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Nucleophilic Substitution Reactions Using Phosphine Nucleophiles: An Introduction to Phosphorus-31 NMR

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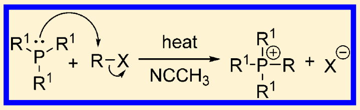
S *Supporting Information*



ABSTRACT: Nuclear magnetic resonance (NMR) spectroscopy is commonly used in modern synthetic chemistry to monitor the conversion of reactants to products. Since instruction in the use of NMR spectroscopy typically does not occur until after the introduction of nucleophilic substitution reactions, organic chemistry students are not able to take advantage of this technique to measure and quantify important concepts such as relative electrophile and nucleophile reactivity. A phosphorus-31 (^{31}P) NMR spectroscopy experiment is reported that allows undergraduate students to monitor product formation for a number of different alkyl halide electrophiles and phosphorus nucleophiles. In this experiment, students are able to use reactant-to-product ratios obtained by simple ^{31}P NMR spectroscopy to explore the relative reactivities of these compounds. This exercise serves as an introduction to both NMR spectroscopy and the specific advantages of heteronuclear NMR spectroscopy.

KEYWORDS: *Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Collaborative/Cooperative Learning, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Main-Group Elements, Molecular Properties/Structure, NMR Spectroscopy, Nucleophilic Substitution*

Nucleophilic substitution reactions are some of the most important reactions discussed in organic chemistry; however, these reactions are often covered before students are exposed to modern reaction monitoring and spectroscopy techniques such as nuclear magnetic resonance (NMR) spectroscopy. Consequently, students have limited tools to explore these fundamental reactions. Many reported nucleophilic substitution laboratory exercises rely on physical properties of the products, such as boiling point[1] or gas chromatography,[2] as a means to monitor product formation. A number of laboratory exercises make use of NMR spectroscopy to study bimolecular nucleophilic substitution (S_N2) reactions using a variety of nuclei including ^{1}H[3] and ^{19}F.[4] However, the interpretation of the NMR spectra for many of these experiments may be beyond the ability of first-semester organic chemistry students.[3c,e,f,h−j,4] These spectra can intimidate novice students and cause them to discount initially the incredible utility of NMR spectroscopy for solving complex problems.

Nucleophilic attack by phosphines on alkyl halides is a well-known and reproducible reaction commonly seen in the synthesis of phosphonium salts.[5] The formation of these phosphonium salts can be easily monitored using phosphorus-31 (^{31}P) NMR spectroscopy by novice organic chemistry students. Both the starting phosphines and phosphonium salts products produce single peaks in decoupled ^{31}P NMR spectroscopy that can be integrated to obtain product ratios. Nuclear magnetic resonance spectrometers with autotunable, multinuclear probes are commonly available and allow rapid access to ^{31}P NMR and other heteronuclear NMR spectra. The ease of conducting these reactions and the simplicity of the resulting spectra make the study of nucleophilic attack by phosphines on alkyl halides an excellent experiment for undergraduate organic chemistry students.

SUMMARY OF PROCEDURE

The pedagogic goal for the experiment is to understand the effects of leaving group ability and steric hindrance on S_N2 reactivity.

Prelab Assignment

Students rank and explain the reactivity of different phosphine nucleophiles (triphenylphosphine and tributylphosphine) in terms of electron richness.[6] Alkyl halide electrophiles (1-chlorobutane, 2-chlorobutane, 1-bromobutane, 2-bromobutane, 1-iodobutane, and 2-iodobutane) in S_N2 reactions are ranked in terms of steric hindrance and leaving group ability.

Lab Experiment

Students work in groups of two. The experiment takes one, 3 h laboratory period to complete. Students are presented with a selection of these same phosphine nucleophiles and alkyl chloride, bromide, and iodide electrophiles. Students groups are assigned a specific nucleophile/electrophile pair for their reaction. The phosphine nucleophile (1.0 mmol) is dissolved in acetonitrile (1.5 mL), and the alkyl halide electrophile (4.0 mmol) is added. The reaction mixture is heated to reflux for 30 min, cooled to room temperature, and diluted with methylene chloride (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 obtain a single scan ^{31}P NMR spectrum in less than 1 min without a workup step or expensive deuterated solvents.

To determine the ratio of products for their reaction, students use the integrations of the ^{31}P peaks that correspond to phosphine, newly formed phosphonium salt, and phosphine oxide; the latter is a commonly occurring byproduct that results from the reaction of phosphines with molecular oxygen. The NMR data collected for all the reactions run by the class are compiled and used to compare the relative reactivities of the different nucleophiles and electrophiles.

