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 the following reaction scheme.

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, butyrylcholinesterase (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 vasodilation. 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 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. Most Efficient Cocaine Hydrolase Designed by Virtual Screening of Transition States. Journal of American Chemical Society, 2008, 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 stared rather sternly 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 someone 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 NaHCO₃ or NH₄OH. 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 2.

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.

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.

![Figure 6](image)

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.)

![Figure 7](image)

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 employed. 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?
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 free base 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 free base from an aqueous reaction 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 Questions

1. Locate and read the article 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)?