

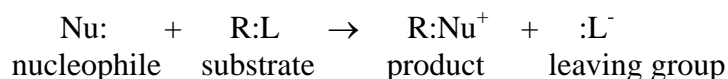
The Mechanism of a Substitution Reaction

Background

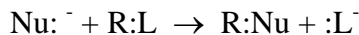
Organohalogenes are mainly laboratory creations. A few compounds of this type have been found in some organisms, especially in the oceans, but for the most part this class of substances has been manufactured for various uses in the modern world: as solvents, insecticides, herbicides, refrigerants (CFCs), etc. This is not always completely good news, especially when these compounds are mishandled.

In the laboratory organohalogenes are important reagents in synthesis because it is easy to convert them into other kinds of compounds. One of the pathways for remaking these substances is known as *nucleophilic substitution*.

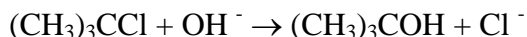
A *nucleophile* (literally "nucleus lover") is a molecule or ion capable of acting as a Lewis base (i.e., an electron pair donor). Nucleophiles can be described as "electron-rich" while their targets or *substrates* can be described as "electron-deficient" (they are Lewis acids, i.e., electron pair acceptors). In a nucleophilic substitution the nucleophile takes the place of--or *substitutes* for--some atom or group on the substrate (called the "leaving group"):



If the nucleophile is neutral (as shown above) the product will be charged since the leaving group takes both bonding electrons away with it. If the nucleophile is an anion then the product will be neutral:



Stronger bases make better nucleophiles (e.g., OH^- is a better nucleophile than H_2O). "Good" substrates include cations, central atoms with incomplete octets or double bonds (like sp^2 carbons) or carbons with partial positive charges. Halogens are generally more electronegative than carbon and so organohalogen compounds are usually subject to nucleophilic attack at the carbon attached to the halogen (which would be the positive end of a dipole). For example, 2-chloro-2-methylpropane (commonly known as *t*-butyl chloride) will undergo nucleophilic substitution with hydroxide ion:

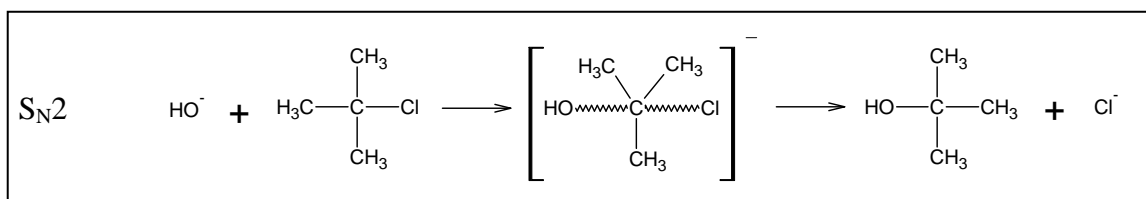
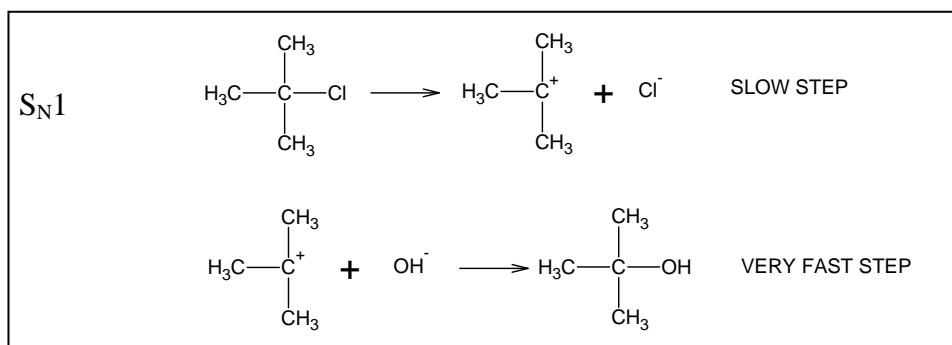


This is a typical synthetic route for producing an alcohol from an alkyl halide.

