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The Role of Water Molecules in the Interfragmental Charge Transfer of the Protolytic Forms of Fluoroquinolones in the Ground and Excited States

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Abstract—Quantum-chemical analysis (TD-DFT/B3LYP/6-31G) of the influence of H-bonding in the donor–acceptor fluoroquinolone compounds with the water molecules on the interfragmentary charge transfer was carried out. The values of charge transfer between the molecular fragments in the transition from the ground into the singlet excited state were calculated. It was found that, depending on the protolytic form of a compound, the frontier molecular orbitals are localized on different fragments, which leads to the specificity of the formation of the electron density transfer channel. The influence of individual substituents in the quinolones on the localization of particular MOs is relatively insignificant.

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The electron and proton transfer in condensed phases is crucial for the occurrence of many chemical and biological processes. Convenient objects in which there is intra- and intermolecular charge transfer between the individual fragments are fluoroquinolone hydrates (fqH). Antimicrobial preparation of the fqH group currently occupy one of the leading places in the chemotherapy of bacterial infections of different genesis. The target of quinolones are the bacterial topoisomerases: topoisomerase-IV and DNA gyrase, the enzymes changing the DNA molecule spatial configuration at the different stages of its replication [1]. Fluoroquinolones in the aquatic environment tend to H-bonding and aggregation [2]. At the action of UV irradiation on fqH solutions a luminescence is observed, individual for each protolytic form [3]. Since the class of quinolone antibiotics is composed of fragments that include a dialkylamino group and quinolone frame the donor-acceptor properties are inherent to them. According to [4] the dialkylamino groups are able to act as electron donors, while 1,4-dihydro-4-hydroxyquinoline-3-carboxylate frame has an electron-acceptor properties. At the photoexcitation of such compounds an intramolecular charge transfer is possible.

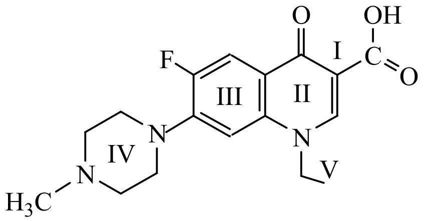
The processes of the fluoroquinolones light absorption and fluorescence usually correspond to the transitions between the ground (S_0) and first excited singlet (S_1) state. The first singlet state plays a leading role in the evaluation of characteristics of fluorescence associated with the photophysical and photochemical processes. They include the formation of excimers and exciplexes, electron density redistribution, transition to the triplet metastable state, and changes in the geometry of the molecules. The dissipative loss of energy due to fluctuations of the individual fragments of the fluoroquinolone molecules, the redistribution of electrons in the solvent molecules surrounding the fluorophore due to the change in the dipole moment of organic molecule at the excitation, the reorientation of solvent molecules around the excited dipole, the hydrogen bonding and forming the charge transfer complexes dictate the necessity of a detailed analysis of the influence of water molecules on the energetics of the ground and excited states of the quinolone antibiotics.

The aim of this work was to perform a theoretical analysis of simultaneous influence of donor-acceptor interaction and H-bonding of fluoroquinolones with the water molecules in the ground and excited states on the interfragmental charge transfer between the individual fragments of the molecules of the composition similar to that of the fqH.

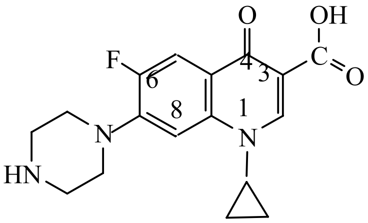
Using quantum-chemical program GAMESS [5] we calculated fluoroquinolone compounds existing in different protolytic forms. The standard procedure for calculating the excited states of molecules is TD-DFT/6-31G scheme with the use of the density functional B3LYP for the full geometry optimization. The numbering of individual fragments of compounds is shown in Fig. 1. The interatomic distances and angles in compounds for which quantum-chemical calculations were carried out were taken from [6–8]. To account for the possible number of reaction centers in fqH interacting with H_2O, the calculation with five water molecules was performed.

