

Ionic Substitution Reactions: S_N2

Suggested Reading

- Review general chemistry kinetics and thermodynamics as needed
- Brown and Foote sections 9.1–9.4
- OCATSA Ionic Substitution Reactions (email instructor to obtain access)

Lecture Supplement

- Ionic Substitution Reactions: S_N2

Optional Reading

- 1999 Nobel Prize in Chemistry: "Photographs" of Transition States (http://nobelprize.org/nobel_prizes/chemistry/laureates/1999/)
- Klein Chapters 8 and 9

Suggested Text Exercises from Brown and Foote

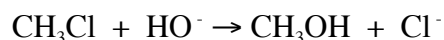
- Chapter 9: 1–3, 11–13, 15–19, 21, 51, and 52

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

- Electrophiles and Nucleophiles
- S_N2 Reaction: Visualizing S_N2 Transition State via Molecular Models

Concept Focus Questions

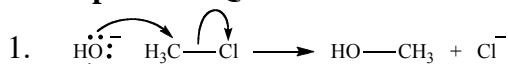
Questions 1–6 refer to this substitution reaction:



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 this reaction.
6. Draw the energy profile for the reaction. Assume the reaction is exergonic. Label all of the important features of the energy profile.
7. What is the relationship between transition state structure and reaction rate?
8. List in order of influence the five important structural features of the nucleophile that control nucleophilicity. Briefly describe how each factor operates.
9. Define "leaving group." What structural factors make for a good leaving group?

- Define "steric effect." Briefly discuss steric effects in the S_N2 reaction.
- Define: Dielectric constant, polar solvent, nonpolar solvent, protic solvent, and aprotic solvent.
- Briefly discuss the relationship between solvent, transition state and S_N2 reaction rate. Include both polarity and hydrogen bonding effects.
- List the four fundamental requirements for an S_N2 reaction to occur. Very briefly describe how each factor controls the rate of an S_N2 reaction.

Concept Focus Questions Solutions

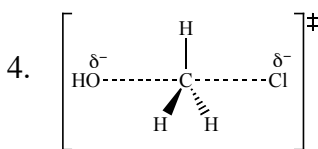


This is a concerted reaction, because it proceeds through a single mechanism step without any intermediates. All bond making and bond breaking occurs within this single mechanism step.

It is not usually necessary to include the leaving group as one of the products. (Its omission is not an error, but rather an acceptable simplification.) However, in some reactions, the leaving group continues to participate in the mechanism after its departure. If you are the kind of student who tends to forget that the leaving group is still present even though it has not been written, then get yourself into the habit of drawing the leaving group.

Does CH_3Cl confuse you, because it implies that the chlorine atom is bonded to hydrogen instead of carbon? By convention, the methyl group may be written as CH_3X or H_3CX .

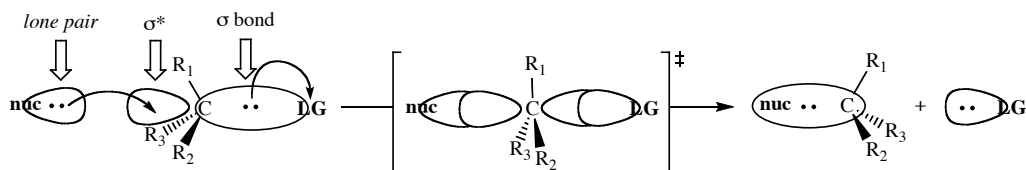
- Rate = k [nucleophile] [electrophile] = k [HO^-] [CH_3Cl]. The reaction is nucleophilic substitution with bimolecular kinetics; hence it is called S_N2 .
- The transition state is the highest energy structure for each mechanism step in the reaction. (Every mechanism step has its own transition state. A reaction mechanism with more than one step has more than one transition states.) 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 (see CFQ 7). Reaction rate is easily observable, and thus a useful tool to verify a proposed mechanism and to ascertain the effects of changing various factors in a chemical reaction.



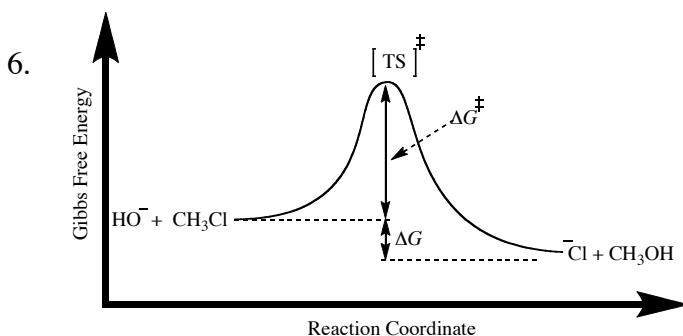
The carbon-oxygen and carbon-chlorine bonds are incomplete and therefore longer than normal sigma bonds. The hydroxide ion has begun to share a lone pair with the carbon, so it has a partial negative instead of a full negative charge. The pair of electrons that were the carbon-chlorine bond has begun to shift toward the chlorine, giving the chlorine a partial negative charge. The carbon has shifted toward sp^2 (or perhaps dsp^3) 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.

It does not matter from what perspective you draw a transition state, unless specified by the problem. For an S_N2 transition state, the partial bonds may be drawn horizontally, vertically, or at any other angle. If you are unsure that your answer and the given answer are equal, use your model kit to build and compare.

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.



The exact structure of the nucleophile and leaving group are not specified, so we cannot specify their charges.



7. For reactants to become products, they must have enough energy to overcome an energy barrier called the Gibbs free energy of activation (ΔG^\ddagger ; see diagram in previous answer). The height of this energy hill is the difference in Gibbs free energy of the reactants and transition state.

Recall that Gibbs free energy (ΔG) is a function of enthalpy (ΔH ; energy changes due to bond changes) and entropy (ΔS ; organization). In equation form:

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

At reaction temperatures up to a few hundred Kelvin the entropy factor is small, perhaps one kcal mol⁻¹. In this temperature range, $T\Delta S^\ddagger$ is small compared to ΔH^\ddagger , and so it can often be neglected when making simple predictions or estimations. Thus we can approximate ΔG^\ddagger as ΔH^\ddagger . (This assumption is valid only when enthalpy changes are more important than entropy changes in a reaction.)

This is a convenient approximation because we cannot measure ΔG^\ddagger in the laboratory. Instead, we can determine a closely related energy value called the energy of activation (E_a). E_a is related to ΔH^\ddagger by the equation: $E_a = \Delta H^\ddagger + RT$. E_a can be measured in the laboratory because of its relationship to reaction rate (something we can easily measure in the lab) by the Arrhenius equation:

$$k = A_0 e^{-E_a/RT}$$

So for our introductory level discussion of reaction rates and variables that influence them, we can discuss transition state energy and not have to be concerned about whether it is ΔG^\ddagger or E_a .

The Arrhenius equation reveals that a lower transition state energy (smaller hill) leads to a faster reaction.

8. Each structural feature is analyzed to see how it influences the ability or driving force of the nucleophile 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 usually (but not always) decreases electron density at the atom that shares electrons with the electrophile.

Atomic radius: An atom is driven to share an electron pair in order to decrease its charge density (electron density per unit of surface area). Everything else being equal, smaller atoms have a higher charge density and thus a stronger drive to form new covalent bonds.

Electronegativity: Electronegativity is defined as an atom's attraction for (or resistance to sharing) electron density. Higher electronegativity means the atom has a greater attraction for (or is less inclined to share) electron density. Since the job of a nucleophile is to share electron density with a carbon atom, higher electronegativity decreases nucleophilicity.

Inductive effect: This is the non-resonance influence that one part of a molecule has on the electron density elsewhere in the molecule. It can be an electron withdrawing or electron donating effect, and can operate both through the sigma bond framework and through space. For a nucleophile, it is the electron density 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.

The previous four factors are listed in order of decreasing influence. Formal charge also plays a significant role in determining nucleophilicity, but its relative influence is not fixed. For example, sometimes formal charge carries more influence than atomic radius and other times its influence is less.

Formal charge: A formal negative charge indicates excess electron density. In the case where all other factors are equal, an atom with a formal negative charge makes the nucleophile stronger than one that is neutral. Formal charge is of variable influence (for example, sometimes it has more influence than resonance, sometimes less) so it does not have a fixed position in this sequence of relative influence.

Because nucleophiles and bases both share electrons, there is a strong (although imperfect) parallel between the structural factors that control them. A thorough review of acids and bases (and the structural features that influence them) can be found in the Supplemental Reading link at the course web site.