Nucleophilic substitution reactions have been studied for many years. It was noticed fairly early that while the overall reaction was similar in the vast majority of cases the kinetics of the process was not always the same. In some substitutions the concentration of the nucleophile had no effect on the rate. In others, the rate was directly proportional to the concentration of the nucleophile. This suggested that two different mechanisms must be at work. The factor which determines the mechanism employed is typically the nature of the substrate itself and NOT the particular nucleophile.

Adapted from [Determining the Reaction Mechanism of a Chemical Reaction Using Kinetics](http://www.udallas.edu/chemdept/hendrickson/3121/solvolysis.htm), Dreyfus Institute
[Solvolysis of *tert*-Butyl Chloride](http://www.udallas.edu/chemdept/hendrickson/3121/solvolysis.htm), <http://www.udallas.edu/chemdept/hendrickson/3121/solvolysis.htm>

The two proposed nucleophilic substitution mechanisms are represented below, using *t*-butyl chloride as the substrate and hydroxide as the nucleophile [note: only one of these is actually correct for *t*-butyl chloride]:



The first mechanism is known as **S_N1** (substitution, nucleophilic, unimolecular) because only one molecule is involved in the first step--the *rate determining step*. Reactions occurring by this mechanism should exhibit first-order kinetics, i.e., the rate law should have the form "rate = k [substrate]¹". Because the nucleophile is not involved until after the slow step its concentration will have no effect on the rate.

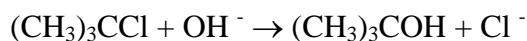
The alternate mechanism is called **S_N2** (substitution, nucleophilic, bimolecular) because two molecules are involved in the rate determining (and only) step. Such reactions exhibit overall second-order kinetics. The rate is proportional to *both* the concentration of the substrate *and* the concentration of the nucleophile. Reactions like this will have a rate law in the form "rate = k [substrate]¹[nucleophile]¹".

In principle it is therefore relatively simple to distinguish between these mechanisms by experiment. If changing the concentration of nucleophile has no effect on the rate of a reaction then it must be S_N1. If there is an effect the reaction must be S_N2.

In addition to the effects of concentration, chemists noted a marked difference in the effect of solvent properties on the rates of these two types of reactions. Strongly polar solvents increase the rate of S_N1 reactions significantly but have little or no effect on S_N2 reactions. To understand why this is so look back at the two mechanisms. In the slow step of the S_N1 mechanism ions must form. Any solvent which facilitates the stability of separated ions will lower the activation energy for this step. Polar solvents possess high *dielectric constants*. This means they have the ability to orient themselves between separated ions in a mixture and prevent these ions from recombining. Water has a high dielectric constant (81) compared to some organic solvents like ethanol (25) or acetone (21). By contrast, in the S_N2 mechanism the same ionic charge is carried through the reactants, transition state and products. There is nothing to be gained from polar solvent molecules. Of course, the solvent effect (or lack of it) should agree with the overall experimentally determined order!

If the solvent is the nucleophile in a substitution reaction the process is sometimes called *solvolysis*. If the solvent is water (as in part of this experiment) the term "hydrolysis" is sometimes used, but this should not be confused with inorganic acid/base chemistry. "Diluting" or "concentrating" water in the usual way is not possible so it does not make a good nucleophile for examining the effect of nucleophile concentration on the rate and subsequent elucidation of the mechanism. However if a small amount of hydroxide ion--which is a stronger nucleophile--is introduced into the mixture then the concentration effect can be examined. The solvent effect can be observed by adding a co-solvent to water (one with a smaller dielectric constant) in various proportions. A co-solvent is necessary in most cases anyway since organohalogenes are generally not water soluble. The reactions with hydroxide and water are actually different, of course, but they both occur by the same mechanism--whichever it is--since the nature of the *substrate* determines the mechanism.

