Monitoring Phosphine Nucleophilic Substitution Reactions with Benchtop $^{31}P\{^{1}H\}$ NMR Spectroscopy

Introduction

Alkyl halides (R-X) are a very important family of organic compounds. Not only are alkyl halides popular, versatile solvents (*e.g.*, $CHCl_3$ and CH_2Cl_2), but they are also vital to a number of common organic reactions, including C-C coupling and nucleophilic substitutions.[1,2] The halogen atom attached to an sp^3 C-X bond (X = Cl, Br, I) creates an electronegativity mismatch where, except in the case of iodine, the carbon-halogen bond carries a positive partial charge.[3] This mismatch is commonly invoked to explain the reactivity of alkyl halides in nucleophilic substitutions, but it is not the only aspect that affects these reactions. The C–I bond is not very polar, but iodoalkanes are the most reactive alkyl halides. Iodine is a highly polarizable atom and this large polarizability compensates for the lower electronegativity, rendering C–I bonds more reactive than C–Br and C-Cl.[4]

C-X	Electronegativity
C	2.5
F	4.0
Cl	3.0
Br	2.8
I	2.5

For this experiment, we will look at nucleophilic substitutions reactions. These are typically introduced in early organic chemistry curriculum, often in both lectures and laboratory. In these reactions the alkyl halide is attacked by a nucleophile. A nucleophile is a species with an unshared electron pair; it could be a negatively charged ion (*e.g.* CH_3O–, CN–) or a neutral species (e.g. PPh_3, H_2O). After the attack, a substitution takes place and the halogen is replaced by the nucleophile, the halogen is called the leaving group (Scheme 1).

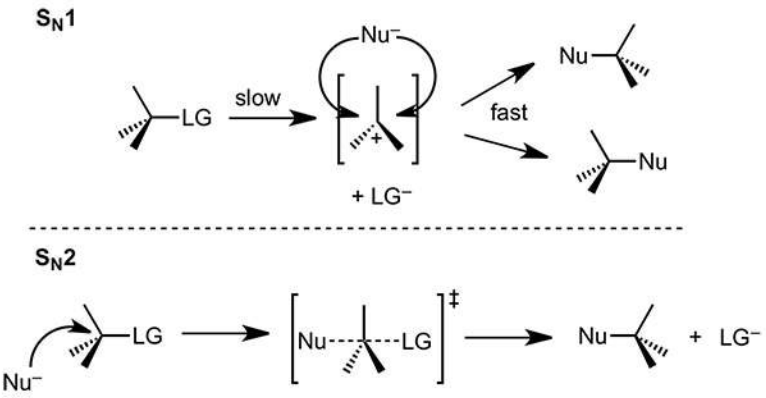
Scheme 1: Nucleophilic Substituion Reaction

It is important to realize that in the overall process the carbon-halide bond breaks and a new carbon-nucleophile bond is formed. Therefore, the strength of the carbon-halide bond is very important in these reactions (Table 2 shows the strengths of several C–X bonds).[4,5] Under the same conditions, the harder it is to break the bond, the slower the reaction will be. That means that iodoalkanes are the fastest to react, followed by bromo-alkanes and chloroalkanes. Fluoro-alkanes are very unreactive and usually don't undergo substitution reactions.

Table 2: Selected Bond Properties

C-X	Strenght (kcal mol^{-1})[4,5]	Covalent Bond Length (pm)[4,6]
F	115	1.39 - 1.43
Cl	83.7	1.78 - 1.85
Br	72.1	1.95 - 1.98
I	57.6	2.15 - 2.18

