

CFQ & PP: Ionic Substitution - S_N2

Reading

- review kinetics, thermodynamics as needed
- Brown and Foote 2nd or 3rd edition: 8.1 - 8.7

Optional Web Site Reading

- Fundamentals of Kinetics and Thermodynamics (<http://www.cchem.berkeley.edu/~chem130a/sauer/outline.html>)
- 1999 Nobel Prize in Chemistry: "Photographs" of Transition States (<http://www.nobel.se/chemistry/laureates/1999/>)

Lecture Handouts

- Steric Effects In the S_N2 Reaction
- Important Organic Solvents

Suggested Text Exercises

- Brown and Foote 2nd edition: Chapter 8: 1 - 5, 9 - 35, 47, 49, 50
3rd edition: Chapter 8: 1, 2, 4, 10 - 18, 47 - 50

Related Tutorials (<http://web.chem.ucla.edu/~harding/tutorials/>)

- Electrophiles and Nucleophiles
 - Vocabulary
 - Electrophiles and Nucleophiles

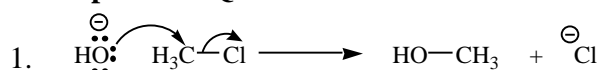
Concept Focus Questions

Consider this substitution reaction: $\text{CH}_3\text{Cl} + \text{HO}^\ominus \longrightarrow \text{CH}_3\text{OH} + \text{Cl}^\ominus$

1. Draw a curved arrow mechanism. Is this a concerted reaction?
2. Write the rate expression and reaction name.
3. Define "transition state." Why is this important in the study of chemical reactions?
4. Draw the transition state for the reaction. Describe in words what this drawing shows.
5. Briefly discuss the stereochemistry of any S_N2 reaction.
6. Draw the energy profile for the reaction. Assume the reaction is exothermic. Label all of the important features of the energy profile.
7. What is the relationship between bond changes and reaction rate?
8. List in order of influence the four structural features of the nucleophile that control nucleophilicity. Briefly describe how each factor operates.

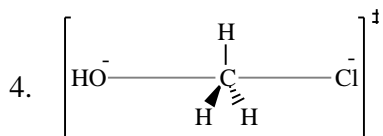
- Define "leaving group." What two structural factors make for a good leaving group?
- Define "steric effect." Briefly discuss steric effects in the S_N2 reaction.
- Define the following terms: Dielectric constant, polar solvent, nonpolar solvent, protic solvent, aprotic solvent.
- Summarize the effect of solvent on nucleophilicity in a single sentence.
- Briefly discuss the effect of solvent on the rate of an S_N2 reaction from the viewpoint of the transition state.
- What three requirements must be met for a substitution reaction to proceed by the S_N2 mechanism?

Concept Focus Questions Solutions



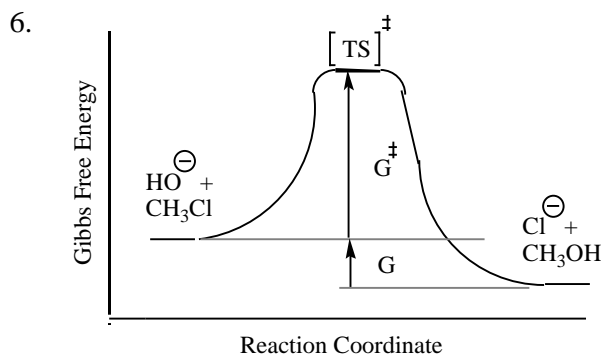
This is a concerted reaction, because it proceeds through a single mechanism step without any intermediates. All bond making and bond breaking occurs within this single mechanism step.

- Rate = $k [\text{HO}^-][\text{CH}_3\text{Cl}]$. The reaction is nucleophilic substitution with bimolecular kinetics; hence it is called S_N2 .
- The transition state is the highest energy point along a single step in the reaction energy profile. The transition state is important in the study of chemical reactions because the amount of energy needed to achieve the transition state, called the energy of activation, controls the rate of a reaction. Reaction rate is easily observable, and thus a useful tool to ascertain the effects of changing various factors in a chemical reaction.



The carbon-oxygen and carbon-chlorine bonds are incomplete and therefore longer than normal sigma bonds. The hydroxide ion has begun to share a lone pair with the carbon, so it has a partial negative instead of a full negative charge. The pair of electrons that were the carbon-chlorine bond has begun to shift toward the chlorine, giving the chlorine a partial negative charge. The carbon has shifted toward sp^2 hybridization as the best geometry to accommodate the five atoms surrounding it. The brackets and \ddagger symbol are used by convention to symbolize that this structure is a transition state.

5. The nucleophile attacks the carbon from the backside of the carbon-leaving group bond so as to allow maximum overlap between the orbital containing the pair of electrons being donated by the nucleophile and the σ^* carbon-leaving group antibonding orbital. This results in net inversion of absolute stereochemistry in an S_N2 reaction.



7. Reaction rate is controlled by the energy of activation, which is a Gibbs free energy term. Recall that Gibbs free energy (G) is a function of enthalpy (H ; energy changes due to bond changes) and entropy (S ; organization). In equation form:

$$G = H - T S$$

The entropy factor is small, perhaps one kcal mol⁻¹ of energy at reaction temperatures up to a few hundred Kelvin. This is significantly less than the enthalpy changes that are typically tens of kcal mol⁻¹. Thus we can approximate the change in Gibbs free energy as the change in enthalpy. Thus, we often discuss reaction rate in terms of the bonding changes.

8. Each structural feature should be analyzed to see how it influences the ability or driving force of the base to donate electron density to an electrophile. Four factors can be listed in order from most influential (resonance) to least influential (inductive effect).

Resonance: Resonance can increase or decrease electron density at the atom that shares electrons with the electrophile.

Polarizability: Loosely defined, polarizability is a measure of an atom's ability to distort its electron cloud. This definition works well for large atoms that are easily distorted (low electronegativity, large size = soft), but fails for small atoms that are not easily distorted (high electronegativity, small size = hard). For reasons derived from quantum mechanics and electrostatics, atoms that are soft react more readily with atoms that are soft, and atoms that are hard react more readily with atoms that are hard. Electrophiles that participate in the S_N2 reaction are fairly soft (due to size and electronegativity of carbon) so atoms of higher polarizability will more readily

donate electrons when participating in an S_N2 reaction. Thus, the best nucleophiles are soft.

Electronegativity: Electronegativity is defined as an atom's attraction for electrons, or conversely, an atom's resistance to giving up electrons. Higher electronegativity means the atom is less willing to share electrons. Since the job of a nucleophile is to share electron density with a carbon atom, higher electronegativity will decrease nucleophilicity.

