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The quantum chemical study of the absorption spectrum of the neutral and charged forms of penicillin G sodium solt

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Received February 15, 2024
Revised June 11, 2024
Accepted June 16, 2024

The methods of spectroscopy and quantum chemistry were used to investigate the nature of absorption spectra and charge distribution of benzylpenicillins. The assumed spatial structure of the complex of benzylpenicillin sodium salt anion with water of composition 1 : 3 has been optimized. It was found that the absorption in the long-wave and middle regions of the spectrum is associated with the penam of the benzylpenicillin molecule. The intensity of the short-wave part of the spectrum is mainly formed by electronic transitions of the benzene part of the molecule. The distribution of effective charges on benzylpenicillin fragments was calculated and analyzed using quantum chemistry methods. The proton-acceptor power of all fragments was determined in benzylpenicillin anion and their complexes with water. The transfer of effective charge was calculated during the transition from a neutral benzylpenicillin molecule to its anion, as well as during complex formation. In the neutral molecule of benzylpenicillin, the donor properties of the penam significantly exceed those of the benzyl fragment, and the side chain has a higher acceptor ability than the carboxyl group. The formation of hydrogen bonds in the benzylpenicillin molecule markedly reduces both the donor properties unit of the penam and the acceptor properties of the side chain. The changes on the benzyl and carboxyl moieties are less significant. Data analysis has established that in the benzylpenicillin anionic form the donor and acceptor properties of fragments change sharply in comparison with the neutral form. The main difference of the charged form is that the penam system becomes practically neutral, and the proton-acceptor center becomes the CCO group in the anionic form.

Keywords: benzylpenicillin sulfoxide, absorption spectra, effective charges, proton acceptor, H-bonding.

DOI: 10.61011/EOS.2024.07.59640.6033-24

Introduction

One of the important problems of physical chemistry is to estimate the correlation between the pharmacological activity of molecular systems and their electronic/spatial structure and spectral manifestations. Estimation of such correlations will make it possible to compare not only therapeutic monitoring tasks, but also the tasks of targeted synthesis of new drugs.

Penicillins — are a broad group of antibiotics containing a β-lactam cycle (Figure 1). Pharmacological properties of this class of molecules are defined by so-called penam group consisting of commonly bonded β-lactam and thiazolidine cycles (Figure 1). Benzylpenicillin sodium salt (penicillin G, $PCNG$) is a natural antibiotic used for treatment of croupous and burn pneumonia, pleuritis, peritonitis, wound and purulent infections of skin, soft tissues and mucous membranes, and other diseases [1]. Biological effect mechanism of penicillins is known to suppress the synthesis of peptidoglycan enzyme that is the major component of bacterial cell wall, thus, killing bacteria [2,3]. The $PCNG$ molecule contains various acid-base functional groups that have a pronounced acidic nature (carboxyl, sulfonic), basic nature — amine, aminothiazole groups, groups weakly involved in acid-base interactions — phenolic and amide groups. dissociation constant of $PCNG$ is equal to 2.56, therefore antibiotic in water solutions (with pH about 5) behaves as an organic acid and is present in human blood (with pH about 7) as single- or double-charged ions [4]. Intermolecular interactions in complex „water–antibiotic“ systems define the solubility and capability of a drug to undergo various biochemical transformations [5,6]. Increased focus is currently made on the issues of drug property control directly in the structure. Studies of cooperative effect of functional groups in the structure are of particular importance [7]. Structural organization control makes it possible to achieve next generation biofunctional injectable drugs.

Antibacterial activity of any antibiotic significantly depends on two factors: geometry that defines possible negotiation of the antibiotic's bioactive fragment into the active center of the target bacteria wall enzyme („key–lock“ relation) and chemical reactivity. The authors of [8,9] have found that, at the first antibiotic action stage, chemical reactivity of the antibiotic is important, while the antibiotic

