Penicillin: From Chemistry to Cure

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Part I – Introduction

Have you ever gotten a bad splinter or blister that became infected? Perhaps it started out small at first, but when the area affected became hotter, started throbbing with pain, and began to swell up, you suspected it had become infected. A quick trip to the doctor's office resulted in a diagnosis of a bacterial infection. Your doctor prescribed some medication to eliminate your infection. She counseled you to take the recommended dose until the bottle of pills was finished.

Less than one hundred years ago, a similar injury may have led to a very different fate. In 1924, the 16-year-old son of President Coolidge developed a blister on his toe, with deadly consequences.

"Calvin Coolidge Jr. didn't tell anyone about the blister that had formed on a toe of his right foot during a strenuous tennis match with his older brother, John, on the White House court. As the son of President Calvin (Silent Cal) Coolidge, and a Boy Scout, he certainly wouldn't have complained about it.

"But the next day, the 16-year-old awoke with a stiff and painful leg. The doctor was called, and his examination revealed that a septic infection had spread to Calvin's bloodstream and throughout his body… [D]uring the next several days, seven doctors tried stomach washings, blood transfusions, an operation, and other methods in desperate efforts to save the teenager. But Calvin only grew weaker. By July 7, he was delirious. Finally, his body began to relax. He said weakly, 'I surrender,' and lapsed into a coma. Four hours later, at 10:30 p.m., he died.

"The entire nation had anxiously followed on the radio the plight of Calvin Coolidge Jr. Now it joined his parents in mourning the loss of a most promising young man."

—Peterson, D.L. 2000. Scouting Magazine*, <http://scoutingmagazine.org/issues/0010/d-wwas.html>*

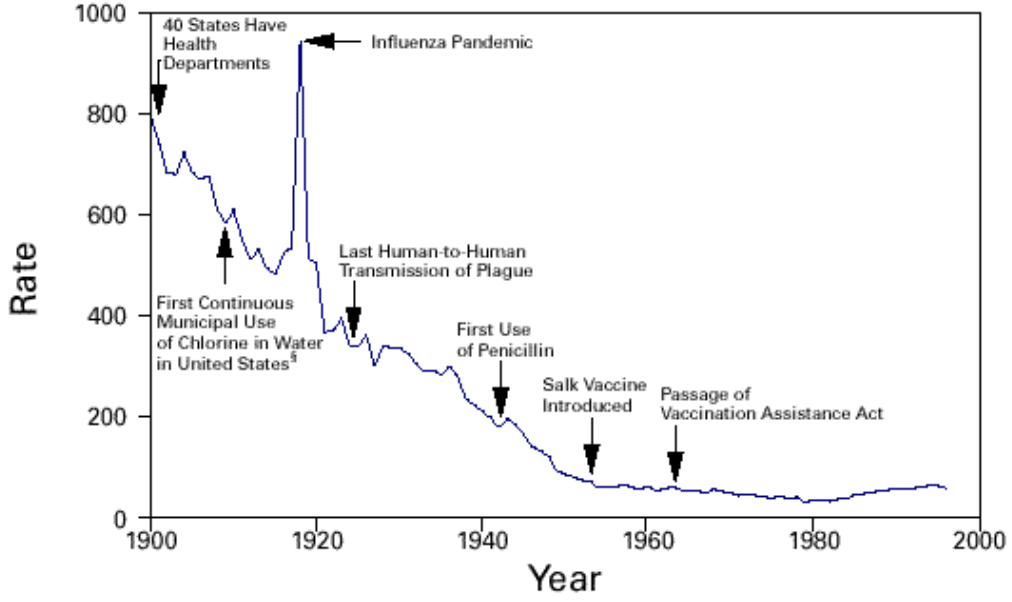
Questions

1. Why do you think the doctors' treatments had little effect on Calvin Jr.'s health?

2. What medications does a doctor prescribe for bacterial infections (e.g., ear infections, urinary tract infections)? What about viral infections, like the common cold?