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. This means the leaving group gains electron density. The best leaving groups are those that can accommodate and disperse this extra electron density most effectively by resonance, atomic size, and inductive effects. Leaving group efficacy is also enhanced when the leaving group atom that accepts the electron pair has high electronegativity or a positive formal charge.

In general the best leaving groups are also poor nucleophiles, but there are exceptions. For example, iodide ion is a good nucleophile and superior leaving group.

10. A steric effect occurs when a chemical phenomenon is influenced by van der Waals repulsion. In an S_N2 reaction steric effects can influence the reaction rate by slowing or preventing approach of the nucleophile. As the number and/or size of substituents on the carbon bearing the leaving group (LG) increases, it becomes increasingly more difficult for the nucleophile to reach this carbon. The S_N2 reaction rate decreases as the number or size of substituents increases. Relative rates: $\text{CH}_3\text{-LG}$ (methyl) > $\text{RCH}_2\text{-LG}$ (primary, 1°) > $\text{R}_2\text{CH-LG}$ (secondary, 2°) \gg $\text{R}_3\text{C-LG}$ (tertiary, 3°). A tertiary carbon is so highly hindered toward backside attack that tertiary substrates do not react by the S_N2 mechanism.
11. Dielectric constant: Dielectric constant (ϵ) is a measure of a substance's ability to insulate opposite charges from each other. In other words, it is a measure of the ability of a substance to separate ions.

Polar solvent: A polar solvent has a high dielectric constant. Solvents with ϵ of approximately 20 or more are labeled as polar.

Nonpolar solvent: A nonpolar solvent has a low dielectric constant. Solvents with ϵ of approximately 20 or less are labeled as nonpolar.

Protic solvent: A protic solvent is a hydrogen bond donor. In common organic solvents, the hydrogen bond donor is an O–H bond. (Review hydrogen bonding from Chem 14C if necessary.)

Aprotic solvent: An aprotic solvent does not have a hydrogen atom that can be shared by hydrogen bonding.

12. Reaction rate is controlled by the energy difference between the reactants and transition state. If the solvent decreases this gap, the reaction is faster. If the solvent increases this gap the reaction is slower. For example, the solvent might stabilize the reactants more than the transition state, causing a larger energy gap and slower reaction.

Most S_N2 reactions involve a negative charged nucleophile and uncharged electrophile. This results in a transition state with δ^- charges on the nucleophile and leaving group. For the fastest reaction, we select a nonpolar solvent, as this provides less stabilization to the nucleophile than to the transition state. However, nonpolar solvents do not dissolve most anionic nucleophiles, so we are forced to choose a polar solvent instead.

A protic solvent surrounds a nucleophile with a hydrogen bonding shell. This hydrogen bonding provides some stabilization. Some of the solvent molecules must move away in order for the nucleophile to come within bonding distance of the electrophile. This desolvation decreases the stability of the nucleophile and the transition state. (Because the nucleophile has greater charge concentration than the transition state, the nucleophile suffers a greater decrease in stability than does the transition state.) Therefore S_N2 reactions are slower in protic solvents than in aprotic solvents of equal polarity.

Overall, the best solvent choice for most S_N2 reactions is polar aprotic. Polar protic is usually acceptable but the reaction is slower. Nonpolar solvents are usually not useful for S_N2 reactions.

13. Moderate or better leaving group: Better leaving groups accelerate an S_N2 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 S_N2 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 bearing the leaving group cannot be tertiary: Steric hindrance slows the approach of the nucleophile, and thus reduces the reaction rate. When the carbon is tertiary, the steric hindrance is sufficient to shift the reaction to a different substitution mechanism.

Solvent: A polar aprotic solvent is best. Polar protic may be acceptable but the reaction is slower. Nonpolar solvents are usually not useful for S_N2 reactions.

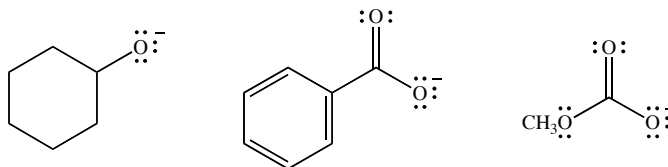
These factors may interact. For example, if the leaving group is superior, then reaction can occur with a poorer nucleophile. There are no exceptions to the "not tertiary" requirement.

OWLS Problems

Please bring your molecular model kit to discussion section this week.

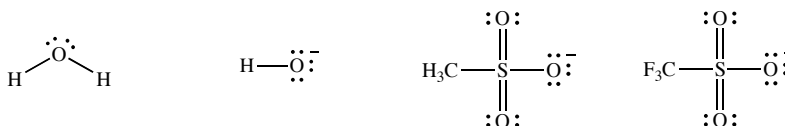
1. Resonance is a common phenomenon in organic molecules. Therefore it is useful for you to recognize its presence, to be able to draw resonance contributors rapidly and accurately, and to understand how resonance influences the structure and reactions of organic molecules.

(a) Draw all of the significant resonance contributors for each of these ions.



(b) Briefly describe how resonance influences each molecule's nucleophilicity and leaving group ability.

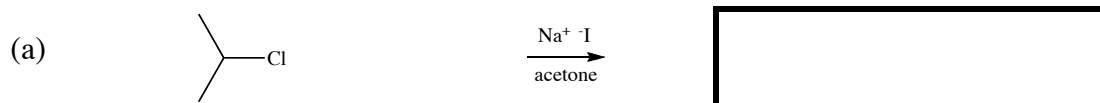
2. (a) Select the best nucleophile and leaving group among these four species:

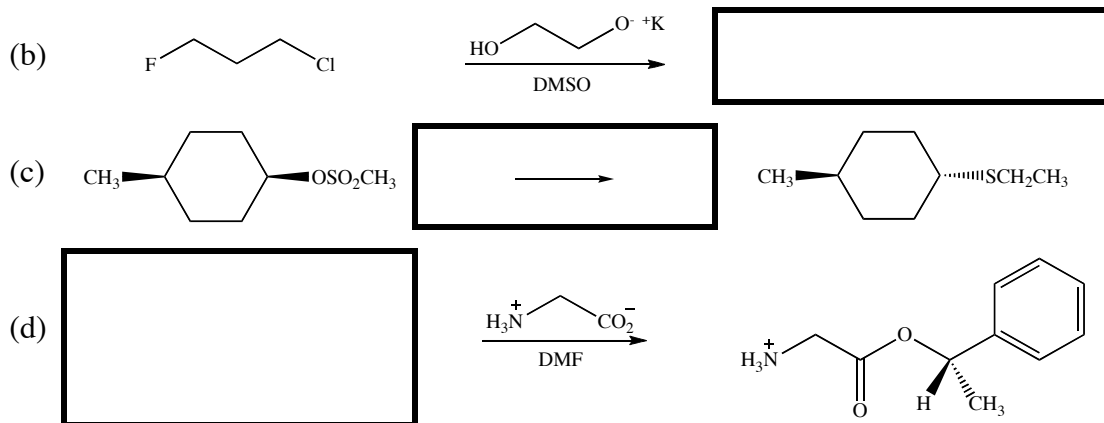


(b) Write an S_N2 reaction including all reactants and products that utilizes both the best nucleophile and the best leaving group from part (a). Your S_N2 reaction must occur at a carbon of the electrophile that is both secondary and a stereocenter.

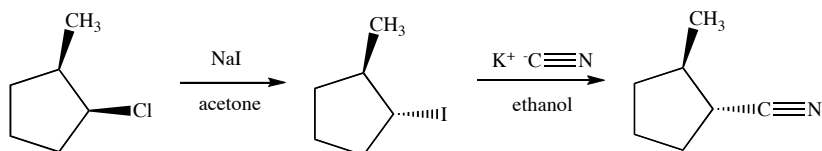
(c) Write the mechanism and transition state for your reaction from part (b).

3. Provide the missing products, reactants, or starting materials in the boxes.

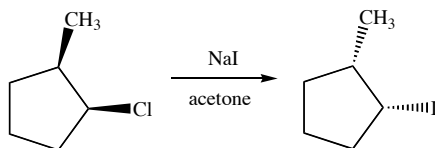




4. Is reaction 3(d) a reasonable S_N2 reaction? Explain.
5. Consider the four reactions of question 3. What one feature is common to all the nucleophiles? What one feature is common to all of the electrophiles?
6. Consider this general statement: "Protic solvents decrease nucleophilicity."
 (a) Give two examples of protic solvents.
 (b) Is the statement true? Briefly explain.
 (c) Write a pair of S_N2 reactions that illustrate this solvent effect. Select the faster reaction.
7. Consider this reaction sequence:



- (a) Evaluate each step in the sequence. Are these reasonable S_N2 reactions?
 (b) An S_N2 reaction proceeds with inversion, so why does the first step not occur as shown below?

