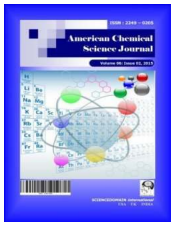

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The Relationship between the Antimicrobial Properties of Benzylpenicillin and the Quantum Chemical Parameters of Its Structure (The DFT Method)

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Authors' contributions

This work was carried out in collaboration between all authors. Author VAB set a target, wrote the abstract and the conclusion, wrote the protocol and participated in the discussions. Author DSA processed and analyzed the results, carried out the graphic design. Author AAP performed quantum chemical calculation of penicillin. Author LML performed the editing and proofreading of the manuscript, an English translation and designed references. Author AIR wrote the following parts: Introduction, materials and methods, experiment, results and discussion. Author NAR wrote the second part of the introduction and participated in the discussions on this part. Author VSB consulted on the medical part of the manuscript. Author GEZ consulted on the chemical part of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The relationship between the antimicrobial properties of benzylpenicillin and its electronic structure, the analysis of which has been carried out by the quantum chemical DFT-PBE0 / 6-311g **method, has been examined for the first time. The carbonyl groups of benzylpenicillin responsible for the blockade of the synthesis by pentodoglikans, which in turn are responsible for the antibacterial properties of benzylpenicillin, have been revealed. Its acid strength (pKa = 12) has been theoretically estimated.

*Keywords: Antimicrobial properties; benzylpenicillin; quantum-chemical calculation; DFT-PBE0 / 6-311g ** method; acid strength; electronic and geometric structure.*

1. INTRODUCTION

Penicillins (the Nobel Prize, Fleming, 1945) are the first antimicrobials developed from the waste products of microorganisms [1]. They belong to a broad class of β-lactam antibiotics (β-lactams). Benzylpenicillin is the ancestor of all β-lactams [2].

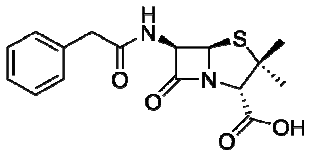

Fig. 1. The structure of the molecule of benzylpenicillin

β-Lactam cycle is the general fragment in the chemical structure of benzylpenicillin. It is associated with the microbiological activity of these drugs [3]. The molecular targets of benzylpenicillin in a microbial cell are trans and carboxyl-peptidase enzymes involved in the synthesis of the main component of the outer membrane of both gram-positive and gram-negative bacteria of peptidoglycan. Due to the ability to be connected with penicillin these enzymes got the second name – the penicillin connecting proteins (PCP). The PCP molecules are rigidly connected with the cytoplasmic membrane of the microbial cell, they carry out the formation of the cross-links. The relationship with the PCP leads to inactivation of the cross-links, cessation of growth and subsequent death of the microbial cells [4]. Thus, the level of activity of specific substances on certain microorganisms is primarily determined by their affinity to the PCP [5]. It is an important fact for practice, that the lower the affinity of the interacting molecules, the higher the concentrations of antibiotic require to inhibit the function of the enzyme [6].

However, in order to be connected with the PCP, antibiotic must penetrate from the outside through the exterior structure of microorganism. The capsule and peptidoglycan of the gram-positive microorganisms are not a significant barrier to the diffusion of penicillin. Virtually insurmountable obstacle for it is the lipopolysaccharide layer of gram-negative bacteria and only by diffusion are outer membrane porin channels which are funnel-shaped structures of a protein nature, and are the main route of transport of nutrients into the bacterial cell. The lipopolysaccharide layer of gram-negative bacteria is virtually insurmountable obstacle for it. The outer membrane porin channels representing funneled structures of a protein nature are the only way for the diffusion and the main route of the transfer of nutrients into the bacterial cell. The β-lactamase enzymes, the hydrolyzing antibiotics, are another factor limiting the access of the substance to the act target. β-Lactamases have probably appeared for the first time in microorganisms as factors which neutralize the action of the synthesizable antibiotic substances. As a result of interspecific gene transfer β- lactamases were widely adopted among various microorganisms, including pathogenic. β-Lactamases localize in the periplasmic space in gram-negative microorganisms and freely diffuse into the environment in gram-positive microorganisms. Blocking the synthesis of peptidoglycan leads to the death of the bacterium. Benzylpenicillin, karboksipenitsillins and ureidopenitsillins are largely collapsed under the influence of hydrochloric acid of the gastric juice, so apply only parenterally.