Nucleophilic substitution reactions can be categorized by the mechanism they undergo. Reactions taking place at saturated carbons are mainly classified as S_N1 or S_N2.[7] S stands for substitution, N for nucleophilic, and the number indicates the molecularity (1 means a unimolecular and 2 a bimolecular process). In the S_N2 reaction the attack of the nucleophile and the elimination of the leaving group take place at the same time, it's a concerted process and its rate is proportional to the concentration of both the alkyl halide and the nucleophile. By contrast, the S_N1 reaction involves two separate steps: first slow loss of the leaving group to generate a carbocation intermediate, and then rapid attack of the nucleophile to form a new bond. Because the first step rate-determining, the rate depends only on the concentration of the alkyl halide. Which mechanism occurs under a certain set of conditions and how fast it occurs depends on several factors, such as the structure of the alkyl halide, the leaving group, the nucleophile, and the solvent. Both mechanisms can be seen in Scheme 2.



Scheme 2: S_N1 reaction showing a two-step process (top). S_N2 reaction showing a concerted process (bottom).

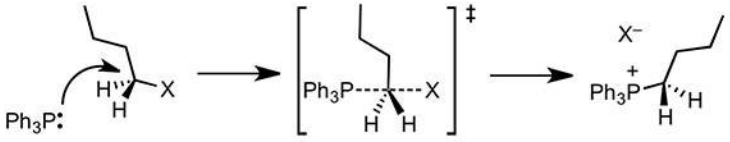
As aforementioned, nucleophilic substitution reactions are frequently included in the experimental part of organic courses.[8,9] However, typically these are introduced prior to spectroscopic methods, and students normally use qualitative observations in order to rate the reactions. For instance, addition of a solution of NaI in acetone to several alkyl halides is frequently used to study the factors that influence an S_N2 reaction. The rate of the reactions is determined by the formation of NaX, which precipitates out of solution (Figure 1). This usually leads to discrepancies between students because the formation of the precipitate is not something they can quantify and highly depends on the person that it is observing the experiment.

Figure 1: Test tubes containing several alkyl halides after the addition of NaI in acetone.

In this experiment, we have chosen phosphine nucleophiles, as this is the first step in formation of a Wittig Reagent, an experiment we highlighted earlier. Phosphines are commonly used as nucleophiles in organic and organometallic chemistry and their reaction with alkyl halides is well-known.[10] Furthermore, the reactions can be easily monitored by ^{31}P NMR spectroscopy because there are no overlapping signals (*e.g.,* solvent) that mask the peaks of interest and the starting materials and the products have distinct chemical shifts. In this experiment we are going to focus on the factors that influence the rate of an S_N2 reaction using triphenyl and tributyl phosphines as nucleophiles. The reactions will be monitored by ^{31}P NMR spectroscopy using the NMReady-60PRO. The following experimental procedure was modified from the experiment reported by Sibbald.[11]

Procedure

In the experiment the alkyl halide electrophile (8.0 mmol) is added to a small round bottom flask containing a solution of the phosphine nucleophile (2.0 mmol) in acetonitrile (1.5 mL). The round bottom flask is fitted with a reflux condenser, to prevent solvent loss, and the reaction mixture is heated to reflux for 30 min. Afterwards, it is cooled to room temperature, and diluted with dichloromethane (1.5 mL) to prevent the newly formed phosphonium salts from precipitating out of solution. An aliquot of the crude reaction mixture (approximately 0.7 mL) is used to acquire the $^{31}P\{^1H\}$ NMR spectrum. No workup is required and the spectra are acquired locking on proton. Figure 2 shows the setup for the experiment.



Scheme 3: S_N2 reaction studied in this experiment

Required Compounds

Phosphines:

- triphenylphosphine
- tributylphosphine

Alkyl halides:

