each pair below is more stable, or if they are expected to be approximately equal.



Answer:

a) First cation is more stable because it is more substituted.

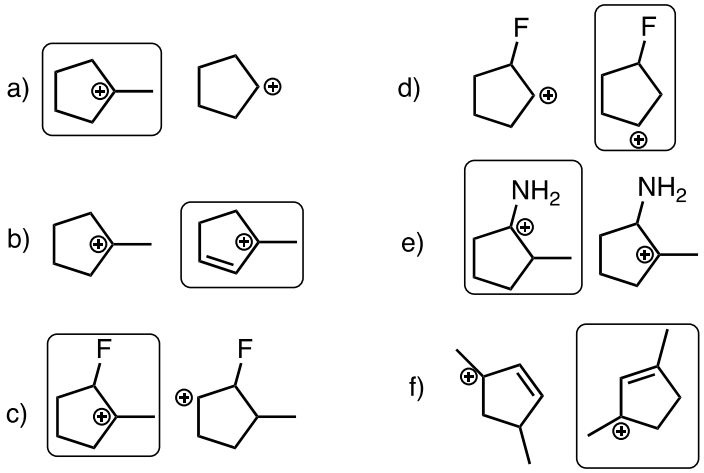
b) Second cation is more stable because it is conjugated.

c) First cation is more stable because it is more substituted.

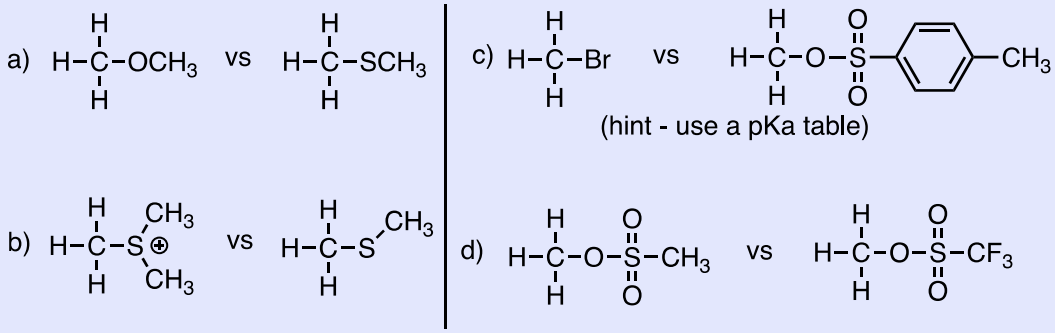
d) First cation is more stable because it is farther in terms of bonds away from the electronegative F atom.

e) First cation is more stable because it is conjugated by the N atom lone pair.

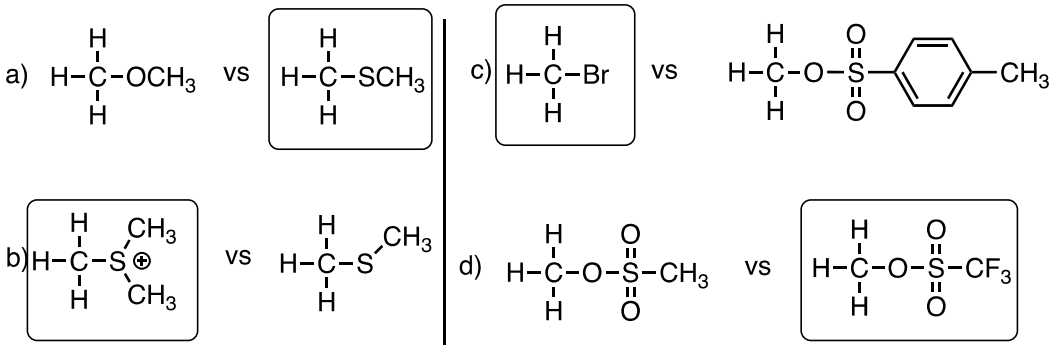
f) Second cation is more stable because it is equally conjugated but is more substituted.



Exercise 9.6.1 In each pair (A and B) below, which electrophile would be expected to react more rapidly with cyanide ion nucleophile in acetone solvent?