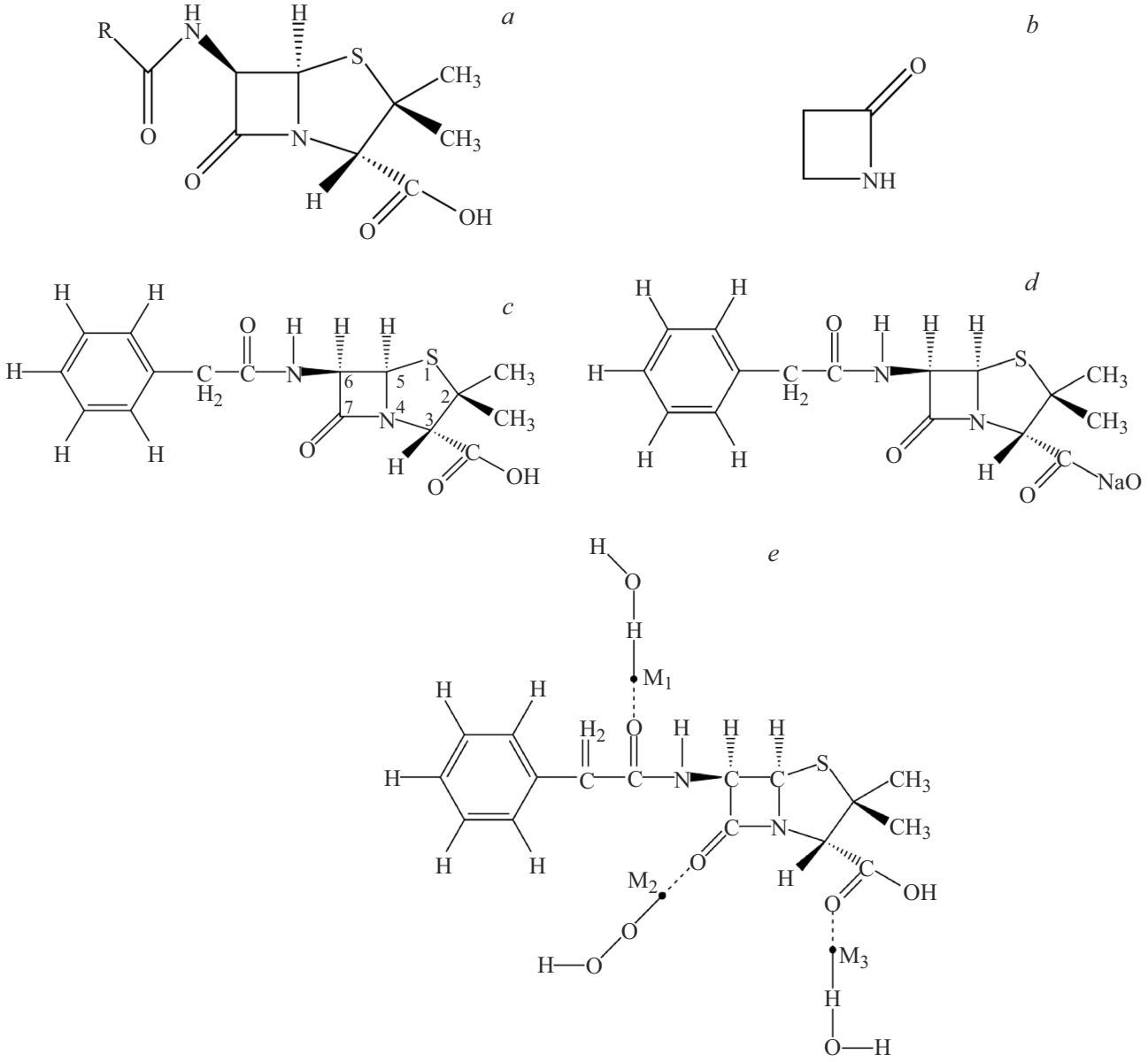

Figure 1. Penicillin structure: (*a*) ring, general view, (*b*) β-lactam cycle, (*c*) benzylpenicillin, (*d*) benzylpenicillin sodium salt (*PCN G*), (*e*) neutral molecule complex *PCN G* (M_1, M_2, M_3 — MESP minimum positions).

structure ranks second. In such situation, each of the above-mentioned factors is important and, from our point of view, it is difficult to give preference to any of them.

Despite the fact that penicillin and penicillin-based antibiotics were discovered long ago, have undergone numerous studies and are successfully used in practical applications, investigation of the correlation between the chemical/geometrical structures and antibacterial activity, and identification of properties of drug compounds responsible for antibacterial activity are of high interest and importance. Water-soluble benzylpenicillin, that has currently lost its wide use in therapy, has been chosen as a subject of research for the following reasons. On the first hand, the physical and chemical properties of the penicillin G molecule are quite well studied experimentally and theoretically [10–12]. But these studies are mostly devoted to the synthesis and pharmacological properties of antibiotics. Absorption spectra calculations and interpretation, and the features of spectra of solutions of this antibiotic class are unknown. Investigation of electronic transitions facilitates deeper understanding of the electromagnetic effects on a substance, in particular, on the photolysis of the *PCN G* molecules that damage the antibiotic's biological activity.

