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Theoretical calculations of natural penicillins: structural and electronic properties

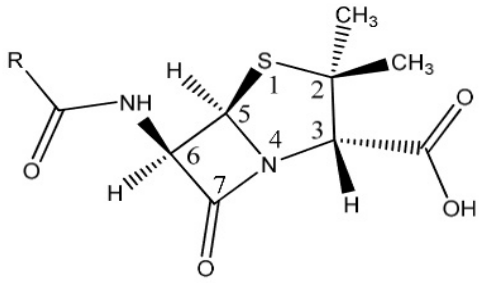
The influence of the calculation method and small structural change in the molecule on the results of geometry and other properties of compounds was studied on the example of known antibiotics. The structural, electronic, and thermodynamic properties of penicillin and phenoxymethylpenicillin were calculated using molecular mechanics and quantum mechanics methods. A comparative analysis of penicillin structures based on experimental data and calculations was carried out. A molecular model of the experimental geometry was considered as the starting structure, which was then optimized. The geometric parameters were computed using the Ellinger MM2 force field method, semi-empirical PM6 one, and *ab initio* Hartree-Fock (HF) method with the Dunning's correlation consistent basis set cc-pVDZ. Although theoretical calculations were carried out in gaseous phase, cc-pVDZ-optimized geometry of the molecules is close to the crystal structure. Some theoretical parameters for optimized structures of the title compounds, such as total electronic energy, zero-point energy, rotational constants and dipole moments were defined by HF method. The electronic properties as HOMO and LUMO energies for both penicillins were calculated. Thermodynamic properties (heat capacity, entropy) of ones were computed by an *ab initio* method that took into account the correlation effects.

Keywords: penicillin, phenoxymethylpenicillin, structure, thermodynamic properties, HOMO and LUMO energies, molecular mechanics, cc-pVDZ basis, quantum mechanics methods.

Introduction

Antibiotics are organic compounds produced in the process of life by bacteria, fungi, molds, yeasts, as well as some higher plants, and possess the property to suppress the growth of microorganisms or kill them. In recent decades, antibiotics have become of great importance for fighting diseases caused by various pathogens. Their study and application in medicine is one of the most remarkable achievements of modern science. The first antibiotic — penicillin was introduced by Scottish scientist Alexander Fleming (1928), and that news had a profound effect on human life. Industrial production and clinical use of penicillin have been achieved thanks to the great work of famous chemists and the collaboration between the pharmaceutical companies of the United States in the 40s of the 20th century [1, 2]. Now a lot of penicillins are known. These are divided into natural (biosynthetic) and synthetic (semi-synthetic) ones. Natural penicillins are fairly selective, semi-synthetic ones manifest a much broader spectrum of antimicrobial action.

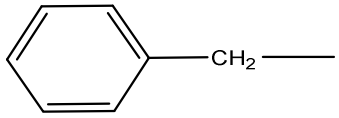
Determination of the structure of penicillins was extremely hampered by their ability to undergo various isomeric transformations even under mild conditions. The question of the structure of penicillin was resolved by X-ray diffraction, a method in which the substance under study does not undergo degradation. The structure of penicillin was established by British chemist and biochemist D. Crowfoot-Hodgkin [3]. The general formula for natural and synthetic penicillins is:



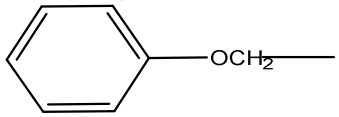
Penicillin core structure

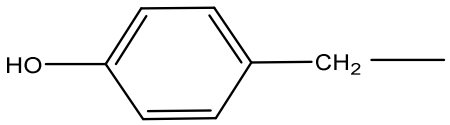
The most important penicillins are natural ones F, G, K, V, and X, which differ by the variable group R:

CH_3-CH_2-CH=CH-CH_2- (F)

 (G)

CH_3-$(CH_2)_5$-CH_2- (K)

 (V)

 (X)

Only two of them, namely, benzylpenicillin (G) and phenoxymethylpenicillin (V) found a wide practical application in medicine [2].