Inductive effect: The inductive effect is label for the electronic effect of atoms in a remote portion of the molecule. In the case of a nucleophile, this would mean the effect of atoms other than the atom that is sharing electron density with the electrophilic carbon. Remote atoms can increase or decrease the electron density on the atom sharing electrons with the carbon, and thus influence nucleophilicity.

Because nucleophiles and bases both share electrons, there is a strong parallel between the structural factors that control them.

9. Leaving group is the portion of the molecule that departs along with the pair of electrons that was the bond between the leaving group and some other atom. A good leaving group is stable after it departs, and the atom that accepts what was the bonding electron pair is soft.
10. A steric effect is a destabilization that results from van der Waals repulsion when two atoms are too close together. The S_N2 reaction is sensitive to increasing steric hindrance at the electrophilic carbon. As the number and/or size of substituents increases, it becomes increasingly more difficult for the nucleophile to reach the electrophilic carbon. Therefore the S_N2 reaction rate decreases as the number or size of substituents increases. Relative rates: CH₃-L (methyl) > RCH₂-L (primary) > R₂CH-L (secondary) >> R₃C-L (tertiary). A tertiary carbon is so highly hindered toward backside attack that tertiary substrates do not react in the S_N2 reaction.
11. Dielectric constant: Dielectric constant (ϵ) is a measure of the ability of a substance to separate ions. (A more rigorous, but less clearly applicable definition is a measure of a substance's ability to insulate opposite charges from each other.)

Polar solvent: A polar solvent has a high dielectric constant. The approximate cutoff is 20 or higher.

Nonpolar solvent: A nonpolar solvent has a low dielectric constant. Solvents with a dielectric constant of approximately 20 or more are considered polar, whereas solvents with a dielectric constant of approximately 20 or less are considered nonpolar.

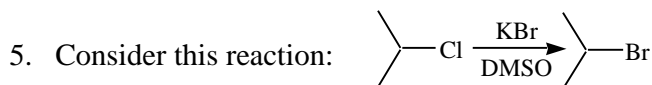
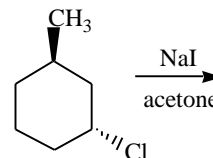
Protic solvent: A protic solvent is capable of donating a hydrogen atom for hydrogen bonding. Usually requires an N-H or O-H bond.

Aprotic solvent: An aprotic solvent does not have a hydrogen atom that can be shared by hydrogen bonding. Does not have an N-H or O-H bond.

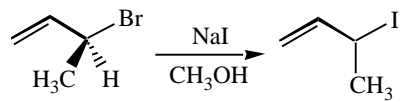
- Nucleophilicity is highest when the solvent is polar and cannot solvate the nucleophile well (usually aprotic). (Hydrogen bonding is much less important in controlling the nucleophilicity of nucleophiles that do not bear a negative charge on the atom that is sharing electrons with the electrophile.)
- The rate of the S_N2 reaction is dependent on the energy of activation. The energy of activation is the difference in energy between the reactants and the transition state. If the solvent stabilizes the reactants more than it stabilizes the transition state, then the energy of activation increases and the reaction is slower. If the solvent stabilizes the transition state more than the reactants, then the energy of activation decreases and the reaction is faster. A polar solvent stabilizes reactants or transition states with large charges more effectively than those with small charges do. A nonpolar solvent stabilizes species more effectively if they have smaller or no charge.
- The three requirements for a substitution reaction to proceed by the S_N2 mechanism are good leaving group, good nucleophile, and the carbon undergoing nucleophilic attack cannot be tertiary. The first two of these factors interact. If the leaving group is superior, then reaction can occur with a poorer nucleophile. There are no exceptions to the "not tertiary" requirement.

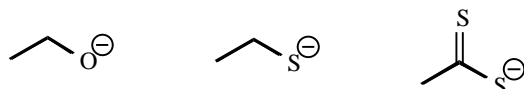
Practice Problems

- For a reaction to occur, molecules must collide with sufficient _____ and correct _____.
- What is the most significant reason that the transition state is the highest energy point between reactants and products in a single mechanism step?
- Briefly discuss the relationship between transition state and reaction rate. Your answer must be clearly illustrated by a properly labeled reaction energy profile diagram.
- Provide the organic product(s) of this reaction. If more than one product is formed, indicate which product (if any) is the major one. If no reaction occurs, write "NR."

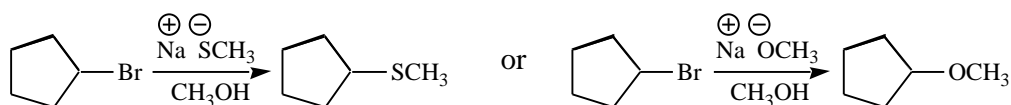


- Write the rate expression for this reaction.
- Write a curved arrow mechanism for this reaction.
- Draw the transition state.

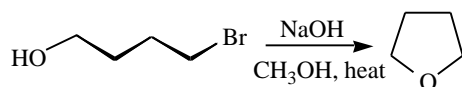
6. Consider this reaction:
- 
- (a) Write the S_N2 mechanism for this reaction. Clearly show product stereochemistry.
 (b) Draw the transition state.
7. What is the single most important factor (more fundamental even than resonance) which controls the nucleophilicity or basicity of any molecule or ion?
8. Rank the nucleophilicity of the following and briefly outline your reasoning.



9. Select the best and worst nucleophiles: $\text{CH}_3\text{CH}_2\text{S}^-$, $\text{CH}_3\text{CH}_2\text{O}^-$, $\text{CH}_3\text{CH}_2\text{OH}$, $\text{CF}_3\text{CH}_2\text{OH}$. Briefly explain your reasoning.
10. Select the strongest nucleophile in each set.
- I^- , Br^- , F^-
 - HS^- , HSe^- , HO^-
 - NH_3 , H_2O , CH_3OCH_3
 - HS^- , HO^- , H_2N^-
 - $\text{CF}_3\text{CH}_2\text{S}^-$, $\text{CH}_3\text{CH}_2\text{S}^-$, $\text{CH}_3\text{CH}_2\text{O}^-$, F^-
 - $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}^-$, $\text{CH}_3\text{CF}_2\text{CH}_2\text{O}^-$, $\text{CF}_3\text{CH}_2\text{CH}_2\text{O}^-$
 - H_2O , H_2S , HO^- , HS^-
 - CF_3CO_2^- , Cl_3CO_2^- , $\text{CH}_3\text{CH}_2\text{CO}_2^-$
 - $\text{CH}_3\text{CO}_2\text{H}$, CH_3CO_2^- , CH_3O^-
11. Select the poorest nucleophile: HO^- , CH_3CO_2^- , CH_3O^- .
12. Select the slowest reaction. Briefly explain your choice.

