

# Unimolecular Nucleophilic Substitution ( $S_N1$ ): Structural Reactivity Evidenced by Colored Acid–Base Indicators

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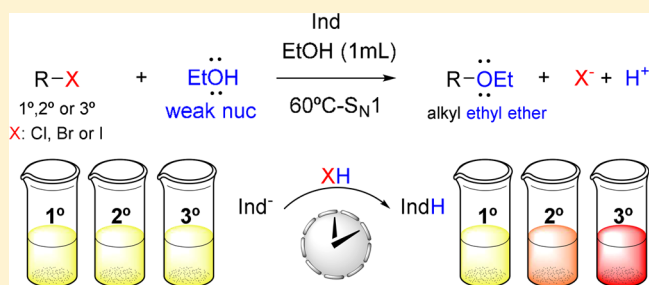
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## Supporting Information

**ABSTRACT:** The different reactivities between 1°, 2°, and 3° butyl chlorides by the unimolecular nucleophilic substitution ( $S_N1$ ) mechanism were easily observed at 60 °C by a solvolysis reaction in ethanol with ether formation. The hydrogen ion from the byproduct HCl reacted with an acid–base indicator such as methyl red to induce a color change. At room temperature, the addition of  $AgNO_3$  was used to detect the released chloride ion by  $AgCl$  precipitation. The reactivity order ( $3^\circ > 2^\circ \gg 1^\circ$ ) was visually confirmed by both a color change in an indicator and precipitate formation by these safe, quick, and easy assays.

**KEYWORDS:** Second-Year Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Nucleophilic Substitution, Acids/Bases



## INTRODUCTION

Nucleophilic substitution mechanisms represent a key topic in undergraduate organic chemistry, stemming from their use in the laboratory for preparative purposes and for the large number of these reactions occurring in living organisms.<sup>1</sup> Both  $S_N1$  (unimolecular) and  $S_N2$  (bimolecular) reaction mechanisms are one of the first subjects studied in organic chemistry courses, as they are useful for understanding kinetic, energetic, and structural aspects of the organic compounds and the basic structure–reactivity relationship.<sup>2</sup> Likewise, the three-dimensional structures of the substrate and the nucleophile, and the nature of the leaving group, are important features to understand the processes involved in nucleophilic substitution reactions.<sup>2</sup>

Because both reaction mechanisms play a central role in organic chemistry, a thorough understanding of them has long been sought.<sup>3</sup> This understanding by students should be developed not only in lectures, but also during lab experiments to illustrate and corroborate the theoretical principles of the reactions.

The  $S_N1$  reaction mechanism requires polar solvents, weak nucleophiles, and enough energy to break a C–X bond (where X is a leaving group such as Cl, Br, or I) to form a carbocation intermediate. Carbocations are stabilized by the degree of substitution, an inductive effect, and hyperconjugation from the alkyl substituents.<sup>4</sup> Thus, tertiary carbocations are the most stable, followed by secondary carbocations, and then primary carbocations, which are highly unstable. In fact, primary

carbocations are so unstable that they probably never form unless they are stabilized by allylic or benzylic groups.

Small alkyl halides are especially suitable for teaching  $S_N1$  and  $S_N2$  reaction mechanisms in both the lecture and laboratory. In the laboratory, the order of reactivity for  $S_N2$  can be demonstrated by way of the Finkelstein reaction (KI or NaI in acetone at room temperature) using 1°, 2°, and 3° alkyl halides<sup>5</sup> (Supporting Information, p S13). However, it is not so easy to demonstrate the order of reactivity for  $S_N1$ . In teaching laboratories, assays with silver nitrate in ethanol are commonly used,<sup>6</sup> yet these experiments can lead to a misunderstanding by students in the differentiation of the substrates' reactivities. Because the formation of silver halide ( $AgX$ ) precipitate is the major driving force in this solvolysis reaction, even some primary substrates can give a positive result either due to a pseudoprimary cation promoted by  $Ag^+$  or due to rearrangements promoted by a slight heating. Either potential cause is effective enough for the reaction to take place; thus, the didactic goal could be missed. As an example, when *n*-butyl bromide has been used for the assay, the good leaving group character of  $Br^-$  accelerates the reaction by formation of the very insoluble  $AgBr_{(s)}$ , which confuses students. Even more confusing results are expected for the structural analog with iodine. The use of other assays with complex kinetic determinations or spectroscopic analyses could be more

