

11.3: CHARACTERISTICS OF THE S_N2 REACTION

OBJECTIVES

After completing this section, you should be able to

1. discuss the role of steric effects in S_N2 reactions.
2. arrange a given series of alkyl halides in order of increasing or decreasing reactivity towards nucleophilic substitution through the S_N2 mechanism.
3. suggest a reason why vinyl halides and aryl halides do not undergo S_N2 reactions.
4. discuss how the nature of the nucleophile affects the rate of an S_N2 reaction.
5. arrange a given series of common nucleophiles (e.g., CN⁻, I⁻, Br⁻, Cl⁻, H₂O) in order of increasing or decreasing nucleophilicity.
6. discuss how the nature of the leaving group affects the rate of an S_N2 reaction.
7. arrange a given series of leaving groups in order of increasing or decreasing ability to leave during an S_N2 reaction.
8. discuss the role played by the solvent in an S_N2 reaction.
9. give examples of the solvents which are commonly used for S_N2 reactions, and identify those that promote a high reaction rate.
10. predict which of two given S_N2 reactions will proceed faster, by taking into account the structure of the substrates, the nucleophiles involved, leaving-group ability, solvent effects, or any combination of these factors.

KEY TERMS

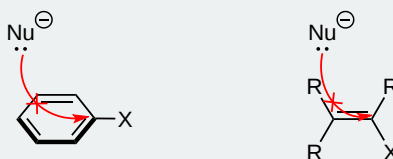
Make certain that you can define, and use in context, the key terms below.

- leaving group
- polar aprotic solvent
- solvation

STUDY NOTES

You may wish to review the discussion of acid-base theory given in Sections 2.7-2.11.

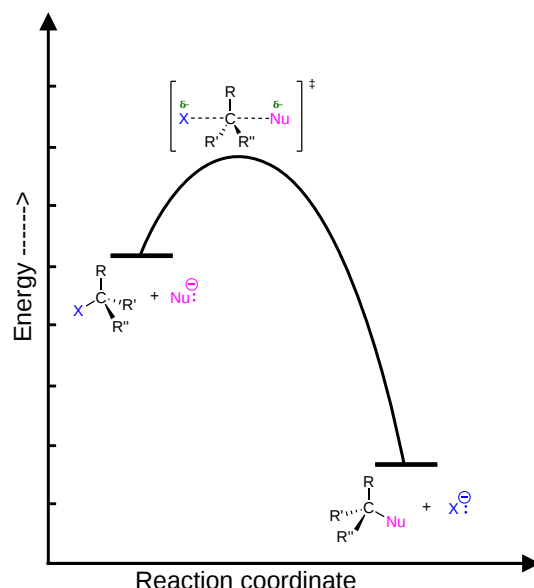
Both aryl and vinylic halides are relatively unreactive in S_N2 displacement mechanisms, mostly because during the backside attack of the molecule the incoming nucleophile is sterically hindered by both substituents and electron density from any double bonds present. Also, leaving groups on sp²-hybridized carbons tend to be held tighter than sp³-hybridized carbons.



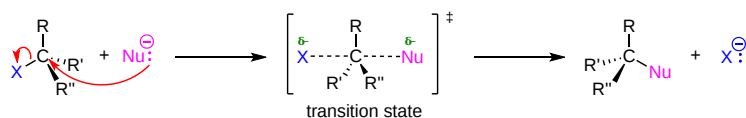
Solvation may be defined as the interaction between molecules of solvent and particles of solute. The result of solvation is to stabilize (i.e., lower the energy of) the solute particles. Solvents with lone pairs of electrons are good at solvating cations. Protic (i.e., hydroxylic) solvents are able to solvate anions through hydrogen bonding. As water has two lone pairs of electrons and is also protic, it is good at solvating both anions and cations.

POTENTIAL ENERGY DIAGRAM FOR AN S_N2 REACTION

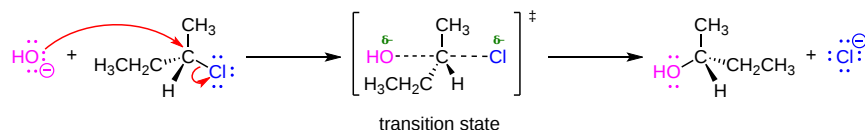
The potential energy diagram for an S_N2 reaction is shown below. This is a single-step, concerted process so a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. For an S_N2 reaction the transition state directly determines the energy of activation which must be overcome for the reaction to occur. Factors which affect the stability of the transition state affect the rate of the S_N2 reaction.