The key structural feature of the penicillins is the four-membered β-lactam ring; this structural moiety is essential for penicillin's antibacterial activity. It undergoes hydrolysis with the disruption of the N4-C7 bond under mild conditions, which leads to a loss of biological activity. The β-lactam ring is itself fused to a five-membered thiazolidine ring [3]. These form a so-called foam-group. X-ray diffraction studies showed that the foam-group of penicillins had a non-planar structure [2]. It was found that antibacterial activity of penicillins depended on the structure of the radical R. The most effective antibiotic is benzylpenicillin (penicillin G), in the molecule of which R is the benzyl radical. A slight change in the structure, the introduction of an oxygen bridge, significantly affects the activity of penicillin. Phenoxymethylpenicillin (penicillin V) is less active against gram-negative bacteria than benzylpenicillin, although it is more resistant to acidic medium [1–4].

Aspects of organic and biological chemistry of penicillins have been well studied [1, 2, 5]. Crystallographic data and the conformational analysis of penicillin molecules are given in Refs [3, 6–9]. In this paper, a comparative quantum-chemical analysis of the above mentioned penicillins, their structural and electronic properties, is performed.

Computational part

The software like ChemBioOffice, GaussView were applied to modelling the structure of molecules. To calculate their characteristics, the molecular mechanics MM2 [10] method, quantum chemical semi-empirical PM6 and *ab initio* methods [11] were used.

Benzylpenicillin has a compact structure according to the X-ray data [3]. We tried to model the crystal structure of penicillin G molecule due to the computer possibilities of above mentioned programs (Fig. 1). Similarly a model of penicillin V was built.

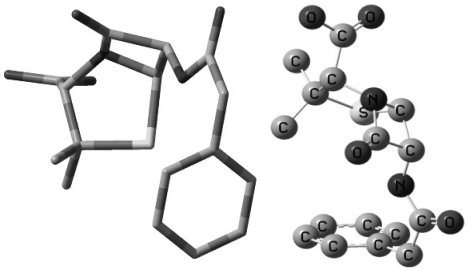
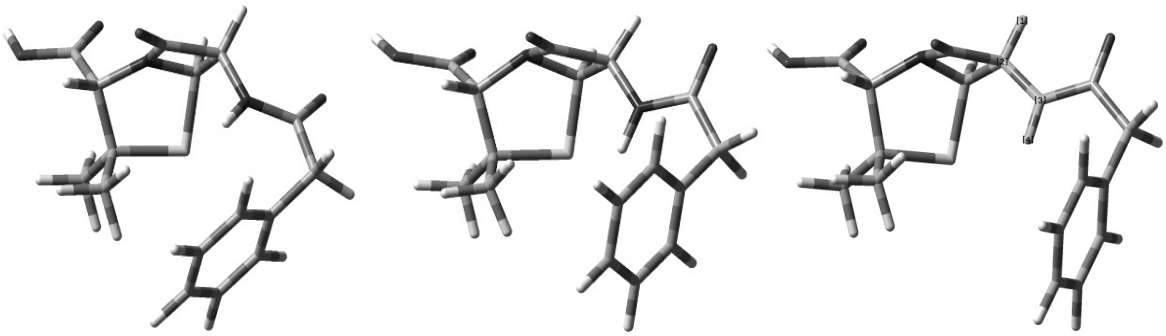


Figure 1. Molecular model of crystal structure of penicillin G
(H atoms are not shown; GaussView 5.0 program)

Using the Hartree-Fock (HF) method with the Dunning's correlation consistent basis set cc-pVDZ, a calculation has been performed on the molecular models of the crystal structure of penicillins to determine the structural, electronic, and thermodynamic properties of ones.

