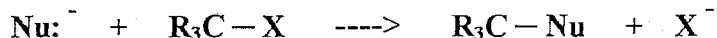


NUCLEOPHILIC SUBSTITUTION REACTIONS / ALKYL HALIDES

Nucleophilic substitution reactions are an important class of reactions which allow the displacement of one functional group or substituent on an sp^3 -hybridized carbon atom with another.



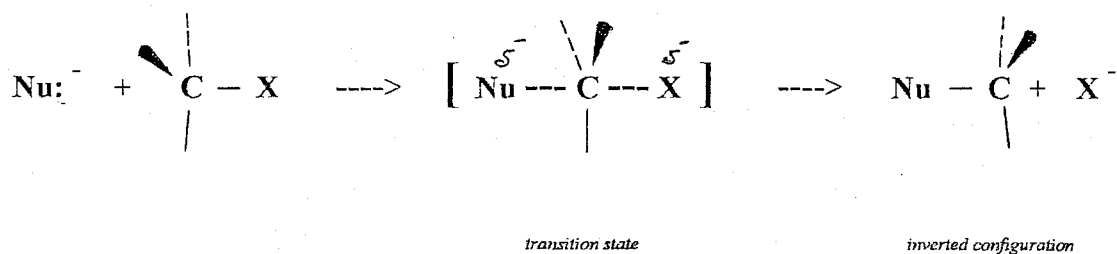
The X group is called the leaving group. In this experiment, X is chloride, but can be any group which can accommodate a negative charge (X^- , an anion is formed). Nu:^- is the nucleophile and is characterized by having an unshared pair of electrons which form a new bond with the carbon atom. Anions which can act as nucleophiles include halides, cyanide, hydroxide, alkoxide, and others. Neutral compounds which can act as nucleophiles include amines, alcohols, and water (with subsequent loss of a proton).



Two classes of nucleophilic substitutions occur at sp^3 -hybridized carbons: S_N1 and S_N2 . In this experiment, you will investigate how reactivity and reaction rates are affected by the different structures of a group of alkyl chlorides under S_N1 and S_N2 conditions

S_N2 Reactions (substitution-nucleophilic-bimolecular)

S_N2 reactions occur as a concerted process. As the nucleophile approaches the carbon atom and bond forming begins, bond breaking between the carbon atom and the leaving group occurs simultaneously.

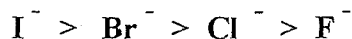


In the transition state both the nucleophile and leaving group are present, hence the kinetics are bimolecular and the reaction rate is proportional to both the concentration of the substrate and the concentration of the nucleophile. If you double the concentration of the nucleophile or the substrate, you double the reaction rate.

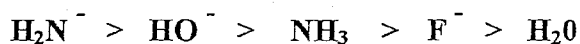
$$\text{rate} = k [\text{Nu:}^-] [\text{Substrate}]$$

Factors other than reactant concentration that may affect S_N2 reaction rates include 1) leaving group ability 2) nucleophilicity of the nucleophile 3) stereochemistry and 4) nature of the solvent.

1) *leaving group ability* - The more an X is able to accommodate a negative charge, the better a leaving group it will be, and the faster the reaction. Anions of this type are weak bases (review acids and their conjugate bases). Leaving group ability in decreasing order is shown below for the halide series. Note that HI is the strongest acid of the group, so I^- is the weakest base and best leaving group.



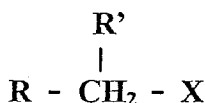
2) *nucleophilicity of the nucleophile* - In general, the higher the basicity of a nucleophile, the more active it will be in displacing a leaving group. Therefore, HO^- is a better nucleophile than water because it is a stronger base. Basicity, thus nucleophilicity, tends to decrease from left to right across the periodic table. Nucleophilicity is shown below for a series of first row elements.



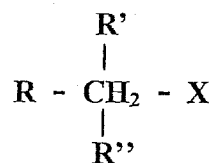
3) *stereochemistry* - The incoming nucleophile can approach the reaction site only from the side opposite the leaving group. Any substituents which can block or hinder the approach of the nucleophile will slow the reaction (or prevent it from occurring altogether). Thus, S_N2 reactions occur only at primary and secondary carbon atoms (where the R groups do not impede the approach of the nucleophile), but never at tertiary carbons.



primary



secondary



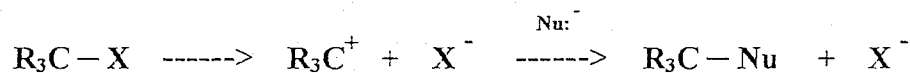
tertiary

As a result of the backside attack by the nucleophile, inversion of configuration (Walden inversion) always occurs in S_N2 reactions.

4) *nature of the solvent* - The solvent in an S_N2 reaction must be polar enough to dissolve the nucleophile and stabilize anion formation, but not so polar as to promote ionization of the substrate. Usually, polar aprotic solvents, e.g. ethers or tertiary amides, are favored.

