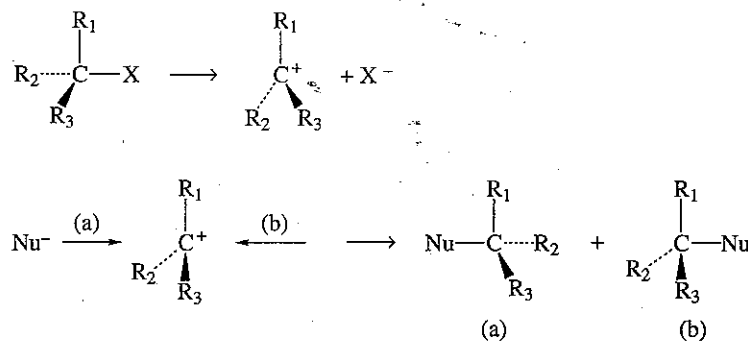


## Nucleophilic Substitution of Alkyl Halides

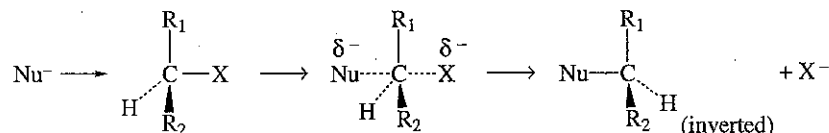
**A**lkyl halides, alkyl sulfates, and alkyl sulfonates serve as reactants or “substrates” in many nucleophilic substitution reactions. These substitution (or displacement) reactions are useful preparative methods, for example, the Williamson synthesis of ethers. For our purpose the term “nucleophilic” will refer to a reaction in which a nucleophile ( $\text{OH}^-$ ,  $\text{X}^-$ ,  $\text{S}^{2-}$ ,  $\text{HS}^-$ , etc.) attacks a carbon atom and displaces a “leaving group,” another nucleophile. Although these reactions proceed in a continuum of slightly different pathways, they can be viewed as occurring in a combination of two limiting mechanisms:

### 1. Substitution: Nucleophilic, Unimolecular ( $\text{S}_{\text{N}}1$ )



This mechanism involves more than one step, the first of which is the ionization of the alkyl halide substrate, yielding a carbocation and an anion. The planar carbocation then reacts with a nucleophile, forming the product (in the case of chiral compounds, racemic product generally results). Since the nucleophile is often a solvent molecule, the process is sometimes called **solvolysis**. A typical  $\text{S}_{\text{N}}1$  reaction is the solvolysis reaction of *tertiary*-butyl chloride with water to form *tert*-butyl alcohol.

## 2. Substitution: Nucleophilic, Bimolecular ( $S_N2$ )



This reaction involves one so-called “concerted” step in which the nucleophile attacks the carbon atom of the substrate on the side opposite the leaving group. An inversion of configuration of chiral compounds results.

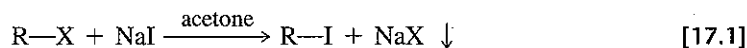
Studies of the mechanisms of these reactions were undertaken in the early 1930s in order to explain the vast differences in the rates of seemingly very similar reactions. Since that time, these findings have been refined to encompass the effects of solvent, ionic strength, added electrolytes, the nature of the alkyl group, and other factors. Some of these factors will be illustrated in this experiment. In addition, the complex methodology of determining the rate of a reaction will be undertaken.



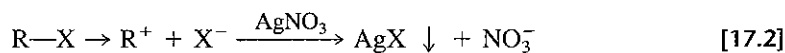
## EXPERIMENTS

### A. STRUCTURAL EFFECTS ON $S_N1$ AND $S_N2$ REACTIVITY

In this experiment the relative reactivities of a series of halides are observed under two sets of conditions, one of which favors the  $S_N1$  mechanism and the other the  $S_N2$ . The  $S_N2$  reaction is observed by the displacement of chloride or bromide by an iodide ion in acetone solution. The iodide ion is a good nucleophile for the  $S_N2$  reaction, whereas acetone is a relatively poor ionizing solvent, and  $S_N1$  dissociation is minimized. Sodium iodide is very soluble in acetone, but sodium chloride and sodium bromide have very low solubilities; so, the course of the reactions can be followed by the formation of crystalline NaCl or NaBr (Eq. 17.1).