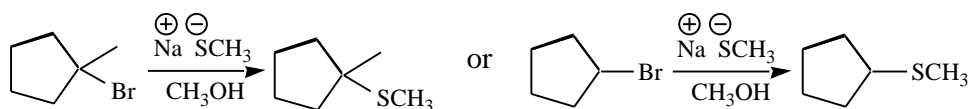


13. Write two detailed S_N2 mechanisms for the following reaction, and select the best one.

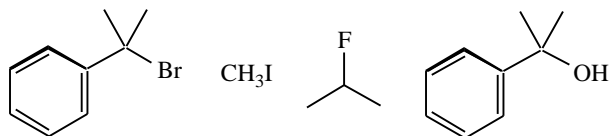


14. Select the best leaving group: CH_3S^- , CH_3O^- , CF_3S^- , F^- .

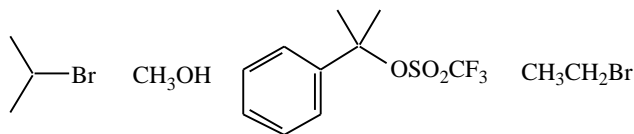
15. Select the worst leaving group: F, I, CH_3^- .
16. Label these leaving groups as best, middle, or poorest: CF_3SO_3^- , CH_3SO_3^- , CH_3CO_2^- .
17. Select the compound that reacts slowest in an $\text{S}_{\text{N}}2$ reaction: CH_3I , $\text{CH}_3\text{CH}_2\text{I}$, $(\text{CH}_3)_2\text{CHI}$.
18. Select the slowest reaction. Briefly explain your choice.



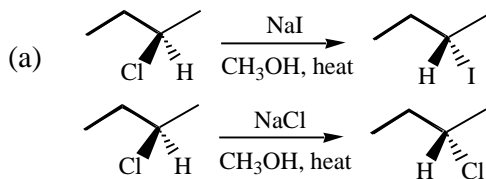
19. Assign the dielectric constants of 80, 33, and 20 to these compounds: $\text{CH}_3\text{CH}_2\text{OH}$, H_2O , CH_3OH .
20. In lecture, three factors were discussed as fundamental requirements for an $\text{S}_{\text{N}}2$ reaction to occur. Name these three factors, and very briefly describe how each factor controls the rate of an $\text{S}_{\text{N}}2$ reaction.
21. Select the molecules that react fastest and slowest by the $\text{S}_{\text{N}}2$ mechanism.

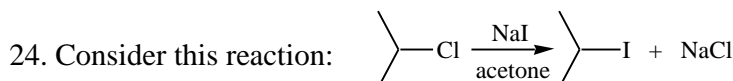
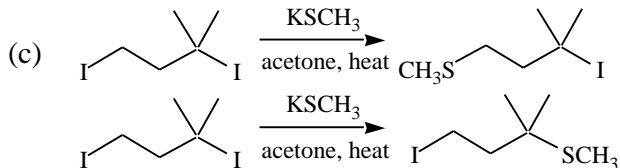
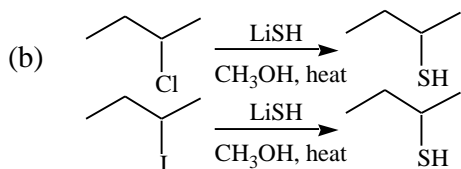


22. Select the molecule that reacts the slowest in an $\text{S}_{\text{N}}2$ reaction:

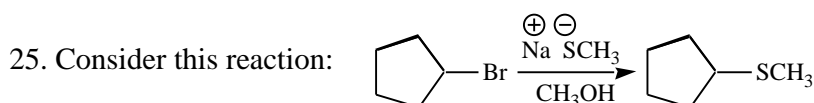


23. For each pair of reactions shown below:
- Decide which reaction would be faster. Briefly explain your choice.
 - Draw a detailed curved arrow mechanism for the faster reaction.
 - Design a reaction that is similar to, but faster, than the faster reaction of part (i). Briefly explain why your designer reaction is faster.





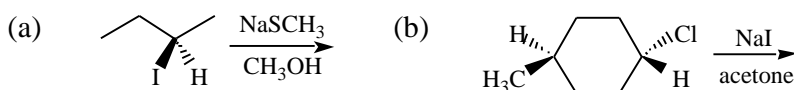
- Write the S_N2 mechanism for this reaction, including all the transition states.
- Write a reaction that is similar to, but obviously faster, than the reaction shown above.



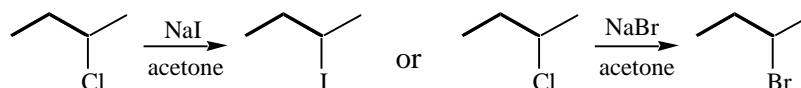
- Write the S_N2 mechanism for this reaction.
- Draw the S_N2 transition state(s) for this reaction.
- Draw the S_N2 energy profile for this reaction. Label all the important parts of the diagram.
- Give an example of an S_N2 reaction that will clearly be slower than the one shown above.

26. For each reaction:

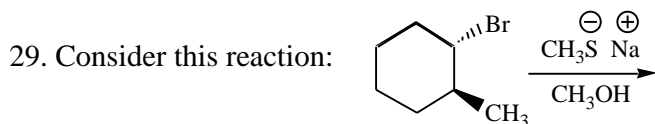
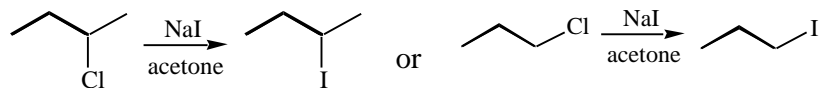
- Write the product of this substitution reaction.
- Write the transition state for this S_N2 reaction.
- Write the S_N2 reaction energy profile for this reaction, and label the important parts.
- Write a substitution reaction that is similar to, but clearly faster than the given reaction.



27. Which reaction is faster? Write a very similar reaction that occurs by the same mechanism but is obviously faster.

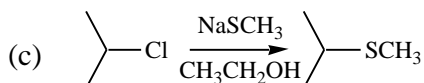
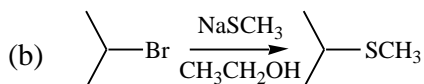


28. Which reaction is faster? Write a very similar reaction that occurs by the same mechanism but is obviously faster.



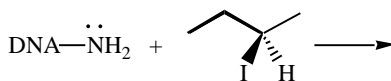
- Draw the product of the reaction.
- Write the curved arrow mechanism for this reaction, including the transition state for each step.
- Changing only the electrophile, write a complete reaction that is clearly slower than the reaction given above. Briefly explain why your new reaction is slower.
- Changing only the nucleophile, write a complete reaction that is clearly faster than the reaction given above. Briefly explain why your new reaction is faster.