S_N1 Reactions (substitution-nucleophilic-unimolecular)

In contrast to S_N2 reactions, S_N1 reactions occur in two steps. In the first step (the rate determining step), the substrate ionizes to form a carbocation and an anion (from the leaving group). In the second step, the nucleophile attacks the carbocation, forming product.

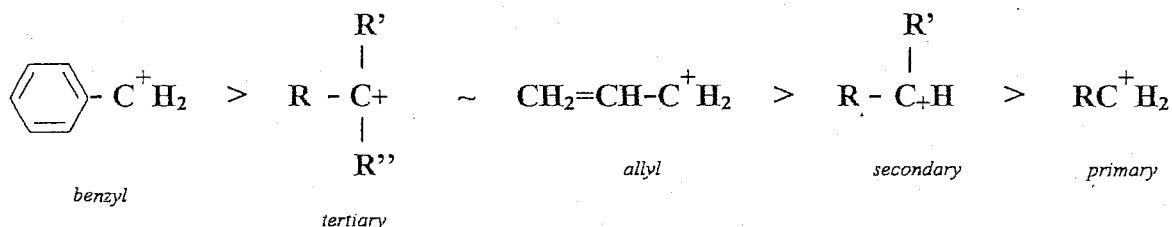


Since only the substrate is involved in the rate determining step, the kinetics are unimolecular and the reaction rate is proportional only to substrate concentration.

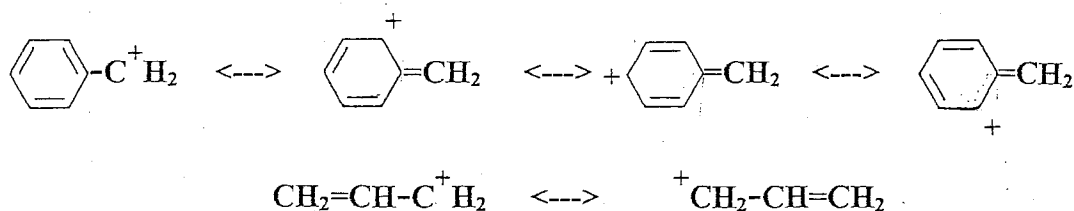
$$\text{rate} = k [\text{substrate}]$$

Doubling the concentration of the substrate will double the rate of reaction, but changing the concentration of the nucleophile will have no effect on reaction rate. Note: do not confuse reaction rate with yield. A slow reaction can give a high yield if given a sufficient time to react. Yield is also affected by isolation techniques which have nothing to do with reaction kinetics.

The S_N1 mechanism is favored by any conditions which promote the formation of the carbocation. The structure of the substrate is of primary importance. Structures which ionize to form stable carbocations facilitate the S_N1 mechanism. Carbocations of decreasing stability as follows:



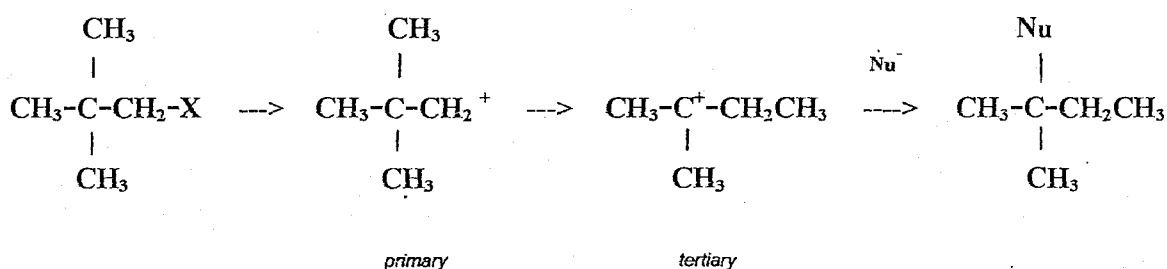
In general, when a charged species (a carbocation) is being formed, the delocalization of that charge over several atoms favors the formation of the charge. The benzylic and allylic carbocations shown above appear to be primary carbocations, but, in fact, are stabilized by resonance overlap with the pi electrons, which delocalizes the positive charge. Therefore, their formation is favored and benzylic and allylic compounds readily undergo S_N1 reactions, in addition to S_N2 reactions.



Reactions at tertiary carbons also occur under S_N1 conditions. First, steric hinderance prevents S_N2 attack. Second, tertiary carbocations are stabilized by hyperconjugation, overlap with the sigma electrons of the neighboring substituents which helps to delocalize the charge. Thus, nucleophilic substitution at a tertiary carbon occurs only by S_N1 chemistry.



Formation of secondary and primary carbocations is much less favored and S_N1 reactions occur only in those cases where steric hinderance inhibits S_N2 attack and an alkyl shift leads to a more stable tertiary carbocation.