Answer:



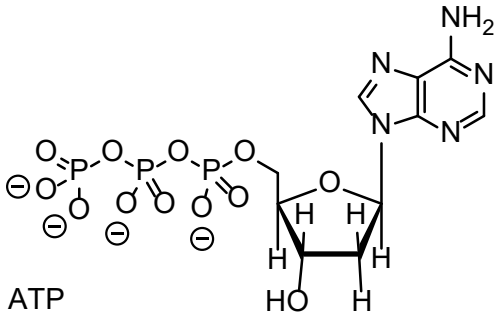
Exercise 9.9.1 Think back to the acid-base chapter: the pKa of a protonated ether is approximately zero, indicating that an ether is a very weak base. Considering periodic trends in acidity and basicity, what can you say about the relative basicity of a sulfide?

Answer: The pKa of $Me_2OH(+)$ = -6.5 whereas the the pKa of $Me_2SH(+)$ = -5.4 Ref: https://www.chem.wisc.edu/areas/reich/pkatable/ This means that once released the lone pair on the O atom is more stable than the lone pair on the S atom in their respective conjugate bases

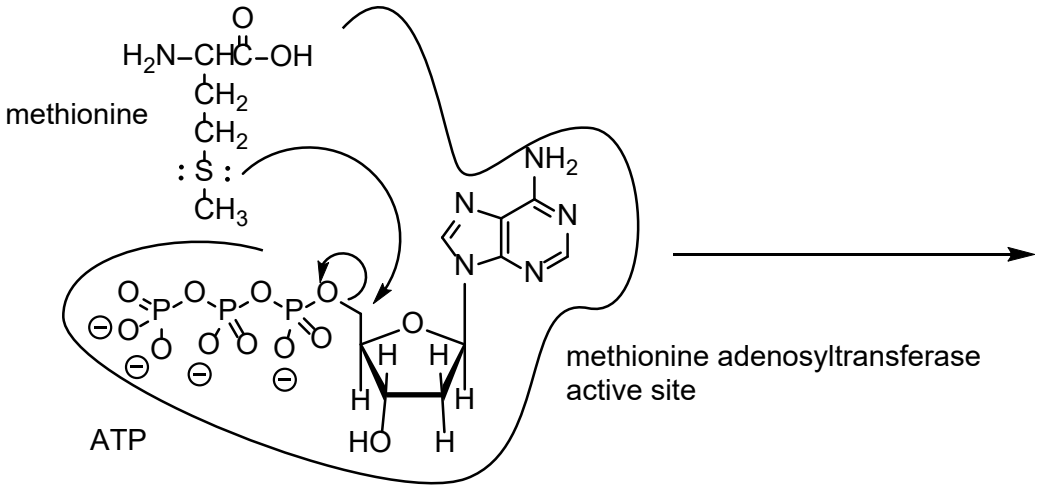
which points to slightly more basicity of the thioether than the ether. Remember that increasing electronegativity as you go up the column in the periodic table decreases the basicity.

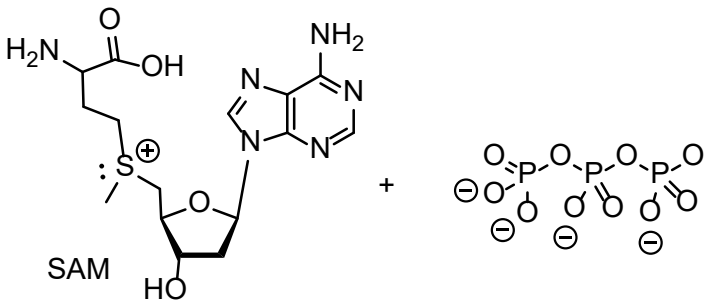
Exercise 9.9.2 SAM is formed by a nucleophilic substitution reaction between methionine and adenosine triphosphate (ATP). Draw a mechanism for this reaction, and explain why you chose either an S_N1 or and S_N2 pathway.

Answer: See section9.10.1. This is an enzyme-catalyzed reaction. The triphosphate group is promoted to leave by the catalytic mechanism. An enzyme-bound cation could be a catalytic intermediate (more like S_N1) or the triphosphate could leave in a concerted fashion to the C–S bond formation (S_N2). This reaction cannot be true S_N1 because ATP is stable to water and becomes activated in the enzyme context and because departure of the triphosphate anion would leave a 1° carbocation.