On the second hand, *PCN G* is included in β-lactam cycle semisynthetic antibiotics and participates in formation of antibacterial properties of these compounds, i.e. impacts the antibacterial activity variation. It is highly likely suggested that at distances exceeding the length of chemical bonds, but

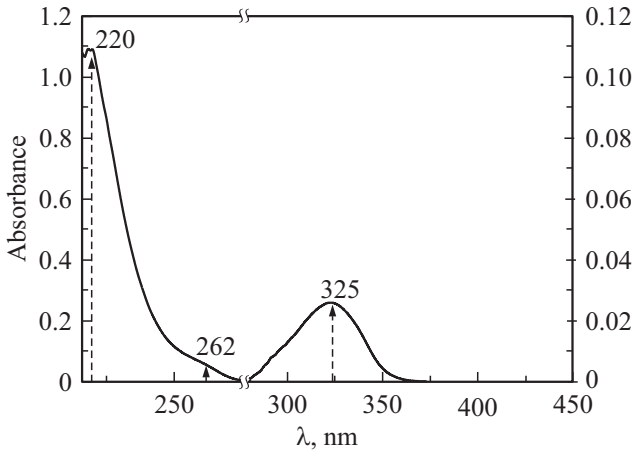

Figure 2. Absorption spectrum of the *PCN G* water solution.

insufficient for exchange interaction, electrostatic interactions play the main role in the interaction between particles. Therefore, understanding of electron density distribution on the antibiotic molecule fragments (and bacterial wall enzyme receptors) will make it possible to identify active regions of antibiotic-receptor interaction and contribute to reasonable construction of complexes between the antibiotic molecules and cell wall enzyme receptors, and will also facilitate the achievement of more specific insight into the mechanism of this interaction. There is little research of this kind [13].

On-the third hand, penicillin family molecules in substance are known to be liable to photolysis mainly over the β-lactam cycle which leads to the loss of biological activity, therefore penicillin salts are used in actual practice because they dissociate in water into antibiotic anions. Thus, the absorption spectrum of the *PCN G* water solution in the spectrum region with $\lambda > 200$ nm is the spectrum of the *PCN G* anion that in turn forms complexes with H-bonds with water molecules.

Considering the above, the aim of our research was to perform quantum chemical study of benzylpenicillin sodium salt water solutions: interpretation of the absorption spectrum of *PCN G*, its anion and their complexes with water involving map calculations by the molecular electrostatic potential (MESP) method for justification of geometry and composition of the complexes. Considering the role of electrostatic interaction at the initial molecule interaction stage, the data on effective charge distribution over the fragments of interacting molecules define the proton acceptor properties of the active *PCN G* fragments and can predict the mechanism o interaction between the antibiotic molecules and environment. Therefore, the objective of our research includes the calculation of effective charge distribution over the neutral and charged *PCN G* molecules and their complexes to evaluate the donor-acceptor properties of these fragments.

Research procedure

Experimental

A *PCN G* substance made by Sigma-Aldrich (CAS Number: 69-57-8) is a poorly water-soluble white powder. Spectral characteristics of the *PCN G* (1.7×10^{-5} M) water solution were recorded at a room temperature of 20°C using the VARIAN Cary 5000 Scan UV-VIS-NIR (AgilentTech, USA-Netherlands-Australia) spectrophotometer. A quartz cell with a 1 mm pathway was used for the measurements.

The experimental absorption spectrum of the *PCN G* water solution is shown in Figure 2, it can be divided into several regions that differ markedly in intensity. Thus, the absorbance of the long-wavelength absorption band in this region does not exceed $D_{\max} \approx 0.025$. The short-wavelength portion — a high-intensity absorption spectrum region with a clearly marked by a peak at ~ 220 nm ($D_{\max} \approx 1.1$ with a concentration of 1.7×10^{-5} M).

The differential spectroscopy method was used to identify band peaks in the experimental absorption spectrum of the benzylpenicillin sodium salt water solution at 325, 262 and $\sim$ 220 nm.