Nevertheless, despite the very deep fundamental experimental researches of its properties, it is well known that penicillin in practice, unfortunately, accompanied by a large number of side reactions that are difficult to lock, so the use of it decreases every year. The research of the structure of penicillins and their relationship with the activity and selectivity of action must undoubtedly lead to the increase of its efficiency.

The quantum chemical calculations of penicillins can certainly contribute to this promising research direction.

2. MATERIALS AND METHODS

To examine the relationship between the antimicrobial properties of penicillin and its electronic structure the quantum chemical DFT-PBE0 / 6-311G ** method was chosen (Perdew-Burke-Ernzerhof 1996 nonlocal, Perdew-Wang 1991 LDA) [7]. It is known that the DFT method (Nobel Prize W. Kohn, 1998), based on the theory of density of functionality, can significantly improve the accuracy of the calculation of the energy of the complex molecular systems to which benzylpenicillin refers [8]. Besides, it makes a good description of the distribution of the electron density in the ground state. Our calculation was carried out in this state. It is the well known advantage of this method.

It is also known that the maximum charge on the hydrogen atom linked to pKa - a universal measure of acidity $pKa = 51.048-150.078q_{max}^{H^+}$ with high correlation coefficient (R> 96%). In our Manuscript the acid strength of penicillin was theoretically estimated. So it was logical to choose the DFT method.

The optimization of geometry was performed in all respects by the gradient method built into the PC GAMESS [7], which is the fundamental basis of the stationary Erwin Schrodinger′s equation. (Nobel Prize, 1933). The calculation has been performed in an approximation of an isolated molecule within the molecular model in the gas phase. It has allowed to estimate its acid strength theoretically, according to the $pKa = 51.048-150.078q_{max}^{H+}$ formula which has been obtained by us for the DFT-PBE0 / 6-311g ** method as analogously described in [9] (but for the AM1 method) (where, q_{max}^{H+} is the maximum charge on the hydrogen atom, pKa is a universal measure of acidity). For a visual representation of the molecular model the MacMolPlt program has been used [10]. The total charge of the molecular system of benzylpenicillin is 0, the multiplicity is M = 2S + 1 = 1 (in the ground state, all electrons are paired, the total spin of the electron is equal to 0).

3. EXPERIMENT, RESULTS AND DISCUSSION

Compulsory component of the outer membrane of prokaryotic microorganisms (except mycoplasma) is peptidoglycan -a biological polymer consisting of parallel polysaccharide chains. The peptidoglycan skeleton acquires rigidity forming between the polysaccharide chains of the cross-links. The carboxyl and transpeptidase enzymes (PCP) bring about the circuit of the links. β-Lactam antibiotics are capable to be connected with the active site of the enzyme and to inhibit its function. The specific activity of antibiotics is determined by the presence of the β-lactam cycle. Side radicals determine the pharmacokinetic characteristics and resistance to β-lactamase.

The target of their action, as has been said before, is the penicillin connecting proteins of bacteria that act as the enzymes in the final stage of the synthesis of peptidoglycan which is biopolymer, the main component of the bacterial cell wall. Blocking of peptidoglycan synthesis leads to the death of bacteria [11].

We have shown (Fig. 3) the role of the β-lactam cycle of benzylpenicillin molecule in the destruction of microorganisms [12]. "Active" PCP becomes "depressed" PCP under the influence of β-lactam cycle of the molecule of benzylpenicillin (PCP) [13].