30. Consider these S_N2 reactions:

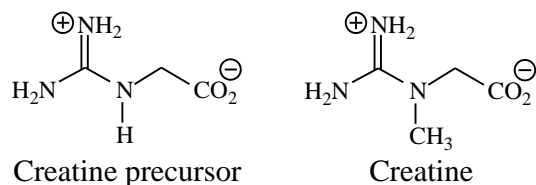


Select the fastest and slowest reactions. Briefly explain your reasoning.

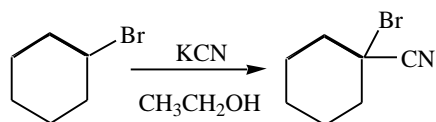
31. Many haloalkanes (alkyl halides) can cause damage to DNA (abbreviated DNA-NH₂) because they can alkylate a free amine group by an S_N2 reaction. Because of this many haloalkanes are carcinogens.



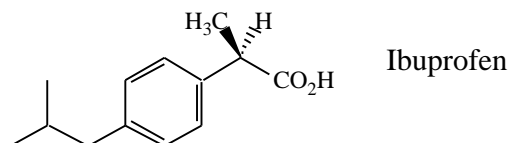
- Write the product, mechanism and all transition states for the S_N2 DNA alkylation reaction shown above.
- Briefly explain why *tert*-butyl iodide, (CH₃)₃CI, is not a very powerful carcinogen.
- Methyl fluorosulfonate (also called Magic Methyl because it seems to be able to methylate just about anything) causes DNA mutations more readily than the iodide in the reaction shown above. Provide two brief reasons for this.



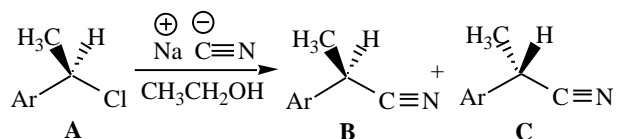
33. The mechanism step shown below contains a significant error. Very briefly describe the error, then write the corrected version of the mechanism step. Try to keep your corrected version as close to the original as possible. If nothing is wrong with the step, write "OK." (Hint: the error is not "missing curved arrows." Curved arrows are used for mechanisms, and are not normally used when the only concern is showing the product of a reaction.)



34. Ibuprofen is an analgesic and anti-inflammatory found in many over-the-counter drugs such as Motrin. Imagine that you have graduated from UCLA and have inherited a factory that manufactures Ibuprofen. You are faced with many problems to improve the factory and its product.

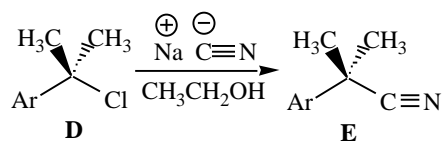


A key step in the synthesis of Ibuprofen in your factory is the reaction of chloroalkane **A** with cyanide ion ("Ar" is a common abbreviation for an aromatic ring.)



- Select the correct product of this reaction: **B** **C** both neither
- Draw the S_N2 mechanism for this reaction including all transition states.
- Is this a reasonable S_N2 reaction? Briefly explain. Clearly state all assumptions.
- Haloalkanes such as compound **A** present environmental hazards if spilled. As a concerned factory owner you want to avoid this problem, and at the same time make the Ibuprofen synthesis faster. Draw an analog of haloalkane **A** that does not have a halogen atom but will undergo a faster S_N2 reaction than **A**. Briefly explain your reasoning.

- (e) One of your employees approaches you with an idea to make an analog of Ibuprofen with an extra methyl group. A key step in the synthesis of this analog would be the S_N2 reaction shown below. Is this employee's idea reasonable or should this employee be fired due to a lack of chemical common sense? Very briefly explain.

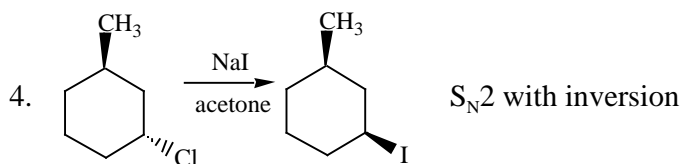
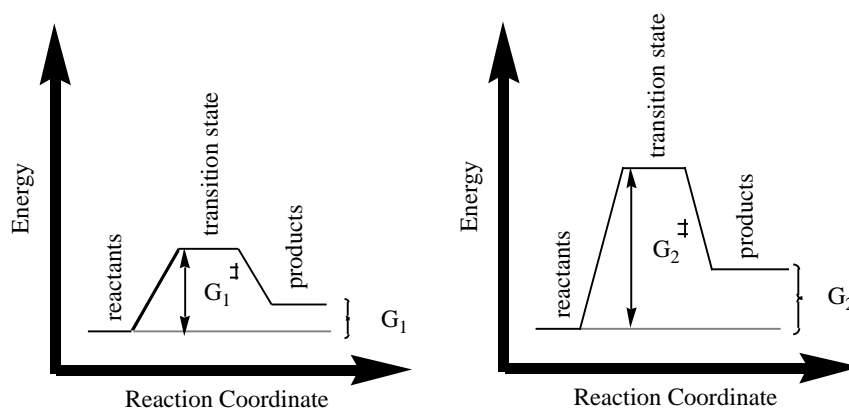


Practice Problems Solutions

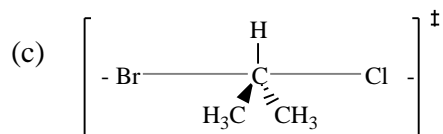
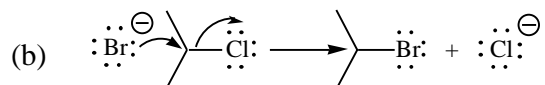
- For a reaction to occur, molecules must collide with **sufficient energy** and **correct orientation**.
- The most significant reason that the transition state is the highest energy point between reactants and products along a mechanism step is the partial bonds (H). That the transition state is highly organized (S) is a less important factor.
- The relationship between transition state energy (G^\ddagger , also called energy of activation, E_{act}) and reaction rate is given by the Arrhenius equation:

$$k = Ae^{-E_{\text{act}}/RT}$$

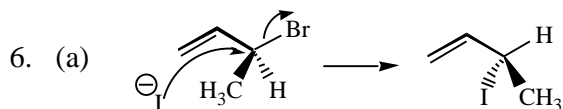
where k is the reaction rate constant. From this equation we see that rate goes down as activation energy increases. From the viewpoint of the reaction energy profile diagram, the higher the hill, the slower the reaction. In this case, $G_2^\ddagger > G_1^\ddagger$ so the rate of reaction 2 is slower than reaction 1.