Analysis of numerical data included examining the degree and site of the localization of the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO). In addition, we studied the distribution of electron density over the individual fragments of molecules and their change during the transition of the molecule into the excited state. The results obtained were compared with the values of change in the bond overlap populations by Mulliken population analysis (which correlate linearly with the bond strength), as well as with the values of charges on the atoms in the ground and excited states.

From the data obtained by the TD–DFT method, for each compound the degree of change in the electron density at the charge transfer between the fragments of molecules and the solvent was calculated that describes quantitatively the charge transfer into the ring π-system.



pfqH



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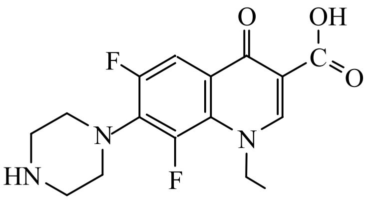

nfqH

The scheme shows the structural formulas of the discussed compounds and the numbering of individual fragments.

Depending on the medium pH, fluoroquinolones may be in the anionic (fq^-), neutral (fqH), and cationic (fqH_2^+) forms.

As shown by X-ray diffraction of fluoroquinolones and their complexes with metals obtained by precipitation from aqueous solutions, in most cases the compound composition includes water molecules [6, 7]. In some cases they are involved in the formation of the coordination polyhedron of the central ion-complexing agent [7, 8]. At the crystallization from acidic media [9] H-bonding is often observed of water molecules with quinolones and acid residues. Water molecules can interact with fqH through the oxygen atoms of the carbonyl and carboxy groups, and by H-bonding with the nitrogen heteroatoms, the reaction centers of the organic molecule. For example, in the case of the zwitter-ionic form of norfloxacin $[nfqH^{\pm}]\cdot 2H_2O$ one of the H_2O molecules forms through its oxygen atom two hydrogen bonds with the NH_2 group protons of the piperazine ring [6]. The second water molecule at the same time is involved into the H-bond with one oxygen atom of the carboxy group.

As an example, Fig. 1 shows a fragment of the structure of the complex compound $(C_{16}H_{20}FNO_3)_2[Bi_2Cl_9]Cl\cdot 2H_2O$, (**I**), and in Table 1 the parameters of hydrogen bonds are given [8]. The structure includes the anion $[Bi_2Cl_9]^{3-}$, the chloride ions Cl^-, the cation $nfqH_3^{2+}$, and water molecules. The water molecules, the uncoordinated chloride ions Cl^6, and the double-protonated cations $nfqH_3^{2+}$ are interconnected by hydrogen bonds. While the interatomic distance D–H is in the range 0.72–0.91 Å, the distance D–A varies in the range 2.58–3.40 Å.

According to [10], the participation of water molecules in the hydration shells in the process of proton exchange may cause the dissociation process. If the incorporation of water molecule by means of two H-bonds leads to the formation of a cyclic system, the intramolecular proton transfer becomes possible through the H_2O molecule. The magnitude of the activation barrier of H^+ transport is very sensitive to the length of the H-bond.

As shown by quantum-chemical calculations, the transition into the excited S_1 state increases the interaction of nfqH with two water molecules, H_2O-1 and H_2O-2 (Fig. 2) involved into the H-bonds with oxygen atoms of the carbonyl and carboxy groups. The