For an S_N2 reaction, the transition state represents the half way point of the reaction. The C-Nu bond is in the process of forming and is represented by a dashed bond. The X-C bond is in the process of breaking and is also represented by a dash bond. The negative charge of the nucleophile is in the process of being transferred to the leaving groups. This is represented by both the nucleophile and the leaving group having a partial negative charge. The electrophilic carbon and the three 'R' substituents all lie on the same plane. Brackets and a double-dagger are placed around the structure to represent that it is a transition state.

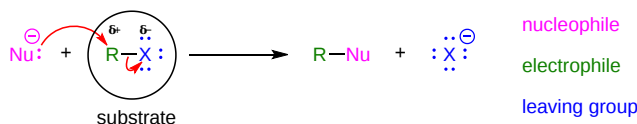


EXAMPLE

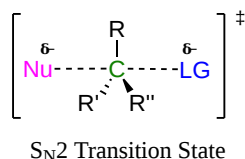


STERICALLY HINDERED SUBSTRATES WILL REDUCE THE S_N2 REACTION RATE

Steric hindrance about the electrophilic carbon, is one of the most important factors Determining the rate of S_N2 reactions. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below we are most interested in the electrophilic carbon that bears the leaving group.



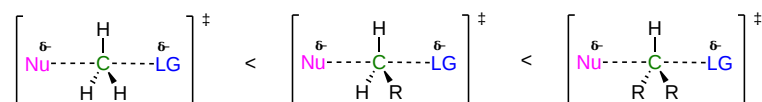
The S_N2 **transition state** is very crowded. Recall that there are a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.



If each of the three substituents were hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion created in the planar portion of the transition state thereby increasing the ease at which the nucleophilic substitution reaction occurs. If one of the hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion created

in the planar portion of the transition state. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion in the transition state.

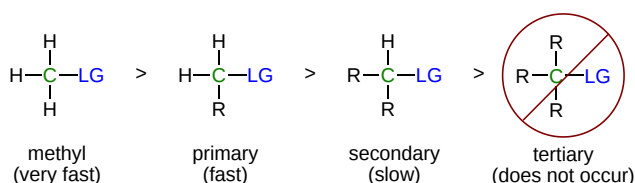
Steric repulsion of S_N2 Transition States



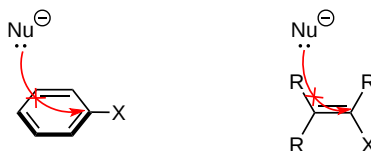
How does steric hindrance affect the rate at which an S_N2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. The increases steric hindrance destabilizes the transition state causing it to become higher in energy. This in turn increases the energy of activation and decreases the reaction rate.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.

S_N2 Displacement Reactivity of Haloalkanes

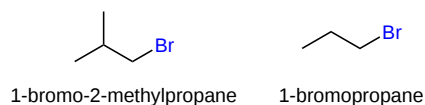


Vinyl and aryl halides are unreactive toward S_N2 displacement due to extreme steric factors. To perform an S_N2 reaction, the incoming nucleophile would have to enter the plane of the C-C double bond and move through the molecule to achieve the backside displacement required.



In addition to alkyl groups being added to the electrophilic carbon, it turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 1-bromo-2-methylpropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.



If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

THE NUCLEOPHILE

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates.

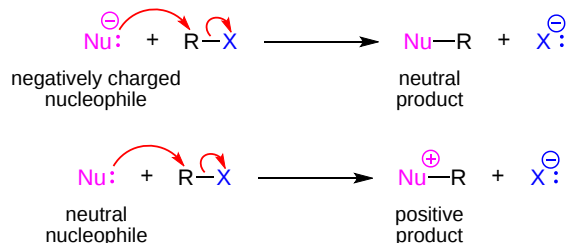
When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it. Basicity refers to the ability of a base to accept a proton. Basicity may be related to the pK_a of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and vice versa. The range of basicities included in the following table is remarkable, covering over fifty powers of ten! In general, as the pK_a of the conjugate acid increases the base becomes a stronger nucleophile. This, however, is not always the case.

Base	I ⁽⁻⁾	Cl ⁽⁻⁾	H ₂ O	CH ₃ CO ₂ ⁽⁻⁾	RS ⁽⁻⁾	CN ⁽⁻⁾	RO ⁽⁻⁾	NH ₂ ⁽⁻⁾	CH ₃ ⁽⁻⁾
Conj. Acid	HI	HCl	H ₃ O ⁽⁺⁾	CH ₃ CO ₂ H	RSH	HCN	ROH	NH ₃	CH ₄
pK _a	-9	-7	0.0	4.8	8	9.1	16	33	48

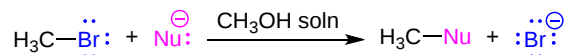


Nucleophilicity is a more complex property. Any compound, neutral or charged, which has lone pair electrons can act a neucophile. After a S_N2 reaction neutral nucleophiles make a positively charges products and negatively charged nucleophiles make neutral products. In general, negatively charges compound tend to make better nucleophilies.



