The Chemistry of Cocaine

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Engaging undergraduate organic chemistry students is often very challenging. It requires special effort to generate enthusiasm for learning such seemingly abstract concepts as functional group chemistry, synthetic routes, and reaction mechanisms. Students often do not see the relevance of these concepts to their own lives or interests. Classroom materials are needed that can be used to connect concepts in organic chemistry to applications that students can relate to. Drug abuse, which is a growing problem, is a topic that many students can connect to emotionally. This case study focuses on the chemistry of cocaine to teach a number of core concepts in organic chemistry, specifically nucleophilic addition reactions, nucleophilic acyl substitution, and cocaine metabolism. It also requires that students read and analyze an original research paper on efforts to develop a treatment for cocaine addiction. Use of the case has the added benefit of raising awareness of cocaine abuse.

The case was designed for the second course in a two-course sequence in undergraduate organic chemistry, as carbonyl group chemistry is normally covered in this course. However, the case could be adapted and used in medicinal chemistry classes.

Objectives

The case teaches these concepts:

- chemistry of aldehydes and ketones: nucleophilic addition reactions (NAR),
- chemistry of carboxylic acids and derivatives: nucleophilic acyl substitution (NAS),
- application of NAR and NAS in multistep synthesis of biologically active compounds,
- metabolism of cocaine, and
- comparison of physical properties of an amine and its salt.

Classroom management

Students are expected to prepare in advance for the case, completing the tasks described next. The in-class portion takes one hour to complete. Students also complete several post–case study homework assignments. I have taught this case in classes with 18 to 25 students. For much larger classes, the help of one or more teaching assistants is recommended.

Pre–case study preparation

At the beginning of the semester, students are informed that the case is available online (*http://sciencecases.lib.buffalo.edu/cs/collection*) and that they will be undertaking the case on a specific date later in the semester. Students are expected to complete the following before the day of the case:

- Read the case study. As part of this, students are told that along with reading the case they should attempt to answer the case questions because they will be required to share their responses with group members during the in-class case study session.
- Locate and read the research article referenced in the case (Zheng et al. 2008). I tell students to read it to understand the key ideas and not worry about all the details in the article.
- Complete the pre–case study questions (see the case). Students are expected do this assignment individually and submit it two weeks prior to the case class date; the assignment is graded and returned to them a week before the case is run in class. This pre–case study assignment requires students to study and write the major mechanisms underlying the reactions in the case study. Students are provided with access to relevant reading resources to help them answer the questions on enzyme function and kinetics (Manoharan and Dreisbach 1988; Voet and Voet 2004).

In-Class Activities

The case is presented in a one-hour class period, and students are allowed to consult their organic chemistry textbook and other materials of their choice. The students are assigned to work in groups of four or five to answer the case study questions. They are asked to select a team member to moderate the discussions. Groups are chosen such that each group has members with a range of subject matter competence. The latter is determined on the basis of the cumulative scores students have earned on exams, labs, quizzes, and homework assignments in the course so far. The instructor works with each of the groups, participating in their discussions as needed to direct students to questions they need to ask themselves in order to come up with the correct solutions.

Post–case study assignments

Each student is required to write up a solution to the case individually and submit it for grading at the next class meeting. In addition, each student is also asked as homework to answer a set of questions related to the scientific paper by Zheng et al. (2008) that they were required to read in advance of the case.

Students indicated that they found the case interesting. Their major criticism of the case was that excerpting the information from the assigned article by Zheng et al. (2008) was challenging and time-consuming. However, this was used as an opportunity to discuss the value of gaining experience in reading (and comprehending) scientific writings. It was also pointed out that one does not need to comprehend all the details of a paper but can often get the gist of the work by reading and understanding selective portions of it.

The case study generated many office visits from students prior to and after the classroom session. Much time was spent guiding students as to the analysis required in order to determine rational mechanisms for the reactions. In addition, the visits were leveraged to motivate students to put even greater effort into studying for and succeeding in the course.

References

Manoharan, A., and J.H. Dreisbach. 1988. Applied enzymology. *Journal of Chemical Education* 65: 98–101.

Voet, D., and J.G. Voet. 2004. *Biochemistry*. Hoboken, NJ: Wiley.

Zheng, F., W. Yang, M.-C. Ko, J. Liu, H. Cho, D. Gao, M. Tong, H.-H. Tai, J.H. Woods, and C.-G. Zhan. 2008. Most efficient cocaine hydrolase designed by virtual screening of transition states. *Journal of American Chemical Society* 130 (36): 12148–12155.

