

7.6: CHARACTERISTICS OF THE S_N2 REACTION

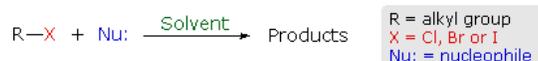


Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N2 reactions
- predict the products and specify the reagents for S_N2 reactions with stereochemistry
- propose mechanisms for S_N2 reactions
- draw and interpret Reaction Energy Diagrams for S_N2 reactions

INTRODUCTION

To understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation where X represents the leaving group (a halide for this chapter).



In order of decreasing importance, the factors impacting S_N2 reaction pathways are

- 1) structure of the alkyl halide
- 2) strength of the nucleophile
- 3) stability of the leaving group
- 4) type of solvent.

The bimolecular transition state of the S_N2 pathway means that sterics are a primary consideration. The orbitals of the nucleophile must be able to penetrate through the reaction solution and create orbital overlap with the orbitals of the electrophilic carbon. The sterics of this mechanism can be determined by applying the bonding theories for individual compounds and ions to the interaction of the nucleophile and electrophile. The strength of the nucleophile will also influence the reaction along with the stability of the leaving group. Solvents can have a subtle yet measurable effect on S_N2 pathway. *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. The role of the solvent is often misunderstood and consequently given way too much importance. Do not drown in the solvent. Solvation effects are less significant than the structure of the alkyl halide, the reactivity of the nucleophile, and the stability of the leaving group.

The following variables and observables can be used to study the S_N2 mechanism.

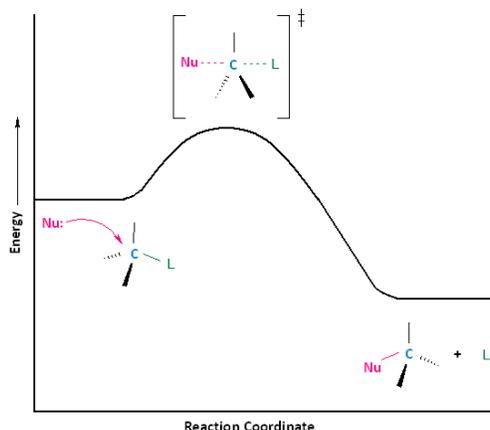
Variables	R change α-carbon from 1° to 2° to 3°
	if the α-carbon is a chiral center, set as (R) or (S)
	X change from Cl to Br to I (F is relatively unreactive)
Observables	Nu: change from anion to neutral; change basicity; change polarizability
	Solvent polar vs. non-polar; protic vs. non-protic
	Products substitution, elimination, no reaction.
	Stereospecificity if the α-carbon is a chiral center what happens to its configuration?
	Reaction Rate measure as a function of reactant concentration.

When several reaction variables may be changed, it is important to isolate the effects of each during the course of study. In other words: **only one variable should be changed at a time**, the others being held as constant as possible. For example, we can examine the effect of changing the halogen substituent from Cl to Br to I, using ethyl as a common R-group, cyanide anion as a common nucleophile, and ethanol as a common solvent. We would find a common substitution product, C₂H₅-CN, in all cases, but the speed or rate of the reaction would increase in the order: Cl < Br < I. This reactivity order reflects both the strength of the C-X bond, and the stability of X⁽⁻⁾ as a leaving group, and leads to the general conclusion that alkyl iodides are the most reactive members of this functional class.

BIMOLECULAR NUCLEOPHILIC SUBSTITUTION REACTIONS ARE CONCERTED

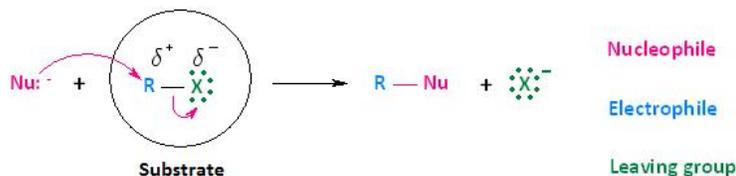
Bimolecular nucleophilic substitution (S_N2) reactions are **concerted**, meaning they are a **one step process**. The bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the halogen.

