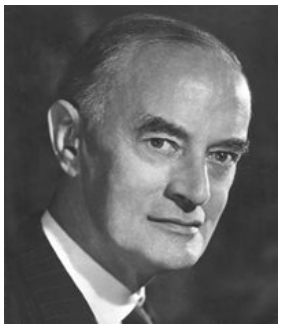
Fig. 15-1



Experiment 15

NUCLEOPHILIC SUBSTITUTION

Sir Christopher Ingold (1893 -1979)
http://www.ucl.ac.uk/chemistry/history/chemical_history/slides/1937

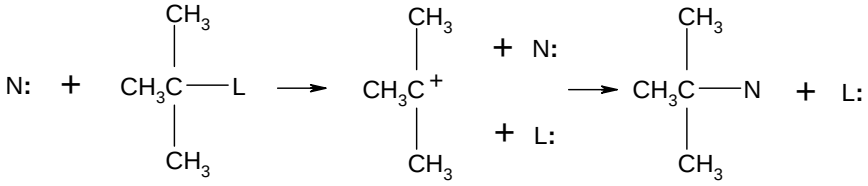
Text Topics

Synthesis and mechanism of nucleophilic substitution reactions.

Discussion

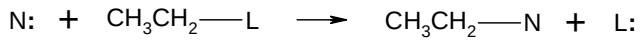
On the surface, nucleophilic substitution reactions at saturated carbons appear to be simple, straightforward conversions. However, investigating further, we find that the mechanism and sometimes the product distribution of the reaction depends on many variables including the structure of the organic compound, the nucleophile, the leaving group, the solvent and the temperature. Thanks to the excellent research of Sir Christopher Ingold and many others, it has been found that the mechanisms of most nucleophilic substitution reactions can be classified according to one of two mechanisms, S_N1 or S_N2. It turns out both mechanisms are common. Based on a careful analysis of the variables, it can be deduced which mechanism should be operative.

These symbols, S_N1 or S_N2, stand for first and second order nucleophilic substitution respectively. Your textbook will thoroughly discuss these two types of reactions and how the variables influence which mechanism predominates. Very briefly, an S_N1 reaction is a two step reaction that involves a rate determining step in which the bond to the leaving group breaks resulting in formation of a carbocation intermediate. In the second and fast step, the carbocation combines with a nucleophile to yield product. As the rate determining step does not involve the nucleophile, the rate of formation of product does not depend on the concentration or nature of the nucleophile and the rate equation is first order.



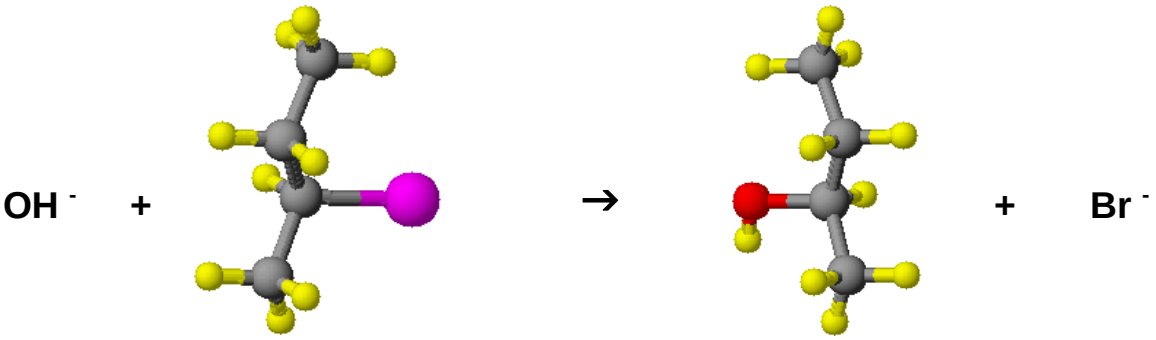
$$\text{rate} = -d[RL]/dt = k_1[RL]$$

An S_N2 reaction involves a backside attack of the nucleophile on the carbon bearing the nucleophile. Thus, in a concerted fashion, the nucleophile pushes off the leaving group. An intermediate is not formed in this reaction but the reaction rate does depend on the frequency of collisions between the nucleophile and the organic substrate. This one step process leads to a rate expression that is proportional to the concentrations of nucleophile and substrate and is second order.