The Table 1 shows the results of quantum chemical calculations of benzylpenicillin molecule. Consider the most important element of this molecule - β - lactam fragment (Figs. 1-3). This fragment is involved in blocking the synthesis of peptidoglycan - the basic component of the bacterial cell wall (the cell walls of the bacterial cells perform a mechanical function, the osmotic protection of the cell and antigen functions). The Table 1 (the numbering of the atoms - Fig. 2) shows that the β-lactam cycle is a quadrangle. The angles (Fig. 2, Table 1) in the β- lactam cycle are: N (12) -C (11) -C (9) - 90deg., C (9) -C (10) -N (12) – 92deg., C (10) -N (12) -C (11) -93 deg., C (11) -C (9) -C (10) -85 degrees. This indicates the presence of the deformation stresses in the four-membered cycle. Furthermore, the high polar bonds between atoms in the β- lactam cycle should be noted: N atomic charge (12) is -0.42, and the adjoining atom C (10) is equal to +0. The displacement of the electron density in the carbonyl group of the β- lactam cycle from the carbon atom C (10) to the oxygen atom, O (20) leads to a high value of the electron density on the carbonyl oxygen and to the charge which is equal to -0.31. The angle O (20) -C (10) -N (12) is equal to 131 degrees. The inclusion of the

β-lactam cycle in the bicyclic structure significantly effects on its properties. In this bicyclic structure in β-position to the nitrogen atom is the sulfur atom (Fig. 2). The angle N (12) -C (11) -S (13) is 107 degrees. On the sulfur atom, S (13), the quantity of the positive charge is equal to +0.18, while on the carbon atom C (11), the quantity of negative charge is equal to -0.16. The carbon atom C (11) is simultaneously connected with the sulfur atom S (13) and the nitrogen atom N (12).

Thus, a negatively charged nitrogen N (12) atom (the node atom in the bicyclic structure) forms a relationship with three carbon atoms: the positively charged atom C (10), C (15) with a small negative charge (-0.04) and negatively charged atom C(11) which is simultaneously connected with a positively charged sulfur atom. This explains the high reactionary ability of the β-lactam cycle. The carbonyl groups C18 = C7 = O19 and O21 also have the same ability and due to the polarity (q_{C18} = + 0.44, q_{O19} = -0.35, q_{S7} + = 0.43, q_{O21} = -0.39) involved in the process of complexation.

So, the structural features of benzylpenicillin examined by the quantum chemical method explain the blocking of peptidoglycan synthesis - the main component of the bacterial cell wall.