The potential energy diagram for an S_N2 reaction is shown below. The one-step mechanism means that only 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.



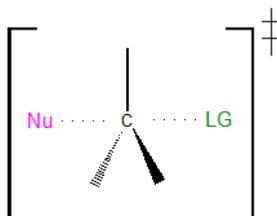
ALKYL HALIDE (SUBSTRATE) STRUCTURE AND S_N2 REACTION RATES

Now that we have discussed the effects that the leaving group, nucleophile, and solvent have on biomolecular nucleophilic substitution (S_N2) reactions, it's time to turn our attention to how the substrate affects the reaction. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below, we will be paying particular attention to the alkyl portion of the substrate. In other words, we are most interested in the electrophilic center that bears the leaving group.



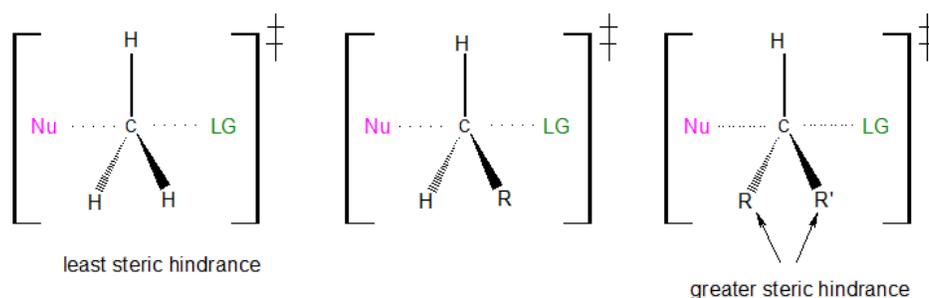
The S_N2 transition state is very crowded with a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.

S_N2 Transition State



If each of the three substituents in this transition state were small hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion between the incoming nucleophile and the electrophilic center, thereby increasing the ease at which the nucleophilic substitution reaction can occur. Remember, for the S_N2 reaction to occur, the nucleophile must be able to overlap orbitals with the electrophilic carbon center, resulting in the expulsion of the leaving group. 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 with the incoming nucleophile. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion with the incoming nucleophile.

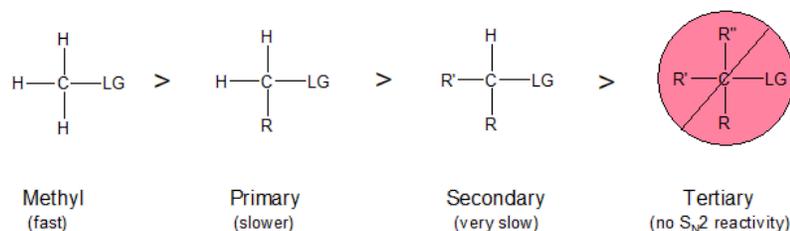
Alkyl Halide Structure and the S_N2 Transition State



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. This is because the addition of one or two R groups shields the backside of the electrophilic carbon impeding nucleophilic penetration.

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.

Alkyl Halide Structure and S_N2 Relative Reactivity



SUBSTITUTES ON NEIGHBORING CARBONS SLOW NUCLEOPHILIC SUBSTITUTION REACTIONS

Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

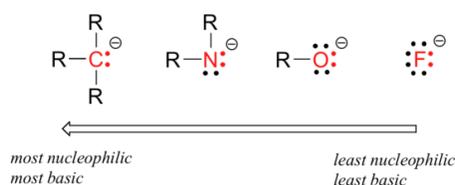
In the example below, 2-methyl-1-bromopropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.



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.

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:



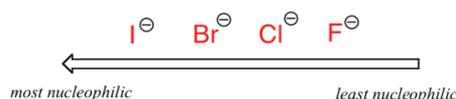
The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond. This horizontal trend also tells us that amines are more nucleophilic 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).