Case study

Professor Martinez entered the classroom with a livelier step than usual. Her morning students were accustomed to their instructor's ritual of carefully unpacking her book bag and arranging the contents neatly on the desk before beginning a lecture. But this time Martinez simply set her bag down on the chair, turned to the class, and began.

"Today, I want to share with you something exciting that I was reading."

The room grew suddenly silent. The word *exciting* was not one that students usually associated with Professor Martinez's lectures. The class looked intently at the blackboard as she drew a reaction scheme (see Figure 1).

Professor Martinez turned to the class, peered through her glasses, and continued. "Currently, there is no effective medication to treat cocaine abuse. However, I have just read a paper that describes a research breakthrough that may lead to the development of a treatment for cocaine addiction."

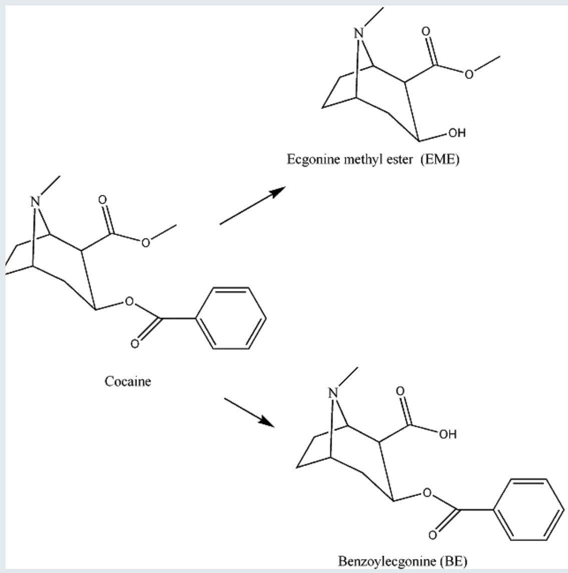
The class remained silent as Professor Martinez continued. "Cocaine has two ester functionalities. Hydrolysis of the benzoyl ester yields ecgonine methyl ester (EME) and hydrolysis of the methyl ester yields benzoylecgonine (BE). An enzyme in the blood, butylcholinesterase (BChE), catalyzes the hydrolysis of benzoyl ester, and this is believed to be the major metabolism pathway for cocaine *in vivo*. In addition, two liver enzymes (denoted by hCE-1 and hCE-2) catalyze hydrolysis at the methyl ester and the benzoyl ester, respectively. EME is less active than cocaine and is believed to cause vasodilatation. BE, on the other hand, appears to be similar to cocaine and causes vasoconstriction as well as lowers the seizure threshold. The researchers developed a mutant form of BChE, which they found could metabolize cocaine 2,000 times faster than the body's natural version of that enzyme. The enzyme that they developed was shown to also prevent convulsions and death when injected into mice that had been given overdoses of cocaine."

"Professor, how did they know what modifications to make in the enzyme so that it would metabolize cocaine faster?" asked Ling.

"This is an excellent question and

FIGURE 1

Hydrolysis of cocaine.



the answer is very interesting. I will give you the reference to the paper so that you can look it up and find out the answer. I believe that you will find the paper interesting," Professor Martinez responded. She then wrote on the blackboard "Zheng et al. 2008. Most efficient cocaine hydrolase designed by virtual screening of transition states. *Journal of American Chemical Society* 130: 12148–12155."

"See how she avoided answering the question. I don't think she knows the answer," Karl muttered under his breath to Denise.

Professor Martinez turned and-sternly stared at Karl and Denise.

"Professor, why does cocaine give you a high?" asked Denise, hurriedly, in an attempt to engage Professor Martinez and stem her obviously growing anger.

"Dopamine is a neurotransmitter that affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. Dopamine (like other neurotransmitters) is reabsorbed and recycled, and this serves to regulate the level of neurotransmitter present in the synapse—the gap between neurons. Specific transport proteins bind to neurotransmitters and facilitate their reuptake. Cocaine prevents dopamine reuptake by binding to its transport protein. As a result, more dopamine remains to stimulate neurons, and this causes prolonged feelings of pleasure and excitement. Cocaine's effects on the central nervous system peak within minutes of consumption. As such, rapid reduction of the concentration of cocaine (to a form with less activity) in the blood is a key strategy to fighting overdose in humans," Professor Martinez explained.