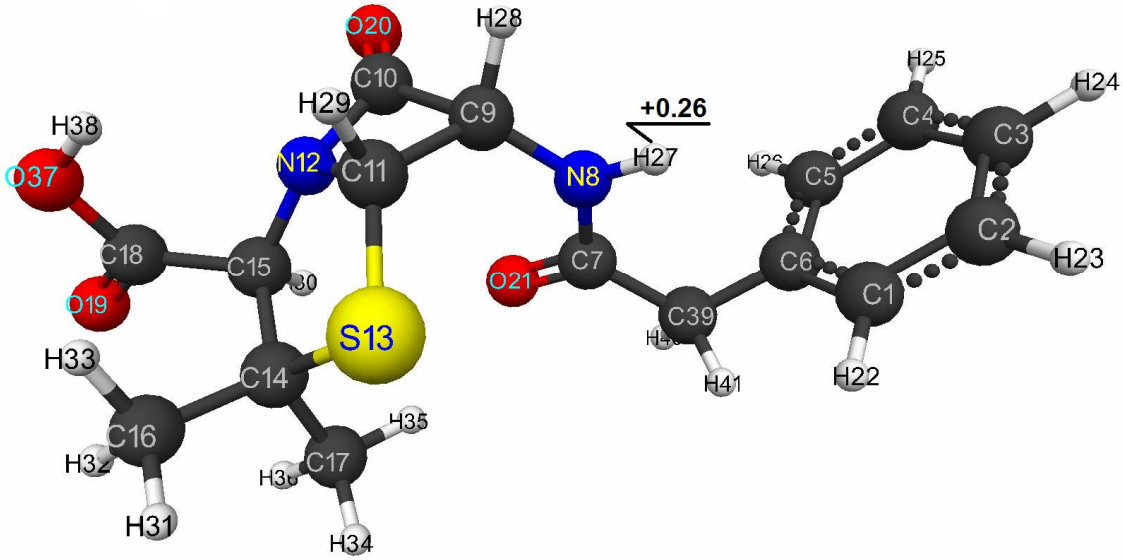

Fig. 2. The geometric and electronic structure of the molecule of benzylpenicillin (E_0= -3748839 kJ / mol, E_{el}= -9407499 kJ / mol)

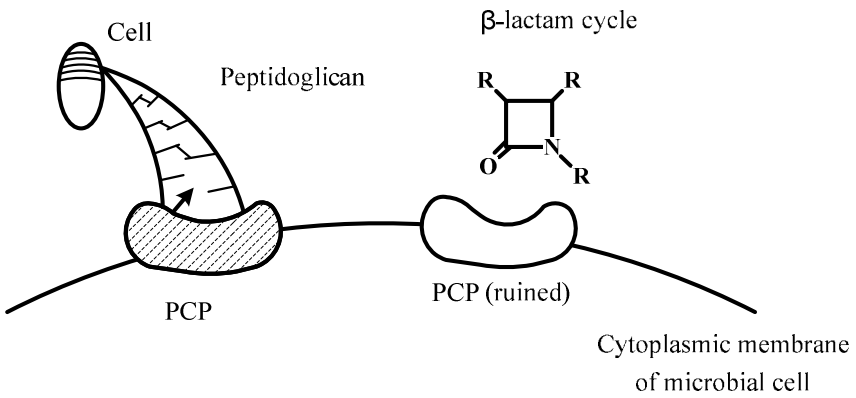

Fig. 3. The relationship scheme of the β-Lactam cycle of benzylpenicillin molecule with the active site of the enzyme

In addition, the strength of the acid of benzylpenicillin within the study of the molecular model, often responsible for the selectivity of any antibiotic, is theoretically evaluated in this manuscript. To do this, the optimized geometric and electronic structure, the total energy, the electron energy and the charges on the atoms of the molecule of benzylpenicillin obtained by DFT-PBE0 / 6-311g ** method have shown on Fig. 2 and in Table 1. Applying pKa = 51.048-150.078 q_{max}^{H+}, (q_{max}^{H+} = +0,26) formula (Table 1) we find the value of acid strength of benzylpenicillin (pKa = 12).

Table 1. The optimized bond lengths, valence angles and the charges on the atoms of the molecule of benzylpenicillin