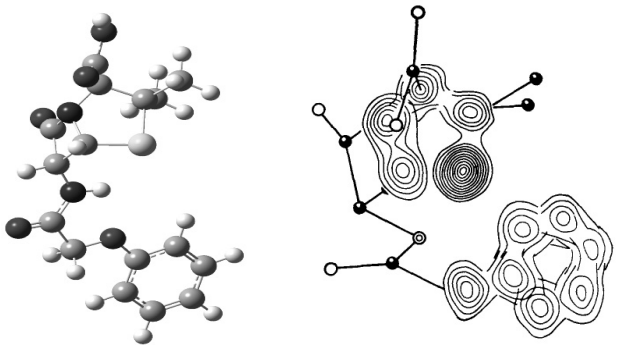
Results and discussion

The optimization of the geometry leads to changes in the positions of atoms and atomic groups. The most important difference is in the orientation of the amide moiety of the side chain. In the crystal structure, oxygen is on the convex face and hydrogen on the concave face of the molecule (<H6-C6-N-H = –156º) [6] (in our calculations, for instance, 178º in the cc-pVDZ structure (Fig. 2*c*)). The locations of these two atoms are altered in the calculated structures. A greater difference is observed in the case of the structure optimized by MM2 method, less for PM6 and cc-pVDZ models (Fig. 2).



a — MM2 model *b* — PM6 model *c* — cc-pVDZ model

Figure 2. Calculated structures of penicillin G



a *b*

Figure 3. Optimized structure (HF/cc-pVDZ method) (*a*) and crystal structure (*b*) [9] of phenoxymethylpenicillin

Optimized structure of penicillin V in comparison with the crystal one is shown in the Figure 3. Differences in spatial structure of molecules in a crystal and other phases can and should be. A preferred conformation is determined by packing in the crystal, but it corresponds to a global minimum in gas. If we compare

three gaseous-phase models the differences can be explained as follows: MM2 structure is considered in the framework of classical mechanics. The molecule is accepted as an electron-nuclear system in quantum-mechanical models. Basis cc-pVDZ takes into consideration the correlation effects.

As we can see on the Figure 2*a* position of benzyl group in space is also not the same for MM2, PM6 and cc-pVDZ models of benzylpenicillin. The corresponding values of angles are shown in Table 1. MM2 method gives mostly smaller angle values and practically perpendicular arrangement of aryl group, while taking into account the correlation effects leads to an increase in the valence and torsion angles. However, according to the method HF/cc-pVDZ, the bonds N-C and $C(H_2)$-C_{Ar} are almost coplanar, whereas MM2 and PM6 show them out of the plane (42º and –41º, respectively).

Another significant difference in the geometry calculated at different levels is the position of the amide group relative to the β-lactam ring: in accordance with the molecular mechanics method they are located nearly orthogonally, semi-empirical and non-empirical methods provide approximately twice as much angle (140º and 130º respectively). Introduction of the oxygen bridge leads to transfer the benzene ring from the position perpendicular to the amide group to the coplanar one. Relevant angle data are listed in Table 1.

T a b l e 1

Some theoretical geometric parameters for penicillins at different levels

Angles (º)	MM2	PM6	HF/cc-pVDZ
C6-N-C	122.026[a] 121.747[b]	120.351 120.160	122.015 122.127
N-C-$C(H_2)$	113.688 114.156	115.556 116.235	117.000 116.214
C-$C(H_2)$-C_{Ar} C-$C(H_2)$-O	109.215 110.420	114.269 106.455	118.005 110.887
C5-C6-N-C	76.863 63.730	140.174 137.687	129.784 132.159
H6-C6-N-H	126.045 107.877	–172.476 –168.035	177.831 –178.047
C6-N-C-$C(H_2)$	–176.903 –179.093	–179.326 –179.793	179.513 178.961
N-C-$C(H_2)$-C_{Ar} N-C-$C(H_2)$-O	42.099 –21.041	–41.224 14.749	–11.154 3.311
C-$C(H_2)$-C_{Ar}-C C-$C(H_2)$-O-C_{Ar}	–97.101 179.807	–64.594 –178.427	–81.770 179.477

Note. [a] — Parameters for penicillin G; [b] — Parameters for penicillin V.

