

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/258245978>

NMR Studies of Structure–Reactivity Relationships in Carbonyl Reduction: A Collaborative Advanced Laboratory Experiment

DATASET *in* JOURNAL OF CHEMICAL EDUCATION · OCTOBER 2012

Impact Factor: 1.11 · DOI: 10.1021/ed3002573

CITATION

1

READS

35

5 AUTHORS, INCLUDING:



Simona Marincean

University of Michigan-Dearborn

11 PUBLICATIONS 27 CITATIONS

SEE PROFILE



Sheila R Smith

University of Michigan-Dearborn

20 PUBLICATIONS 386 CITATIONS

SEE PROFILE



Zeinab Rizk

University of Michigan-Dearborn

1 PUBLICATION 1 CITATION

SEE PROFILE

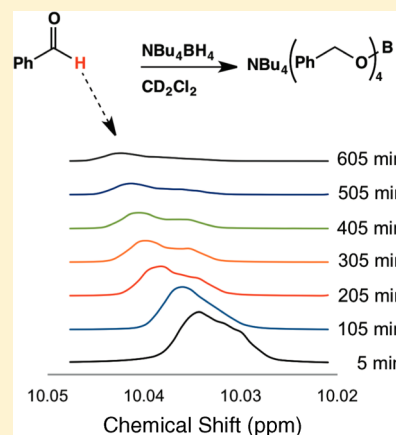
NMR Studies of Structure–Reactivity Relationships in Carbonyl Reduction: A Collaborative Advanced Laboratory Experiment

Simona Marincean,* Sheila R. Smith, Michael Fritz,[†] Byung Joo Lee, and Zeinab Rizk

Department of Natural Sciences, University of Michigan—Dearborn, Dearborn, Michigan 48128, United States

S Supporting Information

ABSTRACT: An upper-division laboratory project has been developed as a collaborative investigation of a reaction routinely taught in organic chemistry courses: the reduction of carbonyl compounds by borohydride reagents. Determination of several trends regarding structure–activity relationship was possible because each student contributed his or her results to an overall data set in a situation similar to a research environment. The students learned to use ¹H NMR techniques for in situ kinetic determinations and collaborated with classmates to develop a complete theory for structure–activity effects in the kinetics of this fundamental organic reaction.



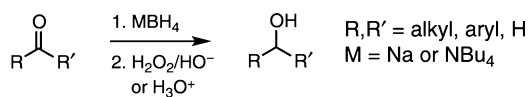
KEYWORDS: Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Physical Chemistry, Collaborative/Cooperative Learning, Hands-On Learning/Manipulatives, Aldehydes/Ketones, Kinetics, Mechanisms of Reactions, NMR Spectroscopy

Upper-division undergraduate chemistry laboratory courses have a dual mission: to introduce advanced techniques and to provide research-like experiences for the student. Although most experiments in such courses satisfy the former goal, fulfilling the latter one is often challenging. An authentic collaborative research endeavor can be time-consuming and hard to control due to unforeseen challenges or student mistakes and thus is often avoided by instructors. The experiment presented here aims to replicate a research environment while studying a vital reaction in organic chemistry: reduction of carbonyl compounds. An important part of the project is the role of an individual's contribution to achieving a common goal. Although each student makes his or her experimental determinations, the final analysis is conducted on the full data set generated by *all* the students.

Reduction of carbonyl compounds to the corresponding alcohols is a common reaction in organic synthesis¹ and borohydride compounds, especially NaBH₄, have been used extensively as reducing agents (Scheme 1). Treatment of the carbonyl substrate with borohydride followed by an acidic or basic workup yields the corresponding alcohol in high yield.

Several factors are known to affect the rate of reaction: carbocation identity, nature of the carbonyl, presence of proximal functional groups, and solvent. Mechanistic investigations have shown that the reaction is first order with respect to carbonyl and that the rate-determining step is the attack of the first borohydride with no disproportionation steps.² Rate

Scheme 1. Reduction of Carbonyl Compounds with Borohydride Reagents



constants were reported for reduction by NaBH₄ of steroid ketones,³ acetone,⁴ substituted cyclohexanones,⁵ and unsaturated ketones⁶ in protic solvent or solid state⁷ at various pH values. NaBH₄ reacts faster than tetrabutylammonium borohydride due to complexation between the oxygen from the carbonyl compound and the sodium cation.^{2b,8} Aldehydes are more reactive than ketones in accordance with their lower stability. Groups capable of intermolecular interactions that activate the reducing borohydride, such as dihydrogen bonding,⁹ accelerate the reaction.¹⁰ Protic solvents accelerate¹¹ the reaction rate by appearing in the rate expression with a 1.5 reaction order.