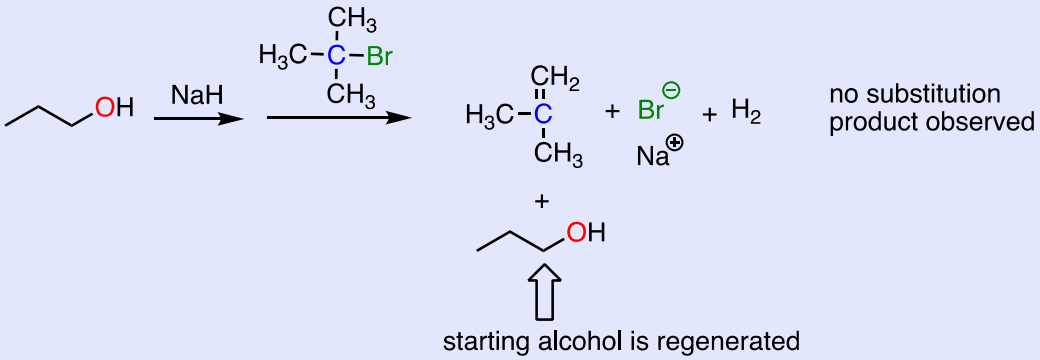
ATP + methionine adenosyltransferase + methionine ⟶ SAM



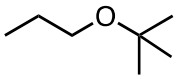


Exercise 9.10.1 A rookie organic chemist ran the reaction shown above, hoping to synthesize an ether. Instead, he got the alkene shown above. What alkyl halide/alcohol combination should he have used instead to get the ether product he was trying for?

The reaction:



Answer:



KEY TO CHAPTER 9 PRACTICE PROBLEMS

PP 9-01 Answer: D > B > A > C

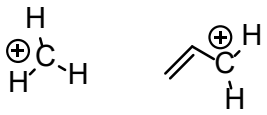
PP 9-02 Draw line structures representing the *most stable* cation with the given molecular formula:

a) $C_3H_7^+$ b) $C_4H_9^+$ c) $C_3H_8N^+$ d) $C_4H_7^+$

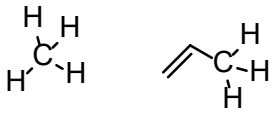
Answer:

When going from formula to structure DU is always the first step.

Think about



Add H:(-)



DU = 0 and 1 respectively .

For a) $C_3H_7^+ + H:(-) \rightarrow C_3H_8$

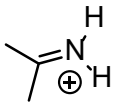
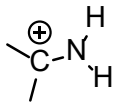
b) $C_4H_9^+ + H:(-) \rightarrow C_4H_{10}$ DU = 0

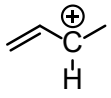
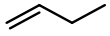
c) $C_3H_8N^+ + H:(-) \rightarrow C_3H_9N$ DU = 0

d) $C_4H_7^+$ + H:(-) —► C_4H_8 DU = 1

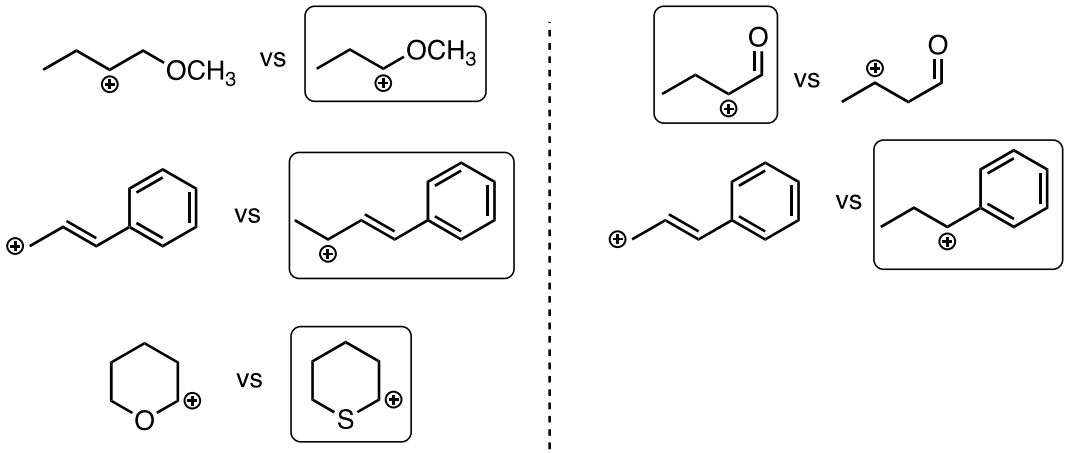
a) 

b) 

c)  most stable resonance representation of 

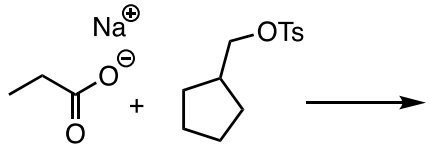
d)  subtract H:(-) from  or  to make the most stable cation

