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### Spectral Analysis of Pellicillin G

Ioana Stanciu

Department of Physical Chemistry, Faculty of Chemistry, University of Bucharest, 4-12 Elisabeta Blvd, 030018, Bucharest, Romania

Corresponding Author: Ioana Stanciu

#### Abstract

Penicillin was the first antibiotic used by doctors. The discovery of penicillin was one of the great achievements of mankind, this drug saved millions of lives. The discovery was made by accident in 1928, by the Scottish bacteriologist Alexander Fleming. In this article we determined the composition of penicillin G by FTIR spectroscopy using a

Bruker spectroscope. The spectrum of penicillin G contains bands between the wave numbers  $1700\text{cm}^{-1}$  and  $3500\text{cm}^{-1}$ . Penicillin drugs contain bands due to vibration of the  $\beta$ -lactam carbonyl, side amide bond and ionized carboxylate group.

**Keywords:** Spectral, IR, Pellicillin g

#### Introduction

Penicillin was the first antibiotic used by doctors. The discovery of penicillin was one of the great achievements of mankind, this drug saving millions of lives. The discovery was made by chance in 1928, by the Scottish bacteriologist Alexander Fleming. The term "penicillin" is used both to designate the class of antibiotics, and to name certain types of drugs in this class. Examples of penicillins are: Penicillin G (injectable form), penicillin V (oral form), ampicillin, amoxicillin, dicloxacillin, oxacillin, carbenicillin, piperacillin and ticarcillin.

Penicillins are important drugs in the therapeutic armamentarium of antibiotics, having a good effect with relatively limited toxicity. Penicillins have a bactericidal effect (kill bacteria), most likely acting by destroying the bacterial wall. Less than 1% of patients may have a severe form of allergy to penicillins (anaphylaxis). Although penicillins remain the drug of first choice for many infections, resistance to penicillins in some bacteria is increasing. Penicillin antibiotics, like all antibiotics, can only be purchased from pharmacies with a prescription<sup>[1-6]</sup>.

Penicillin is the first antibiotic discovered that was successfully used to treat people with infectious diseases.

The discovery was made by accident in 1928 by Scottish bacteriologist Alexander Fleming.

Returning from vacation on September 3, 1928, Fleming began sorting Petri dishes containing colonies of *Staphylococcus*, a bacterium that causes boils, abscesses, and tonsillitis. On one of the plates, Fleming noticed something unusual. It was full of colonies of bacteria, except for a small area where mold had grown. The area immediately surrounding the mold—later identified as a rare strain of green mold *Penicillium notatum*—was clear, as if the mold had secreted something that inhibited bacterial growth. *Penicillium notatum* had accidentally contaminated the cultures through a window that had been left open. Fleming later discovered that this "mold juice" was capable of killing a wide range of harmful bacteria, such as streptococcus, meningococcus, and diphtheria bacillus.

By discovering this mold and understanding its effect on bacteria, Fleming laid the foundation for the development of one of the most useful drugs in medical history. Previously, infections from wounds and diseases such as pneumonia and syphilis were almost always fatal.

In March 1942, 33-year-old Anne Miller became the first patient to be successfully treated with penicillin. This prevented death, which would have surely occurred as a result of a severe infection after a miscarriage. Anne Miller died at the age of 90. In late 1943, mass production of the drug began - just 4 years after the first experiments on mice and despite the Second World War, a sign of Howard Florey's determination. By the end of the war, many laboratories were manufacturing penicillin, including Merck, Squibb and Pfizer in the United States and Commonwealth Serum Laboratories in Australia. In fact, Australia was the first country to make the drug available for civilian use.

However, within just a few years, several strains of bacteria had become resistant to penicillin by altering the structure of their cells. To overcome this problem, in the 1950s, scientists began producing artificial penicillin (synthetic penicillin) by chemically altering natural penicillin.

In 1945, the Nobel Prize in Physiology or Medicine was awarded jointly to Sir Alexander Fleming, Sir Ernst Boris Chain, and Sir Howard Walter Florey "for their discovery of penicillin and its curative effect in various infectious diseases."