Experiments based on borohydride reduction of carbonyls have been developed,¹² but these experiments focus on the synthetic applications of NaBH₄ or introduction of greener alternatives. This experiment is a collaborative study of the effects of reaction conditions on the rate of carbonyl reduction and incorporates concepts from physical organic chemistry.

Rate constants are determined via in situ ^1H NMR spectroscopy of systems carefully chosen such that trends can be easily observed. The project offers the opportunity to develop independent research skills as the student is assigned a set of reagents and solvent but instructed to develop their own procedure based on the primary literature. Experimental results are shared among the whole class and trends are elucidated through oral presentations and discussions.

The students are expected to apply their prior knowledge of reaction mechanisms, determination of reaction order, and structure elucidation via ^1H NMR spectroscopy. Students learn that ^1H NMR spectroscopy has applications other than structure determination, namely in situ kinetic measurements. Finally, students learn to collaborate in order to complete the data analysis and draw conclusions regarding the observed trends. The experimental work is straightforward; the reaction is conducted in an NMR tube, which has an added benefit of generating a low volume of waste. Finally, students develop chemical literacy and communication skills through an oral presentation and a formal lab report.

PEDAGOGY

The chemistry curriculum at our institution features two advanced “capstone” laboratory courses: organic and inorganic synthesis and characterization. These courses, taken concurrently, are required for chemistry majors and open to biochemistry majors. A pedagogical objective of the courses is to integrate learning from courses both in the chemistry major and the rest of the curriculum. The students are presented with complex problems and must use their knowledge to find solutions and report those solutions both in formal written reports and oral peer-reviewed presentations. The two courses have an open-laboratory policy, which allows the students to work on their own schedule (outside of the regular four-hour meeting times) and to develop organizational skills and independence in a safe working environment (minimum two students present at all times in laboratory and stocked stockroom). The project presented here illustrates an authentic research environment in which a detailed picture of a complex phenomenon is obtained through collaborative sharing of experimental results. It would be impossible for a single student to complete the series of comparative studies in the laboratory setting, but through collaborative work a full set of data is generated in only two weeks.

EXPERIMENTAL METHODOLOGY

The deuterated solvents, CD_2Cl_2 and CD_3OD , tetrabutylammonium borohydride, and carbonyl compounds (list included in the Supporting Information) were purchased from Sigma-Aldrich and used without further purification. Each student was assigned a system composed of a carbonyl substrate, NBu_4BH_4 , and solvent and directed to develop a procedure. The student was responsible for finding relevant articles regarding reduction of carbonyl by borohydride reagents. Although there are many articles regarding carbonyl reductions in protic solvents, use of chlorinated solvents and NBu_4BH_4 has been reported in refs 8b and 10. The majority of the students were able to locate pertinent articles and roughly estimate the expected length of their reaction based on the structure of their substrate and solvent. A range of carbonyl compounds was selected so that there would generally be large differences in reaction rates

among data sets, allowing room for student error while maintaining the expected trends.

The substrate was characterized via ^1H NMR spectroscopy on a Bruker Avance 400 MHz spectrometer. Upon selecting a peak to monitor through the course of the reaction (a list with appropriate peaks for each carbonyl compound is included in the Supporting Information), the student acquired spectra at time intervals that he or she considered appropriate at room temperature ($25\text{ }^\circ\text{C}$).¹³

Reactions were run under pseudo-first-order conditions with the limiting reagent, the carbonyl substrate, at an initial concentration of 0.25 M. Following data collection and rate constant determination for her or his own substrate, the student compared his or her results to those of a colleague with one identical variable out of the two variables: substrate and solvent. The student provided an explanation for the observed trend based on the primary literature in an oral, peer-reviewed presentation and formal report. All experimental results were accessible via a collaborative Google document.

A two-week period was needed for all of the students to collect the NMR data. In departments where the NMR instrument is shared among several courses, this experiment would require a dedicated spectrometer for the duration of the laboratory period and the selection of substrates and solvents should be done so the reductions are complete within the laboratory time frame. Hydroxyacetone/ CD_2Cl_2 or acetone/ CD_3OD systems are good candidates because their reactions require 0.5 h at the most. More information regarding instrument and scheduling requirements as well as data acquisition is provided in the Supporting Information for instructors.

HAZARDS

Deuterated methylene chloride is a potential carcinogen and an irritant to eyes, skin, and respiratory tract. Deuterated methanol is toxic upon inhalation or ingestion. Chloroacetone is a lachrymator and *trans*-cinnamaldehyde a skin irritant. Tetrabutylammonium borohydride is an eye, skin, and respiratory tract irritant. Acetone, hydroxyacetone, acetophenone, and benzaldehyde are flammable and may cause eye, skin, and respiratory tract irritation. Students should wear gloves when handling these chemicals. Safety goggles should be worn at all times. Chemicals should be disposed of in designated waste containers.