Quantum chemical calculations

Quantum-chemical calculations performed using the semi-empirical method of intermediate neglect of differential overlap (INDO) with original parametrization [14]. The method was implemented in the software package developed by the photonics department of the Siberian Physical and Technical Institute, Tomsk State University. This software package is oriented to the study of spectral luminescent properties of polyatomic molecules and photochemical processes in them using various classes of chemical compounds. The package's programs calculate the electronic spectra of singlet and triplet excited states, induced absorption spectra, fluorescence and physical and chemical properties of molecules (electron density distribution on atoms and chemical bonds, dipole moment in the ground and excited states as well as proton acceptor ability of the molecule in the ground and excited states using the MESP method [15,16].

The molecule structure geometry was simulated using ChemDraw Ultra software. Austin Model 1 geometry optimization method (Austin Model № 1 or *AM*1) [17,18] was defined using Chem3D Ultra and Hyper Chem programs.

Findings and discussion

1. Geometry of the isolated *PCN G* molecule and complex with water

To understand the mechanism of effect induced by *PCN G* on a bacterium, molecular level study is required. Such study implies that the structural features of *PCN G*

conformations and correlation between the antibiotic's spatial structure and biological activity are known. Most molecule conformation determination methods are based on the search of geometrical structures with the least full system energy, X-ray diffraction data obtained for the crystalline structure of substance is the determination criterion. As far as antibiotics, including *PCN G*, are in major cases used in the form of solutions, deviations of the observed solution properties from solid substance properties may occur. Dexter [19] pointed out that the *PCN G* molecule conformation depends greatly on the local environment (solvent) impact. According to [12,13], activity of *PCN G* is also influenced by the side chain composition and carboxyl group.

The first stage of any quantum chemical calculation implies as far as possible accurate geometry calculation of the studied molecule. An insight into the literature data has shown that focus at the first stage of the *PCN G* geometry calculation was made on the study of the penam-group structure. The research was initiated by V.S.R. Rao et al, and the main findings are summarized in [20].

Authors of [20] made the following conclusions from the full energy calculations of biologically active penicillins (including the *PCN G* molecule).

1) Biologically active conformations have a compact structure with the minimum full energy (so-called global minimum) most often inherent in it.

2) It was shown that the thiazolidine cycle flexibility by changing the spatial position of the COOH-group affects the antibiotic's biological activity. This means that biological activity is provided not only by the penam-group, but also by the carboxyl group.

3) A concept of two types of thiazolidine ring was introduced: pseudo-axial and pseudo-equatorial conformations. In the pseudo-equatorial conformation, the C_3 atom of the thiazolidine ring exits the plane of this ring, in the pseudo-equatorial conformation — the S atom exits the plane (Figure 1). It has been found experimentally that both conformations may exist in solid state, while the pseudo-equatorial conformation primarily exists in solution [10,11]. However, the specified conformity between the design and X-ray diffraction data is not always suitable for addressing the molecule properties in solution. Thiazolidine cycle flexibility also leads to the exit of the lactam nitrogen atom from the molecular plane creating uncertainty in selecting the atom hybridization between the sp^2-type and sp^3-type.

According to the X-ray diffraction study, R.B. Woodward introduced a stereometry parameter of the β-lactam cycle nitrogen as the height h of a triangular pyramid with nitrogen in its apex. The pyramid apex defines the strength of amide bonds in the β-lactam cycle, breaking of any of which damages the antibiotic's antibacterial activity [2]. According to R.B. Woodward, in penams $h = 0.4-0.5$ Å, i.e. hybridization of the β-lactam nitrogen is of sp^3-type. The value of h calculated by various quantum chemical methods according to [10], varies from 0.17 to 0.48 Åfor *PCN G*. Though the degree of exit of the nitrogen atom from the β-lactam fragment plane leads to an increase in interaction between the nitrogen atom and π-system of the molecule's aromatic portion affecting the distribution o effective charges on the fragments, the role of this factor in the occurrence of antibacterial activity has not been reliably determined yet [1].

Geometrical calculations of several penicillins by some semi-empirical methods in order to determine the *PCN G* molecule conformation [10] have shown that various methods do not provide a single conformation: thus, the MNDO and MINDO/3 methods give the pseudo-equatorial conformation as the main one, and the AM1 method — gives the pseudo-axial confirmation, while the geometrical structure obtained by the CNDO/2 method is not assigned to any of the above-mentioned conformations.