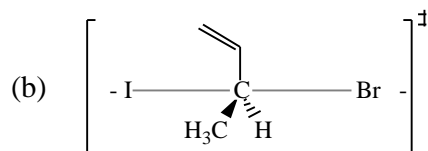
5. (a) rate = $k [\text{R-Cl}] [\text{Br}^-]$ or rate = $k [\text{R-Cl}] [\text{Br}^-]$



Your transition state drawing should clearly show the spatial arrangement of the groups attached to the carbon that bears the leaving group.



An S_N2 reaction proceeds via backside attack of the nucleophile on the carbon bearing the leaving group, resulting in net inversion of configuration. If the starting allylic bromide is optically active, then the product will also be optically active, and have the opposite (inverted) absolute configuration.



Important features:

- Partial negative charges on the nucleophile and leaving group,
- Trigonal planar arrangement of the hydrogen, methyl, and vinyl group on the central carbon atom,
- 180° I---C---Br bond angle, and
- Careful representation of the three-dimensional structure

7. The role of a nucleophile or base is to share an electron pair to form a new covalent bond with the electrophile or proton, so the single most important factor that controls nucleophilicity or basicity is the ability, desire, or driving force to share an electron pair.

8. The most important factor that controls nucleophilicity is the nucleophile's ability to share an electron pair with an electrophile to form a new covalent bond. In class we discussed four structural features that influence this. These features are, in order of decreasing influence, are resonance, polarizability, electronegativity and the inductive effect. If resonance delocalizes the electron density or charge shared with the electrophile, then resonance decreases nucleophilicity. (Alternately, resonance is a stabilizing feature, so loss of resonance inhibits the nucleophile's driving force to share the electron pair.) The dithioacetate ion (CH_3CS_2^-) has resonance and the other

two do not, so dithioacetate is the least nucleophilic. The difference between ethoxide ion ($\text{CH}_3\text{CH}_2\text{O}^-$) and ethanethiolate ($\text{CH}_3\text{CH}_2\text{S}^-$) is one of polarizability of the atom sharing electrons with the electrophile. Because oxygen is harder than sulfur, ethoxide is a poorer nucleophile than ethanethiolate. Thus the order of nucleophilicity is: CH_3CS_2^- (poorest nucleophile) $<$ $\text{CH}_3\text{CH}_2\text{O}^-$ $<$ $\text{CH}_3\text{CH}_2\text{S}^-$ (best nucleophile).

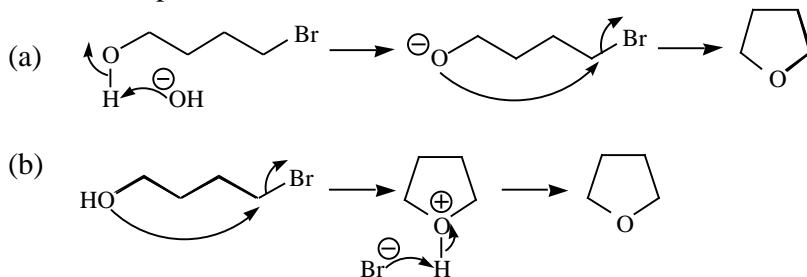
9. The role of a nucleophile is to share electrons with an electrophile. Using the factors discussed in class, we can evaluate the relative nucleophilicity of the species in this question. The first four factors discussed below are presented in order of influence.
- Resonance: Not factor here; not possessed by any of these species.
 - Polarizability: Sulfur is softer than oxygen, so the nucleophile that donates electrons from sulfur will be the best one.
 - Electronegativity: Of the three remaining nucleophiles, all have an oxygen atom as the electron source. Because there is no difference in electronegativity between oxygen atoms, this is not a useful criterion here.
 - Inductive effect: Trifluoroethanol ($\text{CF}_3\text{CH}_2\text{OH}$) is a weaker nucleophile than ethanol because the three fluorine atoms are withdrawing electron density from the oxygen.

Charge must also be considered. When everything else is equal, a molecule bearing a negative charge will be more nucleophilic or basic than one without. Thus, ethoxide ion ($\text{CH}_3\text{CH}_2\text{O}^-$) is more nucleophilic than the conjugate acid, ethanol ($\text{CH}_3\text{CH}_2\text{OH}$).

This analysis suggests the following ranking: $\text{CH}_3\text{CH}_2\text{S}^-$ (strongest) $>$ $\text{CH}_3\text{CH}_2\text{O}^-$ $>$ $\text{CH}_3\text{CH}_2\text{OH}$ $>$ $\text{CF}_3\text{CH}_2\text{OH}$ (weakest).

10. (a) I^- (b) HSe^- (c) NH_3 (d) HS^- (e) $\text{CH}_3\text{CH}_2\text{S}^-$ (f) $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}^-$ (g) HS^-
(h) $\text{CH}_3\text{CH}_2\text{CO}_2^-$ (i) CH_3O^-
11. The structural factor that has the most influence over nucleophilicity is resonance. Acetate ion (CH_3CO_2^-) has resonance that reduces the electron density on the oxygen atoms that would share electrons with an electrophile. Hydroxide and methoxide (CH_3O^-) do not have this resonance dilution of charge. (Alternately, upon reaction with an electrophile, acetate ion loses resonance stabilization whereas the other do not.) Acetate ion is therefore worst nucleophile in this group.
12. The difference between these two reactions is the nucleophile. Methanethiolate (CH_3S^-) is a better nucleophile than methoxide (CH_3O^-) because sulfur is more polarizable than oxygen. Therefore the second reaction will be slower under $\text{S}_{\text{N}}2$ reaction conditions.

13. Mechanism possibilities:



Mechanism (a) is a better choice because an alkoxide (RO^-) has a negative charge and is therefore a better nucleophile than an alcohol (ROH) which is neutral.

14. A good leaving group is stable after departure, and has a polarizable atom to easily accept the electrons that once were the carbon-leaving group bond. Methanethiolate (CH_3S^-) and trifluoromethanethiolate (CF_3S^-) meet the polarizability requirement, but both have a negative charge to stabilize. The three electron-withdrawing fluorine atoms of trifluoromethanethiolate will help stabilize the negative charge by the inductive effect, making the negative charge of trifluoromethanethiolate more stable than the negative charge of methanethiolate. Therefore trifluoromethanethiolate is predicted to be the best leaving group.