- 1-chlorobutane
- 2-chlorobutane
- 1-bromobutane
- 2-bromobutane
- 1-iodobutane

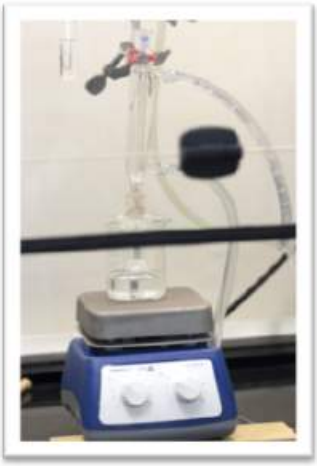


Figure 2: Experimental setup

Results & Discussion

The first factor that we decided to investigate was the leaving group in the alkyl halide. To evaluate that, 1-chlorobutane, 1-bromobutane, and 1-iodobutane were used as the electrophiles and triphenylphosphine as the nucleophile. Figure 3 shows the stacked spectra and Table 3 shows the integration ratio for the unreacted starting material and the phosphonium product.

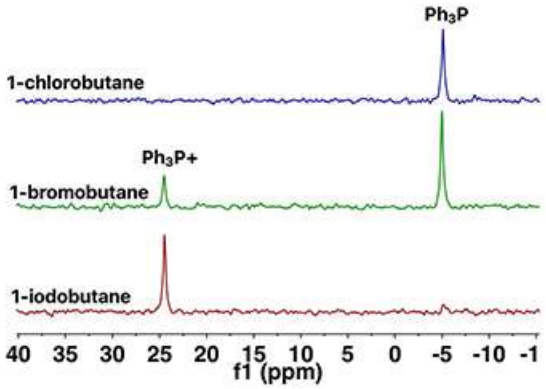


Figure 3: $^{31}P\{^{1}H\}$ NMR spectra from leaving group comparison.

Table 3: % Product formation taken from relative integration of product and reactant

Nucleophile (Nu^-)	Electrophile (E^+)	% Product
PPh_3	1-chlorobutane	0
PPh_3	1-bromobutane	25
PPh_3	1-iodobutane	100

The results show that alkyl halides with larger, more polarizable halogens are more reactive substrates towards S_N2 reactions. 1-chlorobutane and 1-iodobutane are the extremes. The first one shows no reaction at all and the second one shows pretty much 100% formation of the phosphonium salt product.

Subsequently we evaluated the influence of the nucleophile by reacting 1-bromobutane with two different phosphines (triphenylphosphine and tributylphosphine). The experiment demonstrates that tributylphosphine is a considerably stronger nucleophile as only phosphonium product was observed in the reaction mixture. But, in the case of triphenyl phosphine, only 25% of product was present (Figure 4 and Table 4).

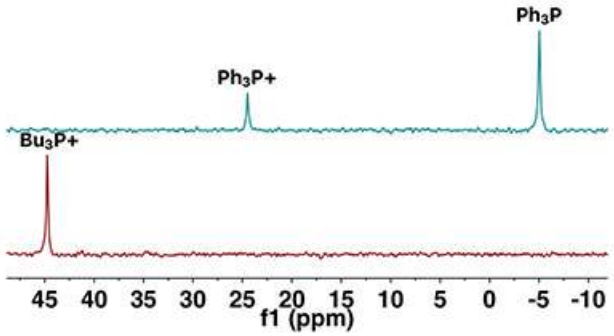


Figure 4: $^{31}P\{^{1}H\}$ NMR spectra comparing nucleophilicity of alkyl and aryl

Table 4: % Product formation taken from relative integration of product and reactant

Nucleophile (Nu^-)	Electrophile (E^+)	% Product
PPh_3	1-bromobutane	25
PBu_3	1-bromobutane	100

We then investigated the role of steric hindrance in the rate of the reaction (Figure 5 and Table 5). Clearly, more sterically encumbered substrates show slower reactivity. Tributylphosphine quickly reacts with 1-bromobutane forming 100% of product, but the reaction with 2-bromobutane only produces 88% of product in the same time. Similarly, the weaker nucleophile triphenylphosphine does not form any product when reacted with 2-bromobutane and only forms 25% of phosphonium salt when the less sterically hindered 1-bromobutane is the substrate.