Our AM1 calculations of the *PCN G* geometry optimization give the pseudo-equatorial conformation with the lactam atom pyramidality not exceeding ~ 0.20 Å, which is closer to the sp^2-type hybridization. Variations of h during the calculation by the INDO method had no significant impact on the effective charges, but changed the energy of electronic transitions to excited states, in particular this was related to the $S_0 \rightarrow S_1$-transition of *PCN G* and its complex with water: variation of h by 0.1 Å changed λ $(S_0 \rightarrow S_1)$ by 22 nm.

When building the spatial geometry of the H-bond complexes, two aspects were considered. The calculated coordinates of the MESP minima were used to define more validly the direction of water molecule approach to the proton acceptor centers of the *PCN G* molecule and its anion. A strong H-bond formation condition, according to which the atoms involved in the H-bond shall be aligned, was also considered. Interatomic distances for this type of hydrogen bond were taken according to [21].

2. Interpretation of absorption bands of the isolated *PCN G* molecule and anion-water complex

As mentioned above, *PCN G* is not soluble in nonpolar solvents and exists as anion in water solutions. Such active particle as anion likely forms complexes with H-bonds with water molecules. As a result, the experimental absorption spectrum is the spectrum of complexes, and the accuracy of calculations shall be compared specifically with this spectrum. Before proceeding to the interpretation of the absorption spectrum of the *PCN G* anion complex with water, it is necessary to determine its geometry.

Therefore, the first stage included the MESP minima calculation to define active proton acceptor centers of the *PCN G* molecule and structure of the complex. Table 1 shows the MESP minima of the neutral *PCN G* molecule and its anion. MESP is an integral characteristic of the interaction between the proton and spatially distributed molecule charge, however, taking into account localization of the MESP minimum in proximity of an individual atom, MESP of this atom is suggested. According to the calculation, the neutral *PCN G* molecule and is anion

Table 1. MESP minima (U) of the proton acceptor centers of the $PCN\,G$ molecule and anion in the ground state

Proton acceptor center	U, kJ/mol	
	$PCN\,G$	Anion $PCN\,G$
O (side chain)	−378	−581
O (penam)	−329	−602
O (COOH or COO)	−346	−1100

have three proton acceptor centers: oxygen atoms in the side chain carboxyl group, β-lactam group and carboxyl fragment. Nitrogen atoms in the β-lactam fragment and side chain as well as carboxyl's hydroxyl group oxygen have a lower negative charge. However, the charge of these centers is lower than the effective charges of the carbonyl oxygen atoms, and these centers are arranged such that the nearby positive charges block their negative charge, consequently the MESP values turn to be lower by an order of magnitude than the MESP value of the carbonyl oxygen atoms. The obtained highest MESP minima of the proton acceptor centers suggest that penicillins may form 1 : 3 complexes in proton donor solvents.

Transition from neutral molecules to their anionic form increases the MESP values on the proton acceptor centers by changing the MESP value ratio between these centers compared with the neutral form: in the neutral molecule and $PCN\,G$ anion, the maximum proton acceptor capability is connected with the side chain oxygen and COO-group, respectively (Table 1). As follows from Figure 1, the benzyl and side (C=O- and N-H-groups) fragments of the penicillin molecule are virtually an aromatic structure, while the penam-group that provides the biological activity is a non-aromatic and non-planar fragment [10], which generally makes the $PCN\,G$ molecule non-planar and hinders the absorption band interpretation on the orbital basis, when only assignment of the identified electronic transitions of the absorption spectrum to a particular molecule fragment is allowed. Absorption at 262 nm assigned to the penam-fragment of the $PCN\,G$ anion agrees with the experimental spectrum of this group [22].

Therefore, when interpreting the experimental absorption spectra of the $PCN\,G$ water solution, we though good to divide the molecule as follows: benzyl fragment (phenyl + CH_2), side chain (C = O + N-H bonds), penam-group, and carboxyl group. Table 2 shows the calculated and experimental absorption spectra of the $PCN\,G$ anion+ $3H_2O$ complex.