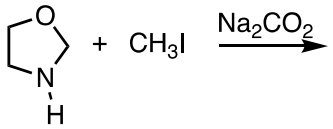
PP 9-03 Answer:

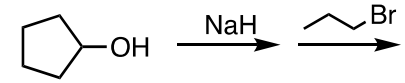


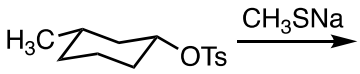
PP 9-04 Answer: C > A > B > D

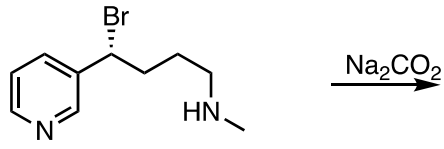
PP 9-05 Predict the organic products of the following nucleophilic substitution reactions, all of which are carried out in polar aprotic solvent. Show stereochemistry at chiral carbons. Hints: Na_2CO_3, sodium carbonate, is a weak base. For part (f): What is the conjugate acid of NH_2^-? What is the pKa of this conjugate acid, and what is the pKa of a terminal alkyne?

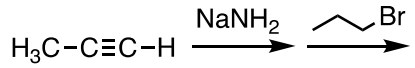
a) 

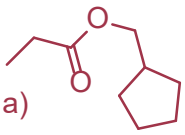
b) 

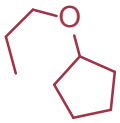
c) 

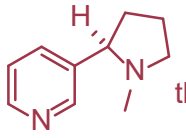
d) 

e) 

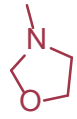
f) 

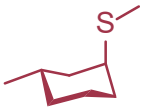
a) 

c) 

e) 

this enantiomer

b) 

d) 

f) 

PP 9-06 Which of the reactions in the previous problem has a *unimolecular* rate determining step? Explain.

The only possible S_N1 reaction is e). There is a good leaving group (Br(-)). The hypothetical carbocation is π-stabilized (benzylic), and the base CO_2(-2) is not strong enough to evolve a strong nucleophile form the amine. These three arguments favor S_N1 mechanism. If stereochemistry is inverted cleanly, see hypothetical S_N2 product above, then the mechanism is S_N2. To the extent that optically pure reactant gives rise to racemic product then the mechanism is pure S_N1 or a mix between S_N1 and S_N2.

PP 9-07 From the following pairs, select the compound that would react more rapidly with bromomethane in acetone solvent.

a) water or hydroxide ion

b) CH_3S^- or CH_3OH

c) CH_2S^- or CH_3SH

d) acetate ion or hydroxide ion

e) diethyl sulfide or diethyl ether

f) dimethylamine or diethylether

g) trimethylamine or 2,2-dimethylpropane

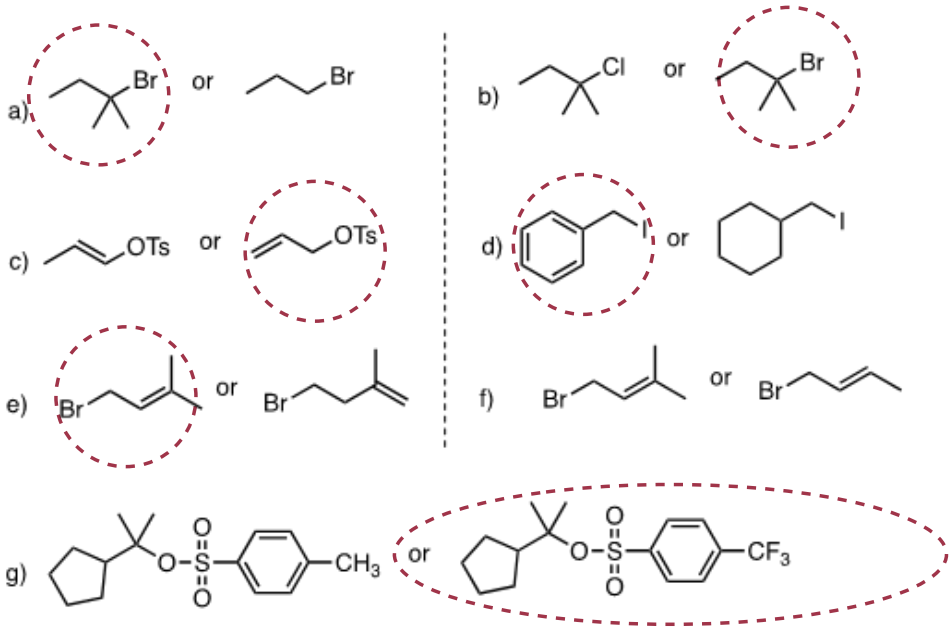
Look for the best nucleophile. Look for reactive lone pairs.