Following a reaction for kinetic studies is often an interesting challenge. Chemists look for some kind of change in the mixture which can be easily measured without interfering with the reaction. In the reaction of *t*-butyl chloride with sodium hydroxide the mixture begins basic but will become neutral or slightly acidic when all of the hydroxide has been consumed:



This situation lends itself to the method of initial rates. If the concentration of *t*-butyl chloride is very much greater than the concentration of hydroxide then it will remain essentially "constant" during the reaction allowing a comparison to be made in the rates for different hydroxide concentrations. An indicator in the mixture can be used to signal when the hydroxide is consumed. The amount of hydroxide which reacts is equal to the amount of *t*-butyl chloride which reacts in the same time period. This provides a rate for comparison purposes whether the change is in hydroxide concentration or the polarity of the solvent mixture.

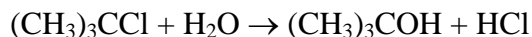
In the method of initial rates various mixtures are chosen to facilitate comparison of rates and concentrations. Consider the hypothetical reaction and mixture table below.



initial [A]	initial [B]	initial rate, [C]/min
0.10	0.0010	0.050
0.20	0.0010	0.10
0.10	0.0020	0.10

In this example when the concentration of A doubles while the concentration of B remains constant the rate also doubles. This indicates that the reaction is first order with respect to A. The same thing happens when the concentration of B is doubled and the concentration of A remains the same. So the reaction is also first order with respect to B. The rate law would look like "rate = $k[\text{A}]^1[\text{B}]^1$ " and the reaction is overall second order. Clearly a similar analysis of the *t*-butyl chloride reaction with hydroxide could reveal whether the reaction is $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ (i.e., first order or second order overall).

In the reaction of *t*-butyl chloride with water, hydrochloric acid is a by-product:



[this reaction actually passes through a very fast intermediate in which the species $(\text{CH}_3)_3\text{COH}_2^+$ donates a proton to water, forming H_3O^+ ; the formation of acid is represented here by the $\text{HCl} \rightarrow \text{Cl}^-$ being the leaving group]

The stoichiometry of the reaction shows that for every molecule of *t*-butyl chloride that reacts, one unit of HCl is produced. Since water is the solvent no information can realistically be obtained concerning its effect on the rate--other than as a very polar solvent compared to a less polar mixture. But once the form of the rate law has been determined for the reaction with hydroxide as a nucleophile, the reaction with water is well-suited for the determination of the rate constant and the activation energy of the solvolysis of *t*-butyl chloride.

As the reaction proceeds *t*-butyl chloride is converted into HCl on a 1:1 basis. This means the pH of the mixture will change with time. The K_a for 2-propanol/water solvent is so small as to be negligible so the pH of the mixture starts at essentially 7.0. If the pH is monitored over time the increase in HCl can be interpreted as the *decrease* in *t*-butyl chloride. Data of this sort can be used to determine graphically both the order of the *t*-butyl chloride in the reaction and the rate constant.

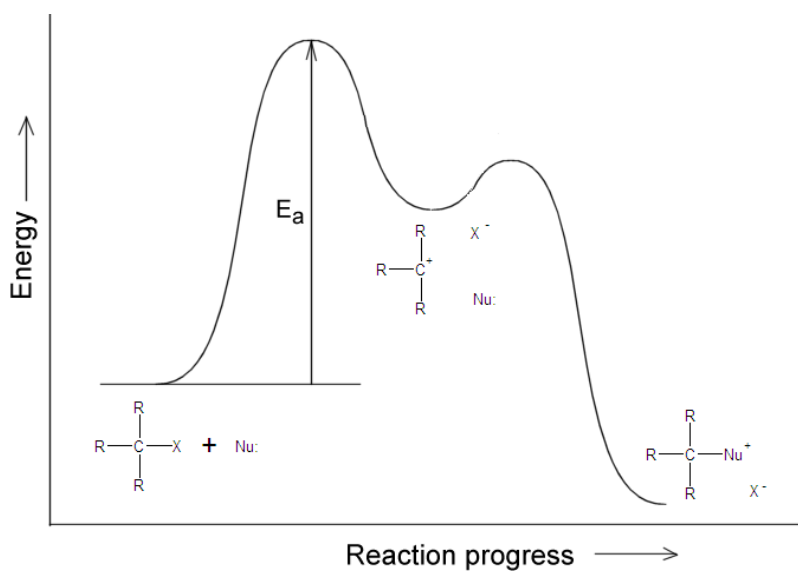
The graphical determination of reaction orders is applicable to situations in which direct (or nearly direct, as in this case) measurement of reactant concentration at fixed time intervals is possible. The standard rate law forms for zero, first and second order behavior are only good for calculating rates or amounts at a fixed time. To determine changes in concentration during time intervals these equations must be integrated (via calculus). This conversion reveals that each rate law expressed in integrated form can be written as a linear equation with a slope equal to $\pm k$.