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difficult for students. Understanding these complicated and time-demanding experiments could likely confound the main goal of the lab experiment for students: learning concepts about structure–reactivity relationships.

In this context, solvolysis of an alkyl halide in hot ethanol (Scheme 1) proceeding by an  $S_N1$  mechanism<sup>7</sup> can be exploited, but the isolation and product characterization is time-demanding, making lab work more expensive and less didactic. However, in the  $S_N1$  solvolysis reaction, a hydracid is also produced as a byproduct and its formation can easily be observed by the change in color of an acid–base indicator. In this way, students can easily associate changes in color intensity with acid release while the reaction takes place.

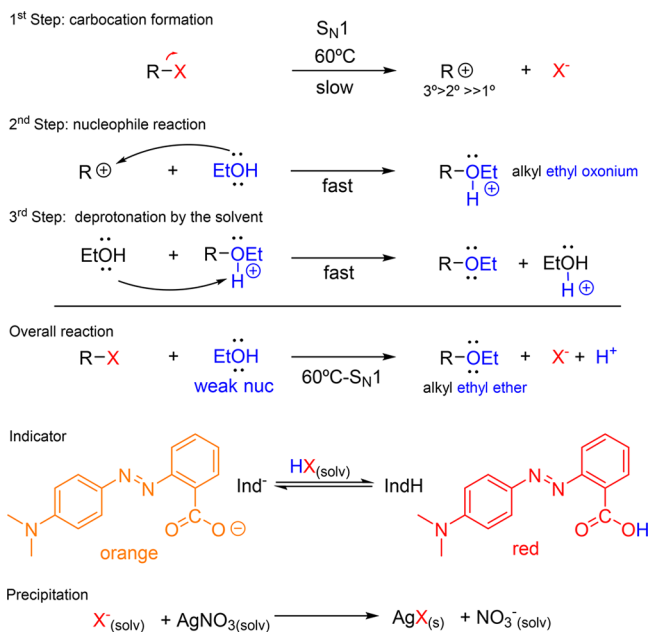
In the present work, a very simple methodology is reported to illustrate the reactivity of alkyl halides and their relationship to structure in an  $S_N1$  reaction. Using this assay, great educational results were obtained, implying a significant improvement over other methodologies previously reported.

### ■ $S_N1$ TEST WITH ACID–BASE INDICATOR

In this experiment, an alkyl ethyl ether is formed after heating for 10 min at 60 °C in the reaction between an alkyl halide and ethanol, the latter acting as a weak nucleophile and solvent. In a positive reaction, a hydracid is formed as a byproduct in the substitution reaction. The acid released is detected by an acid–base color indicator present in the reaction media. Several acid–base indicators were tested (Supporting Information, pp S3–S4): methyl red and methyl orange showed an appropriate color change to visualize the reaction progress. In addition, the halide could be detected with the subsequent addition of silver nitrate at room temperature.

Students can record the reaction evolution using information and communicational technologies (ICTs) such as digital photographs and videos to illustrate in their lab reports.

### Scheme 1. Reaction Steps in $S_N1$ Solvolysis of Alkyl Halides and Ethanol at 60 °C To Form Alkyl Ethyl Ethers and Hydracid<sup>a</sup>



<sup>a</sup>Positive reaction was evidenced by the presence of methyl red acid–base indicator and with the precipitation reaction with silver nitrate.