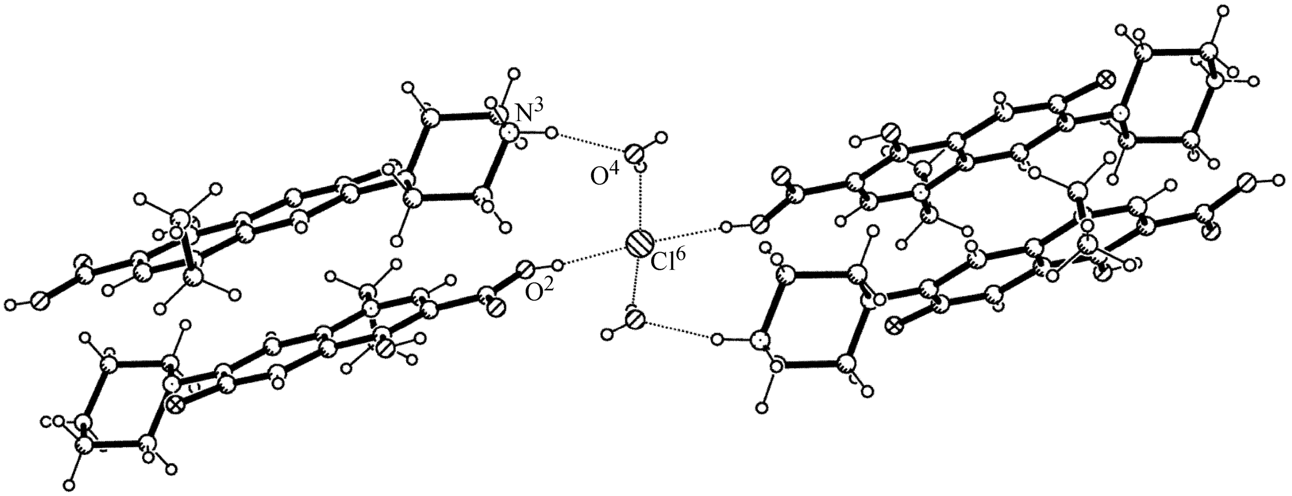

Fig. 1. The structure of a fragment of the norfloxacin cation in structure **I**.

electron density is distributed unevenly over the **I-IV** fragments of the nfqH molecule.

The charge transfer numbers [$\Delta q(e)$] that describe quantitatively the transfer of electron density between fragments of the studied compounds and the solvent are given in Table 2. The numbering of atoms of the compounds for which the quantum-chemical calculations were performed is shown on the left side of Fig. 2.

As show the results given in Table 2 (compounds nfqH-a and nfqH-b), depending on the method and on the location of the coordination site of water molecules relative to the reaction centers of the antibiotic, there is a difference in the degree of participation of water molecules in the donation of a part of electron density to fqH. For example, if the nitrogen atom N^3 is involved into the H-bond with the proton of the water molecule H_2O-4 (Fig. 2a), the H_2O-1 and H_2O-2 donate electron density to the fragments **I–IV** through a chain of conjugated bonds. At the same time, due to a substantial transfer of electron density (0.7 *e*) from the solvent molecules to the π-system of the rings, the interaction of the electron-donor solvent molecules with the charged nfqH fragments increases. This electron density is distributed as follows: the maximum amount is transferred to the ring **I** and somewhat less to the other fragments (including the fluorine atom) (Table 2). This leads to a change in the vector and the modulus of the dipole moment of the molecule.

Table 1. Geometric parameters of hydrogen bonds (Å) in complex **I**

D–H···A[a]	D–H	H···A	D···A	D–H···A
O^3–H^3···O^1	0.83	1.85	2.583 (2)	146
O^2–H^2···Cl^{6ii}	0.83	2.19	3.0150 (15)	173
O^4–H^{4A}···Cl^5	0.715 (18)	2.563 (18)	3.270 (2)	170 (4)
O^4–H^{4B}···Cl^6	0.717 (19)	2.47 (2)	3.146 (2)	157 (4)
N^3–H^{3A}···Cl^{2iii}	0.91	2.51	3.3961 (19)	165
N^3–H^{3B}···O^{4iv}	0.91	1.82	2.693 (3)	160

[a] Symmety transformations in Table 1: (ii) x + 1, *y, z*; (iii) *x* + 1/2, *y* + 1/2, *z*; (iv) *x*, –*y* + 1, *z* + 1/2.

In the case of attaching two protons to the nitrogen atom N^3 (the zwitter-ionic form $fqH^{\pm}$ or a modification of the monoprotonated form), a water molecule H_2O-4 is associated with the protons H-bonded through the oxygen atom (Fig. 2b). In such a case the transfer of electron density from H_2O-1 and H_2O-2 to $fqH^{\pm}$ was not observed. In this group of compounds the electron transport proceeds through the H_2O-3 molecule, and the transfer of electron density on quinolone frame (fragments **I–III**) occurs from the piperazine ring (fragment **IV**).