RESULTS AND DISCUSSION

Sixteen students performed the experiment over two semesters in our advanced laboratory courses as a common project for the two courses; the experimental conditions used and the observed rate constants are summarized in Table 1. The rate constants given are based on an average of three student runs

Table 1. Rate Constants for Reduction Reactions

Entry	Substrate	Solvent	Rate Constant/ (10^{-6} s^{-1})
1	Acetone	CD_2Cl_2	10 ± 0.2
2	Hydroxyacetone	CD_2Cl_2	1800 ± 130
3	Chloroacetone	CD_2Cl_2	9.4 ± 0.7
4	Acetone	CD_3OD	4700 ± 200
5	Acetophenone	CD_2Cl_2	7.3 ± 0.4
6	Benzaldehyde	CD_2Cl_2	64 ± 3.8
7	<i>trans</i> -Cinnamaldehyde	CD_2Cl_2	32 ± 2.0

for each substrate/solvent pair. The results for fast reactions (see Table 1, entries 2 and 4) varied among students more than the results for the slow reactions, which were reproduced easily, presumably due to the lower number of spectra acquired for the short reaction times. Figure 1 depicts selected ^1H NMR spectra for reduction of benzaldehyde.

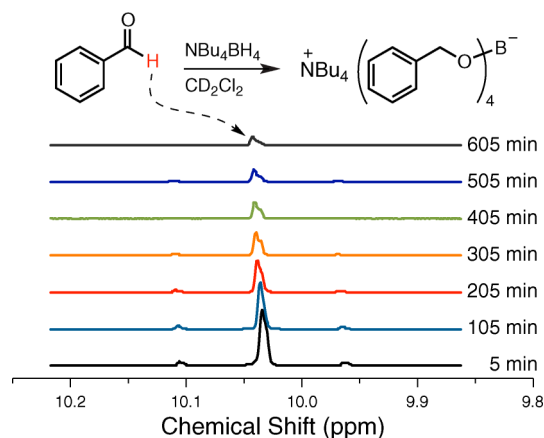


Figure 1. Selected spectra for reduction of benzaldehyde by NBu_4BH_4 in CD_2Cl_2 .¹⁴

Students determined the reaction order with respect to carbonyl and found it to be first order; this required students to apply knowledge concerning graphical determination of reaction orders. The half-lives are on the same order of magnitude with those in the literature.^{5–10} Common student pitfalls in the determination of the rate constant included improper selection of the monitored peak, poor spectral analysis, and incorrect estimation of the reaction time, that is, recording for a time interval that was not large enough to determine a significant conversion of the substrate. Students were asked to show one processed spectrum with integration values in which they identified the peak of interest; if the choice was incorrect, they were led to the correct choice. Regarding the reaction-time interval, students were informed that their system was either a slow or fast reaction that required monitoring for up to 24 or 0.5 h, respectively. The importance of choosing a proper ratio between the frequency of spectral acquisition and length of the reaction was pointed out, but specific values were not given.

When analyzing the functional groups present in the structure of the carbonyl compound, students evaluated them with respect to resonance or inductive effects and compared the results from that perspective. Students were, for example, able to connect the higher reactivity of benzaldehyde over acetophenone to the superior thermodynamic stability of a ketone compared to an aldehyde. The students were surprised to find that presence of an electron withdrawing group (EWG) such as chlorine in the α position to the carbonyl caused essentially no change in the reaction rate constant, although there are reports in literature that other EWG groups such as hydroxyl and methoxy in α position to carbonyl accelerate the rate of reduction by NaBH_4 in isopropanol.¹⁵ The instructor emphasized during group discussion that the inductive effect of functional groups present in the carbonyl substrate are not the sole factor in the reaction mechanism. Recent literature has suggested that the ability of the borohydride counterion to complex with either the oxygen of the carbonyl moiety or the

heteroatoms on the functional groups also plays a role.^{2b} When tetrabutylammonium is used as the counterion instead of sodium, this ability is lost. Students were confronted with the complexity of an apparently simple reaction routinely introduced in introductory organic chemistry.

When the carbonyl substrate was hydroxyacetone, a large rate acceleration was observed (see Table 1, entry 2). With instructor guidance to pertinent literature, students discovered the specific intermolecular interactions involved. This enabled the introduction of the new concept *dihydrogen bonding*, not typically covered in organic chemistry. This is a specific class of hydrogen bonds in which a traditional proton donor such as OH interacts with a proton acceptor such as BH_4^- . On the basis of examples from primary literature, students identified that the hydroxyl groups can participate in dihydrogen bonding with the NBu_4BH_4 and thus activate the carbonyl substrate for reduction. Moreover, the lack of rate increase in the case of chloroacetone supported the explanation of the hydroxyacetone results, as chlorine cannot participate in dihydrogen bonds with borohydride. The students used the concept of dihydrogen bonding to explain the large difference in the rate constants for reduction of acetone in CD_3OD and CD_2Cl_2 as in the former case several dihydrogen bonds can be formed between methanol molecules and BH_4^- .