In Fleming's Nobel Prize acceptance speech, he warned that the overuse of penicillins could one day lead to bacterial resistance. This has proven to be the case and is now a serious public health problem.

Penicillins are used to treat infections caused by gram-positive bacteria (such as streptococcal infections) and some gram-negative bacteria (such as meningococcal infections). Gram-positive bacteria are a group of bacteria that retain the gentian violet stain as a result of the Gram stain method, so they are "positive" as a result of this stain. A bacterium is considered to be Gram-positive when it is purple-violet in the microscopic field. Common examples of pathogenic gram-positive bacteria are: *Streptococcus pneumoniae*, *Clostridium tetani*, *Clostridium difficile*, *Staphylococcus aureus* and *Bacillus anthracis*. On the other hand, Gram-negative bacteria are a group of bacteria that do not retain the gentian violet stain as a result of the Gram stain method. Among the most common species of pathogenic gram-negative bacteria are: *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Vibrio cholerae*, *Chlamydia trachomatis* and *Yersinia pestis*. Infections with such bacteria are difficult to treat because the outer membrane of Gram-negative bacteria protects them from certain agents, such as antibiotics (including penicillins), detergents, or lysozyme, a natural bacteriolytic substance that destroys the bacterial wall.

The spectrum of activity against bacteria of penicillins is as follows:

- Natural penicillins
- Penicillin G (benzylpenicillin) - administered by injection
- Penicillin G (benzathine benzylpenicillin) - delayed-release preparation administered by injection
- Penicillin G (procaine benzylpenicillin) - delayed-release preparation administered by injection
- Penicillin V (phenoxymethylpenicillin) - administered orally
- Penicillin G is a natural penicillin that is produced directly from the fermentation of *Penicillium chrysogenum*. Penicillin V is a derivative of penicillin G and, due to the similarities in the spectrum of activity, is considered a natural penicillin.

Natural penicillins act mainly on: Gram-positive bacteria (e.g., streptococci) and some Gram-negative bacteria (e.g., meningococci).

Natural penicillins have activity against gram-positive cocci (spherical in shape) that do not produce beta-lactamases, such as: Viridans streptococci, group A streptococci, *Streptococcus pneumoniae* and anaerobic streptococci (*Peptostreptococcus*, *Peptococcus* sp.). *Enterococcus* sp. is most susceptible to natural penicillins.

Other potentially susceptible bacteria are strains of *Staphylococcus aureus* that do not produce penicillinase and

coagulase-negative *Staphylococcus*.

However, due to the high probability of resistance, it is not recommended to use natural penicillins as empirical treatment (without antibiogram testing) for a possible staphylococcal infection, unless the susceptibility of the staphylococci to penicillin is known.

Natural penicillins have activity against Gram-positive bacilli (rod-shaped bacteria), such as *Clostridium* sp. (excluding *Clostridium difficile*) and *Actinomyces* sp. Activity against Gram-negative cocci is limited and includes *Neisseria meningitidis*, penicillinase-nonproducing *Neisseria gonorrhoeae*, and *Pasteurella multocida*.

Similar to staphylococcal infection, natural penicillins should not be used for the treatment of gonorrhea (*Neisseria gonorrhoeae*) because of the increased potential for bacterial resistance and subsequent treatment failure.

The anaerobic coverage of penicillin V is lower than that of penicillin G. Natural penicillins also have excellent activity against the spirochete *Treponema pallidum*, the organism that causes syphilis<sup>[5-8]</sup>.

Penicillin G is the first-line antibiotic for syphilis. The extended-release form of penicillin G (benzathine penicillin, Moldamin) is recommended for the treatment of syphilis and for the prevention of rheumatic fever.

Penicillinase-resistant penicillins

Methicillin - rarely used now because of the risk of interstitial nephritis

Dicloxacillin - given orally

Nafcillin - given orally or by injection

Oxacillin - given orally or by injection

These antibiotics are known as antistaphylococcal penicillins.

They were obtained by modifying the penicillin compound with a structure that protects the beta-lactam ring from destruction by penicillinases produced by *Staphylococcus* sp.