15. Methide (CH_3^-) is the least stable of these three ions, and is thus the worst leaving group of these three. (Methide is never a leaving group.)

16. Best: CF_3SO_3^- Trifluoromethanesulfonate (triflate) ion has three resonance contributors and the inductive effect (electron withdrawing) of the CF_3 group to stabilize the negative charge.

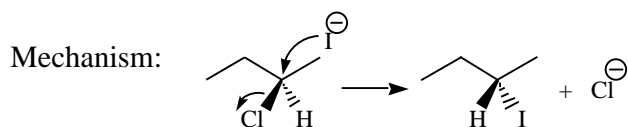
Middle: CH_3SO_3^- Methanesulfonate (mesylate) ion has three resonance contributors as well, but is destabilized by weak inductive electron density donation by the CH_3 group.

Poorest: CH_3CO_2^- Acetate ion has only two resonance contributors to delocalize the negative charge, as well as the same methyl group electron donation as in mesylate ion.

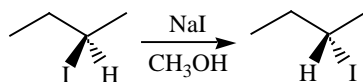
17. The rate of an $\text{S}_{\text{N}}2$ reaction is influenced by the degree of steric hindrance at the carbon undergoing substitution. The more highly substituted this carbon is, the slower the reaction will be. In isopropyl iodide, $(\text{CH}_3)_2\text{CHI}$, this carbon is secondary (2°) and thus isopropyl iodide will react more slowly than ethyl iodide ($\text{CH}_3\text{CH}_2\text{I}$; primary) or methyl iodide (CH_3I ; methyl).

18. If the reaction occurs by the $\text{S}_{\text{N}}2$ mechanism, the first reaction is the slowest because the electrophilic carbon is more sterically hindered.

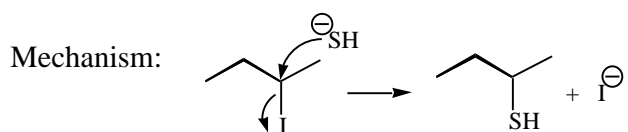
19. Dielectric constant (ϵ) is controlled by molecular structure. A molecule with a greater percentage of polar bonds versus nonpolar bonds will have a greater dielectric constant. Water consists of only polar bonds. Methanol has two polar bonds (C-O and H-O) and three nonpolar bonds (C-H), and thus a smaller ϵ than water. Ethanol has the same number of polar bonds as methanol, but more nonpolar bonds, and thus ethanol has a smaller ϵ than methanol. So: $\text{CH}_3\text{CH}_2\text{OH}$ $\epsilon = 20$, H_2O $\epsilon = 80$ and CH_3OH $\epsilon = 33$. (It is not necessary to have memorized dielectric constants to answer this question. In fact, you are strongly discouraged from wasting your time by memorizing such data. However, the more problems you do, the more often you will see this kind of data, and the more familiar with it you will become.)
20. Good leaving group: Better leaving groups accelerate an $\text{S}_{\text{N}}2$ reaction by allowing for more bonding between the nucleophile and carbon atom accepting the nucleophile. This increased bonding stabilizes the transition state, thus lowering the activation energy and increasing the reaction rate.
- Good nucleophile: Better nucleophiles accelerate an $\text{S}_{\text{N}}2$ reaction by increasing the degree of bonding between the nucleophile and carbon undergoing substitution in the transition state. This increased bonding stabilizes the transition state, thus lowering the activation energy and increasing the reaction rate.
- The carbon undergoing substitution must not be tertiary: Steric hindrance slows the approach of the nucleophile, and thus reduced the reaction rate. When the carbon is tertiary, the steric hindrance is sufficient to stop the reaction entirely.
21. $\text{S}_{\text{N}}2$ reactions work best on substrates that are less hindered. Thus we rank CH_3I (methyl) as fastest. We would like to rank isopropyl fluoride (secondary) second fastest, but fluoride ion a very poor leaving group; so poor that it will probably not undergo an $\text{S}_{\text{N}}2$ reaction at all. The other two molecules are tertiary at the reacting carbon, so they will also not undergo $\text{S}_{\text{N}}2$ reactions. Thus, we can say CH_3I is fastest and the other three are slower because they don't react!
22. These molecules differ both in degree of substitution at the carbon attacked by the nucleophile, and in the leaving group. Increasing the steric hindrance at the carbon bearing the leaving group slows the $\text{S}_{\text{N}}2$ reaction. Based on this criterion, the molecule that would react the slowest in an $\text{S}_{\text{N}}2$ reaction would be the benzylic triflate. From the perspective of leaving group, Br^- and CF_3SO_3^- are both sufficient leaving groups, whereas HO^- is a very poor leaving group. Based on the leaving group criterion, CH_3OH would react the slowest. (Either answer is acceptable.)
23. (a) Iodide is more polarizable than chloride, and is thus a better nucleophile, so the first reaction will be faster.



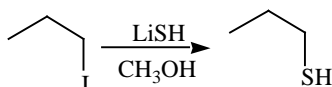
Replacing chloride with a better leaving group (iodide) will make the reaction go faster.



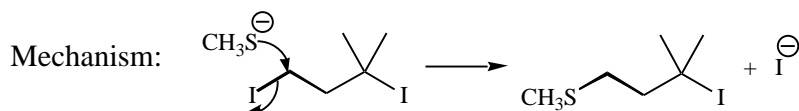
(b) Iodide (more polarizable) is a better leaving group than chloride, so the second reaction will be faster.



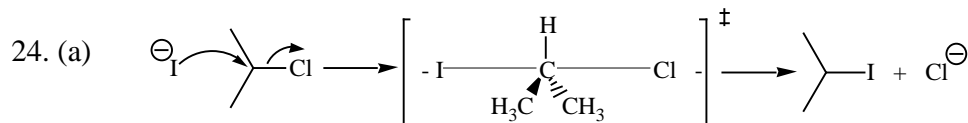
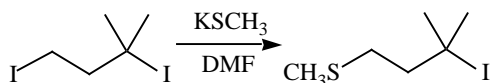
Replacing the 2° halide with a 1° halide will make an S_N2 reaction go faster, because of reduced steric hindrance to nucleophilic attack.