Although the product is not purified, the assay is easily scalable for a demonstration by the lab coordinator and could be complemented by the NMR spectral analysis of the reagents and the expected products<sup>8</sup> (Supporting Information, pp S14–S20).

### ■ EXPERIMENT

Five vials are placed in a rack. Ethanol (1 mL, 96%) is placed in each vial, and 1 drop of acid–base indicator (~2 mM) is added. Under this condition, methyl red is in the basic orange form. Methyl orange can also be used, see Supporting Information, pp S5–S6. The alkyl halide (1°, *n*-butyl chloride; 2°, *sec*-butyl chloride; and 3°, *tert*-butyl chloride) (3 to 6 drops) is added separately to three of the vials. The vials are loosely capped to avoid vapors and placed in a water bath at 60 °C for 10 min, where the progress of the reaction is observed. The remaining two vials are used as control assays: one without alkyl halide substrate, and the other with *tert*-butyl chloride at room temperature (20–25 °C). After 10 min, the vials are removed from the bath and allowed to reach room temperature; the color of each vial is observed. Subsequently, 1 or 2 drops of  $\text{AgNO}_3$  (5% w/v in ethanol) are added and silver halide precipitate formation is observed.

### ■ HAZARDS

The major hazards of this experiment come from the use of alkyl halides, which, by inhalation, cause dizziness and stomach ache. Alkyl halides are usually highly hazardous in case of skin contact (irritant, permeator), eye contact (irritant), and ingestion.<sup>9</sup> Inflammation of the eye is characterized by redness, watering, and itching. Alkyl halides are toxic to liver and mucous membranes. Repeated or prolonged exposure to the substance can produce target organ damage.

The chemical risks related to these compounds involve the formation of toxic and corrosive fumes due to their decomposition in contact with hot surfaces or with flames. Alkyl halides, ethers, and alcohols are highly flammable in the presence of heat, open flames, and sparks.<sup>9</sup>

Although no large quantities of the products are produced, similar considerations must be taken with butyl ethyl ether. It may cause drowsiness or dizziness;<sup>9</sup> therefore, vials or test tubes must be capped when they are under observation as a precaution. In addition,  $\text{AgNO}_3$  is very hazardous in case of skin contact (irritant) or ingestion,<sup>10</sup> furthermore, the product  $\text{AgCl}$  is an irritant in case of skin or eye contact.<sup>10</sup>  $\text{HCl}$  is a strong acid;<sup>10</sup> however, it is produced in low quantities and concentrations. All risks are minimized if reactions are performed on capped vials or prepared under a fume hood. In the heating step, the vials should be loosely capped, or the vials should have a large empty volume above the liquid phase to avoid an increase in internal pressure to prevent the lid from opening suddenly. Waste generated in this assay should be discarded in a stream suitable for halogenated organic solvents. The use of lab protection, such as personal protective equipment, lab coat, gloves, and goggles for eye protection, and adequate ventilation are mandatory.

### ■ RESULTS AND DISCUSSION


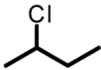
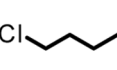















#### Ether Formation Evidenced by Acid–Base Indicator

In this experiment, three structural isomers of butyl chloride were used: *tert*-butyl, *sec*-butyl, and *n*-butyl chlorides. Analysis of the results was simple and easy to observe by students. The