The rate laws and their integrated forms are shown below [t = time]:

		<u>integrated form</u>
Zero order	$\text{rate} = -\frac{\Delta[\text{A}]}{\Delta t} = k[\text{A}]^0$	$-[\text{A}] = kt + [\text{A}]_0$
First order	$\text{rate} = -\frac{\Delta[\text{A}]}{\Delta t} = k[\text{A}]^1$	$\ln [\text{A}] = -kt + \ln[\text{A}]_0$
Second order	$\text{rate} = -\frac{\Delta[\text{A}]}{\Delta t} = k[\text{A}]^2$	$1/[\text{A}] = kt + 1/[\text{A}]_0$

In each case the "constant" arises from the integration of the original rate law. This constant is related to the original concentration of the reactant, $[\text{A}]_0$. If substance A is zero order in a rate law then a plot of $-[\text{A}]$ vs. time should yield a straight line with slope k . If instead A is first order, a plot of $\ln [\text{A}]$ vs. time will be linear. For second order behavior a plot of $1/[\text{A}]$ vs. time will give a straight line. So this method will not only confirm the result from the method of initial rates but will also give the rate constant. Of course, the rate constant may be determined from the method of initial rates as well but not all reactions can be accurately followed by that method.

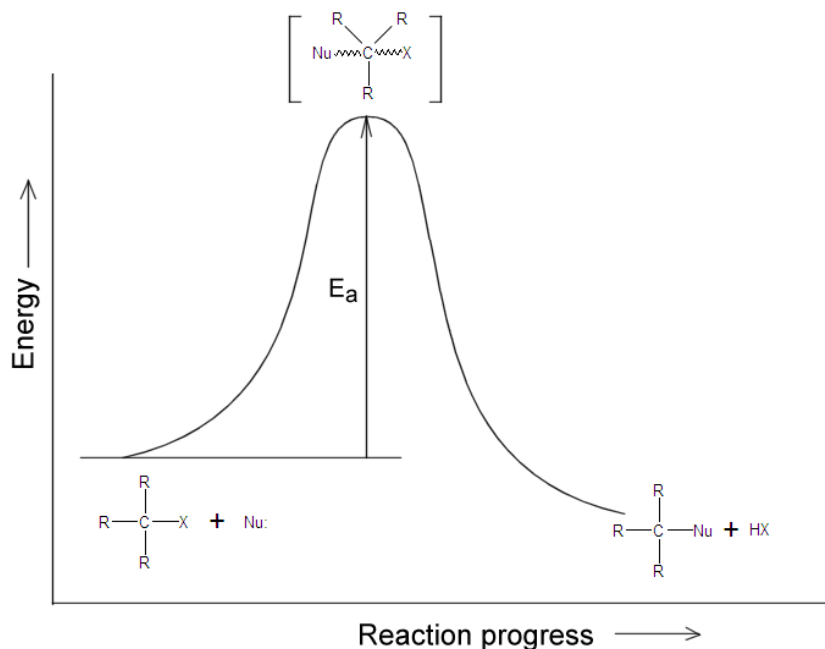
Reaction rates are also influenced by temperature, of course. In a two-step mechanism like the S_N1 , the first step has the higher activation energy:



If the substrate has already reached this energy level there will be sufficient energy for the second step. Therefore the energy requirement of the first or slow step is the overall activation energy for the reaction.