PP 9-08 Methyl iodide (0.10 mole) is added to a solution that contains 0.10 mole $NaOCH_3$ and 0.10 mole $NaSCH_3$.

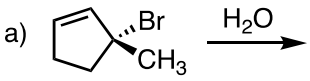
a) Predict the most abundant neutral organic product that would form, and explain your reasoning.

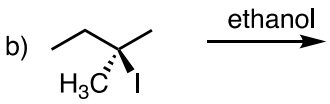
b) Assume that you isolate a mixture the major product (which you predicted in part) along with a smaller amount of a different nucleophilic substitution product. Explain briefly but specifically how you could use ^1H NMR to determine the ratio of the two products in the mixture.

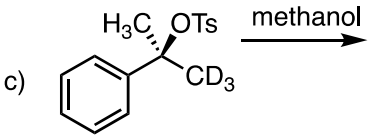
PP 9-09 For each pair of compounds, predict which will more rapidly undergo solvolysis in methanol solution.



PP 9-10 Predict the solvolysis product(s) of each of the reactions below. Consider both regiochemistry and stereochemistry.

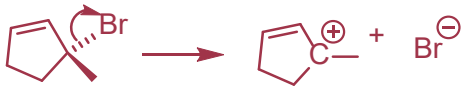
a) 

b) 

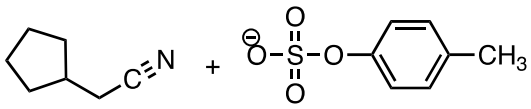
c) 

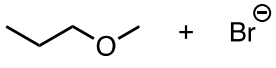
all racemic

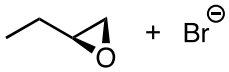
e) Draw a complete curved-arrow mechanism for the formation of the secondary allylilc alcohol product in part (a).

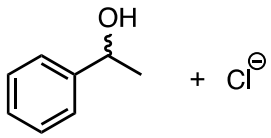


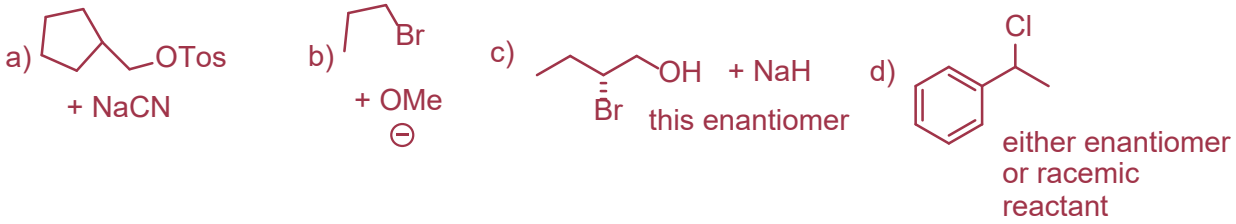
PP 9-11 Show starting compounds that would lead to the following products through nucleophilic substitution reactions.

a) 

b) 

c) 

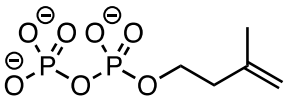
c) 



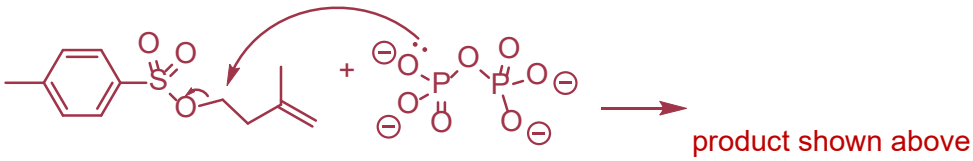
PP 9-12 The fused ring compound shown below is very unreactive to nucleophilic substitution, even with a powerful nucleophile. Explain. (Hint: consider bond geometry - a model will be very helpful!)