The vertical periodic trend for nucleophilicity is somewhat more complicated because the solvent can influence the nucleophilicity trend in either direction. Let's take the simple example of the S_N2 reaction below:



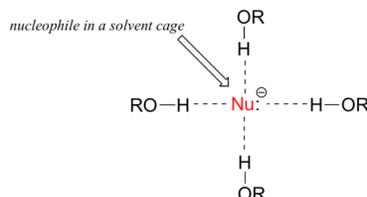
...where Nu⁻ is one of the halide ions: fluoride, chloride, bromide, or iodide, and the leaving group I* is a radioactive isotope of iodine (which allows us to distinguish the leaving group from the nucleophile when both are iodide). If this reaction is occurring in a **protic solvent** (that is, a solvent that has a hydrogen bonded to an oxygen or nitrogen - water, methanol and ethanol are the most important examples), then the reaction will go fastest when iodide is the nucleophile, and slowest when fluoride is the nucleophile, reflecting the relative strength of the nucleophile.



Relative nucleophilicity in a protic solvent

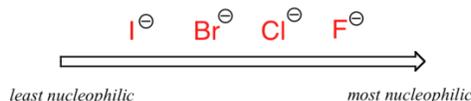
This of course, is opposite that of the vertical periodic trend for basicity, where iodide is the *least* basic. What is going on here? Shouldn't the stronger base, with its more reactive unbonded valence electrons, also be the stronger nucleophile?

As mentioned above, it all has to do with the solvent. Remember, we are talking now about the reaction occurring in a *protic* solvent like ethanol. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile:



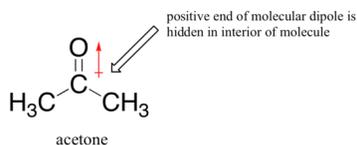
In order for the nucleophile to react with the electrophile, it must break free, at least in part, from its solvent cage. The lone pair electrons on the larger, less basic iodide ion interact less tightly with the protons on the protic solvent molecules resulting in weaker solvation - thus the iodide nucleophile is better able to break free from its solvent cage compared the smaller, more basic fluoride ion, whose lone pair electrons are bound more tightly to the protons of the solvent cage.

The picture changes if we switch to a **polar aprotic solvent**, such as acetone, in which there is a molecular dipole but *no hydrogens bound to oxygen or nitrogen*. Now, fluoride is the best nucleophile, and iodide the weakest.



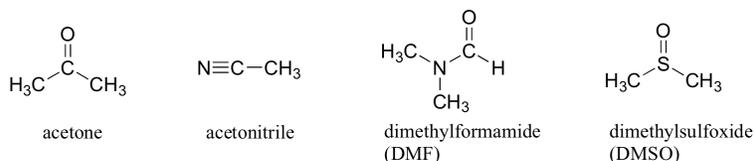
Relative nucleophilicity in a polar aprotic solvent

The reason for the reversal is that, with an aprotic solvent, the ion-dipole interactions between solvent and nucleophile are much weaker: the positive end of the solvent's dipole is hidden in the interior of the molecule, and thus it is shielded from the negative charge of the nucleophile.



A weaker solvent-nucleophile interaction means a weaker solvent cage for the nucleophile to break through, so the solvent effect is much less important, and the more basic fluoride ion is also the better nucleophile.

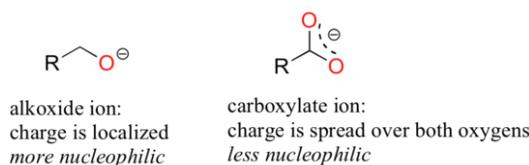
Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not 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).



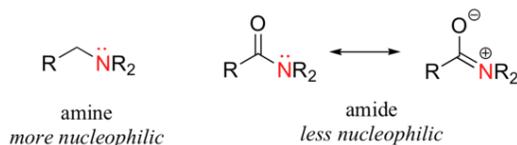
In biological chemistry, where the solvent is protic (water), the most important implication of the periodic trends in nucleophilicity is that thiols are more powerful nucleophiles than alcohols. The thiol group in a **cysteine amino acid**, for example, is a powerful nucleophile and often acts as a nucleophile in enzymatic reactions, and of course negatively-charged thiolates (RS^-) are even more nucleophilic. This is not to say that the hydroxyl groups on serine, threonine, and tyrosine do not also act as nucleophiles - they do.

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.