3. The chart below shows death rates from infectious diseases (per 100,000 people) over time. How many times higher was the death rate from infectious diseases during Calvin Jr.'s lifetime versus your lifetime? Can the difference be attributed solely to the introduction of antibiotics? Why or why not?

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†



*Per 100,000 population per year.
†Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999:281;61–6.
§American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.

Credit: Centers for Disease Control. 1999. Achievements in public health, 1900–1999: control of infectious diseases. *MMWR* 48(29):621–629. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm>

The curative abilities of antibiotics with minimal side effects suggests that they are lethal to certain bacteria, but do not harm your own cells. Why is this? Chemistry is key! Through this case study you will examine the chemistry underlying these life-saving molecules. To prepare for the next part of the case, watch the following videos and complete any reading assignments as directed by your instructor.

- Video #1: *Common Elements in Living Things* <https://youtu.be/U0-MQlJhbbc>
- Video #2: *The Chemical Bond* <https://youtu.be/PoQjsnQmxok>
- Video #3: *Representing Molecule Structures* <https://youtu.be/qwjCFOZbR_E>

Part II – Deciphering Molecules

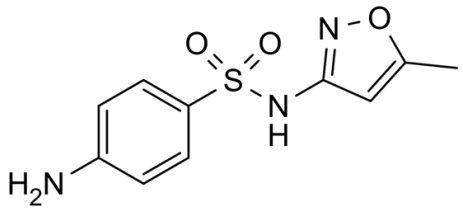
One hundred years ago, nobody knew the chemical structure of antibiotics. Today we do know these chemical structures. Chemists and biologists have worked together to synthesize new kinds of antibiotics, and in order to do so they need to understand the structure of these molecules.

Examine the structures of the four antibiotic molecules below (referred to here as Molecules A, B, C, and D). (*Note:* some of the bonds are drawn as solid or dashed wedges. These are just different ways of showing the 3-D structure of a covalent bond, and are not needed to solve the following questions.)

Questions

1. In your group, compare and contrast the molecules below. For example, do the molecules contain the same elements? Are the atoms bonded to one another in similar or different ways?

A.



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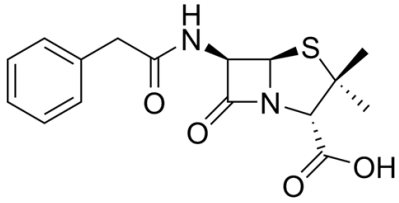
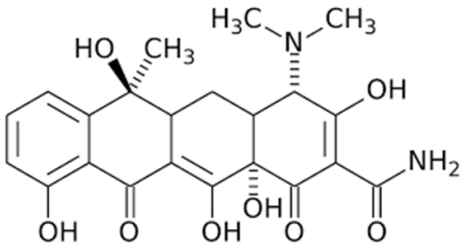
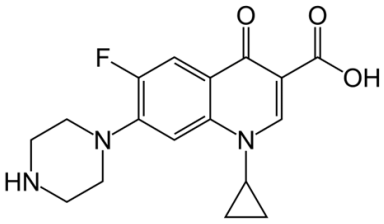


C.



D.



Similarities:

Differences:

Your group will be assigned to focus on one molecule. Record which one here _____ .

2. Remember that the presence of some atoms are implied, but not explicitly shown, in a skeletal diagram. Why is this the case? How do you know to look for them? Draw any implied atoms into the diagram of your assigned molecule.

3. What is the molecular formula of your assigned molecule (for example, the molecular formula for glucose is $C_6H_{12}O_6$)?

4. What element provides the "backbone" for your assigned molecule? Why?

5. Locate a polar covalent bond and a nonpolar covalent bond within your assigned molecule. The electronegativity values given in the table to the right will help you decide.

Element	*Electronegativity value*
Carbon	2.55
Hydrogen	2.20
Nitrogen	3.04
Oxygen	3.44
Phosphorus	2.19
Sulfur	2.58
Fluorine	3.98

6. Molecules containing lots of polar covalent bonds are usually hydrophilic ("water loving"), and those containing mostly nonpolar covalent bonds are usually hydrophobic ("water hating"). Based on the bonds in your assigned molecule, would you expect your assigned molecule to be more hydrophilic or hydrophobic?