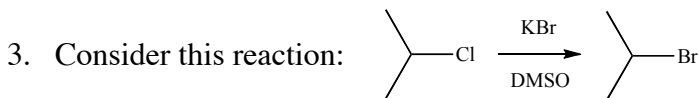


- (c) Considering the given reaction sequence, evaluate this statement: "In an S_N2 reaction, the term 'inversion' means that if the electrophile has the *R* configuration, the product always have the *S* configuration."

Practice Problems

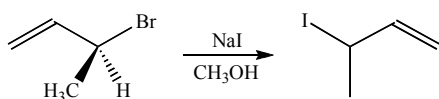
1. For a reaction to occur, molecules must collide with sufficient _____ and correct _____.

2. Give at least one significant reason that the transition state is the highest energy structure between reactants and products in a mechanism step.

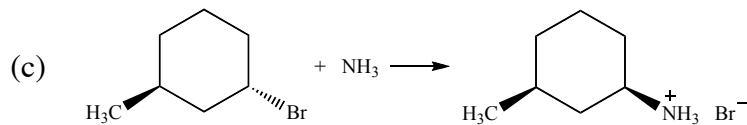
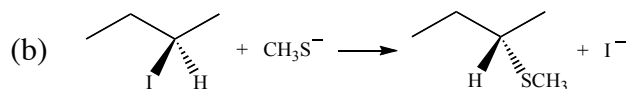
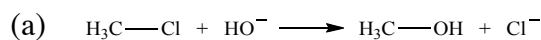


- (a) Write the rate expression for this reaction.
 (b) Write a curved arrow mechanism for this reaction, including the transition state and all lone pairs.

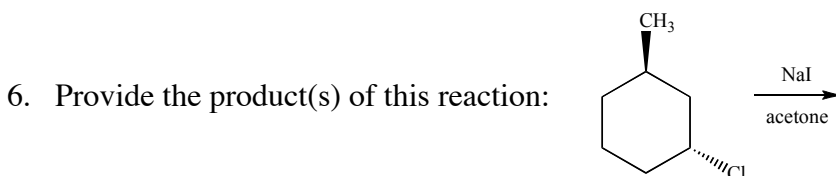
4. Write the S_N2 mechanism, including the transition state for the following reaction. Clearly show product stereochemistry.



5. Build models of the transition states for the following S_N2 reactions.



The product of reaction (c) is a salt, in which RNH_3^+ is the cation and Br^- is the anion. We normally do not write a plus sign between the cation and anion of a salt, even if they are reaction products. Example: $2 \text{Na} + \text{Cl}_2 \rightarrow 2 \text{NaCl}$, not $2 \text{Na}^+ + 2 \text{Cl}^-$.



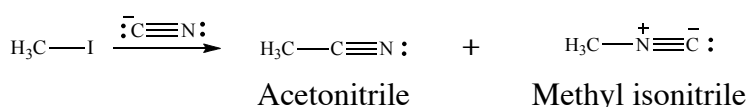
7. What is the single most important factor (more fundamental even than resonance) that controls the nucleophilicity or basicity of **any** molecule or ion?
8. Select the poorest nucleophile: HO^- , CH_3CO_2^- , and CH_3O^- .
9. Select the best and worst nucleophiles in an aprotic solvent: $\text{CH}_3\text{CH}_2\text{S}^-$, $\text{CH}_3\text{CH}_2\text{O}^-$, $\text{CH}_3\text{CH}_2\text{OH}$, and $\text{CF}_3\text{CH}_2\text{OH}$. Briefly explain your reasoning.

10. Select the strongest nucleophile in aprotic solvent in each set. List the most important factor(s) that influenced your decision. Illustrate each nucleophile in a reasonable S_N2 reaction, using a different electrophile in each case.

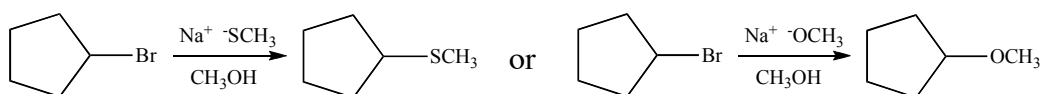
- (a) I^- , Br^- , F^- (e) $CF_3CH_2S^-$, $CH_3CH_2S^-$, $CH_3CH_2O^-$
 (b) HS^- , HSe^- , HO^- (f) $CH_3CH_2CH_2O^-$, $CH_3CF_2CH_2O^-$, $CF_3CH_2CH_2O^-$
 (c) NH_3 , H_2O , CH_3OCH_3 (g) H_2O , H_2S , HO^- , HS^-
 (d) HS^- , HO^- , H_2N^- (h) $CF_3CO_2^-$, $Cl_3CO_2^-$, $CH_3CH_2CO_2^-$

11. Cyanide ion ($C\equiv N^-$) is an excellent nucleophile.

- (a) Suggest the structural feature(s) that account for its high nucleophilicity.
 (b) Select the major product of the following reaction, and briefly explain your reasoning.



12. Select the slowest reaction. Briefly explain your choice.



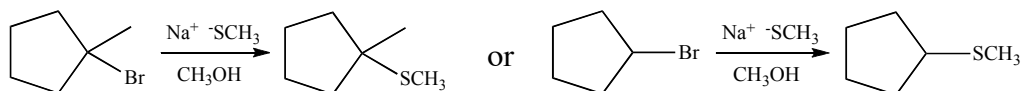
13. Select the best leaving group: CH_3S^- , CH_3O^- , CF_3S^- , or F^- . Illustrate the best leaving group in a reasonable S_N2 reaction at a secondary carbon.

14. Select the poorest leaving group: F^- , I^- , or $^-CH_3$.

15. Label these leaving groups as best, middle, or poorest: $CF_3SO_3^-$, $CH_3SO_3^-$, and $CH_3CO_2^-$.

16. Select the compound that reacts slowest in an S_N2 reaction: CH_3I , CH_3CH_2I , $(CH_3)_2CHI$.

17. Select the slowest S_N2 reaction. Briefly explain your choice.

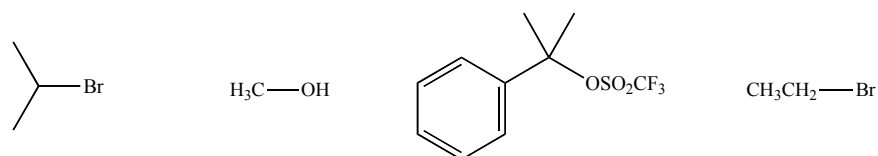


18. Without using any reference material such as a table of solvents or your lecture notes, assign the dielectric constants of 80, 33, and 25 to these compounds: CH_3CH_2OH , H_2O , and CH_3OH .

19. Select the molecules that react fastest and slowest by the S_N2 mechanism.

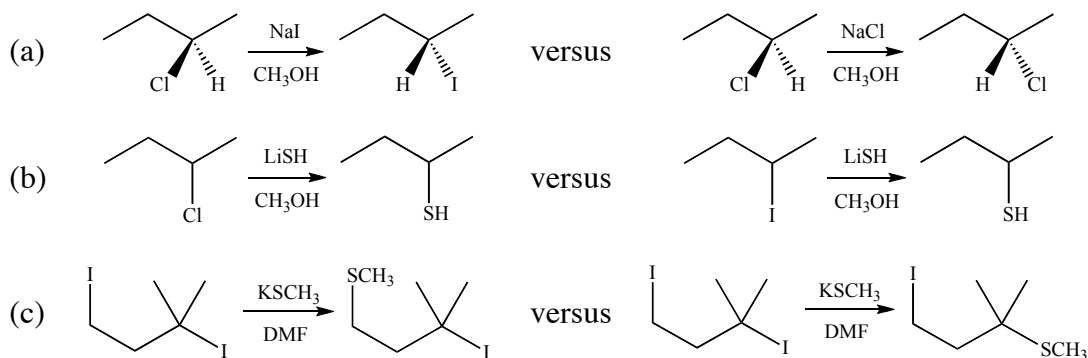


20. Select the molecule that reacts the slowest in an S_N2 reaction:



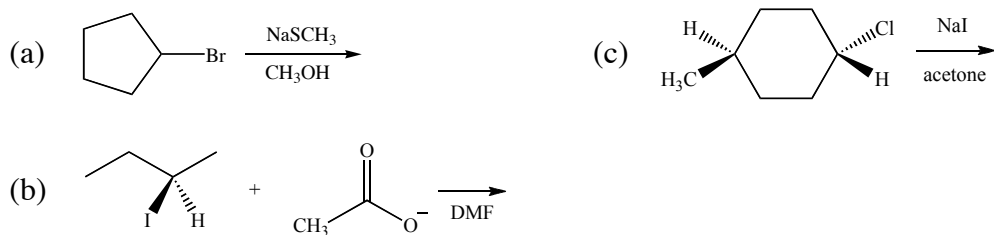
21. For each pair of S_N2 reactions shown below:

- Decide which reaction is faster. Briefly explain your choice.
- Write the mechanism of 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.