ADDITIONAL LABORATORY MODIFICATIONS

To incorporate the experiment into an introductory organic chemistry laboratory course with a large enrollment or in departments where access to an NMR spectrometer is limited, the rate of the reduction reaction of only one carbonyl substrate can be determined by the entire class (hydroxyacetone/ CD_2Cl_2 or acetone/ CD_3OD). Including this experiment at the introductory level would provide a timely review of kinetics and emphasize the usefulness of NMR for other than structural determinations.

CONCLUSIONS

This laboratory project afforded a collaborative investigation of a reaction that is routinely taught in organic chemistry courses: reduction of carbonyl compounds by borohydride reagents. The main goal of this experiment was to introduce NMR spectroscopy as a tool for kinetic determinations. In that context, additional goals were (i) developing independent and collaborative skills and (ii) using primary literature and prior knowledge to tackle complex projects.

At the completion of the project, students were aware of, and proficient in, the application of ^1H NMR spectroscopy for *in situ* kinetic studies. More significantly, they succeeded in developing an independent procedure and analysis methodology. They learned the importance of collaboration, as determination of several reactivity trends was possible *only* because every student contributed his or her results to a pool in a situation similar to a research environment. Their understanding of both known and new concepts was improved significantly by their literature surveys. Each individual presentation based on comparison of two data sets proposed a specific structure–activity relationship. Group discussion at the conclusion of the presentations allowed for the synthesis of a detailed analysis of the many factors that affect the reaction. In summary, this experiment provided the students with a research-like experience, serving as a culmination of their learning process.

■ ASSOCIATED CONTENT

■ Supporting Information

Instructor notes, a student handout, list of required reagents with CAS numbers, a set of data obtained by the student for rate order determination. This material is available via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: simonam@umd.umich.edu.

Present Address

[†]Department of Chemistry and Biochemistry, University of California—Los Angeles, Box 951569, Los Angeles, California 90095, United States

Notes

The authors declare no competing financial interest.

■ REFERENCES

- (1) Magano, J.; Dunetz, J. R. *Org. Process Res. Dev.* **2012**, *16*, 1156–1184.
- (2) (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449–462. (b) Suzuki, Y.; Kaeneno, D.; Tomoda, S. *J. Phys. Chem. A* **2009**, *113*, 2578–2583.
- (3) (a) Brown, H. C.; Wheeler, O. H.; Ichiwava, K. *Tetrahedron* **1957**, *1*, 214–220. (b) Brown, H. C.; Ichiwava, K. *Tetrahedron* **1957**, *1*, 221–230.
- (4) Adams, C.; Gold, V.; Reuben, D. M. E. *J. Chem. Soc. Perkin Trans. 2* **1977**, 1466–1472.
- (5) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894–6904.
- (6) Geribaldi, S.; Decouzon, M.; Boyer, B.; Moreau, C. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1327–1330.
- (7) Cho, B. T.; Kang, S. K.; Kim, M. S.; Ryn, S. R.; An, D. K. *Tetrahedron* **2006**, *62*, 8164–8168.
- (8) (a) Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, *41*, 690–696. (b) Raber, D. J.; Guida, W. C.; Shoenberger, D. C. *Tetrahedron Lett.* **1981**, *51*, 5107–5110.
- (9) Custelcean, R.; Jackson, J. E. *Chem. Rev.* **2001**, *101*, 1963–1980.
- (10) Gatling, S. C.; Jackson, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 8655–8656.
- (11) (a) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1977**, *42*, 1108–1109. (b) Zeynizadeh, B.; Behyar, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 307–315. (c) Kayser, M.; Eliev, S.; Eisenstein, O. *Tetrahedron Lett.* **1983**, *24*, 1015–1018.
- (12) (a) Cunningham, A. D.; Ham, E. Y.; Vosburg, D. A. *J. Chem. Educ.* **2011**, *88*, 322–324. (b) Peeters, C. M.; Deliever, R.; De Vos, D. *J. Chem. Educ.* **2009**, *86*, 87–90. (c) Pohl, N.; Clague, A.; Schwarz, K. *J. Chem. Educ.* **2002**, *79*, 727–728.
- (13) For the experiments with long reaction times, the spectral acquisition can be done in an automated manner for the duration of the reaction if the software of the instrument allows it or at 0.5 h intervals for the first 8 h to collect relevant data.
- (14) The shown reaction is monitored by in situ ¹H NMR. The borate would lead to the corresponding alcohol upon workup.
- (15) Krishnan, K.; Chandrasekaran, J. *Indian J. Chem.* **1982**, *21B*, 595–597.