Nucleophiles cannot access σ* doe to the ring behind the C—Cl bond.

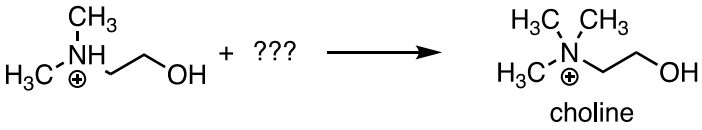
PP 9-13 Laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules (section 1.3A) - was accomplished by first converting isopentenyl alcohol into an alkyl tosylate then displacing the tosylate group with an inorganic pyrophosphate nucleophile. Based on this verbal description, draw a mechanism for the second (nucleophilic substitution) step, showing starting and ending compounds for the step and curved arrows for electron movement



isopentenyl diphosphate



PP 9-14 Choline, an important neurotransmitter in the nervous system, is formed from 2-(*N,N*-dimethylamino)ethanol:



a) Besides the enzyme and the starting compound, what other important biomolecule do you expect plays a part in the reaction?

SAM see above

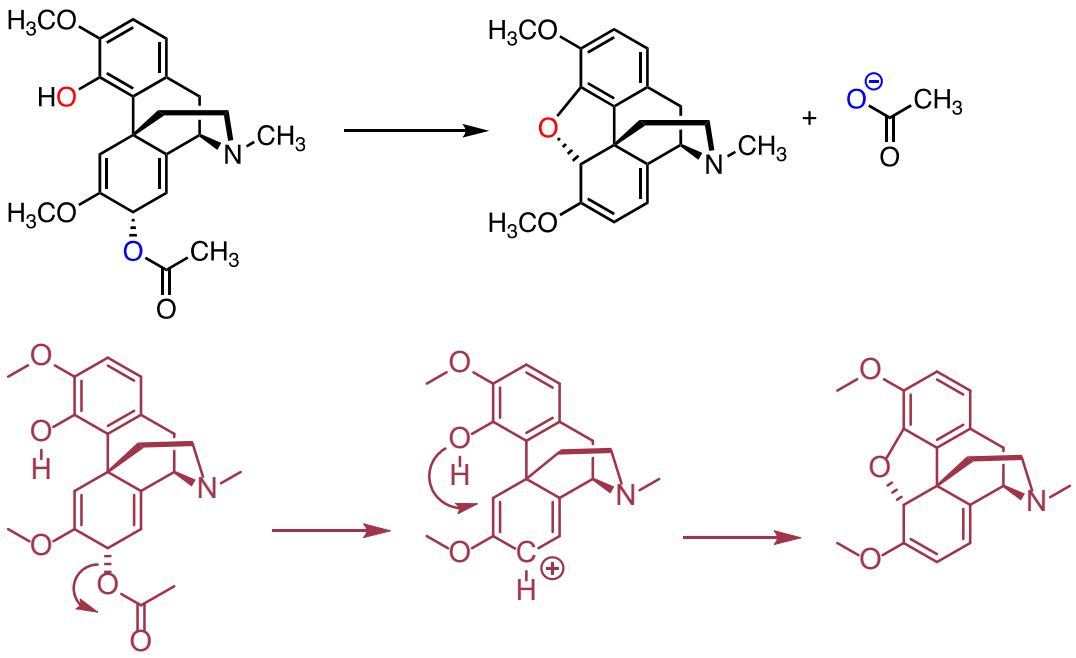
b) Draw a mechanism for the reaction.

See above. Use the mechanism in Exercise 9.9.2 except 2-(N,N-dimethylamino)ethanol is the nucleophile.

c) Briefly explain how ^{1}H NMR could be used to distinguish between the substrate and the product of this reaction.

In protonated 2-(N,N-dimethylamino)ethanol there will be a singlet for the CH_3 groups that integrates to 6: 2: 2 vs. the two CH_2 groups. In the product choline there will be a singlet for the CH_3 groups that integrates to 9: 2: 2 vs. the two CH_2 groups.