Specifically, nucleophilicity refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH₃-Br. The nucleophilicity of the Nu⁽⁻⁾ reactant in the following substitution reaction varies as shown in the chart below:

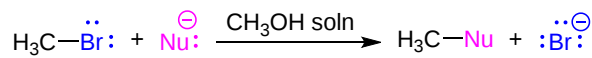
Nucleophilicity is a more complex property. It commonly refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH₃-Br. Thus the nucleophilicity of the Nu⁽⁻⁾ reactant in the following substitution reaction varies as shown in the chart below:



NUCLEOPHILICITY: H₂O < CH₃CO₂⁽⁻⁾ < NH₃ < Cl⁽⁻⁾ < Br⁽⁻⁾ < HO⁽⁻⁾ < CH₃O⁽⁻⁾ < I⁽⁻⁾ < CN⁽⁻⁾ < CH₃S⁽⁻⁾



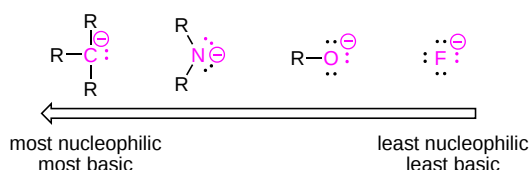
The versatility of the S_N2 reaction is shown by the wide variety of functional groups which can be formed.



Nucleophile			Products	
Formula	Name	Formula	Name	Functional Group
CH ₃ S ⁽⁻⁾	Methanethiolate	CH ₃ SCH ₃	Dimethylsulfide	Sulfide
CN ⁽⁻⁾	Cyanide	CH ₃ CN	Acetonitrile	Nitrile
I ⁽⁻⁾	Iodide	CH ₃ I	Iodomethane	Alkyl Halide
CH ₃ O ⁽⁻⁾	Methoxide	CH ₃ OCH ₃	Diethylether	Ether
HO ⁽⁻⁾	Hydroxide	CH ₃ OH	Methanol	Alcohol
Br ⁽⁻⁾	Bromide	CH ₃ Br	Bromomethane	Alkyl Halide
Cl ⁽⁻⁾	Chloride	CH ₃ Cl	Chloromethane	Alkyl Halide
NH ₃	Ammonia	CH ₃ NH ₃ ⁽⁺⁾	Methylammonium ion	Ammonium
CH ₃ CO ₂ ⁽⁻⁾	Acetate	CH ₃ O ₂ CH ₃	Methyl acetate	Ester
H ₂ O	Water	CH ₃ OH ₂ ⁽⁺⁾	Methylhydronium ion	Protonated Alcohol

PERIODIC TRENDS IN NUCLEOPHILICITY

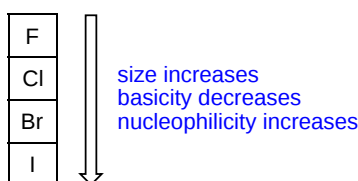
There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:



The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond. This horizontal trend also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.

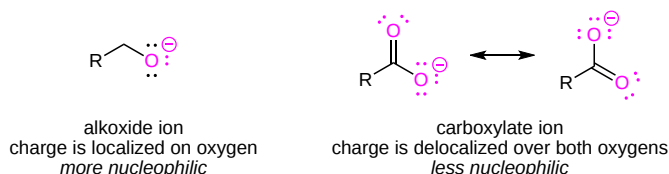
Recall that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons and act as a nucleophile.

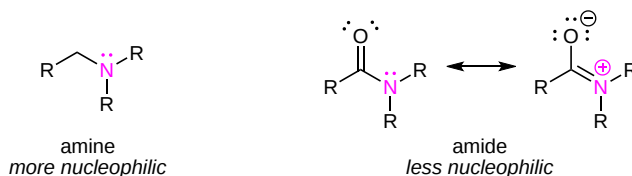


RESONANCE EFFECTS ON NUCLEOPHILICITY

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.



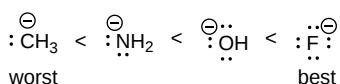
The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



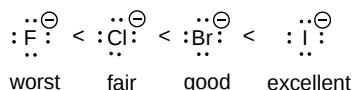
THE LEAVING GROUP

As Electronegativity Increases, The Ability of the Leaving Group to Leave Increases

As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basicity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing CH_3^- to be the worst leaving group and F^- to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that $\text{S}_{\text{N}}2$ reactions of fluoroalkanes are rarely observed.