■ HAZARDS

All reactants, products, and solvents must be handled in a manner consistent with the information available on their material safety data sheets. Eye protection and gloves must be worn at all times, all manipulations must be conducted in a fume hood, and all waste should be collected and disposed of according to safety regulations.

Triphenylphosphine and butyltriphenylphosphonium salts are toxic. Tetrabutylphosponium salts are toxic and corrosive. Tributylphosphine is toxic, corrosive, and flammable. Acetonitrile, 1-bromobutane, 1-iodobutane, and 2-iodobutane are toxic and flammable. 1-Chlorobutane, 2-chlorobutane, and 2-bromobutane are flammable. Dichloromethane is an irritant and harmful by inhalation and if swallowed. Hazards for other phosphonium salt products are unknown, and students should assume that these products are toxic.

■ RESULTS AND DISCUSSION

The results of these experiments were highly reproducible over six sections of 14–24 students. All students were able to complete this experiment in a single 3 h laboratory period, and most students were finished within 2 h.

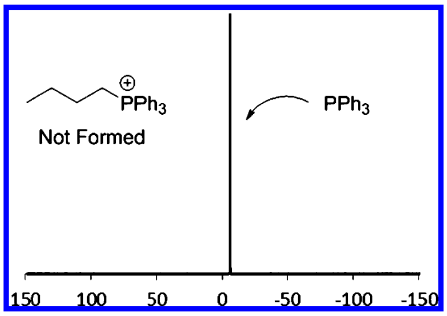


Figure 1. Student ^{31}P NMR spectrum for the reaction of triphenylphosphine with 1-chlorobutane (Table 1, entry 1).

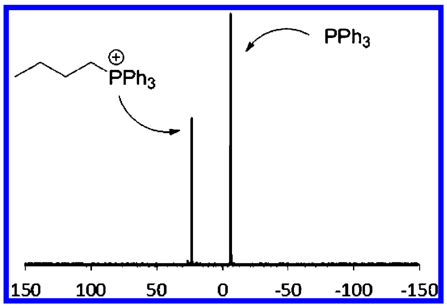


Figure 2. Student ^{31}P NMR spectrum for the reaction of triphenylphosphine with 1-bromobutane (Table 1, entry 2).

Experiment

Student reactions produced a clear, colorless solution that formed a precipitate unless diluted with dichloromethane. Cooling the reactions stopped further conversion to products as the rate of these reactions at room temperature was not significant. Electron-rich phosphines, such as tributylphosphine, were especially prone to oxidation when heated in an open-air reaction.

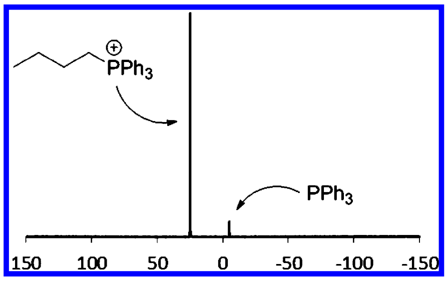
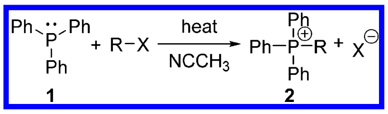


Figure 3. Student ^{31}P NMR spectrum for the reaction of triphenylphosphine with 1-iodobutane (Table 1, entry 3).

Scheme 1. Reaction of Triphenylphosphine (1) with Primary and Secondary Alkyl Halides



NMR samples were made by removing an aliquot of the crude reaction mixture without concentration of the reaction mixture or the use of deuterated solvents. These NMR samples were sufficiently concentrated so that ^{31}P NMR spectra could be generated with a single scan, which allowed each sample to be run in less than 1 min. This allowed students to complete these reactions and obtain NMR data in a single lab period. By using a single scan, integration values can be used to determine product/reactant ratios as differences in relaxation time were no longer a factor.

Spectra were referenced to residual starting phosphine or product phosphonium salts using chemical shift data provided in a student handout.[7] The peaks of interest were then integrated and used to determine relative reaction rates.