$$\text{rate} = d[RL]/dt = k_2[RL][N:]$$

At times it may seem that organic chemists probe mechanisms simply because they are curious and want to understand what is going on. This in itself is sufficient reason to investigate the mechanism of a reaction. But there are very important practical reasons for wanting to understand the mechanism. First, substitution reactions compete with elimination reactions. If substitution is desired, it is necessary to optimize conditions that will achieve a maximum yield of the desired substitution product. Second, even for substitutions, rearrangements and different product distributions are possible. For example in the following nucleophilic substitution of hydroxide on *(S)*-2-bromobutane, an S_N1 reactions would yield a racemic mixture but an S_N2 reaction should yield exclusively the inversion product *(R)*-2-butanol. It is highly probable that careful selection of the solvent and temperature could cause the S_N2 reaction to predominate.



There are many ways of investigating the mechanism of a reaction. Rate studies are versatile and are capable of providing considerable insight into the mechanism of the reaction. For example, in the above reaction, determining if there is a dependence of the reaction rate on the hydroxide concentration should distinguish between S_N1 or S_N2 reactions. Another option for the above reaction is to determine if the product from *(S)*-2-bromobutane is a racemic mixture or *(R)*-2-butanol. The latter method has limitations as many compounds of interest do not have a stereogenic carbon. Changing the structure to one that does can change the mechanism of the reaction. Also, optically pure compounds are usually expensive.

An interesting alternative to rate and polarimetry studies that should provide useful insight into the reaction involves running a nucleophilic substitution reaction as a synthesis with two nucleophiles present (instead of one) at equal molar concentrations. As a result, the product will be a mixture of two compounds. Clearly, this is not a useful way to synthesize a compound but analysis of the product ratio will help elucidate the mechanism of the reaction. The techniques utilized could have been used with just one of the nucleophiles to synthesize a desired product. Thus, in addition to providing mechanistic insight, this experiment provides a meaningful laboratory experience.

To gain the maximum insight for the system you will study, it will be necessary to collaborate with at least two other students. Each of you will run different reactions and then you will share and analyze the results. The reaction to be studied will be the substitution of halide for hydroxide in 1-butanol, 2-butanol and 2-methyl-2-propanol (*t*-butyl alcohol). Consider what should happen if equal molar mixtures of bromide and chloride are used to displace water (hydroxide is a very poor leaving group and will leave as a water molecule only after it has been protonated). For S_N2 reactions, the rate expression includes the concentration of the halide and the rate constant, k_2, should be very dependent on the nature of the halogen. Thus, S_N2 reactions should yield a bromide to chloride ratio significantly different than unity. On the other hand, the rate of an S_N1 reaction does not depend on the concentration of the halide. The very reactive carbocation intermediate is expected to rather indiscriminately react with the first nucleophile encountered. Since the bromide and chloride will be the same concentration, it is expected that the bromide to chloride product ratio should be close to unity.

Nucleophilicity (strongest at top)	Leaving group ability
SH^-	OTs^- (tosylate)
I^-	I^-
CN^-	Br^-
NR_3	H_2O
OH^-	ROH
OR^-	Cl^-
Br^-	NR_3
PhO^-	F^-
N_3^-	OAr^-
NH_3	OH^-
Cl^-	OR^-
$CH_3CO_2^-$	NH_2^-
F^-	
NO_3^-	
H_2O, ROH	

March, J., *Advanced Organic Chemistry*, 4th ed., **1992**, p. 351.

