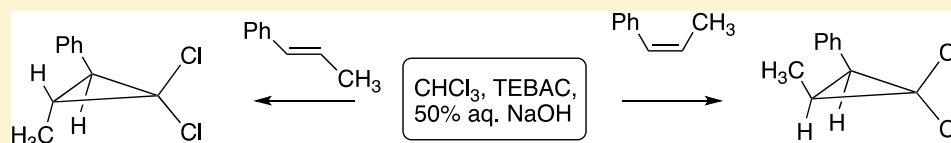


Stereochemistry of Dichlorocarbene Addition to Alkenes: A Collaborative, Discovery-Based Experiment for the Organic Chemistry Laboratory

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Supporting Information



ABSTRACT: A multifaceted experiment, accessible to students either in an introductory organic chemistry course or in a more advanced laboratory setting, is described for investigating the addition of dichlorocarbene to *E*- and *Z*- β -methylstyrenes. The innovative exercise, which integrates elements of synthesis, mechanisms, instrumental analysis, computational chemistry, and collaboration, provides students with an opportunity to learn important laboratory skills while highlighting key concepts covered in class. In particular, the coupling constants from ^1H NMR spectroscopy are used to diagnose the stereochemistry of addition, and integral ratios are evaluated to determine percent conversion of the starting alkenes into dichlorocyclopropanes. The experimental observations are correlated with results from calculations of the singlet–triplet energy gap in the carbene.

KEYWORDS: Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Laboratory Instruction, Inquiry-Based/Discovery Learning, Collaborative/Cooperative Learning, Reactive Intermediates, Stereochemistry, NMR Spectroscopy, Molecular Modeling

INTRODUCTION

Carbenes (1) are an important class of reactive intermediates that many students encounter in their introductory organic chemistry courses (Figure 1). The generation, structure, and

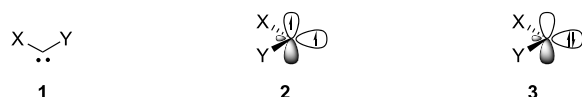


Figure 1. Generic carbene (1) represented as a triplet (2) and singlet (3).

reactivity of carbenes have been extensively studied by theoreticians and experimentalists, and these species have considerable synthetic value, either by themselves or as ligands for catalysts.¹ As shown in Figure 1, carbenes typically have two common electronic ground states, triplet (2) or singlet (3), and their relative stabilities are dependent on the natures of the substituents. Although triplets might be favored on the basis of Hund's rule and minimization of electronic repulsion, carbenes bearing p donor substituents (e.g., dichlorocarbene 4), prefer singlet ground states because of the additional resonance stabilization imparted by structures such as 4' (Figure 2).

The Skell–Woodworth hypothesis provides a means of distinguishing between singlet and triplet carbenes on the basis of their cyclopropanation reactions with stereochemically tagged alkenes.^{2,3} According to this hypothesis, exemplified

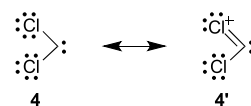


Figure 2. Resonance stabilization of singlet dichlorocarbene.

in Scheme 1, the addition of singlet carbene 5s to alkene 6 proceeds in a concerted fashion to produce cyclopropane adduct 7, which retains the stereochemistry of the original alkene. By contrast, the addition of triplet carbene 5t to 6 proceeds in a stepwise manner by initially forming a triplet biradical 8t, which then needs to undergo a spin inversion to form singlet 8s before closing to produce 7. There is the possibility, however, that 8t could undergo bond rotation to form 9t, which subsequently undergoes a spin flip to form 9s. Ring closure of 9s gives cyclopropane 10, in which the stereochemistry of the original alkene is no longer preserved. Thus, the reaction of 5t with 6 could lead to both 7 and 10 in the product mixture.

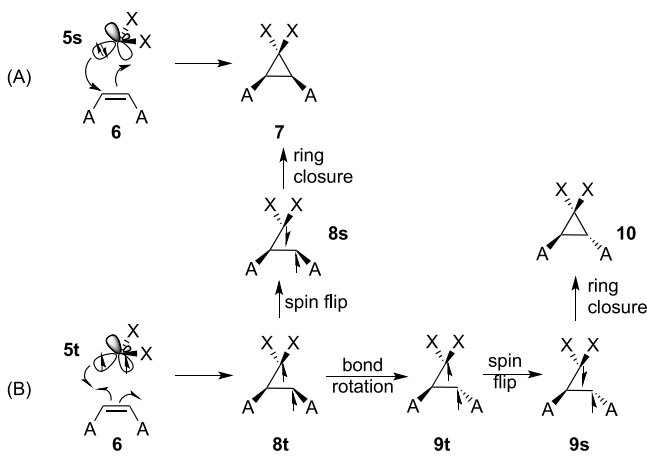
Although there have been a few sporadic experimental reports about carbene reactions in this *Journal*,^{4–9} there is no mention of an investigation into the stereochemistry of their addition to alkenes. Herein, a pedagogical experiment is described, suitable both for an introductory undergraduate