figures in Table 1 show typical reaction performance. At initial stages, the reaction vials were slightly orange. After 10 min heating, *tert*-butyl chloride gave a positive reaction when the indicator turned red by HCl formation (Scheme 2); *sec*-butyl chloride gave a slight color change due to its lower reactivity. The color change for *sec*-butyl chloride was not that evident, unless under careful observation, which, for students, indicated an apparent lack of reaction (Supporting Information, pp S7–S8), while *n*-butyl chloride remained unchanged. Progress of the reaction for *sec*-butyl chloride was difficult to observe only with the indicator color change. To compensate for this, a precipitation reaction was used to provide evidence for the different reactivity. When vials were removed from the bath and a  $\text{AgNO}_3$  solution was added at room temperature, the presence of  $\text{Cl}^-$  anions was confirmed by precipitation of  $\text{AgCl}_{(s)}$ . Without heating, silver nitrate instantly reveals the presence of the chloride ions generated by the reaction of the butyl chlorides. Thus, in the vial with *tert*-butyl chloride, the reaction progress was confirmed, and two phases were formed: an intense red liquid phase and a large quantity of white precipitate. For the *sec*-butyl chloride, with the addition of  $\text{Ag}^+$ , the solution became turbid in the presence of  $\text{AgCl}_{(s)}$  in suspension and showed little progress of the reaction, while the primary halide remained unchanged.<sup>11</sup>

The silver ion must be added after and not before heating because silver cation assists the release of the leaving group

**Table 1. Chloro Butyl Solvolysis Reactions in Ethanol Form Butyl Ethyl Ethers and HCl in the Presence of Methyl Red, Followed by Addition of  $\text{Ag}^+$**

	Control Ind				Control Heating
Starting conditions					
After 10 min at 60°C					
+ $\text{AgNO}_3$ 5% (EtOH)					

<sup>a</sup>Note: Typical results of the  $\text{S}_{\text{N}}1$  solvolysis reaction of butyl chloride isomers in ethanol. The photographs show the changes of each vial: from the beginning; after 10 min at 60 °C; and finally, with silver nitrate addition at room temperature. Control indicator (Ind.) and control heat were made without *tert*-butyl chloride, and without water bath heating, respectively.

chloride for primary alkyl halides (Supporting Information, Instructor's notes, pp S7–S8). In addition, two control vials were used: one containing ethanol and indicator that was heated at 60 °C and the other that contained *tert*-butyl chloride and indicator that was kept at room temperature. After heating and  $\text{Ag}^+$  addition, the two vials remained unchanged. The first control showed that the acid–base indicator does not change its color by any solvent effect or reaction temperature unless an acid is present. In the second control after 10 min at room temperature, some color change was observed; upon the addition of  $\text{Ag}^+$ , the reaction became red and  $\text{AgCl}_{(s)}$  was formed, but with less intensity compared to the heated vial. This was attributed to the high reactivity of the *tert*-butyl isomer.

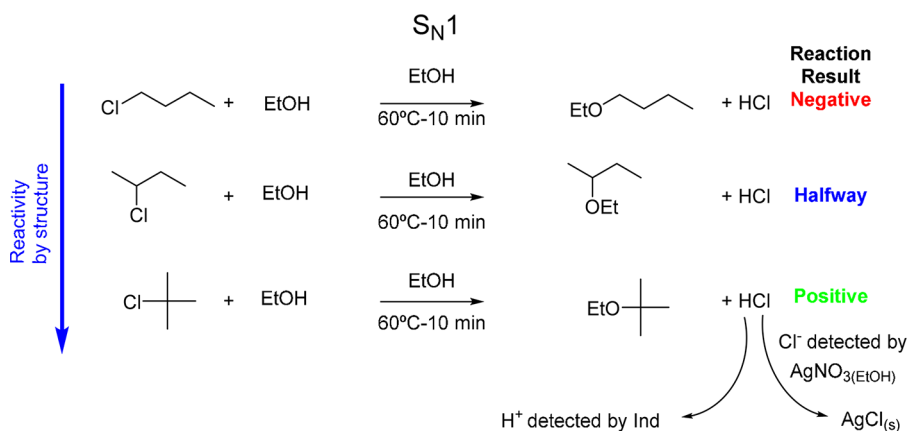
It was easily observed by students that the more substituted substrates showed the fastest reactivity by an  $\text{S}_{\text{N}}1$  mechanism. It can be corroborated that both change in color intensity and precipitate formation followed the order of stability of the intermediate carbocation involved:  $3^\circ > 2^\circ \gg 1^\circ$ , while the latter remains unchanged due to its lack of reactivity (Scheme 2). The results were discussed according to the different reactivities with no purification step. In addition, discussion of the mechanism was complemented by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral analysis (Supporting Information, pp S7 and S14–S20).