"Professor, when they make freebase, they do an organic synthesis. Can we make it as a lab?" Karl interjected, much to the delight of the class.

"Well, it's not a good idea," Professor Martinez replied.

"Is it because freebase can burst into flames? I once heard that some-

FIGURE 2

Conversion of cocaine to its freebase.

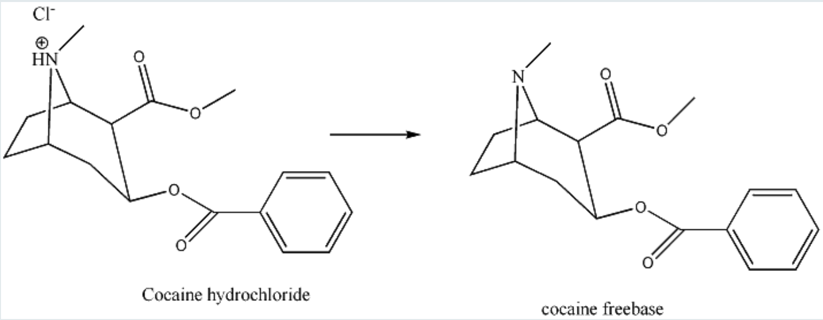
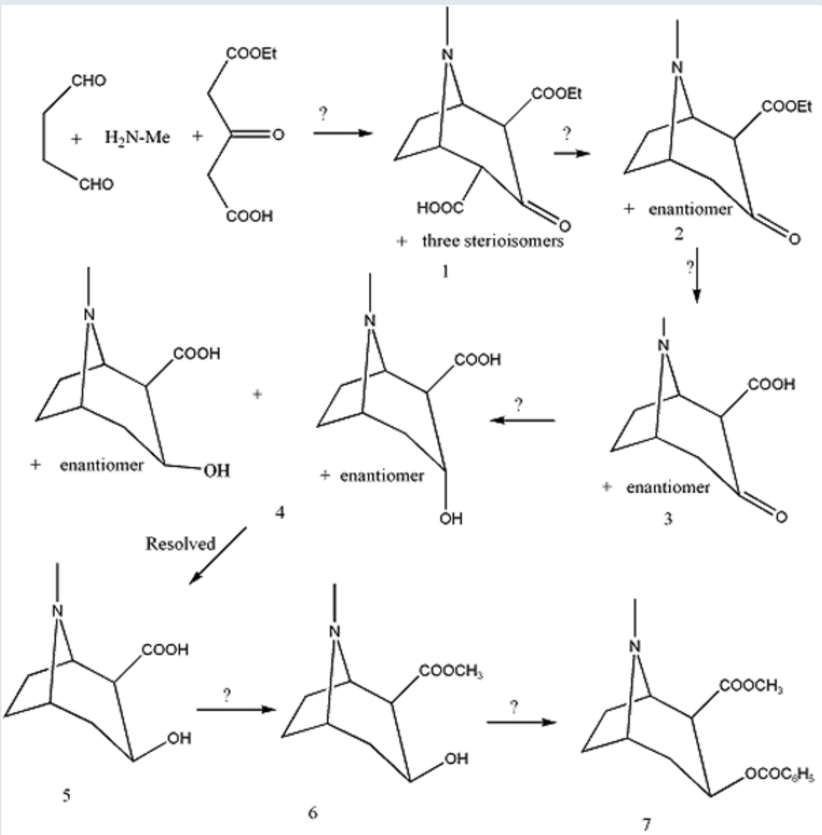


FIGURE 3

Synthesis of cocaine.



one caught fire while smoking it," added Karl with apparent innocence.

Professor Martinez waited for the laughter to subside, turned to the board, and wrote the next reaction (see Figure 2).

She continued. "Cocaine is extracted from the leaves of the coca plant in the form of its salt, cocaine hydrochloride. How would you make the freebase of cocaine from cocaine hydrochloride?"

"By reacting cocaine hydrochloride with a base," answered Kunle, who always seemed to have the correct answer.

"Any base?" Professor Martinez countered.

"You have to react it with either ammonium hydroxide or baking soda," Karl interjected, much to the surprise of the class, as it was the first time he had ever responded to a question in Professor Martinez's class.

"You're right. Could one use caustic soda (NaOH) instead?" Professor Martinez asked.

"Maybe we can make crack cocaine; it doesn't burst into flame," Karl countered, in an attempt to deflect the question.