The  $S_N1$  reaction can be observed by treating the alkyl halide with a solution of silver nitrate in aqueous ethanol. Nitrate ion is a very poor nucleophile so there is little opportunity for  $S_N2$  displacement. Dissociation of the alkyl halide by the  $S_N1$  process is followed by the precipitation of the insoluble silver halide (Eq. 17.2); the carbocation is then captured by alcohol or water.



## PROCEDURE



### SAFETY NOTE

Alkyl halides are toxic and flammable; avoid breathing them or spilling them on the skin. Insure that there is proper ventilation.

Label two series of five clean, thoroughly dry test tubes with numerals 1 to 5. In each series of tubes, place 0.2 mL of the following halides: (1) *n*-butyl chloride, (2) *n*-butyl bromide, (3) *sec*-butyl chloride, (4) *tert*-butyl chloride, and (5) crotyl chloride [ $\text{CH}_3\text{CH}=\text{CHCH}_2\text{Cl}$ ]. Keep the tubes stoppered with corks or parafilm and leave them covered at all times, before and after adding reagents. Obtain 15 mL of 15% NaI-acetone solution and 15 mL of 1% ethanolic  $\text{AgNO}_3$  solution from the side shelf.

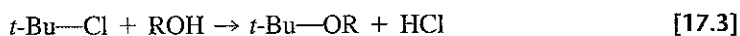
Arrange one series of tubes in order, from 1 to 5. Add 2 mL of the NaI solution to tube number 1 and note the time. (Add the solution from a pipet as rapidly as possible—not dropwise.) After 2 to 3 minutes, add 2 mL of NaI solution to the second tube and again note the time. Continue the addition at 2- to 3-minute intervals with the remaining tubes. After each addition, watch for any rapid reaction and then inspect the other tubes for signs of a precipitate. Note the time as closely as possible when precipitation begins to occur, recording the data in tabular form in your notebook. Cover the tubes and allow them to stand, observing them periodically while the next series is run.

Arrange the second series of tubes, and in the same way add 2-mL portions of the  $\text{AgNO}_3$  solution to each tube at 2-minute intervals. Again, watch closely for any that change rapidly and then observe the others periodically. If possible, note the time both for the first appreciable turbidity and also for a definite precipitate. If any tubes in the NaI series are still clear at this point, loosen the covers slightly and place the tubes in a water bath at  $50^\circ\text{C}$ ; note any changes that occur. Record the data in tabular form with column headings: tube number, time turbidity appears, and time of definite precipitate.

When you have completed these test tube reactions, pour the contents of all of the test tubes into the liquid waste container for halogenated solvents.

## B. EFFECTS OF SOLVENT ON $\text{S}_{\text{N}}1$ REACTIVITY

In addition to structural features of the halide, reaction conditions can have a large effect on the rate of nucleophile substitution. For example, the solvent plays a major role in both  $\text{S}_{\text{N}}1$  and  $\text{S}_{\text{N}}2$  reactions, and in this experiment the effect of solvent on the rate of the  $\text{S}_{\text{N}}1$  solvolysis of *tert*-butyl chloride will be studied. For this purpose, the most suitable method for comparing solvolysis rates is based on the fact that a strong acid is liberated in the reaction (Eq. 17.3). To determine the extent to which the reaction has proceeded, enough base is added to the reaction mixture to neutralize a small fraction of the acid produced. The solution becomes acidic after that fraction of the *tert*-butyl chloride has reacted, and the change in pH is detected with phenolphthalein indicator. The time required for neutralization is inversely proportional to the rate constant of the reaction,  $k_1$ , as shown in Equation 17.4.



The rate of formation of HCl by  $\text{S}_{\text{N}}1$  solvolysis of an alkyl chloride is equal to the rate of disappearance of alkyl chloride and is proportional to the concentration of the alkyl halide (Eq. 17.4).

$$\frac{d[\text{HCl}]}{dt} = k_1[\text{RCl}] = \frac{-d[\text{RCl}]}{dt} \quad [17.4]$$

Integration of this equation from 0 to 50% reaction (100 to 50% of the RCl) provides Equation 17.5 where  $t_{1/2}$  is the time required for 50% of the alkyl halide to react. If 0.50 equivalents of hydroxide ion were present at the start of the reaction,  $t_{1/2}$  will be the time at which the solution becomes acidic.

$$\int_{1.0}^{0.5} \frac{d[\text{RCI}]}{[\text{RCI}]} = - \int_0^{t_{1/2}} k_1 dt$$

$$2.3 \log 0.5 = -k_1 t_{1/2} \quad [17.5]$$

$$k_1 = -2.3 \log 0.5 / t_{1/2} = 0.69 / t_{1/2}$$

In the procedure to be used, the amounts of alkyl halide and hydroxide are not accurately measured, since only relative rates are desired. If the alkyl halide used were weighed and the NaOH solution were standardized and accurately dispensed, actual rate constants could be obtained.