The bond lengths	R,A	The valence angles	Degree	Atom	The charges on the atoms
C(2)-C(1)	1.39	C(1)-C(2)-C(3)	120	C(1)	-0.06
C(3)-C(2)	1.39	C(2)-C(3)-C(4)	120	C(2)	-0.10
C(4)-C(3)	1.39	C(6)-C(5)-C(4)	121	C(3)	-0.09
C(5)-C(4)	1.39	C(3)-C(4)-C(5)	120	C(4)	-0.10
C(5)-C(6)	1.40	C(1)-C(6)-C(5)	119	C(5)	-0.04
C(6)-C(1)	1.40	C(39)-C(6)-C(5)	121	C(6)	-0.25
C(7)-C(39)	1.52	C(2)-C(1)-C(6)	121	C(7)	+0.43
N(8)-C(7)	1.36	C(6)-C(39)-C(7)	117	N(8)	-0.39
C(9)-N(8)	1.43	C(39)-C(7)-N(8)	116	C(9)	-0.11
C(9)-C(11)	1.56	O(21)-C(7)-N(8)	123	C(10)	+0.42
C(10)-C(9)	1.55	C(11)-C(9)-N(8)	120	C(11)	-0.16
C(11)-N(12)	1.48	C(7)-N(8)-C(9)	122	N(12)	-0.42
N(12)-C(10)	1.42	N(12)-C(11)-C(9)	90	S(13)	+0.18
S(13)-C(11)	1.81	S(13)-C(11)-C(9)	120	C(14)	-0.51
C(14)-C(15)	1.55	N(8)-C(9)-C(10)	116	C(15)	-0.04
C(14)-S(13)	1.86	C(11)-C(9)-C(10)	85	C(16)	-0.24
C(15)-N(12)	1.46	C(10)-N(12)-C(11)	93	C(17)	-0.26
C(16)-C(14)	1.53	C(9)-C(10)-N(12)	92	C(18)	+0.44
C(17)-C(14)	1.52	O(20)-C(10)-N(12)	131	O(19)	-0.35
C(18)-C(15)	1.53	N(12)-C(11)-S(13)	107	O(20)	-0.31
O(19)-C(18)	1.20	C(15)-C(14)-S(13)	104	O(21)	-0.39
O(20)-C(10)	1.19	N(12)-C(15)-C(14)	107	H(22)	+0.11
O(21)-C(7)	1.21	C(11)-S(13)-C(14)	91	H(23)	+0.11
H(22)-C(1)	1.09	C(18)-C(15)-C(14)	111	H(24)	+0.11
H(23)-C(2)	1.08	C(10)-N(12)-C(15)	122	H(25)	+0.11
H(24)-C(3)	1.08	C(15)-C(14)-C(16)	112	H(26)	+0.11
H(25)-C(4)	1.08	S(13)-C(14)-C(16)	109	**H(27)**	**+0.26**
H(26)-C(5)	1.09	C(17)-C(14)-C(16)	111	H(28)	+0.17
H(27)-N(8)	1.01	C(15)-C(14)-C(17)	111	H(29)	+0.19
H(28)-C(9)	1.09	S(13)-C(14)-C(17)	109	H(30)	+0.22
H(29)-C(11)	1.09	N(12)-C(15)-C(18)	113	H(31)	+0.14
H(30)-C(15)	1.09	C(15)-C(18)-O(19)	122	H(32)	+0.15
H(31)-C(16)	1.09	O(37)-C(18)-O(19)	123	H(33)	+0.13
H(32)-C(16)	1.09	C(9)-C(10)-O(20)	137	H(34)	+0.13
H(33)-C(16)	1.09	C(39)-C(7)-O(21)	121	H(35)	+0.15
H(34)-C(17)	1.09	C(2)-C(1)-H(22)	120	H(36)	+0.16
H(35)-C(17)	1.09	C(1)-C(2)-H(23)	120	O(37)	-0.29
H(36)-C(17)	1.09	C(2)-C(3)-H(24)	120	H(38)	+0.26
O(37)-C(18)	1.33	C(3)-C(4)-H(25)	120	C(39)	-0.22
H(38)-O(37)	0.97	C(4)-C(5)-H(26)	120	H(40)	+0.18
C(39)-C(6)	1.50	C(6)-C(5)-H(26)	119	H(41)	+0.17
H(40)-C(39)	1.09	C(7)-N(8)-H(27)	118		
H(41)-C(39)	1.09	N(8)-C(9)-H(28)	109		
		C(11)-C(9)-H(28)	113		

The bond lengths	R,A	The valence angles	Degree	Atom	The charges on the atoms
		N(12)-C(11)-H(29)	113		
		N(12)-C(15)-H(30)	109		
		C(14)-C(16)-H(31)	110		
		C(14)-C(16)-H(32)	110		
		C(14)-C(16)-H(33)	112		
		C(14)-C(17)-H(34)	111		
		C(14)-C(17)-H(35)	111		
		C(14)-C(17)-H(36)	109		
		C(15)-C(18)-O(37)	115		
		C(18)-O(37)-H(38)	106		
		C(1)-C(6)-C(39)	121		
		C(6)-C(39)-H(40)	111		
		C(6)-C(39)-H(41)	111		