Some theoretical parameters calculated for optimized structures of the title compounds by *ab initio* HF method, such as total energy, zero-point energy, entropy, heat capacity, rotational constants and dipole moments are given in Table 2.

T a b l e 2

Theoretically calculated physical-chemical parameters for the compounds (HF/cc-pVDZ method)

Parameters	Penicillin G	Penicillin V
Total energy (Hartree)	–1422.3671554	–1497.2201151
Zero-point energy (kcal/mol)	231.623	235.530
Entropy (cal/(mol×K))	158.037	161.240
Heat capacity (C_V, cal/mol×K)	76.423	79.499
Rotational constant (GHz)		
A	0.4341207	0.4597905
B	0.1476509	0.1029334
C	0.1291843	0.0913024
Dipole moment (Debye)		
μ_{total}	5.40	4.49
μ_x	1.0285	–0.2300
μ_y	5.2714	–4.4706
μ_z	–0.5204	–0.3566

The data of Table 2 permit the following conclusions: a) the values of the total electronic energy show an energetical stability of penicillin V, and are consistent with its reduced activity; b) when increasing a number of atoms, a correction to the electronic energy of the molecule, which accounts for the effects of molecular vibrations at 0 K, rises; c) when appearing of additional degrees of freedom in an anisotropic molecule, entropy of penicillin V increases; d) the constant volume molar heat capacity is in the same dependence on the molecular mass; e) both molecules are asymmetric tops due to the different rotational constants; f) penicillin V has a lower polarity.

The ability of electron giving is characterized by the highest occupied molecular orbital (HOMO) energy and the ability of electron accepting is characterized by the lowest lying unoccupied molecular orbital (LUMO) energy. These correspond to the ionization potential (I) and the electron affinity (A), respectively: in the Hartree-Fock approximation, the ionization potential is equal to the orbital energy of the ionized molecule taken with the opposite sign, the electron affinity is defined by the same way. The values $E_{HOMO} < 0$ correspond to the positive ionization potentials. The gap between HOMO and LUMO characterizes the molecular chemical stability [12]. Some of the molecular properties have been calculated theoretically by using HOMO and LUMO energy difference, for example, electronegativity (χ), chemical hardness (η) and chemical softness (S) (Table 3).

Table 3

The calculated frontier orbital energies, the absolute electronegativity, the absolute hardness and softness of the compounds (HF/cc-pVDZ method)

Parameters	Penicillin G	Penicillin V
E_{HOMO} (a.u.)	–0.34034	–0.32318
E_{LUMO} (a.u.)	0.12085	0.12414
$\Delta E_{HOMO-LUMO}$ (eV)	12.55	12.17
I (eV)	9.26	8.79
A (eV)	–3.29	–3.38
χ (eV)	2.99	2.71
η (eV)	6.28	6.09
S (eV)	0.080	0.082

The absolute electronegativity has been calculated as a half-sum of the ionization potential and the electron affinity, the absolute chemical hardness has been identified as their half-difference. The chemical softness is the inverse of the hardness. Benzylpenicillin is a fairly strong acid (pKa = 2.7–2.76). Therefore, it has the greater ionization potential, electronegativity, the negative electron affinity (as well as penicillin V). The HOMO-LUMO gap value indicates a lower polarizability of the benzylpenicillin molecule, which is consistent with the value of its permanent dipole moment (Table 2). The measure of resistance to change in the electronic configuration, the so-called hardness of the substance, is higher in the case of penicillin G, and, respectively, its softness is lower than that of penicillin V.

Conclusions

A comparative analysis of penicillin structures based on experimental data and calculations showed, on the one hand, the significant influence of the calculation method on the results of geometry and other properties of compounds, on the other hand, the influence of the structural change in the molecule on the same properties. Although theoretical calculations were carried out in gaseous phase, Hartree-Fock calculations with a correlation basis allowed us to determine structures close to the experimental ones. The addition of a single oxygen bridge caused a marked change in the physico-chemical properties of the substance. Electronic and thermodynamic properties are also calculated by *ab initio* method that took into account the correlation effects.