22. For the S_N2 reactions shown below:

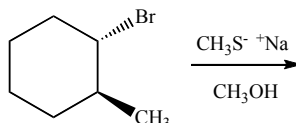
- Write the S_N2 mechanism, transition state(s) and product.
- By adding, subtracting, or transmuting at most four atoms of the electrophile or nucleophile, rewrite the reaction so that it is obviously slower.



23. For the reaction shown below:

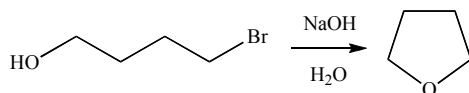
- Write the product and reaction mechanism including all transition states.

- (b) By changing only the electrophile, write a reaction (including product) that is clearly slower. Briefly explain why your new reaction is slower
- (c) Changing only the nucleophile, write a reaction that is clearly faster. Briefly explain why your new reaction is faster.

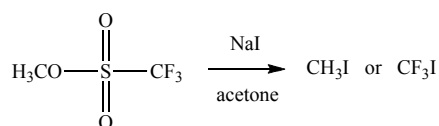


24. Rank the S_N2 reaction rates of the following molecules with NaSCH_3 in ethanol: 2-iodo-2-methyl propane, 2-bromopropane, and 2-chloropropane.

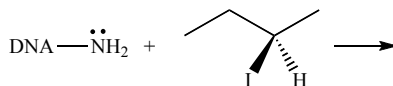
25. Consider this intramolecular substitution reaction:



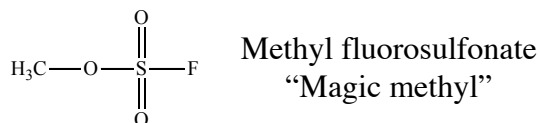
- (a) Write two mechanisms for this reaction, but avoid carbocations.
- (b) Which of these mechanisms is most reasonable?
- (c) Write the transition state for the carbon-oxygen bond-forming step of the most reasonable mechanism. *Use a model to visualize the transition state!*
- (d) Write the rate expression for this reaction. Is it an S_N2 reaction?
- (e) Draw another S_N2 product that might be formed in this reaction.
26. Select the major product of this reaction. Write a mechanism, and briefly explain your choice of major product.



27. Many haloalkanes (alkyl halides) can cause damage to DNA (abbreviated DNA-NH_2) because they can alkylate a free amine by an S_N2 reaction. Because of this many haloalkanes are carcinogens.



- (a) Write the product, mechanism, and all transition states for the S_N2 alkylation of DNA by (*R*)-2-iodobutane (reaction shown above).
- (b) Briefly explain why *tert*-butyl iodide is not a very powerful carcinogen.
- (c) Methyl fluorosulfonate causes DNA mutations more readily than the iodide in the reaction shown above. Provide two brief reasons for this. (Methyl fluorosulfonate is also called “magic methyl” because it is such a powerful methylating reagent.)

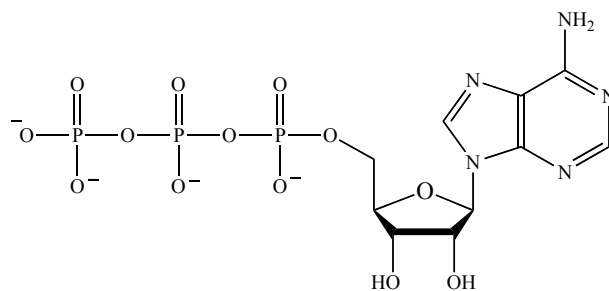


28. Methylation is an important step numerous biosynthetic pathways. This question deals with one step in the biosynthesis of creatine, a molecule that is essential for the functioning of muscles.

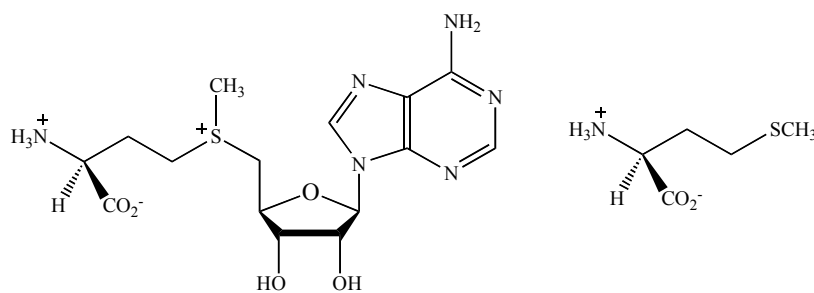
(a) Phosphate ions are used extensively in biosynthesis as leaving groups. Why is triphosphate a good leaving group?



(b) Write a mechanism that shows the conversion of ATP (adenosine triphosphate; structure shown below) and methionine into SAM (*S*-adenosyl methionine).



ATP

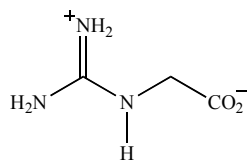


SAM

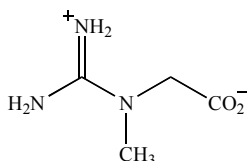
Methionine

(c) Why is methionine alkylated on the sulfur and not the oxygen atom, even though the oxygen bears a negative charge and the sulfur is neutral?

(d) Write a mechanism that shows how SAM reacts with guanidoacetate to form creatine.

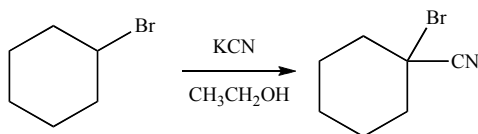


Guanidoacetate

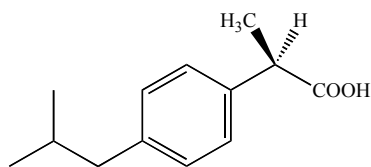


Creatine

29. 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.)

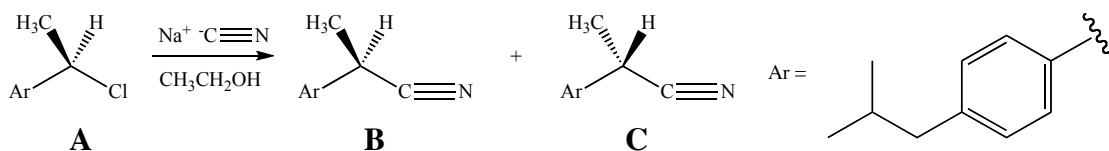


30. Ibuprofen is an analgesic and anti-inflammatory found in many over-the-counter drugs such as Motrin. Imagine that you have inherited a factory that manufactures ibuprofen. You are faced with many problems to improve the factory and its product.



Ibuprofen

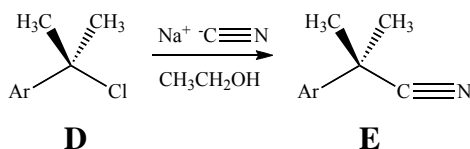
A key step in the synthesis of ibuprofen in your factory is the reaction of chloroalkane **A** with cyanide ion ("Ar" is a common abbreviation for an aromatic ring. Chemical common sense tells us it is not an abbreviation for argon, because argon is a noble gas and does not form chemical bonds.)



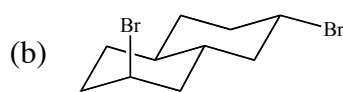
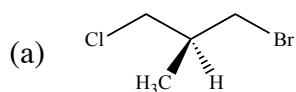
- Select the major product.
- Draw the S_N2 mechanism including all transition states.
- Is this a reasonable S_N2 reaction? Briefly explain. Clearly state all assumptions.
- Haloalkanes such as compound **A** present environmental hazards if spilled. As a concerned factory owner you want to avoid this 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 undergoes a faster S_N2 reaction than A. Briefly explain your reasoning.