[if the mechanism above were a specific representation for solvolysis with water as the nucleophile there would be a third step with a very small E_a in which the extra proton is lost from the cationic product]

In a single-step process like the S_N2 mechanism, the activation energy of the transition state is all that is required for the reaction to occur:



The rate constant, k , is strongly dependent on temperature. That dependence takes a form which is already familiar:

$$\ln k_1 - \ln k_2 = - \frac{E_a}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right)$$

where E_a is the activation energy in J/mol, $R = 8.31 \text{ J/mol}\cdot\text{K}$ and the temperatures are in kelvins. This, too, is a linear equation [shown here in point-slope form] and if values for k can be determined at several different temperatures a plot of $\ln k$ vs. $1/T$ will give a straight line with slope $-E_a/R$ from which the activation energy can be calculated.

The Experiment

There are three parts to this experiment:

- determination of the mechanism for the solvolysis of *t*-butyl chloride
- determination of the effect of solvent polarity on the rate
- determination of the effect of temperature on the rate

The following non-locker materials will be provided:

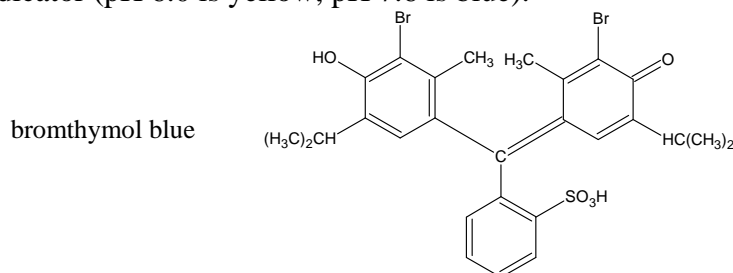
- 0.4 M *t*-butyl chloride in anhydrous 2-propanol [record exact concentration]
- 0.004 M NaOH in water [record exact concentration]
- 45% 2-propanol/55% water mixture (by volume)
- anhydrous 2-propanol
- bromthymol blue solution
- micropipettor w/tips
- 10 mL volumetric pipet w/bulb
- standard thermometer
- ice
- expanded polystyrene container for water bath
- timer

The Chemicals

2-chloro-2-methylpropane or *t*-butyl chloride is a volatile liquid (bp = 51°C) which is sparingly soluble in water but miscible with alcohol and ether. Boiling with water yields 2-methyl-2-propanol or *t*-butyl alcohol. It is a mild irritant and narcotic in high concentrations. May cause liver damage.

2-propanol or isopropyl alcohol is a flammable liquid, miscible with water and common organic solvents. It forms a low-boiling azeotrope with water and can also be used to make low-freezing mixtures (i.e., as an antifreeze). It is a solvent in many quick-drying commercial preparations (inks, shellacs, oils, etc.) and is used as a topical antiseptic in a 70% solution (*rubbing alcohol*). Ingestion of as little as 100 mL can be fatal.

Bromthymol blue ($C_{27}H_{28}Br_2O_5S$) or 3,3'-dibromothymolsulfonphthalein consists of cream-colored crystals which are sparingly soluble in water but soluble in alcohol and alkaline solutions. It is used as an indicator (pH 6.0 is yellow, pH 7.6 is blue).



Sodium hydroxide is commonly known as lye or caustic soda. It is a very hygroscopic white solid (absorbs water from the air rapidly) and also absorbs CO_2 . It is very corrosive to vegetable and animal matter and aluminum metal, especially in the presence of moisture. Dissolving NaOH in water generates considerable heat.

Besides its use in the laboratory, sodium hydroxide is used in commercial drain cleaner preparations, to treat cellulose in the manufacture of rayon and cellophane and in the manufacture of some soaps. It is corrosive to all tissues and can be detected on skin by the "slimy" feeling associated with bases. It should be rinsed off thoroughly upon contact. It can damage delicate eye tissues and cause blindness.

Technique Discussion

Although the experiment is divided into three parts, the last "logical" part should be done first since once set up it requires very little monitoring and takes about 30 minutes for data collection alone.