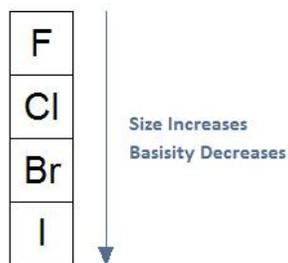
The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



THE LEAVING GROUP

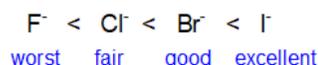
The more stable the leaving group, the lower the transition state energy, the lower the activation energy, the faster the reaction rate. Evaluating leaving group stability is analogous to determining relative acidity by evaluating conjugate base stability. The considerations are the same: identity of the atom(s) and relative position on the periodic table, resonance delocalization, and electronegativity. Orbital hybridization is rarely relevant.

As Size Increases, Basicity Decreases, Leaving Group Stability Increases: 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.

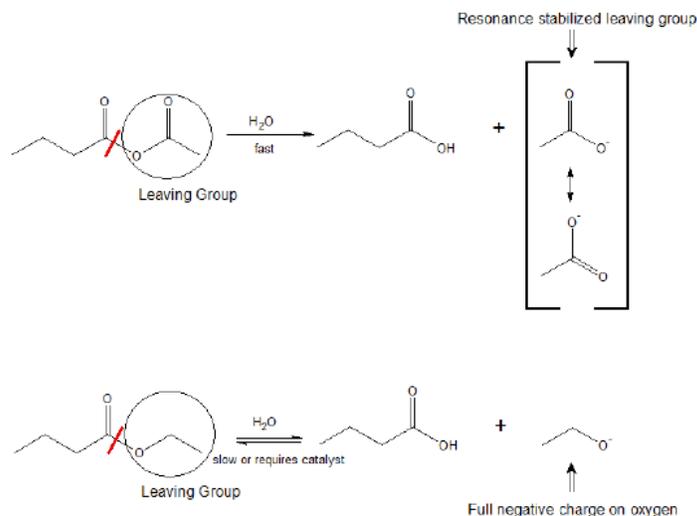


When evaluating halogens as leaving groups, the same trend is significant. Fluoride has the highest electron density and is considered the worst leaving group to the point of no reactivity. As move down the column, the leaving groups have lower electron density and greater stability with iodide considered an excellent leaving group.

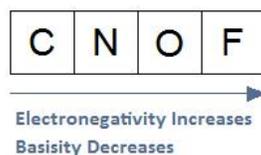
Leaving Group Comparison



Resonance Decreases Basicity and Increases Leaving Group Stability: The formation of a resonance stabilized structure delocalizes the electrons over two or more atoms lowering the electron density of the leaving group and increases its stability. For halides as leaving groups there are no applications for this consideration, so we will look briefly at carbonyl chemistry to illustrate this effect. When comparing the hydrolysis rates of anhydrides and esters, anhydrides react spontaneously with water and undergo hydrolysis to form a resonance stabilized carboxylate ion. Whereas, ester hydrolysis is a much slower reaction and requires a catalyst to overcome the alkoxides as poor leaving groups. The details of these two reactions will be studied in greater detail later in this text.

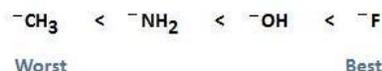


As Electronegativity Increases, Basicity Decreases and Leaving Group Stability Increases: In general, if we move from the left of the periodic table to the right of the periodic table as shown in the diagram below, **electronegativity** increases. As electronegativity increases, basicity will decrease, meaning a species will be less likely to act as base; that is, the species will be less likely to share its electrons.



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 S_N2 reactions of fluoroalkanes are rarely observed.

Leaving Groups Across a Period



SOLVENT EFFECTS ON 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 through strong solvation. We can view the nucleophile as being locked in a solvent cage through the strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. 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. Below are several polar aprotic solvents that are commonly used in the laboratory:

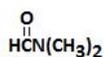
Polar Aprotic Solvents



Acetone



Ethanenitrile (Acetonitrile)



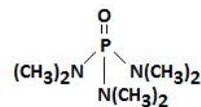
N,N-Dimethylformamide (DMF)



Dimethyl sulfoxide (DMSO)