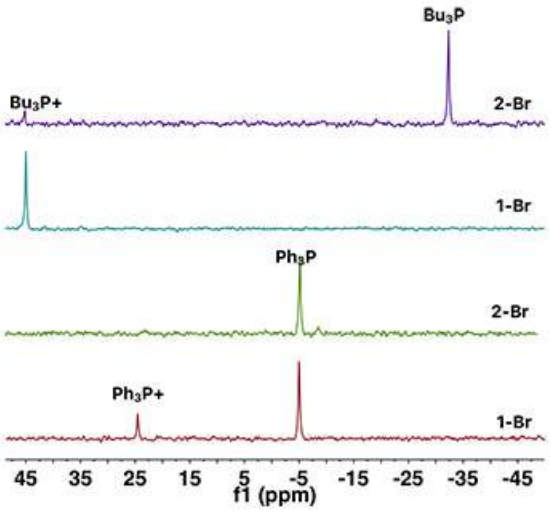


Figure 5: $^{31}P\{^{1}H\}$ NMR spectrum of PPh_3 and PBu_3 nucleophiles with 1- and 2-bromobutane.

Table 5: % Product formation taken from relative integration of product and reactant

Nucleophile (Nu^-)	Electrophile (E^+)	% Product
PBu_3	2-bromobutane	88
PBu_3	1-bromobutane	100
PPh_3	2-bromobutane	0
PPh_3	1-bromobutane	25

Finally, we decided to quickly test the role of the solvent in rate of reaction. For consistency, instead of heating each solvent to reflux, we headed each reaction to 90°C. The reaction of triphenylphosphine and 1-bromobutane did not occur in toluene. The more polar solvent acetonitrile only shows 25% of product and the significantly more polar DMF shows 65% of product under the same conditions (Figure 6 and Table 6). These results are consistent with the theory that SN2 reactions are favoured in polar aprotic solvents.

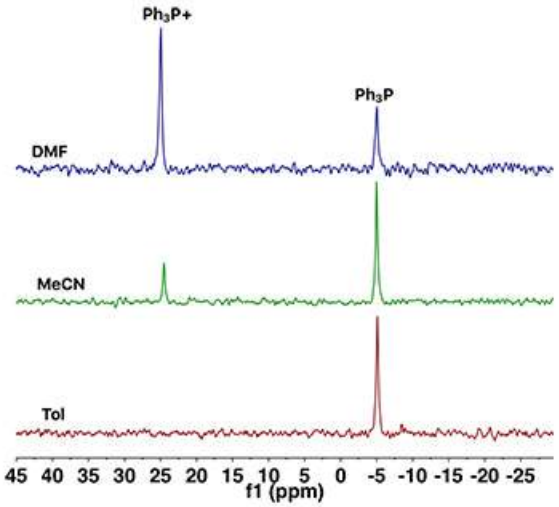


Figure 6: $^{31}P\{^{1}H\}$ NMR spectrum of PPh_3 and 1-bromobutane in different solvents.

Table 6: % Product formation taken from relative integration of product and reactant

Nucleophile (Nu^-)	Electrophile (E^+)	Solvent (Polarity Index)	% Product
PPh_3	1-bromobutane	DMF (6.4)	66
PPh_3	1-bromobutane	MeCN (5.8)	25
PPh_3	1-bromobutane	Tol (2.4)	0

Conclusions

In this quick and easy experiment we have been able to investigate the role of the most important factors determining the rate of an S_N2 reaction. As expected, less sterically hindered substrates, better leaving groups, and stronger nucleophiles favour the S_N2 mechanism and speed up the reaction in polar aprotic solvent. The experiment allows individuals or groups of students to simply monitor their reaction in a timely fashion by ^{31}P NMR spectroscopy using cheap proteo-solvents. Since all the spectra generate singlets students don't need a have a deep understanding of NMR spectroscopy in order successfully complete the laboratory experiment. Furthermore, this is a great experiment to introduce student to one of the most powerful techniques used in re search to monitor reactions.

References

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