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Табиғи пенициллиндердің теориялық есептеулері: құрылымдық және электрондық қасиеттері

Белгілі антибиотиктердің мысалында қосылыстардың геометриясы мен басқа қасиеттеріне есептеу әдістері және молекуладағы кішігірім құрылымдық өзгерістерінің әсері зерттелді. Молекулалық және кванттық-механикалық әдістерін пайдалана отырып, пенициллин мен феноксиметилпенициллиннің құрылымдық, электрондық және термодинамикалық қасиеттері есептелді. Тәжірибелік деректер мен есептеулер негізінде пенициллиндердің құрылымдарына салыстырмалы талдау жүргізілді. Бастапқы құрылым ретінде тәжірибелік геометриясының молекулалық үлгісі қарастырылды. Құрылым одан әрі оңтайландырылды. Геометриялық параметрлері Эллинджер ұсынған ММ2 модификацияланған күштер өрісіне негізделген әдісімен, PM6 жартылай эмпирикалық әдісімен және Даннингтің корреляциялы-реттелген базистік cc-pVDZ жиыны бар эмпирикалық емес Хартри-Фок әдісімен есептелінді. Газ фазасындағы молекулалар үшін орындалған теориялық есептеулерге қарамастан, cc-pVDZ-оңтайландырылған геометриясы кристалдық геометрияға жақын. Жоғарыда аталған қосылыстардың оңтайландырылған құрылымдары үшін толық электрондық энергия, нөлдік тербеліс энергиясы, айналмалы тұрақтылар, диполь моменттері сияқты кейбір теориялық параметрлер анықталған. Сондай-ақ екі пенициллин үшін шекаралық молекулалық орбитальдардың электрондық қасиеттері есептелді. Корреляциялық әсерлерін ескеретін *ab initio* әдісімен қосылыстардың термодинамикалық қасиеттері (жылусыйымдылығы, энтропиясы) анықталды.

Кілт сөздер: пенициллин, феноксиметилпенициллин, құрылым, термодинамикалық қасиеттер, ЖТМО мен ТБМО энергиялары, молекулалық механика, cc-pVDZ базисі, кванттық механика әдістері.

Л.К. Абуляисова, М.С. Касымова, Е.В. Минаева

Теоретические расчеты природных пенициллинов: структурные и электронные свойства

На примере известных антибиотиков изучено влияние метода расчета и небольшого структурного изменения в молекуле на результаты по геометрии и другим свойствам соединений. С использованием методов молекулярной и квантовой механики рассчитаны структурные, электронные и термодинамические свойства пенициллина и феноксиметилпенициллина. Выполнен сравнительный анализ структур пенициллинов на основе экспериментальных данных и расчетов. В качестве стартовой структуры была рассмотрена молекулярная модель с экспериментальной геометрией, которая далее была оптимизирована. Геометрические параметры были рассчитаны методом молекулярной механики с модифицированным силовым полем ММ2, разработанным Эллинджером, полуэмпирическим PM6 методом и неэмпирическим методом Хартри-Фока с корреляционно-согласованным базисным набором Даннинга cc-pVDZ. Несмотря на то, что теоретические расчеты были выполнены для молекул в газовой фазе, cc-pVDZ-оптимизированная геометрия близка к кристаллической. Методом ХФ определены некоторые теоретические параметры для оптимизированных структур названных выше соединений, та-

кие как полная электронная энергия, энергия нулевых колебаний, вращательные постоянные, дипольные моменты. Для пенициллинов были рассчитаны также электронные свойства граничных молекулярных орбиталей. *Ab initio* методом, учитывающим корреляционные эффекты, определены термодинамические свойства соединений (теплоемкость, энтропия).

Ключевые слова: пенициллин, феноксиметилпенициллин, структура, термодинамические свойства, энергии ВЗМО и НСМО, молекулярная механика, базис cc-pVDZ, методы квантовой механики.

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