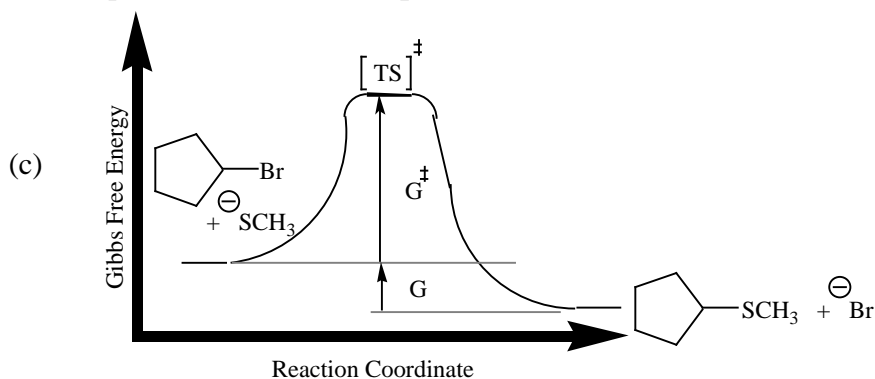
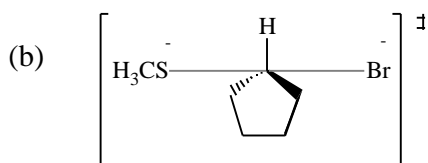
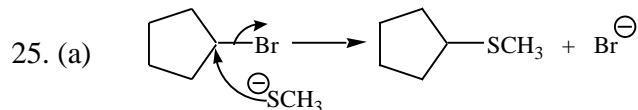
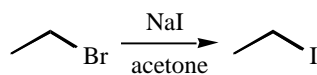
(c) An S_N2 reaction is sensitive to steric crowding. The second reaction is substitution of a 3° iodide, which does not proceed at all by the S_N2 mechanism. The first reaction, substitution at a 1° carbon, is therefore the faster one.



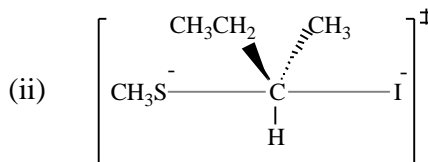
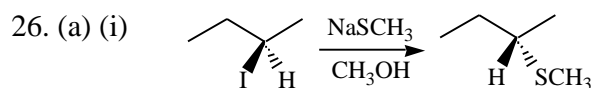
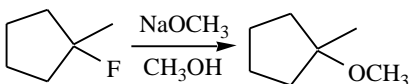
The reaction could be made to go faster in an aprotic solvent that is more polar than acetone. This results in greater nucleophilicity for the nucleophile.

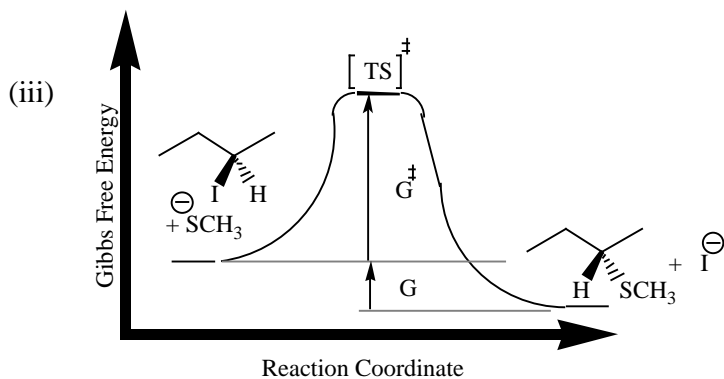


(b) Anything that improves the reaction rate is acceptable: better leaving group, less steric hindrance, and so forth. A case employing both is shown below.

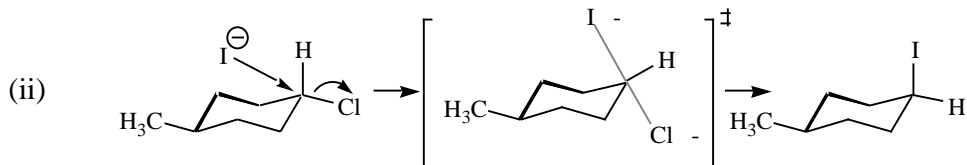
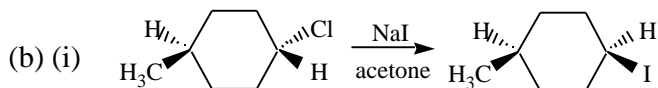
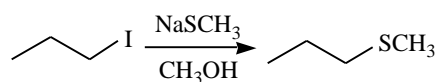


(d) An S_N2 reaction with a weaker nucleophile ($^-\text{OCH}_3$), poorer leaving group (F^- instead of Br^-) and greater steric hindrance (3° instead of 2°) will be much slower.





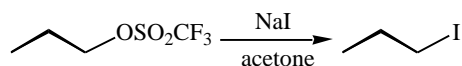
(iv) There are many possibilities. In the example shown below, the secondary alkyl iodide has been replaced by a primary alkyl iodide.



(iii) Your energy profile should look very much like the energy profile in part (a) of this question.

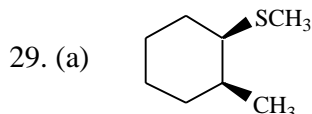
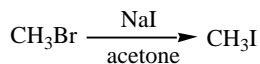
(iv) There are many possible answers, including changing to a better leaving group.

27. These are both S_N2 reactions (reasonably good nucleophiles; acceptable leaving groups; carbon bearing the leaving group is secondary). The difference is the nucleophile. Iodide is a better nucleophile than bromide. Therefore the first reaction is predicted to be faster. To design a reaction that is faster we can use a better leaving group or reduce the steric hindrance at the carbon bearing the leaving group. Both of these factors are incorporated in the faster reaction shown below.

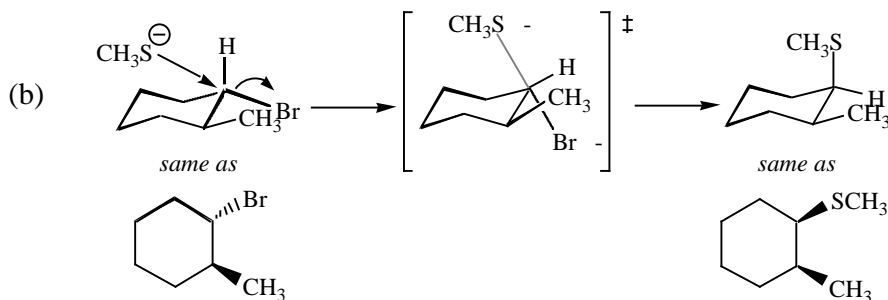


28. Both of these substitution reactions can occur by the S_N2 mechanism (iodide is an excellent nucleophile; chloride is a moderate leaving group, and neither is tertiary). The difference is the degree of substitution at the carbon bearing the leaving group. A primary halide is less crowded and therefore reacts faster than a secondary halide, so the second reaction is faster. The reaction rate can be improved by further decreasing the steric crowding (replacing primary with methyl) and use of a better

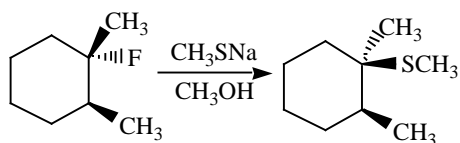
leaving group. Both of these factors are incorporated in the faster reaction shown below.