Lastly, solvent can be important in facilitating an S_N1 reaction. Solvents which can help stabilize the carbocation are generally used and include polar, protic solvents, such as alcohols and water.

The stereochemistry of S_N1 reactions is also different from that of S_N2 reactions. The positively charged carbon atoms of carbocations are sp^2 hybridized and are planar (all the substituents around the positively charged carbon atoms lie in the same plane). The incoming nucleophile can approach the carbon atom from either side of the plane giving a product mixture which is 50% inverted and 50% retained configuration. Such a mixture is called a racemate or racemic mixture. The product from an optically active starting material will lose its optical activity under S_N1 conditions, but show opposite optical activity under S_N2 .

Experiments

Objective: to determine the effects of structure on the rate of reaction of various alkyl chlorides under S_N1 and S_N2 conditions.

Materials and Equipment:

1-chlorobutane	water bath <i>or</i>
2-chlorobutane	hot plates w/ 400 mL beaker
2-chloro-2-methylpropane	thermometer
	small test tubes
18% sodium iodide in acetone	pasteur pipets and rubber bulbs
1% silver nitrate in ethanol	test tube rack

Students: Reagents are water sensitive. Please keep all containers closed as much as possible. All glassware very clean and dry.

Procedures:

S_N2 Reaction

Iodide ion is an excellent nucleophile and will displace chloride from alkyl chlorides. Acetone is used as a solvent because sodium iodide (NaI) is readily soluble and the product sodium chloride (NaCl) is not. Thus when NaI reacts with an alkyl chloride in acetone, a positive indication of reaction is the formation of an insoluble white solid. Anything from a slight haze to a heavy precipitate should be considered a positive result.

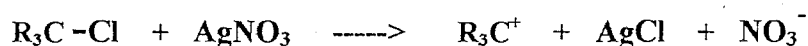
First, set up a 50°C water bath. Fill a 400mL beaker with 200mL water and place it on a hot plate (setting of 2 to start). Monitor the temperature with a thermometer. If the temperature rises above 50°C , turn down the heat and add some cold water to adjust the temperature. It is important not to overheat the bath because acetone readily evaporates and this may cause 'false positives'.

Label four test tubes, one for each alkyl chloride. Add 25 drops of 18% NaI in acetone to each test tube. Then add 6 drops of the appropriate alkyl chloride to each tube and mix by shaking back and forth, noting the time of addition. If a precipitate forms on the addition of the first few drops, but redissolves on shaking, ignore this. Time 2 minutes and note any changes. If nothing has happened, place the tubes in the water bath and again note the time to any changes. It is important to stay focused because changes may occur rapidly. Heat no longer than 5 minutes. Record the time to form a precipitate and under what conditions for each alkyl chloride.

Repeat the above experiment with 25 drops NaI in acetone and 18 drops of each alkyl chloride.

S_N1 Reaction

In the reaction of an alkyl chloride with silver nitrate (AgNO₃) to form silver chloride and an alkyl nitrate, the silver atom coordinates with the chloride facilitating the formation of the carbocation. Nitrate ion is such a weak nucleophile, that direct S_N2 displacement cannot occur.



1% AgNO₃ in ethanol is strictly S_N1 conditions. Again, a positive indication of reaction is the formation of a white precipitate (AgCl) ranging from a haze to a heavy solid. Ignore any precipitate which redissolves on mixing.

Label four test tubes, one for each alkyl chloride and add 25 drops 1% AgNO₃ in ethanol to each. Then add 6 drops of the appropriate alkyl chloride to each tube with shaking and note the time of addition. Time 2 minutes. If no change has occurred, place the tubes in the water bath and note the time to any changes. Heat no longer than 5 minutes.

Clean Up

Wash the test tubes into the waste solvent container. Glassware must be free of all chemical residue and contaminants before disposal in solid waste container.

Pre-lab Questions

1. Draw the structures of the alkyl chlorides in this lab and label the substitution (primary, secondary, tertiary, allyl).
2. Rank the order of reactivity you expect (fastest to slowest) for the alkyl chlorides when reacted with NaI in acetone.
3. Rank the order of reactivity you expect (fastest to slowest) for the alkyl chlorides when reacted with AgNO₃ in ethanol.
4. Predict the change, if any, in the following rates of reaction:
 - a. The concentration of NaI reacted with 1-chlorobutane is doubled.
 - b. The concentration of NaI reacted with 1-chlorobutane is doubled and the concentration of 1-chlorobutane is halved.

Post-lab Questions

1. Did your results confirm your expectations for the reactivity of the alkyl chlorides with NaI?
2. Did your results confirm your expectations for the reactivity of the alkyl chlorides with AgNO₃?
3. What changes in the rate of reaction occurred, if any, when the concentration of alkyl chloride was tripled in the reaction with NaI?