### Pedagogical Considerations

The objective of the experiment is to show structure–reactivity relationships among a series of isomers in a solvolytic  $\text{S}_{\text{N}}1$  reaction by a quick and easy assay. The experiment was developed as part of a laboratory lesson on nucleophilic substitution for second-year undergraduate students. Students had previously received a lecture on the topic and had solved and discussed problems with their teaching assistants.

Usually, in these laboratory experiments, groups of 20 students are formed (20 groups and around 400 students each year). Usually, students worked in pairs in the lab. The experiment was evaluated with a brief test and with a journal-style lab report. The ether formation assay was conducted in 2016 as a demonstration assay by the instructor in each laboratory lesson. The demonstration was well received by students and did not considerably increase lab work. In 2017, the experiment was established as one of the regular activities to be carried out by each student group. Thus, this experiment has been carried out successfully 20 times in 2016 and about 200 times in 2017, which reached 800 students. This colorful experiment encouraged the use of ICTs by students. The didactic value of this experiment was evidenced in the lab reports that were actually improved with the inclusion of ICTs; moreover, students were able to integrate in a simple experiment the theoretical concepts introduced in organic chemistry lecture and the experimental results obtained in the laboratory.

The use of a chameleon acid–base indicator to evidence an  $\text{S}_{\text{N}}1$  solvolysis reaction used together with the Finkelstein reaction (and other assays: Supporting Information, pp S12–S13) allowed students to gain a better understanding of  $\text{S}_{\text{N}}1$  and  $\text{S}_{\text{N}}2$  reaction mechanisms. In addition, as some authors have recommended,<sup>12,13</sup> students were able to apply their basic NMR spectroscopy skills (knowledge acquired the previous lesson) to identify the number and multiplicity of signals from both reactants and the expected reaction products.

Scheme 2. S<sub>N</sub>1 Solvolysis Reaction of Butyl Chloride Isomers (*n*-Bu, *sec*-Bu, and *tert*-Bu) in Ethanol<sup>a</sup>

<sup>a</sup>Byproduct HCl was detected by methyl red acid–base indicator and later on AgCl precipitation by AgNO<sub>3</sub> addition at room temperature. Both color change and solid formation depends on the butyl chloride isomers reactivity. Important: *n*-Butyl chloride is not reactive under the indicated reactions conditions.

## CONCLUSION

A simple and safe experimental procedure was developed as a practical lab experiment to illustrate the structure–reactivity relationship in undergraduate chemistry courses. In the experiment, ethanol was used as a solvent and as a weak nucleophile in the unimolecular nucleophilic substitution reaction with three butyl chloride isomers. The outcome of the combination of an acid–base indicator with a silver halide precipitation reaction allowed students to differentiate the three isomers visually. The whole activity took about 20 min in total (10 min reaction plus 10 min for experimental set up and analysis). Although the results are qualitative, this experiment unambiguously discriminated the reactivity in the butyl chloride family of compounds, which allowed students to discuss and consolidate theoretical concepts about the S<sub>N</sub>1 reaction mechanism previously acquired. On the basis of our experience, it was better to complement this experiment with other experiments for alkyl halides such as the Finkelstein test for the S<sub>N</sub>2 mechanism, the synthesis of *tert*-butyl chloride, Beilstein assay, etc. (Supporting Information, pp S12–S13). The combination of all of these assays allowed the students to understand both key mechanisms (S<sub>N</sub>1 and S<sub>N</sub>2) in organic chemistry.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.7b00903.

Additional resources for instructors and students; *tert*-butyl chloride synthesis; NMR spectra; S<sub>N</sub>1 and S<sub>N</sub>2 activities (PDF, DOCX)

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### Notes

The authors declare no competing financial interest.

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