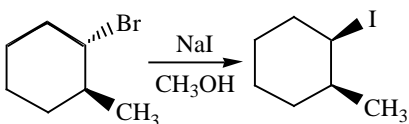
Note inversion of stereochemistry at the carbon undergoing substitution.



(c) Any change in the electrophile that slows the reaction is acceptable. Such changes might include replacing Br with F (poorer leaving group) or adding steric hindrance to the carbon undergoing nucleophilic attack (a tertiary carbon is so hindered as to prevent nucleophilic attack). Both of these are illustrated below.

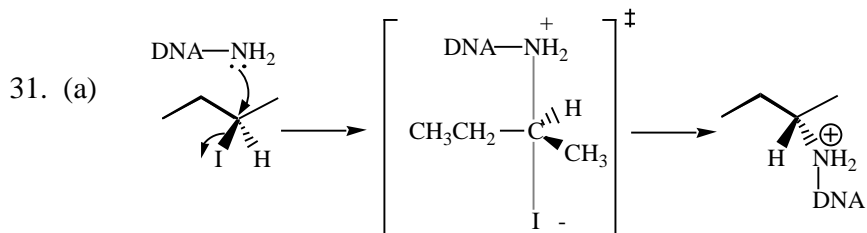


(d) Any change in the nucleophile that makes the reaction faster is acceptable. Replacing methanethiolate with an even better nucleophile (iodide ion) is one solution. (Changing the solvent may change nucleophilicity but it does not change the nucleophile itself.)



30. We need to consider the differences between the three reactions, and how these differences influence the rate of an S_N2 reaction. Reaction (i) occurs at a tertiary carbon, whereas reactions (ii) and (iii) occur at secondary carbons. Increasing steric hindrance at the carbon bearing the leaving group retards the rate of an S_N2 reaction. A tertiary carbon is so highly hindered to S_N2 attack that no reaction occurs. Thus, reaction (i) is the slowest of the three. The difference between reactions (ii) and (iii) is the leaving group. Bromide is a better leaving group than chloride because

bromide is more polarizable. Thus reaction (ii) is faster than reaction (iii). The relative rates are therefore: (ii) is fastest > (iii) > (i) is slowest.

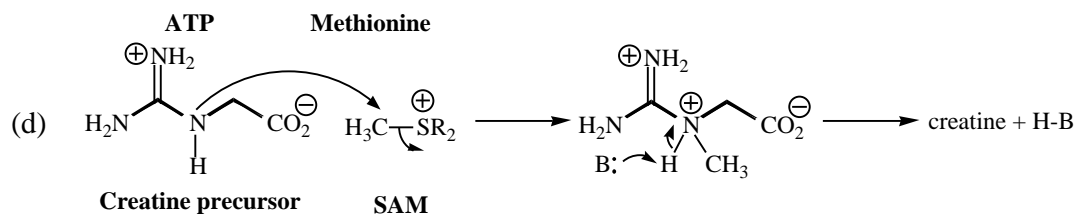
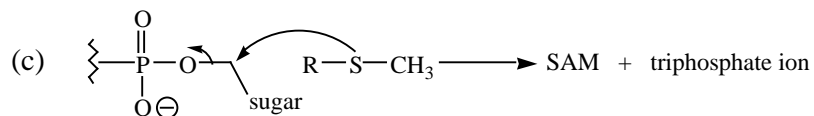


(b) Assuming the DNA alkylation reaction is an S_N2 process, *tert*-butyl iodide would be unreactive because it is a tertiary haloalkane and thus too sterically hindered to allow the nucleophile to approach the backside of the carbon-iodine bond.

(c) Reason #1: Magic methyl is less sterically hindered than 2-iodobutane, a secondary haloalkane. Reason #2: Fluorosulfonate (FSO_3^-) is a better leaving group than iodide due to a combination of resonance and the inductive effect of the fluorine atom.

32. (a) The negative charge gained upon departure is delocalized by resonance. This makes triphosphate ion more stable, and thus a better leaving group.

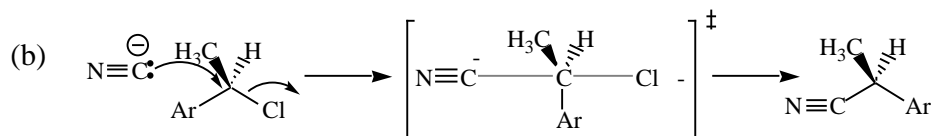
(b) Methylation of methionine occurs on sulfur because sulfur more polarizable than oxygen and therefore sulfur is more nucleophilic than oxygen.



B: is a base of some sort, most probably a nitrogen-containing functional groups such as primary amine within the enzyme active site where this reaction occurs.

33. This reaction cannot occur as written, because the carbon atom that gains the nitrile group (CN) already has a full octet. One solution is to show the Br leaving (an S_N2 reaction).

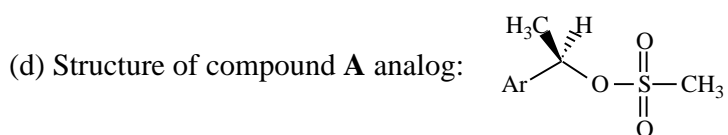
34. (a) An S_N2 reaction proceeds with inversion of configuration so the correct answer is product C.



(c) An S_N2 reaction requires:

- Good leaving group (chloride is a moderate leaving group),
- Good nucleophile (cyanide ion is an excellent nucleophile because the negative charge is localized on carbon and because it is a skinny ion that can readily fit into tight spaces), and
- The carbon that accepts the nucleophile cannot be tertiary (it is secondary in this case).

Thus we conclude this should be a reasonable S_N2 reaction.



S_N2 reaction of this analog will be faster than S_N2 reaction of **A**, as methanesulfonate (CH_3SO_3^-) is a better leaving group than chloride ion. It is a better leaving group due to resonance stabilization of the negative charge. (Other answers may also be acceptable.)

(e) An S_N2 reaction cannot occur at a tertiary center, so this employee should be fired for suggesting this S_N2 reaction.