Methicillin, the first agent synthesized in this group, is rarely used now because of the higher incidence of interstitial nephritis (a severe kidney disease).

Nafcillin and oxacillin are the agents commonly used parenterally, while dicloxacillin is available for oral use.

Beta-lactamase-resistant penicillins have activity against *Staphylococcus* species (including penicillinase-producing strains). Strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE) exist and may be the predominant types of staphylococci in certain settings, such as hospitals or hospital intensive care units. These organisms are not susceptible to penicillinase-resistant penicillins.

Aminopenicillins

Ampicillin - given orally or by injection

Ampicillin/sulbactam - administered orally or by injection

Amoxicillin - administered orally

Amoxicillin/clavulanic acid - administered orally

As a result of the need for better coverage against gram-negative bacteria, the structure of the natural penicillins was further modified. By adding an amino group to the basic penicillin compound, the aminopenicillins were produced.

The spectrum of activity against gram-positive organisms is similar to that of the natural penicillins. These antibiotics retain activity against streptococcal species and have somewhat better activity against *Enterococcus* (ampicillin) and *Listeria monocytogenes* than the natural penicillins.

The improved spectrum of these antibiotics includes activity against gram-negative bacilli, including *H. influenzae*, *E. coli*, *Proteus mirabilis*, *Salmonella* sp. and *Shigella* sp. However, the added side chain does not inhibit destruction by staphylococcal penicillinases or gram-negative beta-lactamases. Combinations of aminopenicillin plus a beta-lactamase inhibitor, such as clavulanic acid or sulbactam, are useful for the treatment of infections caused by beta-lactamase-producing organisms<sup>[8-19]</sup>.

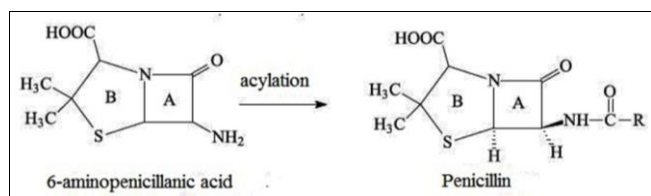
## Materials and methods

Molecular formula:  $C_{16}H_{18}N_2O_4S$

### Pellicillin synthesis

Among the natural compounds with a tetrahydrothiazole (thiazolidine) ring, **penicillin**, the first antibiotic used in therapy (1943), should be mentioned.

At the base of the structure of penicillins is penicillanic acid with two heterocycles:  $\beta$ -lactam (A) and thiazolidine (B). Natural and semi-synthetic penicillins have N-acylated derivatives of 6-aminopenicillanic acid:



The determination of the FTIR (Fourier Transform Infrared Spectroscopy) spectrum of penicillin G requires compliance with specific conditions in order to obtain a clear and interpretable spectrum. The essential conditions for performing this analysis are presented below:

#### 1. Sample preparation

**Physical state:** Penicillin G can be analyzed in solid form (powder) or dissolved in a suitable solvent (if soluble).

**Preparation techniques:**

**KBr pellet:** A small amount of penicillin G is homogenized with dry potassium bromide (KBr) and pressed into a transparent pellet.

**ATR (Attenuated Total Reflectance):** Penicillin G powder can be applied directly to the ATR crystal, without further chemical preparations.

**Film:** For liquid or semi-solid forms, the solvent can be evaporated on a NaCl or KBr plate and the remaining thin film analyzed.

#### 2. Instrumental conditions

**Spectral range:** 4000–400  $\text{cm}^{-1}$  (classical IR range)

**Spectral resolution:** 2–4  $\text{cm}^{-1}$  (for good definition of characteristic bands)

**Number of scans:** 16–64 scans, for good signal-to-noise ratio

**Atmosphere:** Purge with dry nitrogen or use of a desiccant is recommended to reduce interference from water vapor and carbon dioxide.

#### 3. Precautions

**Hygroscopicity:** Penicillin G is hygroscopic and may degrade in the presence of moisture — handling should be rapid and in dry conditions.