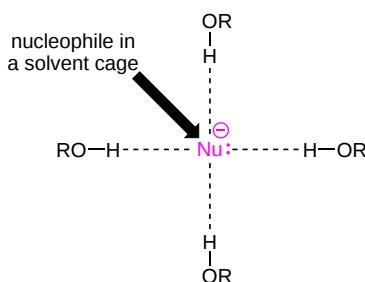


As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.



INFLUENCE OF THE SOLVENT IN AN S_N2 REACTION

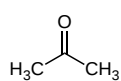
The rate of an S_N2 reaction is significantly influenced by the solvent in which the reaction takes place. The use of **protic solvents** (those, such as water or alcohols, with hydrogen-bond donating capability) decreases the power of the nucleophile, because of strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile. In order for the nucleophile to attack the electrophile, it must break free, at least in part, from its solvent cage. A less powerful nucleophile in turn means a slower S_N2 reaction. S_N2 reactions are faster in **polar, aprotic solvents**: those that lack hydrogen-bond donating capability.



Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not solvate an a charged (or highly polar) nucleophile at all. That is why chemists use polar aprotic solvents for nucleophilic substitution reactions in the laboratory: they are polar enough to solvate the nucleophile, but not so polar as to lock it away in an impenetrable solvent cage. In addition to acetone, three other commonly used polar aprotic solvents are acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).

Below are several polar aprotic solvents that are commonly used in the laboratory:

Polar Aprotic Solvents



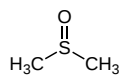
acetone



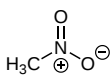
ethanenitrile
(acetonitrile)



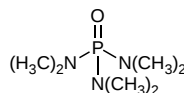
N,N-dimethylformamide
(DMF)



dimethyl sulfoxide
(DMSO)



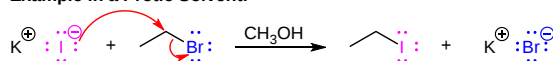
nitromethane



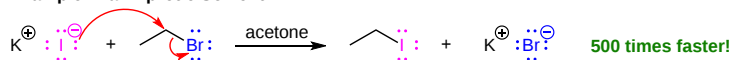
hexamethylphosphoric triamide
(HMPA)

These aprotic solvents are polar but, because they do not form hydrogen bonds with the anionic nucleophile, there is a relatively weak interaction between the aprotic solvent and the nucleophile. By using an aprotic solvent we can raise the reactivity of the nucleophile. This can sometimes have dramatic effects on the rate at which a nucleophilic substitution reaction can occur. For example, if we consider the reaction between bromoethane and potassium iodide, the reaction occurs 500 times faster in acetone than in methanol.

Example in a Protic Solvent:



Example in an Aprotic Solvent:



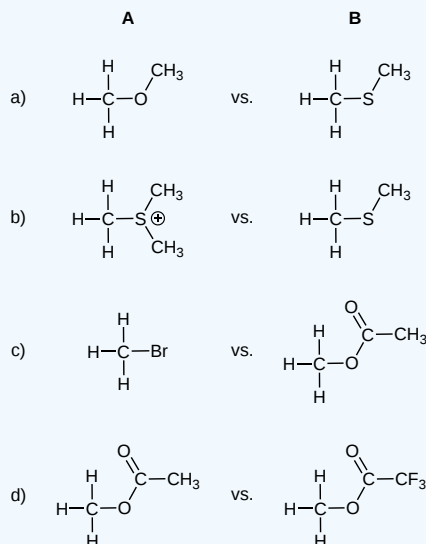
SUMMARY OF FACTORS IN AFFECTING S_N2 REACTIONS

There are four main factors which affect S_N2 reaction:

- 1) The structure of the alkyl portion of the substrate: S_N2 reactions are affected by steric hindrance around the electrophilic carbon. As steric hindrance increases the rate of S_N2 reactions decrease. Methyl and primary substrates work well for S_N2 reactions, secondary substrates react slowly, and tertiary substrates do not undergo S_N2 reactions at all.
- 2) The reactivity of the nucleophile: The rate of S_N2 reaction is increased when strong nucleophiles are used. Strong nucleophiles tend to be negatively charged and good bases. Also, being of an increases size tends to increase the nucleophilicity of an atom.
- 3) The nature of the leaving group: The rate of S_N2 reaction is increased when leaving groups are used in the substrate. Good leaving groups tend to stabilize the electrons gained during an S_N2 reaction. High electronegativity, resonance, and an increases size all can stabilize electrons.
- 4) The solvent: S_N2 reaction are severely hindered when a polar protic solvent is used for the reaction. Instead, polar aprotic solvents tend to be used for S_N2 reaction.

