

11. Nucleophilic Substitution Reactions

A. Introduction

It would be beneficial if you review the chapter on substitution reactions in your textbook prior to lab. This is Ch. 11 in the 9th edition McMurry textbook.

In a substitution reaction, one atom (or group of atoms) is replaced by another atom (or group of atoms). The atom or group that is lost is called the **leaving group** and the atom or group that is added is a **nucleophile**. In the example below, a nucleophilic substitution reaction is carried out between 2-bromopropane and the hydroxide ion. In this reaction, bromide is the leaving group and hydroxide is the nucleophile. It should be noted that the carbon at which substitution occurs is sp^3 hybridized. Nucleophilic substitution only occurs at sp^3 hybridized carbons. sp^2 and sp hybridized carbon atoms do not undergo nucleophilic substitution.

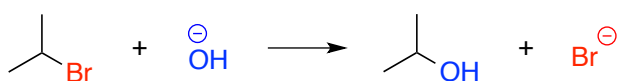


Figure 1. A Substitution Reaction

In practice, nucleophilic substitution reactions can occur via two distinct mechanisms: S_N1 (substitution, nucleophilic, unimolecular) or S_N2 (substitution, nucleophilic, bimolecular). The operative mechanism is dependent on a number of factors including: the substrate, the nucleophile, the leaving group, the solvent, and the temperature. For any given reaction it is possible that one or both substitution mechanism are operative. As you progress through the lecture and laboratory courses, you will begin to develop the knowledge necessary to predict the mechanism that is occurring under the given conditions.

1. The S_N2 Reaction

The S_N2 reaction is a bimolecular process meaning both reactants (the nucleophile and the alkyl halide) are involved in the rate-determining step. This reaction takes place in a single step through a transition state where there is partial bond formation between the nucleophile and electrophilic carbon along with partial bond breakage between the carbon and the leaving group.

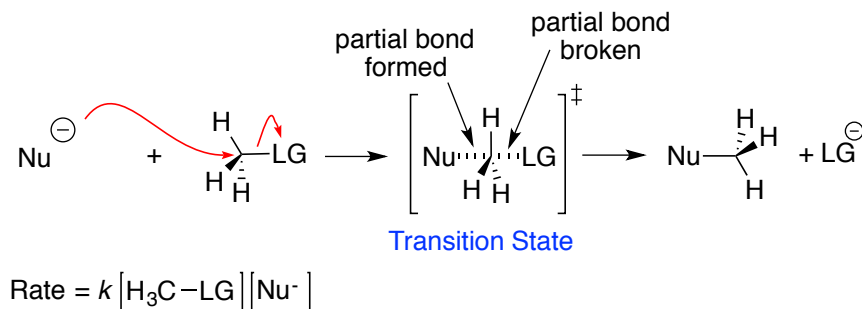
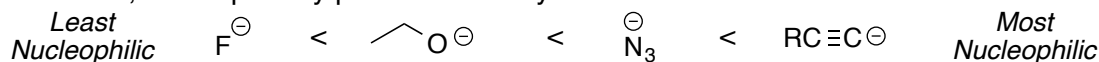


Figure 2. A General S_N2 Reaction

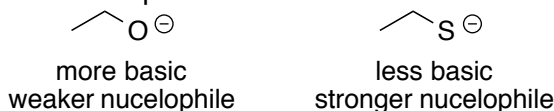
The rate of the S_N2 reaction is influenced by three main factors: the strength of the nucleophile, steric hindrance around the electrophilic carbon, and the leaving group. Solvent effects also play a role in the rate of the S_N2 reaction, but this factor will not be discussed here.

A stronger nucleophile will result in a faster S_N2 reaction.

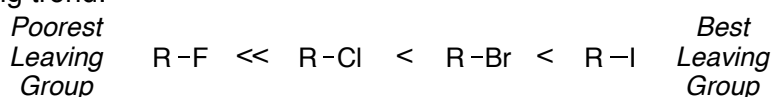
- In a series of nucleophiles where the nucleophilic atoms are from the same row on the periodic table, nucleophilicity parallels basicity.