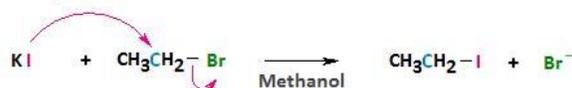
Nitromethane



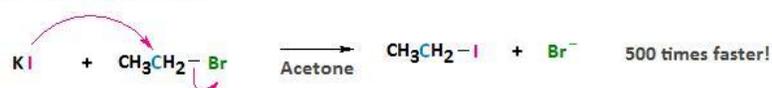
Hexamethylphosphoric triamide (HMPA)

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 - Protic Solvent

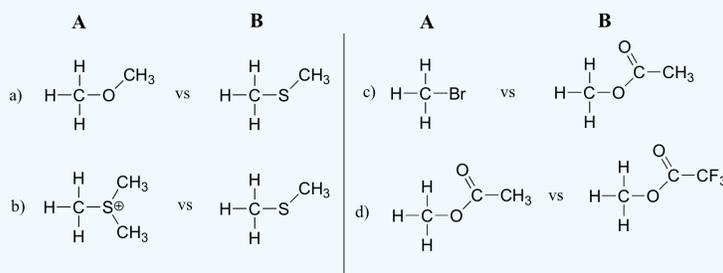


Example - Aprotic Solvent



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?



Explanations to explain differences in chemical reactivity need to discuss structural and/or electrostatic differences between the reactants

a) Cpd B b/c it has a more stable leaving group.

The larger atomic size of S relative to O means the sulfide (CH₃S⁻) will have a lower electron density than the alkoxide (CH₃O⁻).
b) Cpd A b/c it has a more stable leaving group.

The neutral leaving group, (CH₃)₂S, is more stable than the charged sulfide leaving group (CH₃S⁻).

c) Cpd B b/c the leaving group is resonance stabilized delocalizing the negative charge over two oxygen atoms. d) Cpd B b/c the leaving group has inductive electron withdrawal stabilization from the three fluorine atoms in addition to the resonance stabilization.

Exercise

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
- $\text{CH}_3\text{C}\equiv\text{C-Li}$
- NH_3

2. Which in the following pairs is a better nucleophile?

- $(\text{CH}_3\text{CH}_2)_2\text{N}^-$ or $(\text{CH}_3\text{CH}_2)_2\text{NH}$
- $(\text{CH}_3\text{CH}_2)_3\text{N}$ or $(\text{CH}_3\text{CH}_2)_3\text{B}$
- H_2O or H_2S

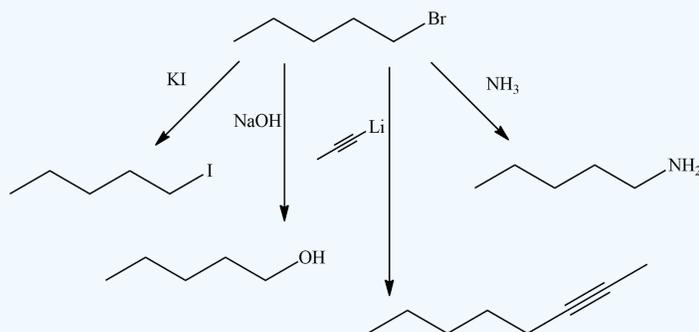
3. Order the following in increasing reactivity for an S_N2 reaction.

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

4. Solvents benzene, ether, chloroform are non-polar and not strongly polar solvents. What effects do these solvents have on an S_N2 reaction?

Answer

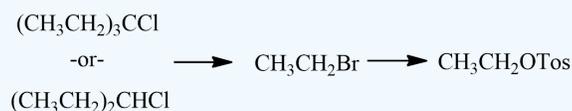
1. (a) - (d)



2.

- $(\text{CH}_3\text{CH}_2)_2\text{N}^-$ as there is a charge present on the nitrogen.
- $(\text{CH}_3\text{CH}_2)_3\text{N}$ because a lone pair of electrons is present.
- H_2O as oxygen is more electronegative.

3.



4. They will decrease the reactivity of the reaction.

CONTRIBUTORS AND ATTRIBUTIONS

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- [Organic Chemistry With a Biological Emphasis](#) by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark ([Chemguide.co.uk](#))

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