According to the calculation, a band with 325 nm peak in the absorption spectrum of the $PCN\,G$ anion complex with water (Figure 2) is formed by two electronic transitions. The $S_0 \rightarrow S_1$-transition is associated with the electron density redistribution between the anion COO-group and penam-fragment carbonyl group oxygens and with the electron density redistribution in the penam-fragment. The $S_0 \rightarrow S_2$electronic transition (in accordance with the molecular orbitals (MO) that form the electronic transition) may be compared with the $n \rightarrow \pi^*$-transition of the penam-fragment carbonyl group.

It is difficult to determine the boundaries of the absorption band at 262 nm due to the proximity of intense absorption at 220 nm. The boundaries of this absorption band are presumably within $\sim 260-300$ nm. Hence, the absorption in this spectrum range of $PCN\,G$ is generated by the electronic transitions from the ground state to the S_3-S_6 states (Table 2). Analysis of the contribution and localization of MO forming the $S_0 \rightarrow S_3$, $S_0 \rightarrow S_5$, $S_0 \rightarrow S_6$ electronic transitions has shown that they are primarily associated with various parts of the penam-fragment and this absorption assignment to 262 nm agrees with the experimental spectrum [22]. The same spectrum range includes the $S_0 \rightarrow S_4$ electronic transition that is formed by the phenyl ring MO and may be compered in the oscillator energy and strength with the benzene absorption band in water at 254 nm [23]. Comparison of the number, configuration and intensity contribution of the electronic transitions forming the absorption band at 262 nm suggests that the intensity of this absorption band is mainly formed by the electronic transitions localized at the penam-fragment. Thus, the absorption bands at 325 and 262 nm are mainly defined by the non-aromatic part of $PCN\,G$.

Absorption at 220 nm (Figure 2) belongs to the benzene ring, the nature of molecular orbitals forming the ring is similar to the charge distribution in the S_{23} state for the H-bonded $PCN\,G$ complex (Table 2).

Differentiation of the short-wavelength portion outline of the experimental absorption spectrum highlights an absorption band whose intensity is much higher than that of the long-wavelength absorption band. The calculation includes weak bands (electronic transitions to the $S_9 - S_{22}$ excited states from the ground state are not shown in Table 2) associated with the penam-fragment into the short-wavelength spectrum range, but the absorption intensity at 220 nm forms the $S_0 - S_8$ transition localized on the phenyl fragment as well as electronic transitions to the S_{23} and S_{31} excited states from the ground state. Whereby the $S_0 \rightarrow S_{23}$ ($\pi\pi^*$) and $S_0 \rightarrow S_{31}$ ($\pi\pi^*$) transitions correspond in the pattern of electron density redistribution on the phenol ring to the short-wavelength absorption band of the benzene water solution at 205 nm [23].

Analysis of the nature and localization of the electronic transitions in the spectra of the neutral and charged $PCN\,G$ form complexes and isolated molecules has shown (Tables 2 and 3) that formation of the H-bonded complexes does not induce considerable absorption spectrum variations. For most electronic transitions, the electronic transition energy in an isolated molecule decreases and the electronic transition intensity increases. These changes shall not have a significant influence on the absorption spectrum view of isolated molecules of the neutral and charged $PCN\,G$ forms.

Table 2. Calculated and experimental absorption spectra of the *PCN G* and PCN G anion complexes with water

Calculation								Experiment	
State	E_i cm^{-1}	λ, nm	f	State	E_i, cm^{-1}	λ, nm	f	E_i, cm^{-1}	λ, nm
PCN G + 3H$_2$O				*PCN G* + 3anion H$_2$O					
S_1	33060	303	0.002	S_1	31010	322	0.007	30770	325
S_2	35130	285	0.001	S_2	36990	278	0.004		
S_3	36570	273	0.009	S_3	37580	266	0.007	38170	262
S_4	37860	264	0.003	S_4	37700	265	0.020		
S_5	38390	260	0.022	S_5	40160	249	0.015		
S_6	41710	240	0.039	S_6	40870	245	0.092		
S_7	45000	222	0.029	S_7	42910	233	0.000		
S_8	45210	221	0.119	S_8	43260	231	0.226	45750	220
S_{14}	50910	196	0.713	S_{23}	50920	196	0.485	48780	205 [23]
S_{15}	51430	194	0.547	S_{31}	53130	188	0.411		

E_i — electronic transition energy, λ — wavelength, f — electronic transition oscillator strength.