By the example of pfqH·5H_2O we performed a quantum-chemical analysis of changes in the total charges on the atoms in the individual fragments in the ground S_0 and excited S_1 states for different protolytic forms of fqH (Table 3). For the compound close by composition to fqH, the results are of similar nature. Analysis of quantum-chemical calculations of the electron density redistribution over the selected fragments of the protolytic forms of compounds upon photoexcitation (Table 3) indicates its generality and

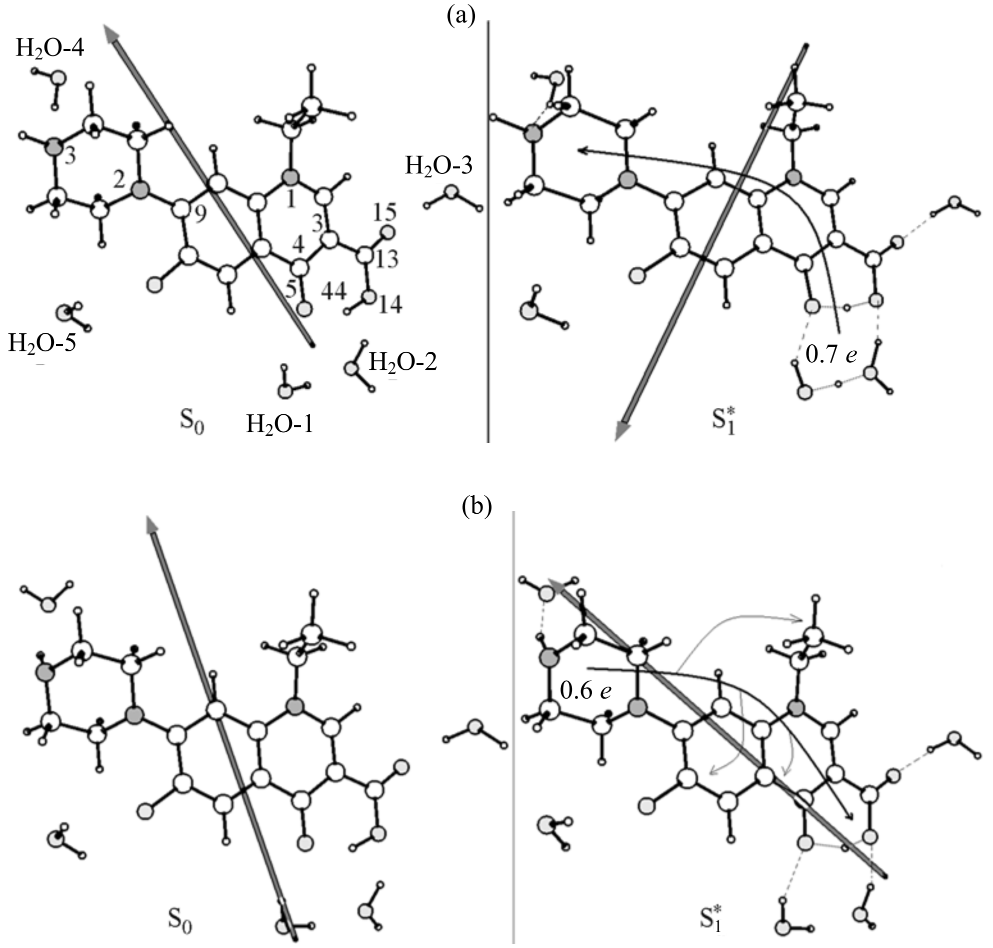

Fig. 2. Structure of nfqH and direction of the dipole moment (thick arrows) in the ground state S_0 (left) and excited state S_1 (right). Top: (a) the H_2O-4 molecule is linked to N^3 by H, bottom: (b) the same via O. Thin arrows indicate the direction of transfer of electron density.

specificity. For example, for the fluoroquinolone hydrates, as a rule, a high degree of charge transfer is found, which is consistent with the experimental data [4].