Suitable solvent systems for this study are mixtures of water with methanol, ethanol, and acetone. The volume percent compositions indicated below will give conveniently measurable reaction rates, with the exception noted for 70% acetone. The following solutions will be available.

#### COMPOSITION (SOLVENT: WATER)

55:45	(all solvents)
60:40	(all solvents)
65:35	(all solvents)
70:30	(not acetone)

## PROCEDURE

Select three to five solvent mixtures, using either different ratios of one solvent or the same ratio with the three solvents, and label each of three to five clean dry 13 × 100-mm test tubes accordingly. To each test tube add 2.0 mL of the solvent system and 3 drops of 0.5 M NaOH solution containing phenolphthalein indicator. Cover the tubes with corks or parafilm, and place them in a bath containing a thermometer and water at 30 ± 1°C. A Styrofoam cup placed in an empty beaker for stability makes a convenient insulated container for the bath. After 4 to 5 minutes in the bath to bring the solvent to bath temperature, add 3 drops of *tert*-butyl chloride to each test tube. Note the time of addition, shake or swirl the test tubes to mix the solutions, and replace them in the bath, swirling intermittently to insure good mixing. Add a few mL of hot water as needed to the bath to maintain the temperature at 30 ± 1°C. Record the time required for the pink (basic) color to disappear in each solvent mixture. Tabulate your results and compare them with those of others in the class to obtain a more complete picture of the solvent effects.

### C. EFFECT OF TEMPERATURE ON REACTION RATES

The rate of any reaction increases with increasing temperature because of the greater kinetic energy of the reacting molecules. The effect of temperature on the rate constant of a reaction is generally expressed in terms of the Arrhenius Equation (Eq. 17.6) where  $E_a$  is the activation energy,  $T$  is the temperature in K,  $A$  is a term related to the probability of a reaction occurring if the molecules have sufficient energy, and  $R$  is the gas constant (1.99 cal/mole deg). The activation energy can be obtained if the rate constant is known at two or more temperatures.

Using the logarithmic form of Equation 17.6 (Eq. 17.7), it is seen that a plot of  $\log k$  versus  $1/T$  gives a straight line with slope equaling  $-E_a/2.3R$ .

$$k = A \exp\left(-\frac{E_a}{RT}\right) \quad [17.6]$$

$$\log k = \log A - \frac{E_a}{2.3R} \left(\frac{1}{T}\right) \quad [17.7]$$

The effect of temperature on the rate of solvolysis of *tert*-butyl chloride can be studied using the procedure and solvent systems of Part B at different temperatures. To obtain conveniently measurable rates, a solvent should be used that gives an end point at about 10 minutes in Part B. Although numerical values of the rate constants are not obtained by the comparative procedure in Part B, the neutralization times measured are inversely proportional to the rate constants (Eq. 17.5). Thus, a plot of  $\log t$  values versus  $1/T$  gives a straight line with slope  $+E_a/2.3R$  from which the value of  $E_a$  can be obtained.

## PROCEDURE

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From your results in Part B, select the solvent system for which the neutralization time at 30°C is closest to 10 minutes. Obtain two 2-mL mixtures of this solvent composition and add 3 drops of phenolphthalein indicator solution as in Part B. (In this part of the experiment, duplicate samples should be run.)

Adjust the temperature of the water bath to  $20 \pm 1^\circ\text{C}$ , insert both tubes, and allow 4 to 5 minutes for temperature equilibration. Note the time, add 3 drops of *tert*-butyl chloride to each tube, mix, and measure the time required for the color to disappear. Repeat the procedure with two other samples after adjusting the bath temperature to  $40 \pm 1^\circ\text{C}$ .

Using the times required for the samples at 20°C and 40°C and the time at 30°C from Part B, make a plot of  $\log t$  versus  $1/T$  (°K), and from the slope, calculate the activation energy for the solvolysis in the solvent used.