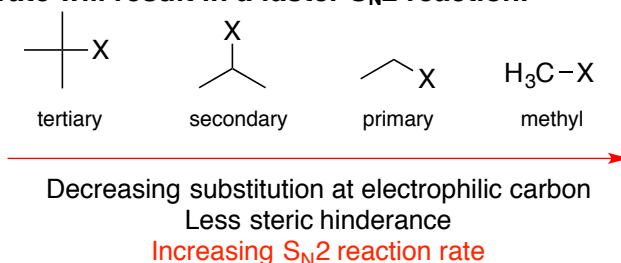
- In a series of nucleophiles where the nucleophilic atoms are from the same column, the less basic nucleophiles are more nucleophilic.



A better leaving group will result in a faster S_N2 reaction. The more stable a leaving group, the more likely it is to leave the molecule. Halides are the most common leaving group and they exhibit the following trend:



A less hindered substrate will result in a faster S_N2 reaction.



2. The S_N1 Reaction

The S_N1 reaction is a unimolecular process meaning only one molecule is involved in the rate-determining step. This molecule is the substrate that contains the leaving group. The mechanism of the S_N1 reaction (figure 3) involves the loss of a leaving group to form a carbocation intermediate. This carbocation intermediate then reacts with the nucleophile to provide the substitution product.

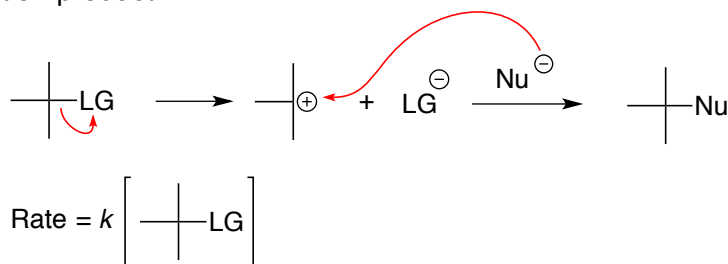
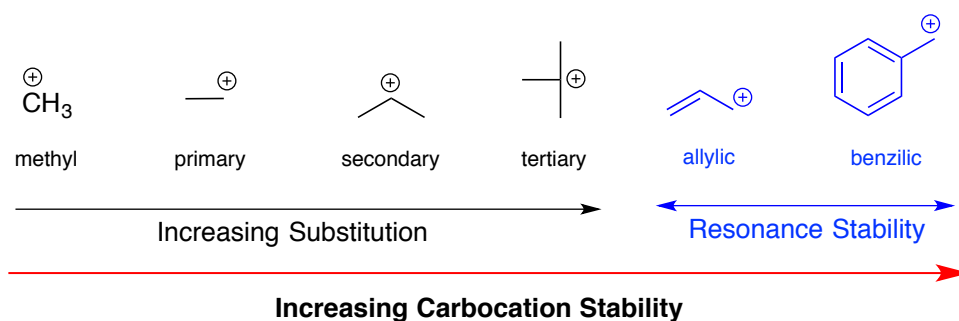


Figure 3. A General S_N1 Reaction

As can be seen from the rate equation, the nature or concentration of the nucleophile has no effect on the reaction rate. Two main factors govern the rate of the S_N1 reaction: the ability of the leaving group to leave and the stability of the resulting carbocation intermediate. Leaving group ability follows the same trend as in the S_N2 reaction. A carbocation is stabilized by increased substitution and by resonance effect. A more stable carbocation intermediate corresponds to a faster S_N1 reaction.



Using the information presented above, it is possible to make predictions concerning the relative rates of various substrates under S_N1 and S_N2 conditions. In this experiment you will confirm your predictions by performing nucleophilic substitution reactions on a variety of different substrates.

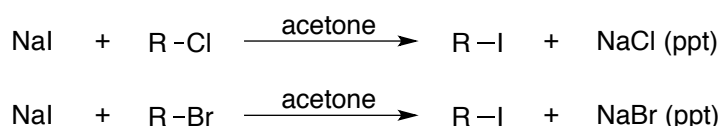
B. Experimental Procedure

You will be investigating ten substrates (organic halides) for their reactivity under S_N2 and S_N1 conditions. Your experiment will reveal the validity of the predictions that you made in the pre-lab questions.