4. CONCLUSION

Thus, we first examined the relationship of the antimicrobial properties of benzylpenicillin with its electronic structure, the analysis of which has been carried by the quantum chemical of DFT-PBE0 / 6-311g ** method. The carbonyl groups of benzylpenicillin responsible for the blockade of the synthesis by pentodoglikans [14], which in turn are responsible for the antibacterial properties of benzylpenicillin, have been revealed. Its acid strength (pKa = 12) has been theoretically estimated. It is found that the molecule of benzylpenicillin refers to a class of weak acids (9 <pKa <14).

Furthermore, the quantum chemical calculations of benzylpenicillin have been previously produced by us by AB INITIO method [15]. The comparison of the results of calculations of benzylpenicillin by the DFT and AB INITIO methods gives the same value (pKa = 12) within the errors of the methods. Ultimately, the quantum chemical calculations of various penicillins may contribute to the development of new, more effective antibiotics, for example, according the algorithms proposed in [16].

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Klets OP, Minokina LM. Antibiotic - Irkutsk: Irkutsk State Medical University. 2013;72.
2. Glushchenko NN. Pharmaceutical chemistry. M.: Akademiya. 2004;84.
3. Nys PS, Kurochkina VP. Beta-lactam compound. Correlation of structure and biological activity. Antibiotics and Chemotherapy. 2000;7.
4. Gilman AG. Clinical pharmacology. Practice - V.3. 2006;1642.
5. Syomina NA, Sidorenko SV, Rezvan SP. Guidelines. Determination of the sensitivity of microorganisms to antibiotics. Clinical, Microbiological, Antimikrobiological Chemotherapy. 2004;6(4):306-359.
6. Atrepeva LV. Properties and receiving of antibiotics of the penicillin line. Pharm. Journal. 2003;5:13-16.
7. Schmidt MW, Baldrosge KK, Elbert JA, Gordon MS, Enseh JH, Koseki S and et al. General Atomic and Molecular Electronic Structure System. J. Comput. Chem. 1993; 14:1347-1363.
8. Tsirel'son VG. Quantum chemistry. Molecules, molecular systems and solids. M.: Publishing House "Binom". 2010;496.
9. Babkin VA, Andreev DS, Fomichyov VT, Zaikov GE, Mukhamedzyanova ER. About the correlation dependence of the universal indicator of acidity with the maximum charge on the hydrogen atom of H-acids. AM1 method. Vestnik of the Kazan Technological University – Kazan. 2012;10:15-19.
10. Bode BM, Gordon MS. A grafic user interface for gamess. J. Mol. Graphics Mod. 1998;16:133-138.
11. Mosolov VV. Proteolytic enzymes. Moscow. 1971;416.
12. Antonov VK, Ginodman LM. Chemistry of Proteolysis. M. 1983;515.
13. Franklin TJ, Snowe J. Biochemistry of antimicrobial activity; transl. from English. M.: Mir. 1984;238.

14. Fouco D. Antibiotics; 2012 [An electronic resource] Available:http://www.mdpi.com/2079-6382/1/1/1 (Accessed 08 November 2015).
15. Babkin VA. Dmitriev VYu, Belousova VS, Zaikov GE. Quantum chemical calculations of benzylpenicillin molecule. Collection of articles "the quantum chemical calculations of unique molecular systems. V1. Volgograd: The VolGU Publishing House. 2010;10-14.
16. Babkin VA, Zaikov GE. Nobel laureates and nanotechnologies of applied quantum chemistry. USA. New York: Nova Science Publishers. 2010;351.

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