The main donor of electron density in the anionic form $pfq^{-}\cdot 5H_2O$ (Table 3) is the piperazine ring (fragment **IV**). The contribution of water molecules in the transfer of electron density is negligible. The negative charge on oxygen atoms O^{14} and O^{15} of carboxy group decreases, and on the atom O^5 increases.

The neutral form $pfqH\cdot 5H_2O$ is characterized by a high degree of electron density transfer from the oxygen atom of H_2O-1 on the fragments **I–IV**. The value of the negative charge on the atoms O^5 and O^{14} increased. The piperazine ring (**IV**) acts as an acceptor of electron density.

At the photoexcitation of the zwitter-ionic form $pfqH^{\pm}\cdot 5H_2O$ the donors of the electron density are the fragments **I** and **III** and the O^{15} atom, the acceptors are fragment **IV** and the H_2O-4 molecule.

In the protonated $pfqH^{2+}$ form the electron density transfer is observed on the fragments **I–III** from the water molecules H_2O-1 and H_2O-2, both involved into the H-bonding with the oxygen atom and interacting with each other. If the proton is fixed at the nitrogen atom of piperazine group (compound $pfqH_2^{\pm}$), the transfer of electron density on fragments **II, III,** and **IV**, and atom O^{15} proceeds from the H_2O-3.

Of particular interest is the fact of preparation of H_2O-1 and H_2O-2 molecules to the shift of electron density on the fluoroquinolone: the former tends to dissociate into H^+ and OH^-, and the latter, to the formation of H_3O^+.

Table 2. The Σq(e) magnitude on atoms of individual fragments of nfqH·5H_2O in the ground and excited states

Fragment	nfqH-a			nfqH-b		
	S_0	S_1^*	Δq	S_0	S_1^*	Δq
I	0.03	−0.31	−0.28	0.03	−0.12	−0.15
II	0.300	0.23	0.07	0.29	0.17	−0.12
III	0.670	0.51	−0.16	0.65	0.43	−0.22
IV	−0.08	−0.14	−0.06	−0.14	0.46	0.60
V	0.33	0.28	−0.05	0.31	0.23	−0.08
O^5	−0.56	−0.76	−0.2	−0.57	−0.65	−0.08
O^{15}	−0.46	−0.47	−0.01	−0.46	−0.50	−0.04
COOH	−0.11	−0.22	−0.01	−0.10	−0.19	−0.09
H_2O-1	−0.07	0.54	0.61	−0.07	−0.08	−0.01
H_2O-2	0.01	0.10	0.09	0.01	0.00	−0.01
H_2O-3	−0.04	−0.04	0.00	−0.04	−0.05	−0.01
H_2O-4	−0.06	−0.06	−0.00	0.04	0.07	0.03
H_2O-5	0.02	0.02	0.00	0.02	0.03	0.01
μ	11.72	5.00	−6.72	15.08	34.58	19.50

Table 3. Change of the total ΣΔq(e) value of the charges on the atoms of the fragments of the pfqH·5H_2O protolytic forms

Fragment	pfq$^-$	pfqH	pfqH$^\pm$	pfqH$_2^+$	pfqH$_2^\pm$
I	0.11	−0.34	0.38	−0.58	0.02
II	−0.01	−0.09	0.05	−0.10	−0.08
III	−0.21	−0.18	0.16	−0.13	−0.23
IV	0.32	−0.08	−0.15	−0.01	−0.08
V	−0.04	−0.04	0.07	−0.03	−0.07
CH_3	0.00	−0.01	−0.07	0.00	−0.03
O^5	−0.09	−0.20	−0.20	−0.10	−0.09
O^{15}	0.12	−0.01	0.19	−0.03	−0.26
O^{14}	0.19	−0.11	0.29	−0.13	0.03
H_2O-1	0.01	0.61	0.04	0.74	0.00
H_2O-2	0.03	0.10	0.03	0.10	0.01
H_2O-3	0.05	0.09	0.05	−0.03	0.73
H_2O-4	0.00	−0.01	−0.81	0.01	0.01
H_2O-5	−0.01	0.01	−0.02	0.00	−0.03
Δμ	−10.22	−0.34	−41.04	0.91	10.26

Upon transition to the excited S_1 state, the dipole moments of the anionic, neutral and zwitter-ionic forms decrease, while that of the protonated form increases.