Table 3. Calculated absorption spectra of *PCN G* and PCN G anion

State	E_i, cm^{-1}	λ, nm	f	State	E_i, cm^{-1}	λ, nm	f
PCN G				*PCN G* anion			
S_1	32830	305	0.003	S_1	32100	312	0.005
S_2	35870	279	0.009	S_2	35880	279	0.006
S_3	36820	272	0.003	S_3	36370	276	0.007
S_4	38370	261	0.006	S_4	38240	262	0.005
S_5	41740	240	0.001	S_5	40000	250	0.010
S_6	44410	225	0.004	S_6	43420	230	0.013
S_7	44900	223	0.140	S_7	44070	227	0.158
S_8	45770	219	0.040	S_8	44120	227	0.071
S_{15}	50750	197	0.736	S_{21}	50150	199	0.663
S_{17}	51730	193	0.396	S_{25}	51220	195	0.634

E_i — electronic transition energy, λ — wavelength, f — electronic transition oscillator strength.

Table 4 shows the effective charges of the studied molecule fragments. Calculation of the effective charge distribution in the isolated neutral *PCN G* molecule has shown that the penam and benzene fragments exhibit donor properties, while the side chain and carboxyl group exhibit acceptor properties. Note that the donor properties of the penam-fragment in the neutral *PCN G* molecule exceed considerable the benzene fragment properties, and the side chain has a higher acceptor capability than the carboxyl group. Formation of hydrogen bonds in the *PCN G* molecule substantially reduces the donor properties of the penam-fragment as well as the acceptor properties of the side chain. Changes on the benzene and carboxyl fragments are less significant.

In the *PCN G* anion, the side chain fragment and COO-group retain their acceptor properties by substantially enhancing them. Priority rests with the COO-group where the main portion of the negative charge of the *PCN G* anion is concentrated. Formation of the *PCN G* anion complex with water molecules makes the penam-groups almost neutral, their donor properties are negligibly low. And the key difference of the charged *PCN G* form in water from the neutral one is in dramatic growth of the acceptor properties of *PCN G* due to the COO-group, the

Table 4. Effective charges (Q) of the *PCN G*molecule fragments, ion and their complexes with water

Structure	Q, e				
	Fragments				
	benzene	side chain	penam (COO-)	COOH	$3H_2O$
PCN G	0.032	−0.149	0.147	−0.030	—
PCN G + $3H_2O$	0.028	−0.108	0.077	−0.007	0.010
*PCN G*anion	0.004	−0.152	−0.007	−0.849	—
PCN G + 3anion H_2O	0.011	−0.154	0.005	−0.863	−0.001

acceptor properties of the side chain increase, but are still much lower than those of the COO-group. Considering the role of electrostatic interaction at the initial molecule interaction stage, the effective charge distribution data may play a substantial role in understanding the mechanism of interaction between antibiotic molecules and bacterial cell wall receptors.

Conclusion

Theoretical interpretation of the absorption spectrum of benzylpenicillin sodium salt water solution has been performed using the semi-empirical quantum-mechanical INDO method with special parameterization. The calculated data analysis has shown that the penam-group mainly defines the short-wavelength low-intensity absorption spectrum region, while the intense short-wavelength spectrum region is mainly formed by the electronic transitions associated with the phenyl ring. In the neutral *PCN G* molecule, the MESP calculations have detected three proton acceptor centers: oxygen atoms of the side chain carbonyl groups, penam- and carboxyl groups. In the neutral *PCN G* molecule and complex with water, the penam-group exhibits the donor properties, while the side chain and carboxyl group exhibit the proton acceptor properties. *PCN G* dissolution in water leads to the formation of the anionic molecule form and its complexes with water molecules. Comparison of the donor-acceptor properties of the anionic benzylpenicillin form fragments has shown that the main difference of the charged form is in significant change in the ptoron donor properties of the *PCN G* molecule fragments. The penam-group becomes almost neutral, and the COO-group becomes the main proton acceptor center of the anionic form with the COO-group's acceptor properties being enhanced during formation of complexes with water.

Funding

The results were obtained in the context of implementation of the state assignment of the Ministry of Education and Science of the Russian Federation, project №AAAA-A19-2020-0033.

Conflict of interest

The authors declare that they have no conflict of interest, financial and other conflicts.