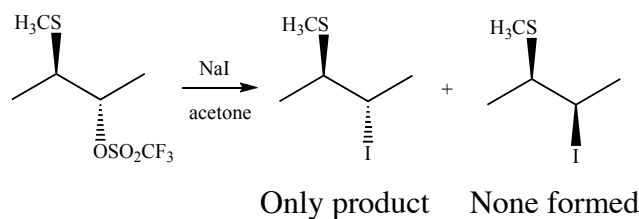
- (e) One of your employees approaches you with an idea to make an analog of ibuprofen with an extra methyl group. A key step in the synthesis of this analog is the S_N2 reaction shown below. Is this employee's idea reasonable or should this employee be fired due to a lack of chemical common sense? Explain.



31. What is the major product formed when each of the following molecules is reacted with one equivalent of sodium cyanide in ethanol?



32. Design an S_N2 reaction in which the molecule bearing the leaving group has a stereocenter, but the product does not.
33. In your studies of organic and biochemistry you will encounter reactions that you have never seen before, for which you need to figure out the mechanism. You can do this by considering the bond changes necessary to convert the starting material into the product(s), and deciding on a reasonable set of curved arrows. In addition, consider the reactants: what have you seen them do in the past? Suggest a mechanism for the following reaction, which produces only the product shown.

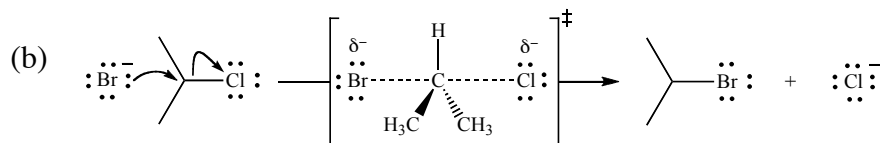


34. Unlike most other S_N2 reactions, the reaction of CH_3I with $(\text{CH}_3)_2\text{S}$ is actually *faster* in a protic solvent than in an aprotic solvent. Explain.

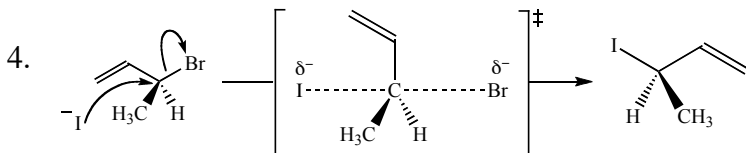
Practice Problems Solutions

- 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 presence of significant van der Waals repulsive forces created between the nucleophile and electrophile.

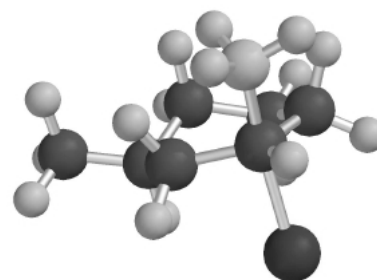
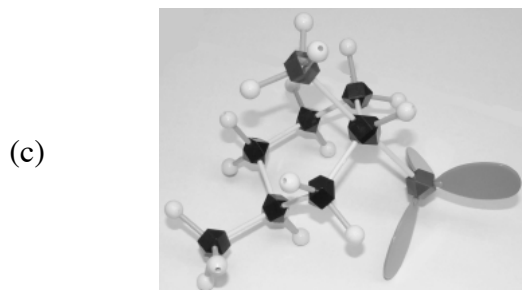
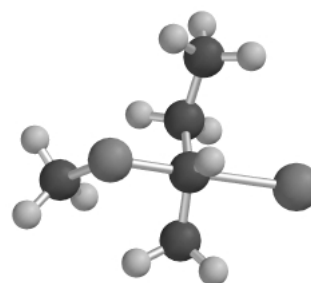
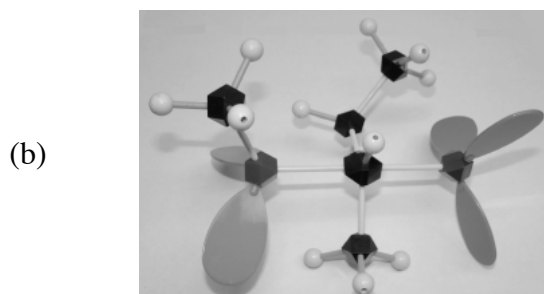
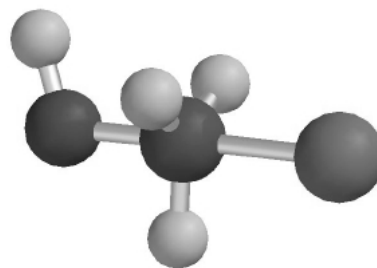
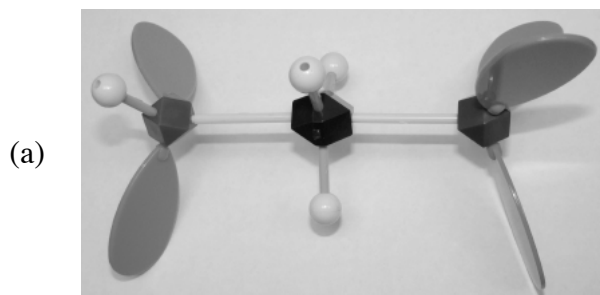
3. (a) $\text{Rate} = k [\text{R-Cl}] [\text{Br}^-]$

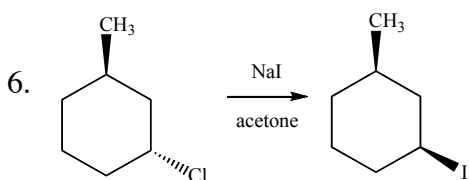


Your transition state drawing must clearly show the three-dimensional spatial arrangement of the groups attached to the carbon that bears the leaving group.



5. In the following models, lone pairs are depicted with orbital paddles. If your model does not appear to be the same as the answer shown here, try changing it's perspective. Make sure your model has the correct absolute configuration at the carbon with the nucleophile and leaving group. The computer-generated models may help you interpret the model photographs.





Note that inversion occurs only at the carbon attacked by the nucleophile and not at any other carbon.

- 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.
- 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 share electrons with an electrophile. Hydroxide ion (HO^-) and methoxide ion (CH_3O^-) do not have this resonance dilution of charge. (Alternately, upon reaction with an electrophile, acetate ion loses resonance stabilization whereas the other two do not.) Acetate ion is therefore worst nucleophile in this group.
- 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.

Atomic radius: Sulfur is larger than oxygen, so in an aprotic solvent the nucleophile that donates electrons from oxygen is 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.

Formal charge: When everything else is equal, a molecule bearing a negative charge is more nucleophilic or basic than one without. Thus, ethoxide ion ($\text{CH}_3\text{CH}_2\text{O}^-$) is more nucleophilic than its conjugate acid, ethanol ($\text{CH}_3\text{CH}_2\text{OH}$).

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

- The best nucleophiles are **in bold**.



- (c) $\text{CH}_3\text{I} + \text{NH}_3 \rightarrow \text{CH}_3\text{NH}_3^+ \text{I}^-$ (electronegativity)
- (d) $\text{CH}_3\text{OSO}_2\text{CF}_3 + \text{H}_2\text{N}^- \rightarrow \text{CH}_3\text{NH}_2 + ^-\text{OSO}_2\text{CF}_3$ (atomic radius; electronegativity)
- (e) $\text{CH}_3\text{CH}_2\text{I} + \text{CH}_3\text{CH}_2\text{O}^- \rightarrow (\text{CH}_3\text{CH}_2)_2\text{O} + \text{I}^-$ (atomic radius; inductive effect)
- (f) $\text{H}_2\text{C}=\text{CHCH}_2\text{Br} + \text{CH}_3\text{CH}_2\text{CH}_2\text{O}^- \rightarrow \text{H}_2\text{C}=\text{CHCH}_2\text{OCH}_2\text{CH}_2\text{CH}_3 + \text{Br}^-$ (inductive effect)
- (g) $\text{PhCH}_2\text{Br} + \text{HO}^- \rightarrow \text{PhCH}_2\text{OH} + \text{Br}^-$ (formal charge, atomic radius)
- (h) $\text{H}_2\text{C}=\text{CHCH}_2\text{Cl} + \text{CH}_3\text{CH}_2\text{CO}_2^- \rightarrow \text{H}_2\text{C}=\text{CHCH}_2\text{O}_2\text{CCH}_2\text{CH}_3 + \text{Cl}^-$ (inductive effect)

11. (a) Recall that nucleophilicity is strongly influenced by charge density at the atom that shares electrons to form the new covalent bond. Consider how various structural features influence the charge density of cyanide.