A consequence of the redistribution of electron density is the modified bond strength in the complexes.

Table 4. The bond overlap population by Mulliken (Q) in the pfqH molecule

Q	S_0	S_1^*
C^4–O^5	0.47	0.32
C^4–C^3	0.14	0.24
C^9–N^{18}	0.23	0.22
C^3–C^{13}	0.09	0.18
C^{13}–O^{14}	0.18	0.17
O^{14}–H^{44}	0.17	0.11
$O^5\cdots H^{44}$	0.09	0.17
$O^5\cdots H_2O$-1	0.03	0.05
$O^{14}\cdots H_2O$-1	0.00	0.09
H_2O-1$\cdots H_2O$-2	0.00	0.14
H_2O-2$\cdots O^{14}$	0.03	0.10
H_2O-3$\cdots O^{15}$	0.04	0.04
H_2O-4$\cdots N^{21}$	0.06	0.06

In Table 4 by an example of compound pfqH the values of the bond overlap populations by Mulliken are shown that correlate directly with the bond strength. In those fragments of the pfqH molecule where the charge transfer is small, the strength of interfragment bond does not change significantly upon the transition to excited state. On the contrary, in the fragments where the charge transfer is large, the changes in the bond strength are significant. For example, there is a weakening of the intramolecular bonds between the oxygen atoms entering into the interaction with the solvent molecules and the carbon atoms of ring **I** as well as strengthening of the bonds of the oxygen atom with the solvent, which leads to a strong association with water molecules. In addition, the population of the bond overlap inside the ring **I** including the bond $O^5\cdots H^{44}$ significantly increases, therefore it is converted from a hydrogen bond into virtually an interatomic bond (Fig. 2). Thus, the ring **I** strives to be closed. In addition, as noted above, the molecular structure of H_2O-1 and H_2O-2 changed: one of the hydrogens of H_2O-1 molecule is "collectivized" and connects two water molecules.

To explain the differences in the processes of the electron density transfer in various compounds we