Investigation of S_N2 Reactivity

Solvent effects in substitution reactions will be fully discussed in your lecture course. S_N2 reactions work best when a polar aprotic solvent such as acetone is used.

In your investigation, sodium iodide (NaI) will be reacted with a variety of alkyl halides. When using NaI, the iodide ion (I^-) acts as the nucleophile. The combination of sodium iodide with the solvent acetone proves especially useful in this investigation because the NaCl or NaBr byproducts are not soluble in acetone, thus the appearance of the precipitate can be used to monitor the progress of the reaction. By comparing the precipitate formation versus time for the various organic halides you will be able to organize them by their relative reactivities.



Take 9 test tubes and number them 1-9. These numbers will correspond to the organic halides listed in table 1. Place approximately 0.5 mL of 18% NaI in acetone in each tube. Next, add 5 drops of each organic halide to the appropriate test tube. Stopper the tube and shake it to mix the reagents thoroughly. Record whether or not a precipitate forms and the amount of time elapsed between addition of the halide and the definitive formation of a precipitate.

Be cautious of false positives. Impurities present with the organic halides can result in the formation of a small amount of initial precipitate. If you observe a small amount of precipitate, but the amount does not steadily increase, then you likely have a false positive.

If no precipitation is observed after 5 min, heat the sample in a 45 °C. If no precipitation is observed after 5 min, record as no reaction. For reactions that require heating, record the elapsed time as the length of time the reaction required heating in order for precipitation to occur.

Table 1: S_N2 Reactivity

	Structure	Name	Reaction ^a	Heating ^b	Time ^c
1	CH ₃ CH ₂ CH ₂ CH ₂ Cl	<i>n</i> -Butyl Chloride			
2	CH ₃ CH ₂ CH ₂ CH ₂ Br	<i>n</i> -Butyl Bromide			
3	CH ₃ CHBrCH ₂ CH ₃	<i>sec</i> -Butyl Bromide			
4	(CH ₃) ₂ CHCH ₂ Br	Isobutyl Bromide			
5	(CH ₃) ₃ CCl	<i>tert</i> -Butyl Chloride			
6	C ₆ H ₅ CH ₂ Cl	Benzyl Chloride			
7	CH ₂ =CHCH ₂ Br	Allyl Bromide			
8	PhBr	Bromobenzene			

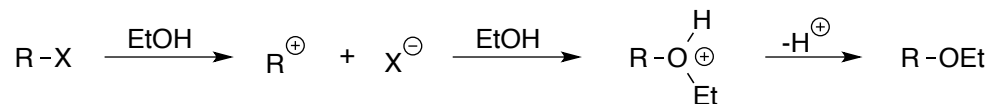
^aRecord whether or not a reaction occurs (yes/no).

^bRecord whether or not it was necessary to heat the reaction.

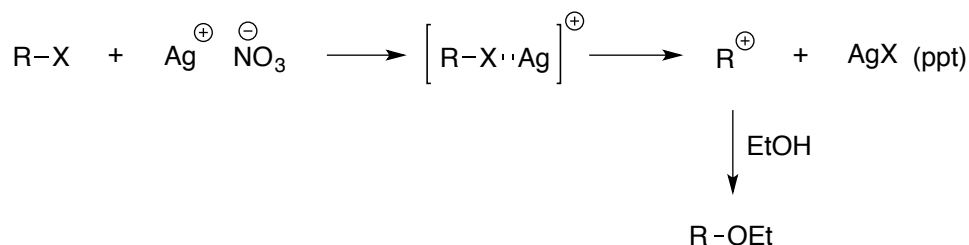
^cIf a reaction is observed, record the elapsed time between halide addition and the definitive observation of a precipitate.