Received: October 1, 2018

Revised: May 15, 2019

Published: June 20, 2019

Scheme 1. Stereochemical Outcome of the Cyclopropanation Reactions of Alkene 6 with (A) Singlet Carbene 5s and (B) Triplet Carbene 5t



laboratory as well as for a more advanced course, where the students generate dichlorocarbene and study the stereochemistry of its cyclopropanation reaction with *Z*- β -methylstyrene (11) and its *E* isomer (12), as shown in Scheme 2. They also calculate the singlet–triplet gap in the carbene and correlate their computational results with the experimental observations. The experiment may be easily performed over two laboratory sessions of 3–4 h each. Students work in pairs with each group assigned one of the alkene isomers. The students from one group then share their results with a different group that worked with the other alkene isomer, thus adding a collaborative element to the activity. This multifaceted experiment is designed to have high instructional value by exposing students to synthesis, mechanistic analysis, instrumentation techniques such as gas chromatography–mass spectrometry (GC-MS) and NMR spectroscopy, and computational studies.

■ PEDAGOGICAL GOALS

The pedagogical outcomes of this experiment are listed below.

- Plan and execute an organic synthetic reaction.
- Learn to use important equipment such as the NMR spectrometer and GC-MS instrument, which are routinely employed by organic chemists in their work.
- Analyze spectral data to draw conclusions about the identities of products in a reaction mixture and estimate conversion.
- Provide a mechanistic rationale for the observed stereochemistry of the products.

(e) Learn to perform theoretical calculations to understand the experimentally observed results and appreciate the synergy between theory and experiment.

(f) Learn to work collaboratively first with a peer partner to perform the experiment and then with other teams to discuss results from different experiments.

■ EXPERIMENT

The first week of the experiment is devoted to synthesizing the cyclopropane adducts of dichlorocarbene with *Z*- and *E*- β -methylstyrenes using benzyltriethylammonium chloride (TEBAC) as a phase transfer catalyst^{10,11} and performing calculations on the singlet and triplet states of the carbene. Analysis of the products by GC-MS and ¹H NMR is carried out the following week.

Synthesis

To a disposable 20 mL scintillation vial equipped with a magnetic stir bar, students add chloroform (3 mL), alkene (0.5 mL), and TEBAC (10–25 mg). The vial is clamped above a magnetic stirring plate, and 50% sodium hydroxide (3 mL) is added over 3 min at room temperature with stirring. After being stirred for 1 h, the reaction mixture is worked up to obtain an oil that is stored for analysis the following week. The next week, a solution of the oil is prepared in CDCl₃ for ¹H NMR and GC-MS analysis. The remainder of the lab period is used for analysis of the data. A detailed procedure is in the Supporting Information (p S3).

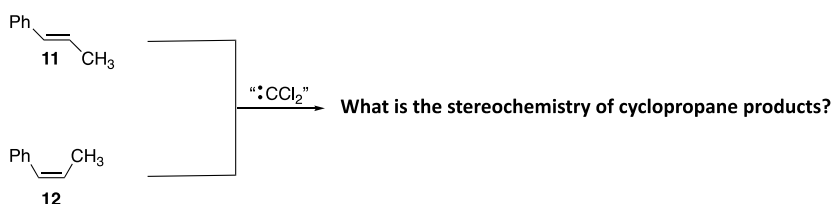
Computational Studies

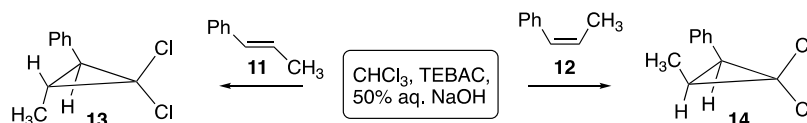
In the first iteration of the experiment, dichlorocarbene was built in GaussView,¹² and the calculations were performed on both the singlet and triplet species with Gaussian¹³ at the B3LYP/6-31G* level of theory.^{14–18} The energies of each carbene as well as key parameters such as bond lengths and bond angles were recorded. In the second iteration, the computational work was performed with the Spartan program¹⁹ with equal success.

■ HAZARDS

The styrenes used in this experiment are flammable and irritants to skin and eyes. Chloroform and chloroform-*d* can be harmful if inhaled or ingested. Concentrated aqueous sodium hydroxide solution is corrosive. The dichlorocyclopropane products are potentially hazardous materials and should be handled with caution. Students should wear appropriate personal protective equipment (gloves, goggles, etc.) while performing this experiment. The reaction should be conducted in a well-ventilated fume hood. Waste chemicals should be disposed of in accordance with existing regulations.