The third part of the experiment is more complex. You will be assigned a temperature at which to run the solvolysis of *t*-butyl chloride. Other students may duplicate this temperature. At the end of the experiment all of the data will be used to determine values for k and E_a . A reacting mixture will be prepared in a pH electrode storage bottle and kept at the assigned temperature in a water bath. A CBL will be used to follow the pH over time. **Be sure to bring your TI-83/84 calculator to lab and have the HCHEM.8XG programs in memory.**

The water bath for the reaction should be set up first and some care exercised to keep the temperature as close as possible to your assigned value. Approximately 1 mL of the 0.40 M *t*-butyl chloride solution in a stoppered test tube should be placed in the water bath. Calibrate a pH electrode with 2 and 6 buffers and rinse and dry the electrode as thoroughly as possible without damaging it. Pipet 10 mL of the 45% 2-propanol/55% water mixture into the clean, dry storage bottle and remove 0.200 mL (200 μ L). Seal the electrode in the bottle and place the assembly in the water bath to come to temperature. Set up the CBL for measuring pH vs. time at 1 minute intervals. The determination should last about 30 minutes. A graphical display will help you decide whether the experiment should continue that long.

When the reactants have reached thermal equilibrium 0.200 mL (200 μ L) of the *t*-butyl chloride solution is added directly to the mixed solvent and mixed thoroughly. Data recording should begin as soon as the solutions make contact and should continue until the pH of the mixture has more or less leveled off.

During this part of the experiment there is nothing much to do so it is a good time to do some initial rate mixtures. Suitable reacting mixtures are prepared which meet the criteria for the method of initial rates with two reactants such that the ratio of 2-propanol [the solvent for the *t*-butyl chloride] to water [the solvent for the NaOH] remains constant for the first part. In the second part similar mixtures are prepared with *different* ratios of solvents. In both parts a very small amount of NaOH is consumed by the reaction leading to a change in indicator color which signals the completion of the reaction (and the timing interval). These reactions may be done at the ambient lab temperature.

Only small amounts of the materials are required and test tubes make acceptable containers. To obtain data on the orders of two reactants only three mixtures are required [see the example in the Background section]. A reasonable maximum volume of the 0.4 M *t*-butyl chloride solution would perhaps be 0.300 mL (300 μ L) combined with 1.000 mL (1000 μ L) of 0.004 M NaOH, 0.400 mL (400 μ L) of water and 0.300 mL (300 μ L) of 2-propanol. This gives a total volume of 2 mL and it is convenient to keep a constant mixture volume to simplify interpretation of the data. To maintain a constant solvent ratio it is only necessary to add 2-propanol if less of the *t*-butyl chloride solution is used in a mixture, or more water if less of the NaOH is used. Separate micropipet tips should be used for each liquid.

Because the *t*-butyl chloride and its 2-propanol solvent are volatile it should be measured last, after mixing the NaOH, additional water or 2-propanol and 1 drop of indicator in a test tube. The *t*-butyl chloride can then be added directly from the pipet. Immediate and thorough mixing is important and timing must commence as soon as the solutions make contact.

Two additional mixtures should be sufficient to determine the effect of solvent polarity. If you have a mixture with less than 0.300 mL of *t*-butyl chloride solution from the first part of the experiment you can use this as a base for comparison. Prepare the same mixture two more times but in one use only water to make the final volume 2 mL and in the other use only 2-propanol. This gives mixtures which are more and less polar than those used in the order determination.

ALL solutions from every part of the experiment should be discarded ONLY in the container designated in the fume hood.

The Report

Your initial calculations should include:

1. The initial concentrations of *t*-butyl chloride and OH⁻ in the mixtures for parts 1 and 2
2. The rates of the reactions in parts 1 and 2 ([OH⁻]/min)
3. A comparison of rates illustrating the orders for *t*-butyl chloride and OH⁻ in the rate law for part 1
4. A comparison of rates illustrating the solvent effect on the rate for part 2
5. The initial *t*-butyl chloride concentration in the reacting mixture for part 3
6. *t*-butyl chloride concentration remaining at each 1 minute interval for part 3
7. An appropriate plot [based on the order determined in #3] for finding *k* (time in minutes)

*8. A plot of $\ln k$ vs. $1/T$ for determining E_a

*class results for the entire range of temperatures will be distributed after data has been collected

Your conclusion to this experiment should include a brief summary of your findings for the mechanism of the substitution reaction. Note any contradictory indications and attempt to explain them (if needed).