7. Would it be advantageous for an antibiotic molecule to be hydrophilic or hydrophobic? Why?

In the next part of the case, you will delve further into the structure of a specific antibiotic, penicillin. To prepare, watch the following videos and complete any reading assignments as directed by your instructor.

- Video #4: *Isomers* <https://youtu.be/z8M4EciPpYI>
- Video #5: *Chirality* <https://youtu.be/JS-iAuCIexk>

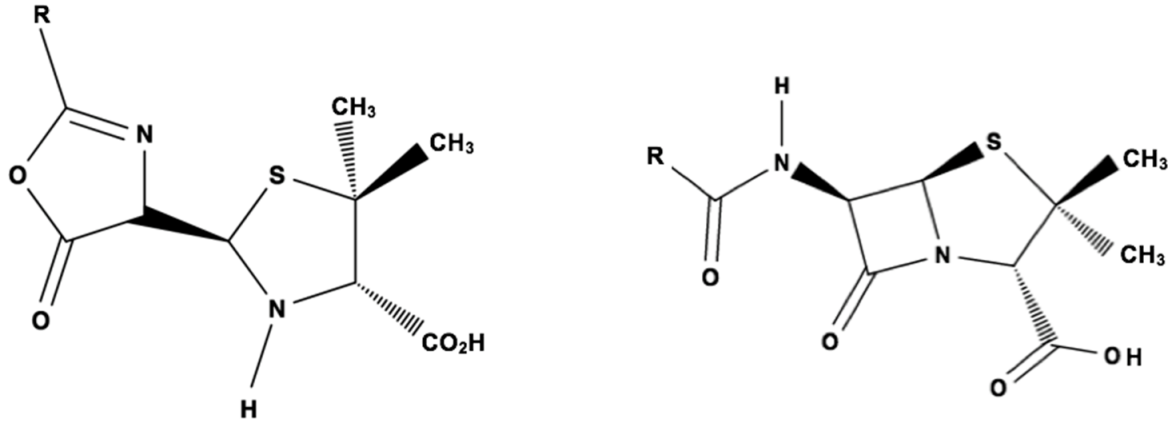
Part III – Synthesizing Penicillin

You may have already learned about Fleming's discovery of penicillin. Fleming noticed a mold growing in one of his petri dishes filled with bacterial growth medium. He observed that no bacteria were growing in the areas directly surrounding the mold. Fleming already knew enough about bacterial growth to hypothesize that the mold was producing an antibacterial molecule.

Almost 30 years passed between Fleming's initial observations (1928) and the ability of organic chemists to synthesize penicillin in the laboratory (1957). Before a total chemical synthesis was found, penicillin was extracted from massive-scale cultures of the Penicillium mold, much of which was taken from moldy cantaloupes! Nevertheless, penicillin remained in short supply, especially during the Second World War. It was so scarce at times that it would be recovered from patients' urine and re-used.

Why did figuring out a laboratory-based chemical synthesis take so long? Synthesizing penicillin, rather than extracting it from a mold culture, depends on knowing the molecule's formula and structure. The molecular structure of penicillin was not confirmed until 1945.

Pictured below are the two leading candidate structures for penicillin in the 1940s. (*Note:* "R" stands for a variable group.) These two molecules have the same molecular formula (i.e., the same number of carbons, hydrogens, oxygens, etc.).

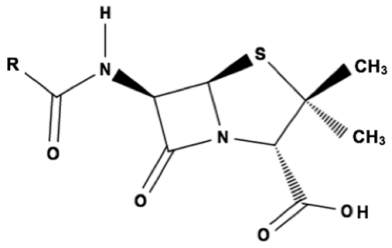


Questions

1. How would you characterize these two structures? Are they different molecules altogether, or are they isomers? If isomers, are they structural isomers or stereoisomers? Explain your answer.