Scheme 2. Probing the Stereochemistry of Cyclopropane Products from the Reaction of Dichlorocarbene with *Z*- or *E*- β -Methylstyrenes



Scheme 3. Stereospecific Addition of Dichlorocarbene, Generated from Chloroform, to *Z*- or *E*-*b*-Methylstyrene

RESULTS AND DISCUSSION

A total of 58 students, working in groups of two, performed this experiment in its first iteration. Of the 29 groups, 14 worked with the *Z* isomer, and 15 worked with the *E* isomer. Every group was able to obtain product, but the conversions varied significantly across the board. The lowest conversion of product from the *Z* alkene was 9%, and the highest was 44%. The average conversion with the *Z* alkene was 22%. With the *E* alkene, the minimum and maximum conversions were 16 and 79%, respectively, with an average conversion of 34%. The second iteration of the experiment involved 80 students and 40 groups. Only one group was unsuccessful in getting any product. The minimum, maximum, and average conversions were 8, 40, and 22%, respectively, for the *Z* alkene and 10, 93, and 40% for the *E* alkene.

The operational simplicity of the reaction is one of the features of this laboratory experiment. The synthesis may be carried out with commonly available laboratory glassware. Instead of purifying the crude product mixture, which would necessarily add time and cost (solvents, silica gel, glassware, etc.) to the experiment, we decided that analysis of the complex reaction mixture provided important teaching opportunities. Accordingly, the students were instructed to prepare NMR samples of their crude product mixtures, acquire ^1H NMR spectra, and analyze the spectra as follows:

- Identify the methyl signals of the starting alkene and the product, and examine their integral ratio to get an estimate of the conversion.
- Identify the olefinic signals of the starting alkene and determine their coupling constant. Although these protons display some fine splitting because of long-range coupling, it is rather straightforward to measure the *J* value for the doublet of the proton signal on the carbon alpha to the phenyl ring. The average value for this *J* was ~ 12 Hz for the *Z* isomer and ~ 16 Hz for the *E* isomer.
- Identify the protons on the cyclopropane ring of the product, and determine their coupling constant. Again, the proton on the benzylic position is the most convenient to analyze. In this case, the average *J* value for the *cis* adduct was found to be ~ 11 Hz, whereas the *trans* adduct showed a noticeably smaller coupling at ~ 8 Hz.

Representative examples of the ^1H NMR spectra of the crude product mixtures obtained with the *Z* and *E* alkenes are shown in the [Supporting Information](#) (pp S7–S8). The coupling constant values comport well with those encountered by the students in class. Furthermore, as the coupling constants provided students with insights into the geometry of the starting alkene and the product cyclopropane,²⁰ they realized that the addition of dichlorocarbene to the alkenes 11 and 12 proceeded in a stereospecific manner to produce cyclopropanes 13 and 14, respectively (Scheme 3). These observations suggested that the carbene was likely reacting as a singlet. The students were able to arrive at this conclusion

after consulting the laboratory handout, analyzing their computational data (*vide infra*), and discussing their results with peers and laboratory staff.

Results of calculations (B3LYP/6-31G*) were consistent with the singlet being the ground state of the carbene, with typical values for the singlet–triplet gap at ~ 16.6 kcal/mol. The Cl–C–Cl bond angle in the singlet was 109.4° , and the Cl–C bond length was 1.753 Å. The corresponding values for triplet $:\text{CCl}_2$ were 128.0° and 1.695 Å, respectively. The calculated structures of the two dichlorocarbenes are shown in the [Supporting Information](#).

Students were also asked to use their NMR solutions to acquire GC-MS data. The *m/z* analysis of the chromatogram peaks revealed that the starting material and product were both present in the crude reaction mixture. The GC-MS conditions, as well as copies of sample data, are provided in the [Supporting Information](#) (p S11).

The laboratory handout provided to students (see the [Supporting Information](#)) required them to complete prelab exercises relevant to the experiment. The handout also provided clear instructions for writing a report on the experimental data.

Achievement of the pedagogical goals (*vide supra*) was evident from the students' performance during the laboratory and in their reports. The fact that virtually all students were able to successfully synthesize the product spoke to their ability to execute the experiment itself. As they had to prepare their own GC-MS and NMR samples and acquire the relevant data, albeit with assistance from the laboratory instructor, the students learned how these instruments are used for analysis. Interpreting the data, however, was perhaps the most challenging element of the experiment, but it also provided students with an opportunity to engage with their peers and the laboratory staff in productive conversations. These conversations ultimately resulted in the students successfully connecting the spin state of the carbene with the stereochemical outcome of its reaction. By performing calculations on the carbenes, the students appreciated the insights that computational studies can provide into experimental work. Finally, the experiment required collaboration, not only between the two students in each group but also among the groups (particularly those that worked on different alkene isomers), in order to grasp the full significance of the results.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the [ACS Publications website](#) at DOI: [10.1021/acs.jchemed.8b00758](https://doi.org/10.1021/acs.jchemed.8b00758).

Handout to students, instructor notes, copies of NMR spectra, GC-MS parameters and data, Gaussian input files, and calculated structures and energies of singlet and triplet dichlorocarbenes ([PDF](#), [DOCX](#))

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Science Foundation for support of this work through grant number CHE-1665278. We thank Jeffrey L. Katz for implementing the second iteration of this experiment.

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