Formal charge: The carbon end of cyanide bears a formal negative charge whereas the nitrogen end is neutral. The formal charge enhances the nucleophilicity of cyanide ion, and suggests that the carbon end is more nucleophilic than the nitrogen end.

Resonance: Cyanide has just one significant resonance contributor, in which each atom has a lone pair and carbon bears a formal negative charge. The lack of resonance dispersion of negative charge enhances the nucleophilicity of cyanide ion.

Atomic radius: Carbon is a second-row element and thus bears a high electron density. This enhances nucleophilicity.

Electronegativity: Carbon's electronegativity is modest (2.5). This does not significantly enhance or decrease the nucleophilicity of cyanide ion.

Inductive effect: Nitrogen is more electronegative than carbon, so nitrogen is pulling some electron density from carbon. This dispersion of charge reduces the nucleophilicity somewhat.

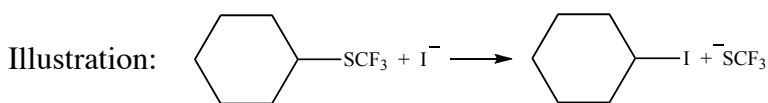
Steric effects: In an $\text{S}_{\text{N}}2$ reaction, steric effects can influence electrophiles as well as nucleophiles. Bulky nucleophiles cause transition state destabilization in the same way as bulky electrophiles. Cyanide ion is thin (like a spear) so it provides very little steric hindrance. This enhances the ion's nucleophilicity.

Hybridization: The carbon atom of cyanide is sp . Electrons in an sp orbital are held more tightly than electrons in sp^2 or sp^3 orbitals. (The orbital becomes more

diffuse with increasing p character. Electrons in more diffuse orbitals are further from the nucleus and thus not held as tightly.) This attenuates nucleophilicity.

(b) The major product depends upon which end of cyanide ion is more nucleophilic. The carbon end bears a formal negative charge whereas the nitrogen end is neutral. Carbon is less electronegative than nitrogen. Taken together these observations suggest that the carbon end of cyanide ion is more nucleophilic than the nitrogen end, so we predict the major product is acetonitrile.

12. The only difference between the reactions is the atom of the nucleophile that forms a bond with the carbon bearing the leaving group. Oxygen has a smaller atomic radius than sulfur. Because this is an atomic radius effect on nucleophilicity, we must also consider the solvent (CH_3OH), which is protic. A protic solvent forms hydrogen bonds with the nucleophile. The strength of these hydrogen bonds is controlled by charge density. Oxygen is smaller than sulfur, so oxygen has greater charge density and therefore forms stronger hydrogen bonds. These hydrogen bonds are broken when the solvent moves out of the way as the nucleophile approaches the electrophile. The stronger hydrogen bonds formed by CH_3O^- cost more energy to break than the hydrogen bonds to CH_3S^- . Therefore the CH_3O^- activation energy is higher than the CH_3S^- case, and the CH_3O^- reaction is slower.
13. A good leaving group is stable after departure, because it can easily accommodate the lone pair that was once the electrons that once were the carbon-leaving group bond. The three electron-withdrawing fluorine atoms of trifluoromethanethiolate (CF_3S^-) help stabilize the negative charge by the inductive effect, making the negative charge of trifluoromethanethiolate more stable than the negative charge of methanethiolate (CH_3S^-). Therefore trifluoromethanethiolate is predicted to be the best leaving group.



14. Carbon and fluorine are both second-row elements so their atomic radii are about equal. Fluorine is more electronegative than carbon, so fluorine can accommodate the formal negative charge more effectively than carbon. We know that fluorine is a very poor leaving group, so methanide (CH_3^-) must be even worse than “very poor.”
15. **Best:** Trifluoromethanesulfonate ion (CF_3SO_3^- , also called triflate) has three resonance contributors and the inductive effect (electron withdrawing) of the CF_3 group, resulting in very effective dispersion of the negative charge.

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

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

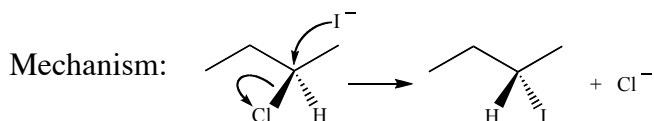
- The rate of an $\text{S}_{\text{N}}2$ reaction is influenced by the degree of steric hindrance at the carbon undergoing substitution. Increasing the degree of substitution at this carbon makes the reaction slower. In isopropyl iodide, $(\text{CH}_3)_2\text{CHI}$, this carbon is secondary (2°) and thus isopropyl iodide reacts more slowly than ethyl iodide ($\text{CH}_3\text{CH}_2\text{I}$; primary) or methyl iodide (CH_3I ; methyl).
- If the reaction occurs by the $\text{S}_{\text{N}}2$ mechanism, the first reaction is the slowest because the carbon bearing the leaving group is more sterically hindered. *A reaction rate of zero is less than a reaction rate of 'slow'.*
- Dielectric constant (ϵ) is controlled by molecular structure. A molecule with a greater percentage of polar bonds versus nonpolar bonds has a greater dielectric constant. Water consists of two polar O–H bonds and no nonpolar 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: $\text{CH}_3\text{CH}_2\text{OH}$ $\epsilon = 25$, 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.

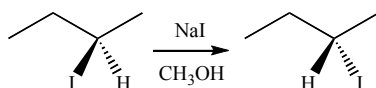
- $\text{S}_{\text{N}}2$ reactions work best on substrates that are less hindered. Thus we rank CH_3I (methyl) as fastest. We might rank isopropyl fluoride (secondary) second fastest, but fluoride ion a very poor leaving group; so poor that $\text{S}_{\text{N}}2$ reactions in which fluoride is the leaving group are very slow and therefore exceptionally rare. The other two molecules are tertiary at the reacting carbon, so they do not undergo $\text{S}_{\text{N}}2$ reactions. Thus CH_3I is fastest and the other three are slower because they don't react at all (the reaction rates are zero).
- These molecules differ in leaving group as well as the degree of substitution at the carbon attacked by the nucleophile. 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 reacts the slowest in an $\text{S}_{\text{N}}2$ reaction is 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 reacts the slowest. (Either answer is acceptable.)

A rate of zero (i.e., no reaction) is slower than any other rate, including very slow.

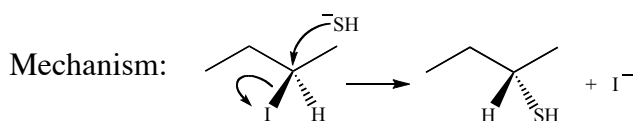
21. (a) Iodide ion has a greater atomic radius than chloride ion, and in a protic solvent (CH_3OH) is more nucleophilic, so the first reaction is faster.



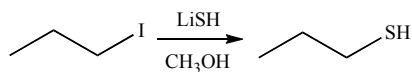
Changing chloride to a better leaving group (iodide) makes the reaction go faster.



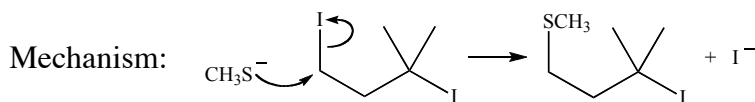
- (b) Iodide ion has a larger atomic radius than chloride ion, so iodide ion is a better leaving group. The second reaction is faster.



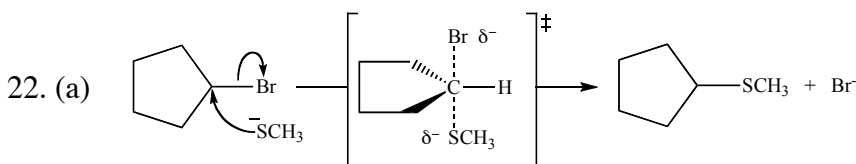
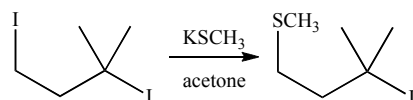
Changing the 2° halide to a 1° halide makes an $\text{S}_{\text{N}}2$ reaction go faster, because of reduced steric hindrance to nucleophilic attack.