PP 9-15 The following is a reaction in the biosynthesis of morphine in opium poppies.



a) Draw a complete mechanism, assuming an S_N1 pathway.

b) What would you expect to be the most noticeable difference between the IR spectrum of the product and that of the substrate?

The hydrogen bonding in the OH stretching region disappears ~3500 cm^{-1}. The carbonyl of the ester disappears at 1700 cm^{-1}.

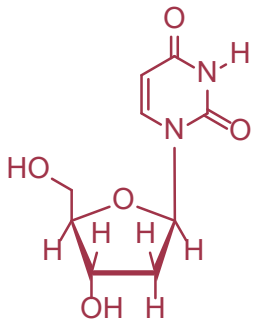
c) This reaction is an example of the regiospecificity of enzymatic nucleophilic substitution reactions noted earlier in the chapter. Draw two alternate nucleophilic, ring-closing steps for this reaction (leading to different products from what is shown above), and explain why these alternate pathways are both less favorable than the actual reaction catalyzed by the enzyme.

All other ring closures are strained. This is best shown by building a model.

PP 9-16 The enzymatic reaction below, which is part of the metabolism of nucleic acids, proceeds by an S_N1 mechanism. The new bond formed in the substitution is indicated.

a) Predict the structures of the two substrates A and B.

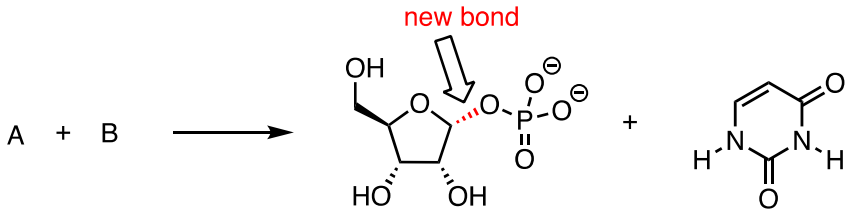
The nucleophile is PO4(-). The electrophile is:



b) Draw a complete mechanism, and use resonance drawings to illustrate how both the carbocation intermediate and the leaving group are stabilized.

The lone pair on the O atom stabilizes the cation with conjugation. —(+)O=C—

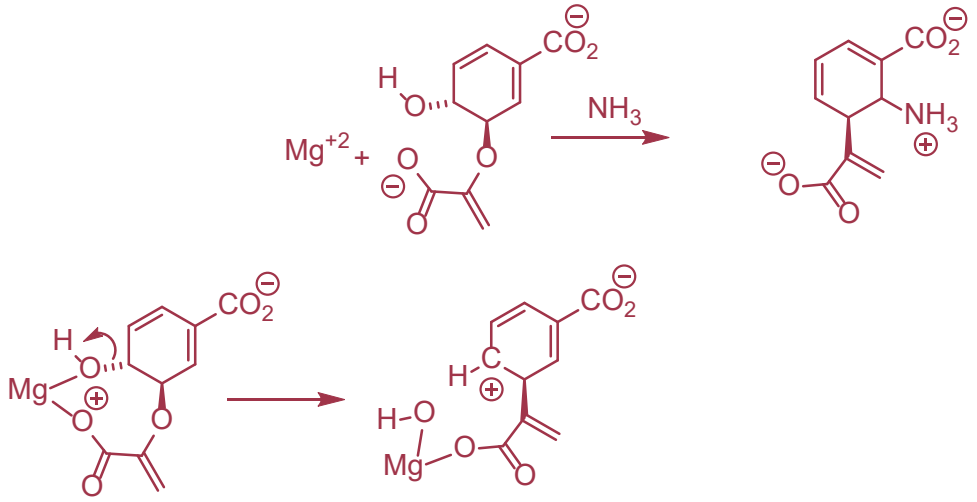
The leaving group is stabilized by the fact that the liberated lone pair is sp2 hybridized at the relatively electronegative N atom.