Procedure

A group of ***three*** should assign one of the three alcohols, 1-butanol, 2-butanol and 2-methyl-2-propanol to each of the collaborators.

Fig. 15-2

In a hood, set up a system for dropwise addition with a 50 mL reaction flask in a heating mantle. Add 22 mL of 8 M H_2SO_4 (if not available in the laboratory, carefully and cautiously prepare this solution by adding 10 mL of concentrated sulfuric acid to 12 grams of ice) in the flask. Add 0.05 moles of ammonium chloride and 0.05 moles of ammonium bromide and a boiling chip or magnetic stirrer to the flask. Warm and stir the mixture until the salts dissolve. Add 0.032 moles (about 3.0 mL) of your alcohol to the dropping funnel. Heat the acid solution until it is slowly refluxing and add the alcohol dropwise while continuing to slowly reflux the mixture. The reflux time varies with the alcohol used (0.25 hours for 2-methyl-2-propanol, 1 hour for 2-butanol and 1.5 hours for 1-butanol).

Allow the mixture to cool to near room temperature and then cool further with an ice bath. Transfer the solution to a separatory funnel. After you confirm which layer is the aqueous layer, the aqueous layer can be discarded. Wash the organic layer twice with 10 mL portions of 3 M sulfuric acid, twice with 10 mL portions of water followed by two 10 mL portions of 5% sodium hydrogen carbonate. Add some anhydrous magnesium sulfate to the top of a Hirsch funnel (on top of the paper) and vacuum filter the halide mixture into a very small filter flask. Transfer the product to a flask or large test tube and tightly stopper it. The chloride to bromide ratio should be determined by as many techniques as possible. If it is necessary to store the solution before analysis, store the container in a refrigerator.

Determine the bromide to chloride ratio by running a gc and determine the ratio of the peak areas. Assume that the gc has the same sensitivity to both compounds. The results for the *t*-butyl halides could have errors due to an elimination reaction during the gas chromatographic process.

For the *t*-butyl halides it is also possible to determine the bromide to chloride ratio by measuring the refractive index and/or nmr of the products. Assume a linear relationship between the ratio and the refractive index of the possible products.

References

Helmkamp, G. K.; Johnson, Jr., H. W., *Selected Experiments in Organic Chemistry*, Freeman, **1968**, pp. 59-61.
Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Engel, R. G., *Organic Laboratory Techniques*, Saunders, **1998**, pp. 211-217.

Prelaboratory Preparation - *Experiment 15*

First, be sure to list all the goals of the experiment. Try to decide if nmr, ir, refractive index, density or boiling point could be used to determine the bromide to chloride ratio. If you think one or more of these techniques will work, you should do the determination in addition to using gc. Decide what kind of information the bromide to chloride ratio will provide. Are there any significant assumptions that have to be made to come to meaningful conclusions? If so, how much confidence do you have that the assumptions are correct? Locate this type of substitution reaction on the *Reaction-Map of Organic Chemistry* in ***Appendix C*** and include the reaction number in your report.

Observations

Report all relevant observations including the results of the gc analysis and if performed, additional types of analysis.

Conclusions

This section should include the following:

1. Were the goals of the experiment achieved? Explain your answer.
2. What was the bromide to chloride ratio for the three sets of products? Do the ratios enable you to decide if the mechanism for each molecule was S_N1 or S_N2? If so, what mechanisms were operative for each halide? If the mechanisms were not the same, explain why the mechanism depends on the structure. Try to make a generalized statement about how the mechanism of substitution reactions depends on structure.
3. Does a percent yield have any meaning in this experiment? Explain your answer.
4. Was the product pure enough for the present application or should additional purification have been performed? If so, what technique would you recommend?
5. Comment on the use of gc, nmr, ir, refractive index, density or boiling point for the determination of the bromide to chloride ratio. Which methods could be used for each alcohol and which should give the most reliable results?.