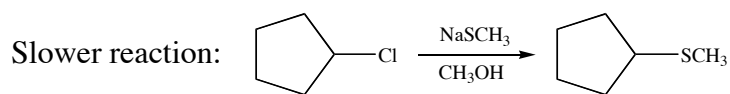


- (c) An $\text{S}_{\text{N}}2$ reaction is sensitive to steric crowding. The second reaction is substitution of a 3° iodide, which does not proceed at all by the $\text{S}_{\text{N}}2$ mechanism. The first reaction, substitution at a 1° carbon, is therefore the faster one.

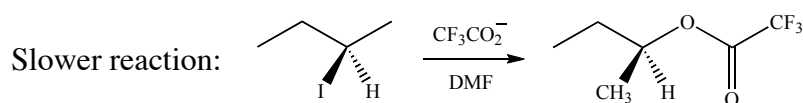
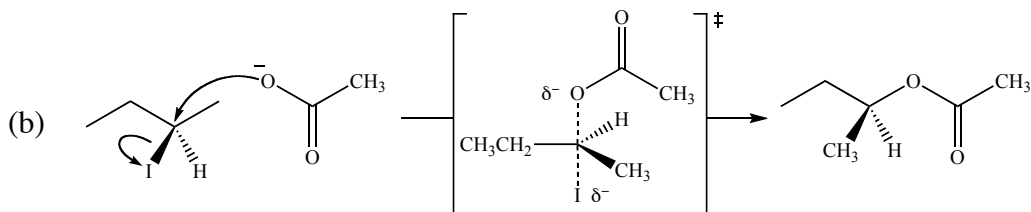


Changing to a less polar solvent increases $\text{S}_{\text{N}}2$ reaction rate when the nucleophile bears a formal negative charge and the electrophile is neutral. The new solvent must still be sufficiently polar to dissolve $\text{K}^+ \text{SCH}_3^-$ (an ionic compound). Acetone ($\epsilon = 21$) is less polar than DMF ($\epsilon = 37$), but still dissolves many ionic substances.

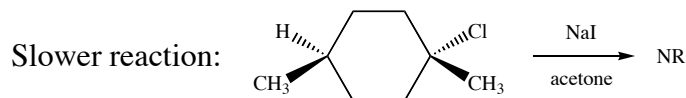
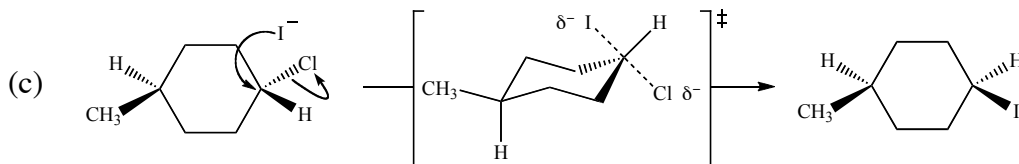




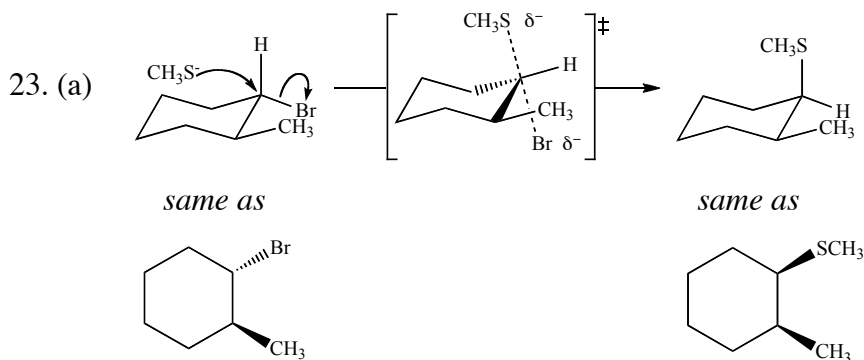
This reaction is slower because chloride ion is a poorer leaving group than bromide ion.



This reaction is slower because trifluoroacetate ion (CF_3CO_2^-) is a poorer nucleophile than acetate ion.

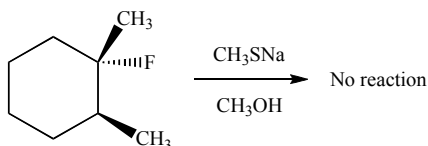


This reaction is slower because a tertiary alkyl halide is more sterically hindered than a secondary alkyl halide. (The reaction is slow that it does not give any detectable amounts of product, hence the label “NR”, which means “no reaction.”)

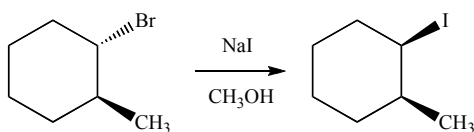


(b) Any change in the electrophile that slows the reaction is acceptable. For example, changing Br to F (a very poor leaving group) or adding steric hindrance to the

carbon undergoing nucleophilic attack (changing a secondary carbon into a tertiary carbon) shuts down the S_N2 mechanism.

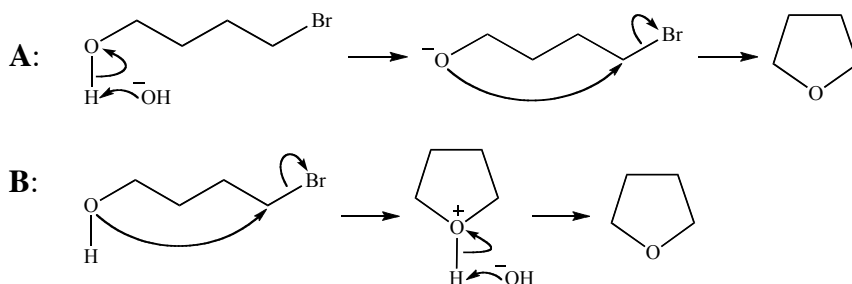


- (c) Any change in the nucleophile that makes the reaction faster is acceptable. Replacing methanethiolate with a nucleophile that suffers less hydrogen bonding (iodide ion) is one solution. (Changing the solvent may change nucleophilicity but it does not change the nucleophile itself.)

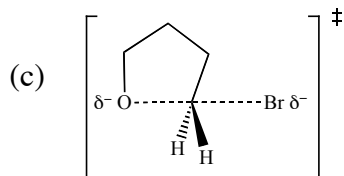


24. We need to consider the differences between the three reactions, and how these differences influence the rate of an S_N2 reaction. In 2-iodo-2-methylpropane (also called *tert*-butyl iodide) the leaving group is bonded to a tertiary carbon, whereas in 2-bromopropane and 2-chloropropane the leaving group is bonded to a secondary carbon. 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 S_N2 reaction occurs. Thus, 2-iodo-2-methylpropane the slowest of the three. 2-Bromopropane and 2-chloropropane differ in their leaving groups. Bromide ion is a better leaving group than chloride ion because bromide ion has a larger atomic radius and can disperse the charge more effectively. Thus 2-bromopropane reacts faster than 2-chloropropane. Therefore the rate ranking is: 2-bromopropane > 2-chloropropane > 2-iodo-2-methylpropane.

25. (a) Mechanism possibilities:



- (b) Due to formal charge, an alkoxide ion (RO^- ; mechanism **A**) is more nucleophilic than an alcohol (mechanism **B**). Therefore mechanism **A** occurs more quickly (i.e., is the pathway most of the reactants follow to become the given product.)

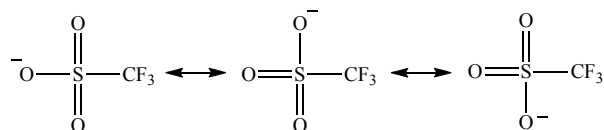


(d) This is a two-step mechanism in which the first step (the proton transfer) is much faster than the substitution (second step). Therefore the second step is rate determining. (We will discuss this issue in greater depth during our studies of the S_N1 reaction.) Therefore the rate expression is $\text{rate} = k [\text{RO}^-]$. Even though the rate expression is unimolecular, it is still categorized as an S_N2 reaction because it is ionic substitution at an sp^3 carbon without the intermediacy of a carbocation.

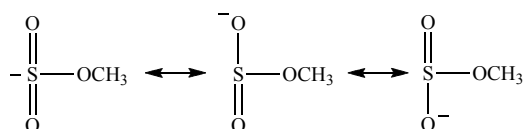
(e) Intermolecular S_N2 with HO^- can form 1,4-butanediol, $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$

26. The reaction products arise from attack by the same nucleophile (iodide ion) at a different site on the electrophile. There are two fundamental differences between these reaction pathways.