Investigation of S_N1 Reactivity

In the second part of this experiment, you will be investigating the S_N1 reactivity of the same nine alkyl halides. The solvent (ethanol) will be the nucleophile. For this reason S_N1 reactions are often referred to as solvolysis reactions. The reaction shown below proves to be difficult to monitor qualitatively because unlike the S_N2 reaction there is no insoluble byproduct, meaning precipitation is not observed.



To work around this issue, we will add silver nitrate (AgNO₃) to the reaction mixture. The benefit is two fold. First, the silver ion will coordinate with the halogen, helping to pull it off the molecule. Second, the AgX byproduct is insoluble in the reaction solvent and precipitation can be observed allowing for the qualitative assessment of the reaction rate.



To nine clean¹ and labeled test tubes, add 0.5 mL of 1% AgNO₃ in ethanol. Next, add 5 drops of the appropriate halide to each tube. Shake the tubes to affect mixing and watch for formation of a precipitate. Record the results in table 2. Just as in the S_N2 reaction, if precipitation is not observed, you should heat the solution in a 45 °C water bath.

¹ You can clean your test tubes from the first experiment by emptying them into the waste container, rinsing with water, and then rinsing them 2-3 times with ethanol.

Table 2: S_N1 Reactivity

	Structure	Name	Reaction ^a	Heating ^b	Time ^c
1	CH ₃ CH ₂ CH ₂ CH ₂ Cl	<i>n</i> -Butyl Chloride			
2	CH ₃ CH ₂ CH ₂ CH ₂ Br	<i>n</i> -Butyl Bromide			
3	CH ₃ CHBrCH ₂ CH ₃	<i>sec</i> -Butyl Bromide			
4	(CH ₃) ₂ CHCH ₂ Br	Isobutyl Bromide			
5	(CH ₃) ₃ CCl	<i>tert</i> -Butyl Chloride			
6	C ₆ H ₅ CH ₂ Cl	Benzyl Chloride			
7	CH ₂ =CHCH ₂ Br	Allyl Bromide			
8	PhBr	Bromobenzene			

^aRecord whether or not a reaction occurs (yes/no).

^bRecord whether or not it was necessary to heat the reaction.

^cIf a reaction is observed, record the elapsed time between halide addition and the definitive observation of a precipitate.

Be sure to record any additional observations in your notebook. The results and analysis will be explored in the post-lab questions.

C. Pre-Lab Questions

1. Draw the skeletal structure of each organic halide in table 1. The common names are given in the table. Write the IUPAC name for each of these molecules.
2. Considering the rate law for the S_N2 reaction given in figure 2, if you were to double the concentration of the nucleophile, how would the rate be affected?
3. Recalling that nucleophilic substitution reactions only occur at sp³ hybridized carbon atoms containing a leaving group, are there any molecules from table 1 that you suspect will not undergo nucleophilic substitution?
4. Based on the theoretical discussion, do you expect *n*-butyl chloride or *n*-butyl bromide to undergo substitution at the fastest rate?
5. Predict the order of both S_N1 and S_N2 reactivity for the alkyl halides in table 1.

D. Post-Lab Questions

1. Based on your results, which substrates do not undergo S_N2 reactions? Can you make any generalizations?
2. Based on your results, which substrates do not undergo S_N1 reactions? Can you make any generalizations?
3. Compare the effect of substrate structure (primary, secondary, tertiary) under S_N2 and S_N1 conditions.

4. Did your prediction about the nature of the leaving group in pre-lab question 4 hold true?
5. Neophyl bromide and *n*-butyl bromide are both primary halides. Was there any observable rate difference between these two substrates under S_N2 conditions? Explain your result.
6. Using your experimental data, rank the halides in table 1 by their S_N2 and S_N1 reactivity. If two substrates have very similar reactivity, you can identify them as equal. You should also be able to identify certain substrates as unreactive.
7. Are there any major differences between your experimental observations and theoretical predictions?

Because the post-lab questions basically walk you through the results and conclusions section of your lab notebook, you can omit the "results and conclusions" notebook section for this experiment to avoid repetition. You can and should however record any additional notes or observations that you find pertinent.