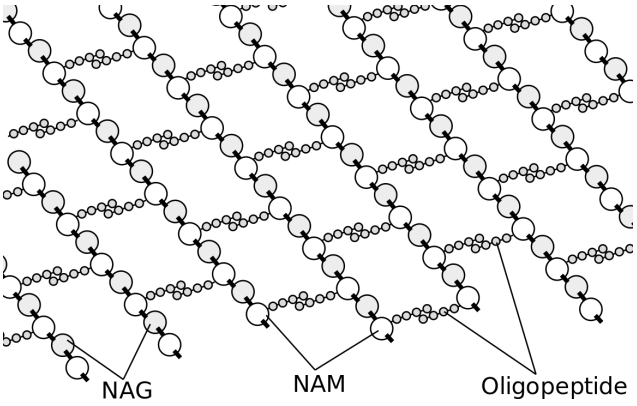
2. The 3-dimensional shape of a molecule can be vitally important to its function. Recall that chiral carbons endow a molecule with a specific 3-D structure. Do the two possible structures above contain chiral carbons? If you find a chiral carbon, circle it and explain why it is chiral. Place a star next to a carbon that is not chiral, and explain why it is not chiral.

3. Only one of these structures is effective at fighting bacteria. Based on the similarities and differences between the structures, can you guess which parts of the structure are likely to be involved in its ability to kill bacteria?

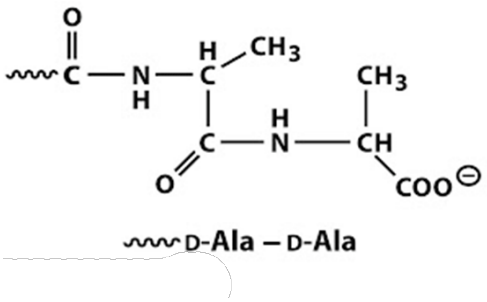


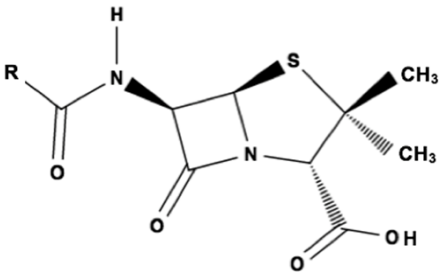
In 1945, Dorothy Crowfoot Hodgkin and colleagues used crystallography (a method of visualizing molecular structures with X-rays) to confirm that penicillin had this structure (left). The fused ring structure is called a β-lactam ring. This ring is crucial for the mechanism of penicillin.

But how does penicillin actually work? To answer this question, we need to know a bit about bacterial cell structure. Here (right) is a diagram showing *peptidoglycan*. Peptidoglycan is an important part of cell wall structure of bacteria and is found in very large amounts in certain bacteria ("gram positive"). Peptidoglycan contains a series of sugars (abbreviated NAM and NAG), which are cross-linked by short chains of amino acids (oligopeptides). An enzyme called a "transpeptidase" is responsible for assembling the peptides. One part of the transpeptidase enzyme interacts with two terminal alanine residues; this is one step in the cross-linking reaction.



4. Examine the structure of the two alanine residues below (left). Compare this structure to that of penicillin (right). Circle the parts of the penicillin molecule that resemble the alanine residues.





5. How could penicillin affect the ability of transpeptidase to link amino acids together? What consequence might this have on peptidoglycan production? Ultimately, how will the bacteria be affected?

Closing

As you have seen, the actions of antibiotics are rooted in chemistry. If Calvin Coolidge Jr. had been alive today, a dose of antibiotics would have made the splinter in his foot no big deal. But the overuse of antibiotics today has selected for bacteria with mutations that provide antibiotic resistance. Some bacteria are now resistant to most major kinds of antibiotics. Today's chemists and biologists must collaborate to find new molecular structures that can kill bacterial cells without killing our cells. Maybe one day, you will help make such a discovery…