Leaving group: Triflate (CF_3SO_3^-) gains three significant and energetically equal (degenerate) resonance contributors upon departure.

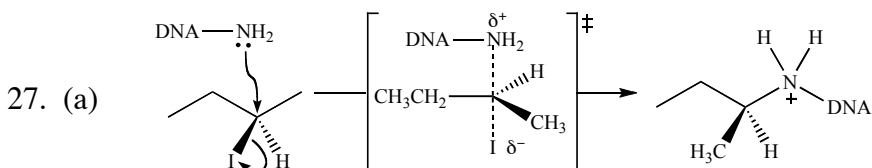
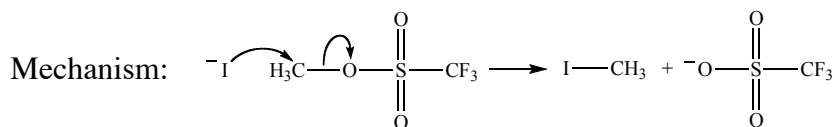


Methyl sulfite ($\text{CH}_3\text{OSO}_2^-$) gains three significant but energetically unequal resonance contributors upon departure.



Recall that degenerate resonance contributors provide more stabilization than do resonance contributors that are not degenerate. (Review the resonance tutorial on the course website if needed.) Therefore CF_3SO_3^- delocalizes its negative charge more evenly (and is thus more stable) than $\text{CH}_3\text{OSO}_2^-$. Triflate is the better leaving group.

Steric effects: Fluorine (van der Waals radius 1.35 \AA) is a bit larger than hydrogen (van der Waals radius 1.2 \AA), so attack at the CF_3 group suffers a bit more steric hindrance than attack at the CH_3 group. (The difference is much smaller than the difference between a CH_3 and a primary carbon.)

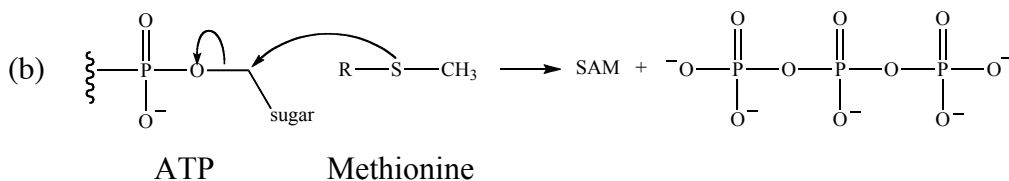


(b) Assuming the DNA alkylation reaction is an S_N2 process, *tert*-butyl iodide is unreactive because it is a tertiary haloalkane and thus too sterically hindered to allow the nucleophile to approach the backside of the carbon-iodine bond.

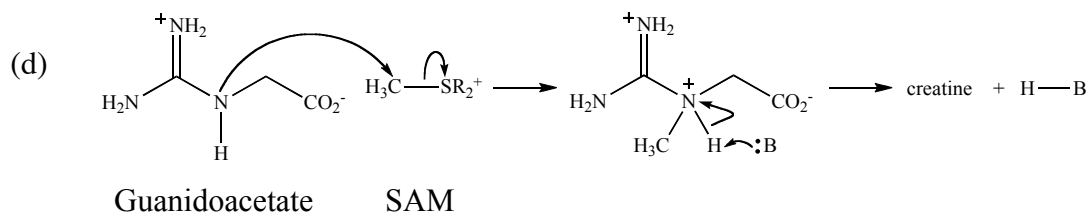
(c) Reason #1: The carbon in magic methyl that bears the leaving group (a methyl carbon) is less sterically hindered than the corresponding carbon in 2-iodobutane (a secondary carbon).

Reason #2: Fluorosulfonate ion (FSO_3^-) is a better leaving group than iodide ion due to a combination of resonance and the inductive effect of the fluorine atom.

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



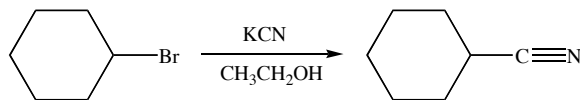
(c) Alkylation at oxygen disrupts the resonance stabilization of the carboxylate ion (RCO_2^-). Alkylation at sulfur does not detract from the existing resonance.



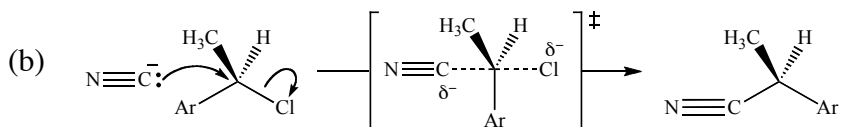
B: is a base of some sort, most probably a nitrogen-containing functional group such as primary amine within the enzyme active site where this reaction occurs.

29. This reaction cannot occur as written because the carbon atom that gains the nitrile group (CN) has eight electrons to begin with. Forming a new bond to the nitrile group without losing an existing bond results in a pentavalent carbon (ten electrons). The reaction also cannot occur as written because hydride ion (H^-) is not a leaving group

(except in the Chichibabin reaction). One way to rewrite this as a valid reaction is to show the Br leaving (an S_N2 reaction).



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

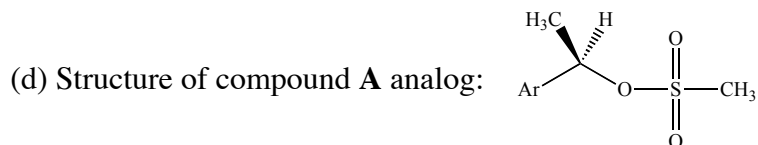


Use models to convince yourself that the product shown here is the same as product C. The only difference is the perspective from which the molecule is viewed.

(c) An S_N2 reaction requires:

- Moderate or better 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;
- The carbon that accepts the nucleophile cannot be tertiary: it is secondary in this case, and
- Solvent: The solvent is sufficiently polar (ethanol $\epsilon = 25$). It is also protic. Hydrogen bonding hinders (but does not necessarily prevent) cyanide ion from being a nucleophile.

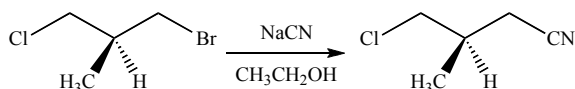
Thus we conclude this is a reasonable S_N2 reaction.



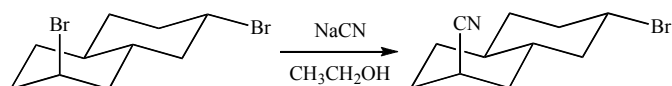
Methanesulfonate ion (CH_3SO_3^-) is a better leaving group than chloride ion due to resonance stabilization of the negative charge. (Other answers may also be acceptable.)

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

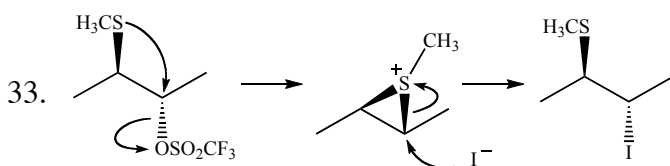
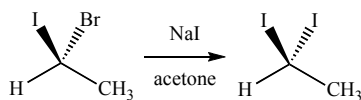
31. (a) Bromide ion is a better leaving group than chloride ion.



(b) Exploration with a model shows that approach to the backside of the axial C–Br bond is less sterically hindered than the equatorial C–Br bond.



32. There are several ways to achieve this, for example, when the stereocenter has an atom or group that is the same as the nucleophile.



A standard S_N2 mechanism is not consistent with the stereochemistry of the major product. Using a model will help you following the stereochemistry of this mechanism. This is an example of neighboring group participation (also called anchimeric assistance).

34. A protic solvent stabilizes a nucleophile to a greater extent than it stabilizes the transition state, because the nucleophile usually has a full negative formal charge whereas the charge in the transition state is a mere δ⁻. Compared to an aprotic solvent, this results in a larger ΔG[‡], and thus a slower reaction rate. Methyl iodide and (CH₃)₂S do not have a negative formal charge or a neutral oxygen or nitrogen atom, so they do not form hydrogen bonds. The transition state of this reaction has δ⁻ on the leaving group (iodide ion), so the transition state does enjoy some hydrogen bonding stabilization from the protic solvent. Because the transition state gains hydrogen bonding stabilization and the reactants do not, ΔG[‡] is decreased, and the reaction is faster.