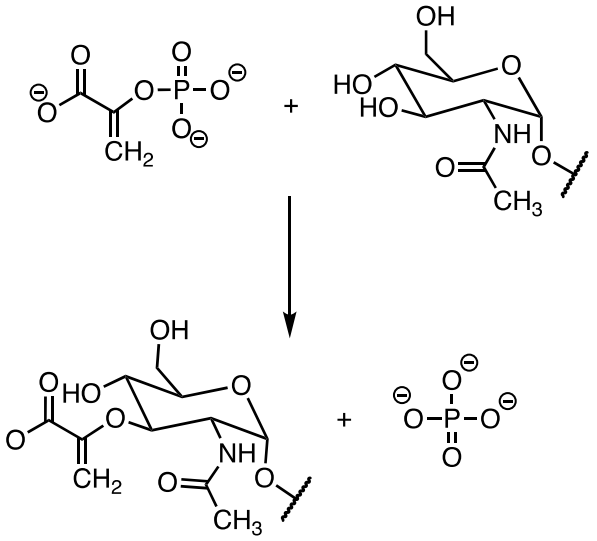
PP 9-17 Below is the first step of the reaction catalyzed by anthranilate synthase, an enzyme involved in biosynthesis of the amino acid tryptophan.

a) This reaction is somewhat unusual in that the leaving group is a hydroxide anion, which is of course is normally thought to be a very poor leaving group. However, studies show that an Mg^{+2} ion is bound in the active site close to the hydroxide. Explain how the presence of the magnesium ion contributes to the viability of hydroxide as a leaving group.

b) Draw a complete mechanism for the reaction, assuming an S_N1 pathway.

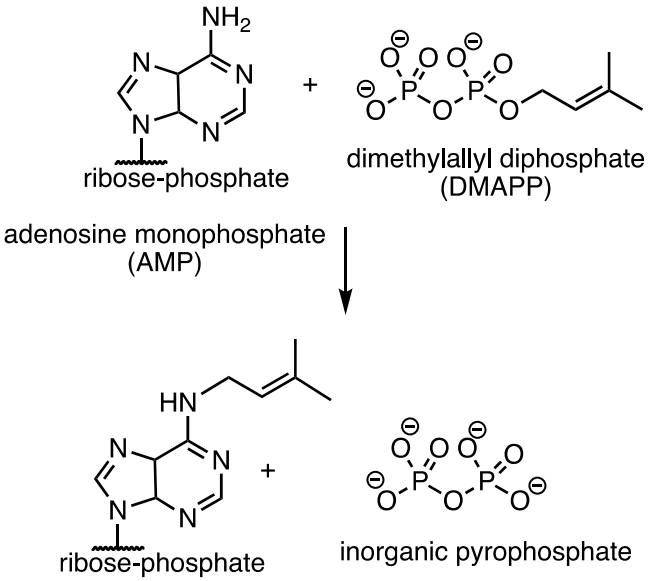


PP 9-18 The reaction below is part of the biosynthesis of peptidoglycan, a major component of bacterial cell walls. Is it likely to proceed by a nucleophilic substitution mechanism? Explain.



No, because the O atom that is displaced is connected to a C atom by an sp^2 hybridized bond at C. Due to σ sp^2 being so low in energy (so stable), the σ*sp^2 orbital is higher energy than the π* orbital, so the π* orbital is likely the LUMO in this reaction.

PP 9-19 Compare the reaction below, catalyzed by the enzyme AMP-DMAPP transferase, to the protein prenyltransferase reaction we learned about in section "*9.9.3 A Biochemical SN1/SN2 Hybrid Reaction*", the mechanism of which, as we discussed, is thought to be *mostly* S_N2-like with some S_N1-like character.



a) Is the AMP-DMAPP transferase reaction below likely to have more or less S_N1 character compared to the protein prenyltransferase reaction? Explain.

The reaction above is likely to have less S_N1 character. The cation is not as stable above as it is in the prenyl transfer. Prenyl is more π-bound (conjugated) than dimethylallyl.

PP 9-20 In a classic experiment in physical organic chemistry, (*R*)-2-iodooctane was allowed to react (non-enzymatically) with a radioactive isotope of iodide ion, and the researchers monitored how fast the radioactive iodide was incorporated into the alkane (the rate constant of incorporation, k_i) and also how fast optical activity was lost (the rate constant of racemization, k_r). They found that the rate of racemization was, within experimental error, equal to twice the rate of incorporation. Discuss the significance of this result - what does it say about the actual mechanism of the reaction?

The rate determining step is the loss of I(-) to produce the achiral cation. The mechanism must be wholly S_N1.