11.3.1 EXAMPLE

In each pair (A and B) below, which electrophile would be expected to react more rapidly in an S_N2 reaction with the thiol group of cysteine as the common nucleophile?



Solution (8.13)

? EXERCISE 11.3.1

1) What product(s) do you expect from the reaction of 1-bromopentane with each of the following reagents in an S_N2 reaction?

- KI
- NaOH
- CH₃C≡C-Li
- NH₃

2)

Which in the following pairs is a better nucleophile?

- (CH₃CH₂)₂N⁻ or (CH₃CH₂)₂NH

b) $(\text{CH}_3\text{CH}_2)_3\text{N}$ or $(\text{CH}_3\text{CH}_2)_3\text{B}$

c) H_2O or H_2S

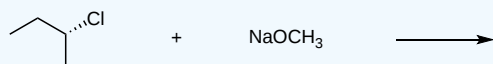
3) Order the following in increasing reactivity for an $\text{S}_\text{N}2$ reaction.

$\text{CH}_3\text{CH}_2\text{Br}$ $\text{CH}_3\text{CH}_2\text{OTos}$ $(\text{CH}_3\text{CH}_2)_3\text{CCl}$ $(\text{CH}_3\text{CH}_2)_2\text{CHCl}$

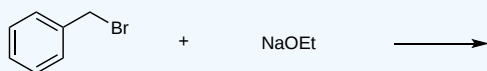
4) Solvents benzene, ether, chloroform are non-polar and not strongly polar solvents. What effects do these solvents have on an $\text{S}_\text{N}2$ reaction?

5) Predict the products of these nucleophilic substitution reactions, including stereochemistry when appropriate.

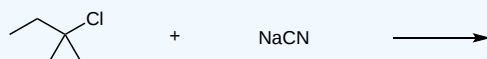
a)



b)



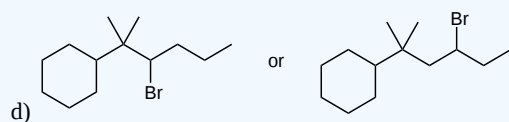
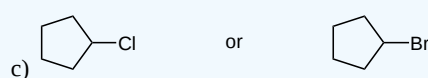
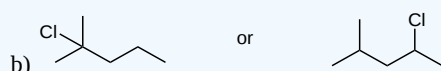
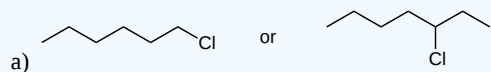
d)



d)

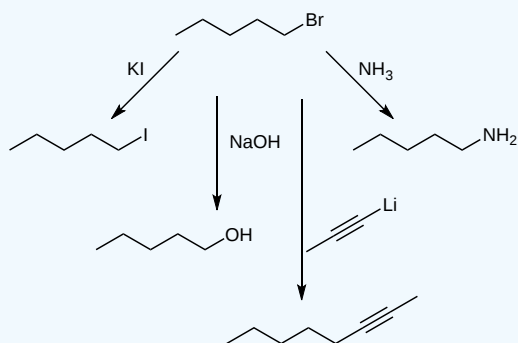


6) Predict which compound in each pair would undergo the $\text{S}_\text{N}2$ reaction faster.



Answer

1)



2)

a) $(\text{CH}_3\text{CH}_2)_2\text{N}^-$ as there is a charge present on the nitrogen.

b) $(\text{CH}_3\text{CH}_2)_3\text{N}$ because a lone pair of electrons is present.

c) H_2O as oxygen is more electronegative.

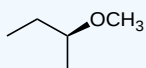
3)

$(\text{CH}_3\text{CH}_2)_3\text{CCl}$ OR $(\text{CH}_3\text{CH}_2)_2\text{CHCl}$ < $\text{CH}_3\text{CH}_2\text{Br}$ < $\text{CH}_3\text{CH}_2\text{OTos}$

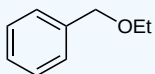
4) They will decrease the reactivity of the reaction.

5)

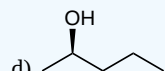
a)



b)



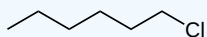
c) No reaction



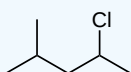
d)

6)

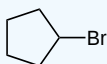
a)



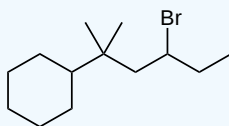
b)



c)



d)



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