The most common errors in this experiment occurred when students did not add the correct quantities of reagents or incorrectly timed the reaction period. ^{31}P NMR spectra for reactions using tributylphosphine as a nucleophile showed the formation of additional phosphorus-containing side products. Fortunately, these additional product peaks were offset from the peaks of interest and excluded from further analysis. Students were, therefore, still able to assign and integrate the relevant peaks in the ^{31}P NMR spectra and compare these data to data collected by their classmates.

Analysis

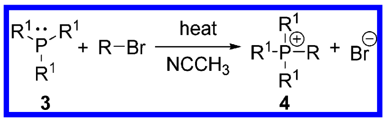
This experiment introduced undergraduate organic chemistry students to NMR spectroscopy as a modern reaction monitoring technique. Phosphorus-31 NMR spectroscopy was a particularly approachable form of NMR spectroscopy for undergraduate students as it illustrated the concepts of chemical shift and integration through easy-to-interpret ^{31}P NMR spectra (Figures 1–3) before the additional complexity of spin–spin splitting seen in ^{1}H NMR spectroscopy is introduced.

Students initially investigated the effects of leaving group ability on S_N2 reactivity using triphenylphosphine as a nucleophile (Scheme 1). As anticipated, electrophiles with larger, more polarizable halogens showed greater reactivity as

Table 1. Student Product Composition for the Reaction of Triphenylphosphine (1) with Primary and Secondary Alkyl Halides

Entry	Electrophile	Unreacted Phosphine (1)	Phosphonium Salt (2)
1	1-chlorobutane	100.0%	0.0%
2	1-bromobutane	74.9%	25.1%
3	1-iodobutane	7.0%	93.0%
4	2-chlorobutane	100.0%	0.0%
5	2-bromobutane	100.0%	0.0%
6	2-iodobutane	98.0%	2.0%

Scheme 2. Reaction of Triphenylphosphine (PPh_3) and Tributylphosphine (PBu_3) with 1- and 2-Bromobutane



S_N2 substrates (Table 1, entries 1−3). Students then investigated the role of increasing steric hindrance on the electrophile. Again, the reduced reactivity predicted by students for more substituted electrophiles was observed (Table 1, entries 4−6).

Students also investigated the role of the nucleophile on S_N2 reactivity by reacting triphenylphosphine (PPh_3) and tributylphosphine (PBu_3) with primary and secondary substituted alkyl bromides (Scheme 2). They observed that the more electron-rich tributylphosphine was a better nucleophile than was the more electron-poor triphenylphosphine (Table 2, entries 1 and 2, 3 and 4).[6] The observation that more hindered electrophiles led to reduced S_N2 reactivity was reconfirmed through using both 1-bromobutane and 2-bromobutane in this screening (Table 2, entries 1 and 3, 2 and 4).

The pedagogic goal for the experiment was to understand the effects of leaving group ability and steric hindrance on S_N2 reactivity. Achievement of this pedagogical goal was assessed using a guided lab report (Supporting Information). Over six laboratory sections, the average score earned on the guided lab report was a 92.7 ± 3.7%, which demonstrates the anticipated student mastery.

■ SUMMARY

This laboratory exercise taught students to use the important NMR concepts of chemical shift and integration through highly approachable ^{31}P NMR spectra. Students were readily able to use the ^{31}P NMR data generated to investigate the effects of leaving group ability and steric hindrance on S_N2 reactivity. After this experiment, students were able to predict S_N2 reactivity better not only in reactions using phosphine nucleophiles and alkyl halide electrophiles, but also in reactions using a variety of reagents. This introduction to NMR spectroscopy provided a valuable foundation for later discussions of ^1H and ^{13}C NMR spectroscopy. Student exit surveys for this modern and innovative laboratory exercise have been highly positive.

■ ASSOCIATED CONTENT

Supporting Information

Handouts for students, notes for instructor, student ^{31}P NMR spectra, and guided lab report. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Table 2. Student Product Composition for the Reaction of Triphenylphosphine (PPh_3) and Tributylphosphine (PBu_3) with 1- and 2-Bromobutane

Entry	Reaction	Unreacted Phosphine (3)	Phosphonium Salt (4)	Phosphine Oxide
1	1-bromobutane/PPh_3	74.9%	25.1%	0.0%
2	1-bromobutane/PBu_3	0.0%	81.8%	18.2%
3	2-bromobutane/PPh_3	100.0%	0.0%	0.0%
4	2-bromobutane/PBu_3	52.0%	12.6%	35.4%

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(7) Refer to Supporting Information on instructions and sample ^{31}P NMR spectra using a 95% H_3PO_4 internal standard.