"You are correct. Crack cocaine is less likely to be flammable than the freebase. When cocaine freebase is made, it is extracted out of the reaction mixture. Crack cocaine is essentially the evaporated reaction mixture after the reaction between cocaine hydrochloride and $NaHCO_3$ or NH_4OH. The extraction step is omitted. There is very interesting chemistry that is involved in the synthesis of cocaine freebase, not from cocaine, but from simple laboratory chemicals," Professor Martinez indicated and drew Figure 3.

On completion of the scheme, Prof Martinez continued. "As cocaine is a controlled substance—and a very dangerous one at that—it would not be a good idea to undertake its synthesis as a laboratory exercise. For your homework, I would like you to fill in the missing reagents and postulate mechanisms for the corresponding reaction steps. You can learn a lot from this exercise, as the synthetic steps and mechanisms are ones that are covered in this course."

"I have heard that drinking alcohol along with taking cocaine makes you feel even better but is also more dangerous. Is there some kind of chemical reaction between the two?" Charonda asked.

"Cocaine and alcohol undergo an enzyme catalyzed transesterification reaction in the body to form cocaethylene. Cocaethylene is euphoric and stays longer in the body than cocaine does. However, it is believed to have a higher cardiovascular toxicity than cocaine. As you can see, the chemistry of cocaine is very fascinating. The transesterification reaction is an example of a nucleophilic acyl substitution. We will discuss reactions that undergo this mechanism today. However, let us revisit the mechanism for nucleophilic addition reactions, as the initial steps are the same as those of nucleophilic acyl substitution" Professor Martinez continued (see Figure 4).

After the class ended, Karl and Denise walked together to the subway station. Denise could not help but remark on the class. "It was very interesting in the beginning, but then she reverted to her old self." Denise was surprised that Karl remained silent and did not join her in his usual bashing of Professor Martinez and her lectures.

"You were really into the class today," Denise persisted.

"Yeah," Karl mumbled sadly and his pace seemed to slacken.

Denise slowed down to keep pace with him, and they walked the rest of the way in silence. As they reached the stop, Denise asked. "What's the matter?

"Nothing," Karl replied.

Denise offered, "Let's go have a coffee, my treat."

Karl looked at his feet and apologized. "I'm sorry, maybe next time."

Denise insisted. "Come on, let's go. We need to go over some of the homework Professor Martinez assigned."

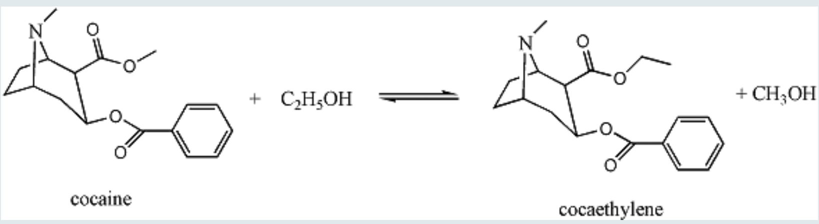
"OK," Karl resignedly replied.

After they finished their coffees and had gone over the homework, Karl made a confession. "I have something to tell you. My dad is a cocaine addict. He tries very hard to quit, but it is almost impossible."

"I am so sorry," Denise said gently as she reached for his hand.

FIGURE 4

Reaction of cocaine with alcohol.



CASE STUDY

Pre–case study questions

1. Aldehydes and ketones undergo nucleophilic addition reactions as illustrated by the reaction shown in Figure 5. Write a mechanism for this reaction.
2. Carboxylic acid derivatives undergo nucleophilic acyl substitution reactions as illustrated by the reaction shown in Figure 6. Write a mechanism for this reaction.
3. The Mannich reaction involves nucleophilic addition of an amine to a carbonyl group followed by dehydration to form a Schiff base. The latter is an electrophile and reacts in a second step in an alpha substitution reaction with a carbonyl compound (see Figure 7). Mannich reactions and their analogues have played an important role in the synthesis of biologically active nitrogen-containing natural products. The earliest example was the synthesis of tropinone as a synthetic precursor to atropine in 1917 by Sir Robert Robinson. Atropine is an important medicinal compound that is still used clinically for cardiac resuscitation and to dilate the pupils during eye examinations. The Mannich reaction proceeds through a variety of mechanisms depending on the reactants and conditions that are used. Figure 8 displays a reaction scheme with key intermediated for the synthesis of tropinone via a Mannich reaction employing an acid catalyst. Propose mechanisms for the reaction scheme.
4. What are enzymes and how do they function?
5. The k_{cat}/K_m provides a measure of the catalytic efficiency of an enzyme for a particular reaction and is useful for comparing different enzymes against each other, or the same enzyme with different substrates. Explain what is meant by K_m and k_{cat}.
6. If the rate of binding of an enzyme to its substrate is inhibited, would this affect the catalytic efficiency of an enzyme?