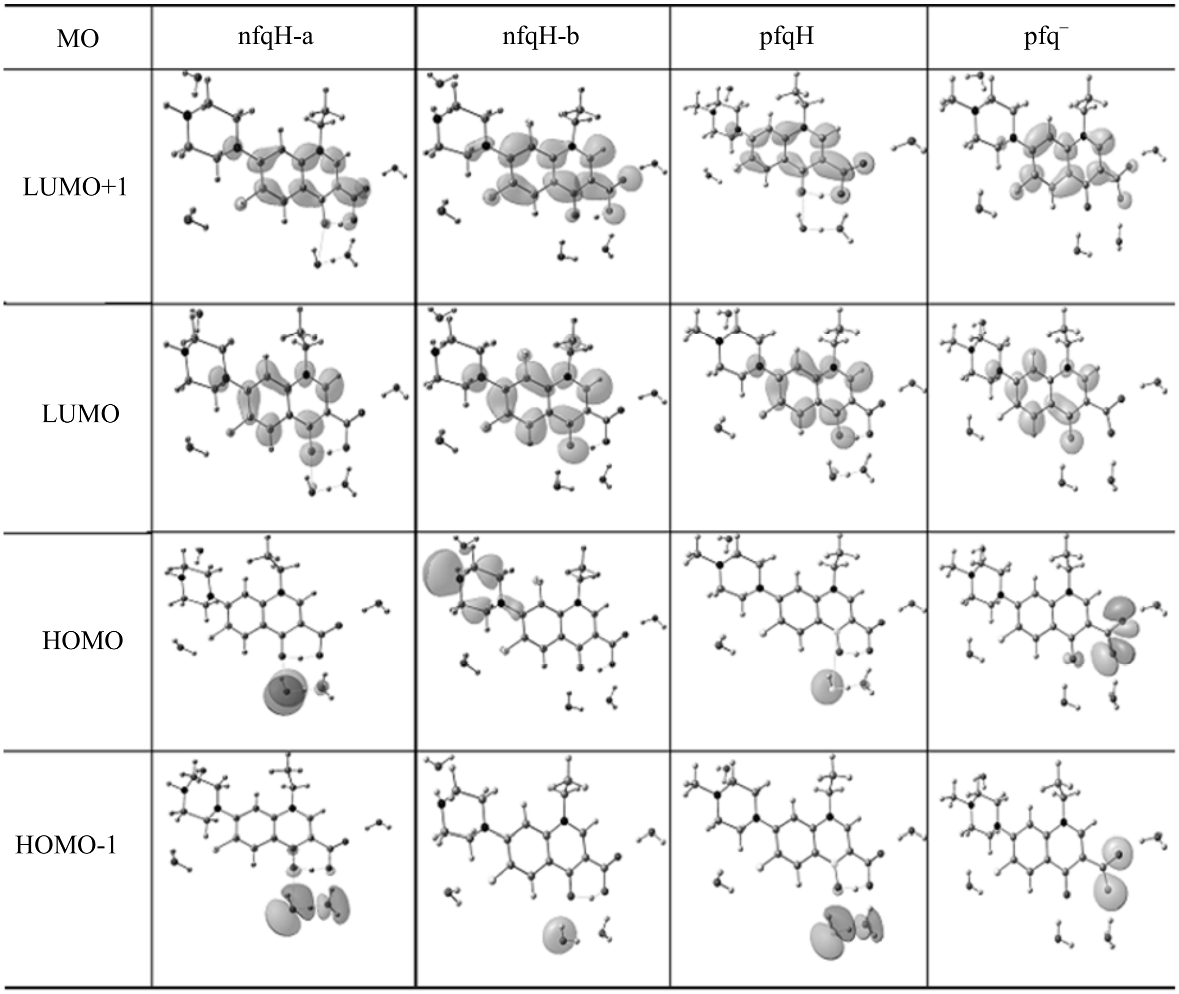

Fig. 3. The nature of the highest occupied (HOMO) and lowest unoccupied (LUMO) orbitals of the protolytic forms fqH·5H_2O.

performed an orbital analysis of compounds nfqH-a and nfqH-b differing in the mode of orientation of the H_2O-3 molecule, as well as of the compound pfqH in the neutral and anionic form. The orbital analysis showed that in the case of H-bonding the H_2O-4 molecule with the nitrogen atom N^3 the highest occupied molecular orbital (HOMO) in the S_1* state is localized on the oxygen atom of the H_2O-1 (Fig. 3). In the case when the molecule H_2O-4 forms H-bond with the proton of piperazine ring (Fig. 2b) the HOMO is localized on the piperazine ring. In compound pfq$^-$ both HOMO and HOMO-1 are localized on the oxygen atoms of the carbonyl and carboxy groups. As for the rest frontier orbitals, their character is not dependent on the protolytic form of the compound and the mode of coordination of the water molecules. HOMO-1 is a group atomic orbital of the rings **II** and **III**, and the AOs of the fluorine atom in a small degree contribute to its formation. Two lower vacant orbitals are localized mainly in the area which includes the rings **II** and **III** of the molecule. Ring **IV** practically does not contribute to these MOs.

Thus, the channel of the electron density transfer is directly dependent on the specific localization of frontier orbitals.

Thus we showed that the compounds of the class of quinolone antibiotics are, in essence, the donor-acceptor complexes, which participate in the electron transfer reactions. The high degree of dependence of the electron density transfer on the composition (degree of protonation) of the antibiotic indicates the possibility of targeted control over the charge transfer between the donor-acceptor systems with hydrogen bonding. A major role of water molecules in the transfer of electron density in the donor-acceptor complexes of quinolone class hydrates is revealed. The general and specific features of the role of H-bonding between the compounds of different protolytic forms are considered.

ACKNOWLEDGMENTS

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