References

[1] V.G. Alekseev. *Bioenergeticheskaya khimiya penitsillinov i tsefalosporinov* (Tverskoy gosudarstvennyi universitet, Tver, 2009)(in Russian).
[2] E. Gale, E. Cundliffe, P. Reynolds, M. Richmond, M. Waring, *Molekulyarnye osnovy deistviya antibiotikov*, (Mir, M., 1975) (in Russian).
[3] L.S. Strachunsky, S.N. Kozlov. *Sovremennaya antimikrobnaya khimioterapiya* (Borges, M., 2002) (in Russian).
[4] V.G. Alekseev. Khimiko-farmatsevticheskij zhurnal, **44** (1) 16 (2010) (in Russian).
[5] V. Gil-Ocaña, I.M. Jimenez, C. Mayorga, I. Dona, J.A. Cespedes, M.I. Montanez, Y. Vida, M.J. Torres, E. Perez-Inestrosa. Frontiers in Immunology, **12**, 750109-1 (2021). DOI: 10.3389/fimmu.2021.750109
[6] S. You, Y. Xie, Q. Yu, H. Chen, Y. Qin, J. Cao, T. Lan. Biochemical Engineering J., **180**, 108335 (2022). DOI: 10.1016/j.bej.2022.108335
[7] O.A. Petrov, A.A. Maksimova,A.E. Rassolova, G.A. Gamov, V.U. Maizlish. Zhurnal fizicheskoy khimii, **93** (9), 1290 (2023) (in Russian). DOI: 10.31857/S0044453723090157
[8] N.C. Cohen. J. Medic. Chemistry, **26** (2), 259 (1989). DOI: 10.1021/jm 00356a 027
[9] J.-M. Frere, J.A. Kelly, D. Klein, J.M. Ghuysen, P. Claes, H. Vanderhaeghe. Biochem. J., **203** (1), 223 (1982). DOI: 10.1042/bj2030223
[10] J. Frau, M. Coll, J. Donoso, F. Munoz, F. Garcia Blanco. J. Molec. Struct. (Theochem), **231**, 109 (1991). DOI: 10.1016/0166-1280(91)85144-V
[11] C.M. Dobson, L.O. Ford, S.E. Sumners, J.P. Williams. J. Chem. Soc., **2**, 1145 (1975).
[12] S. Wolfe, M. Khalil, D.F. Weaver. Can. J. Chem., **66**, 2715 (1988).
[13] S. Wolfe, K. Yang, M. Khalil. Ca. J. Chem., **66**, 2733 (1988).
[14] V.Ya. Artyukhov, A.I. Galeeva, Izv. vuzov. Fizika, **29** (11), 96 (1986) (in Russian).
[15] V.Ya. Artuykhov. J. Struct. Chem., **19**, 364 (1978). DOI: 10.1007/BF 0075 3260
[16] E. Scroco, J. Tomasi. Adv. Quantum. Chem., **11**, 115 (1978).

[17] V.A. Blatov. *Poluempiricheskie raschetnye metody kvantovoy khimii* [uchebnoe posobie] (Univers-grupp, Samara, 2005) (in Russia).
[18] M.J. Dewar, R.C. Dougherty. *The PMO Theory of Organic Chemistry* (Springer, US, 2012).
[19] D.D. Dexter, J.M. Veen. J. Chem. Soc. Perkin I., **3**, 185 (1978). DOI: 10.1039/P19780000185
[20] V.S.R. Rao, T.K. Vasudevan. Critical Reviews in Biochemistry, **14** (3), 173 (1983). DOI: 10.3109/10409238309102793
[21] B.P. Nikol'sky, V.A. Rabinovich *Spravochnik khimika. Tom 1. Obshchie svedeniya; Stroenie veshchestva; Svoistva vazhneishikh veshchestv; Laboratornaya tekhnika* (Khimiya, M.-L., 1966) (in Russian).
[22] A.K. Zhernosek. *Farmatsevticheskaya khimiya: prakticheskoe rukovodstvo*: [uchebno-metodicheskoe posobie]. Ch. 1 (UO „Vitebsky gosudarstvennyi meditsinsky unuversitet", Vitebsk, Ministerstvo zdravookhraneniya Respubliki Belarus, 2010) (in Russian).
[23] E. Stern, K. Timmons. *Elektronnaya absorbtsionnaya spektroskopiya v organicheskoi khimii* (Mir, M., 1974) (in Russian).

Translated by E.Ilinskaya