FIGURE 5

Nucleophilic addition reaction.

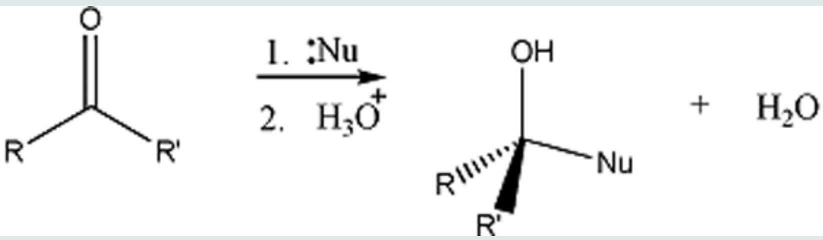


FIGURE 6

Nucleophilic acyl substitution reaction.

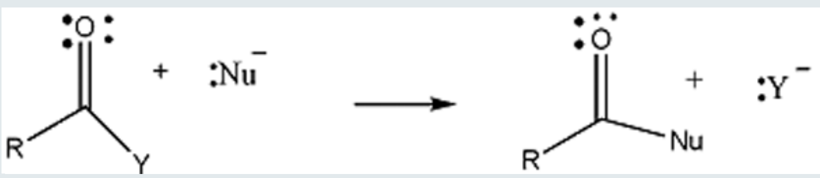
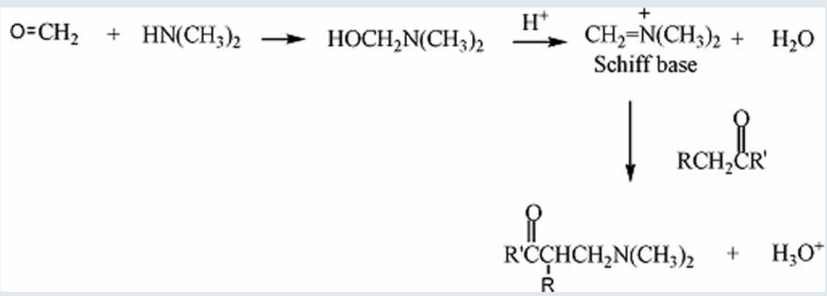


FIGURE 7

The Mannich reaction.



Case study questions

1. Cocaine (in the form of cocaine hydrochloride) is usually consumed by drinking, snorting, or injecting, but not by smoking. However, the freebase form of cocaine is smoked. What is the likely reason for this?
2. The late comedian Richard Pryor performed a skit poking fun at himself for an incident in which he caused an explosion and ignited himself attempting to smoke "freebase." Do you think that such an incident is possible? Before responding, consider the steps that would be required to separate out the freebase from an aqueous re-

action mixture. Explain the reason for your answer.
3. Crack cocaine presumably got its name from the "cracking" sound it makes when being smoked. Why do you think it makes this sound?
4. What chemical reaction(s) would occur if NaOH were used instead of baking soda to make crack cocaine? Write a mechanism for the reaction(s) proposed.
5. Complete the reaction scheme proposed by Professor Martinez for the synthesis of cocaine by adding the necessary reagents/reaction conditions. Write mechanisms for each of the reaction steps that you added the reagents to.
6. A researcher is involved in pharmacological studies of cocaethylene and would like to synthesize it from cocaine. She seeks your advice on a suitable synthetic route. Outline a synthetic scheme that you would suggest to her.

Post–case study questions

1. Locate and read the article (Zheng et al. 2008) that Professor Martinez referred to. Respond to Ling's question in less than 250 words.
2. What is the larger implication of the referenced study (beyond that of a lead for a possible cure for cocaine addiction)?

An extended version of the teaching notes and an answer key to the questions for this case may be found at the National Center for Case Study Teaching in Science at *http://sciencecases.lib.buffalo.edu/cs/collection*.

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FIGURE 8

Reaction scheme for the synthesis of tropinone.