**Photosensitivity and instability:** Should be protected from light and high temperatures.

**Contaminants:** Avoid contamination with plastics or other organic substances that may give interfering IR bands.

SalvateInfrared (IR) spectra were taken in a Bruker EQUINOX 55 Fourier Transform Infrared Raman Spectroscopie (Bruker, Karlsruhe, Germany).



Fig 1: Spectroscopie Bruker

## Results and discussions

The structure of penicillin G (also called benzylpenicillin) is representative of the class of  $\beta$ -lactam antibiotics, having a penam nucleus, formed by a  $\beta$ -lactam ring fused to a thiazolidine ring. This structure is essential for its antibacterial activity. Chemical structure of penicillin G: penam nucleus: A  $\beta$ -lactam ring (4 atoms) with a thiazolidine ring (5 atoms, with one sulfur atom) and a side chain containing a benzyl group ( $\text{C}_6\text{H}_5\text{-CH}_2\text{-}$ ), attached to the penam nucleus through an amide group. The characteristic IR features of penicillin drugs 1, 2, 3 are strong bands due to the  $\beta$ -lactam carbonyl vibration at about 1770  $\text{cm}^{-1}$ , the side amide link at about 1660  $\text{cm}^{-1}$  and the ionised carboxylate group at about 1660  $\text{cm}^{-1}$  (Fig 2).

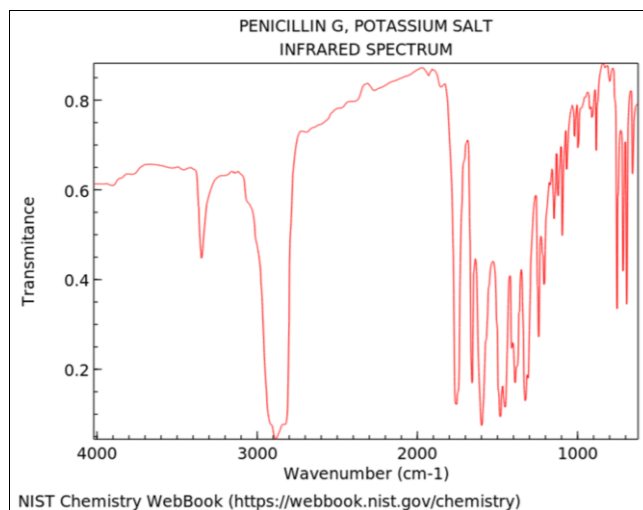


Fig 2: IR spectrum of pellicillin G

The IR (infrared) spectrum of penicillin G (also known as benzylpenicillin) shows bands characteristic of the functional groups in its chemical structure. Penicillin G is an antibiotic of the  $\beta$ -lactam class, and its IR spectrum reflects the presence of  $\beta$ -lactam rings, thiazolidine rings, amide, acidic and aromatic groups (Table 1).

**Table 1:** Characteristic bands in the IR spectrum of penicillin G

Value (cm <sup>-1</sup> )	Assignment
~1770	C=O of the $\beta$ -lactam ring (very strained, so higher than a normal ketone)
~1740	C=O from the ester or carboxylic acid group
~1600–1650	Amide group (C=O and N-H)
~1450–1600	Benzene (aromatic nucleus of benzene from the benzyl residue)
~3200–3400	N-H and/or O-H (wide, due to hydrogen bonds)
~700–900	Aromatic C-H distortions (for the benzene ring)

The  $\beta$ -lactam group is the key to antibiotic activity and is easily identified by the C=O band at ~1770 cm<sup>-1</sup>, which is typical for  $\beta$ -lactam rings. The broad band at ~3400 cm<sup>-1</sup> may indicate the presence of –OH (carboxylic acid) and/or –NH groups. The spectrum may vary slightly depending on the state of the sample (solid, solution, film), but the essential bands are preserved.

### Conclusions

Penicillin was the first antibiotic used by doctors. The discovery of penicillin was one of the great achievements of mankind, this drug saving millions of lives. The discovery was made by chance in 1928, by the Scottish bacteriologist Alexander Fleming. The term "penicillin" is used both to designate the class of antibiotics, and to name certain types of drugs in this class.

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