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Intramolecular Charge Transfer and Electronic Absorption and Luminescence Spectra of Fluoroquinolinones

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Abstract— TD-DFT study on the effect of donor and acceptor substituents on molecular orbital localization and charge distribution in fluoroquinolinone molecules showed that their photoexcitation is accompanied by electron density redistribution over particular fragments. Depending on the protolytic form, frontier molecular orbitals are localized on different fragments, whereas variation of substituents weakly affects localization of these orbitals.

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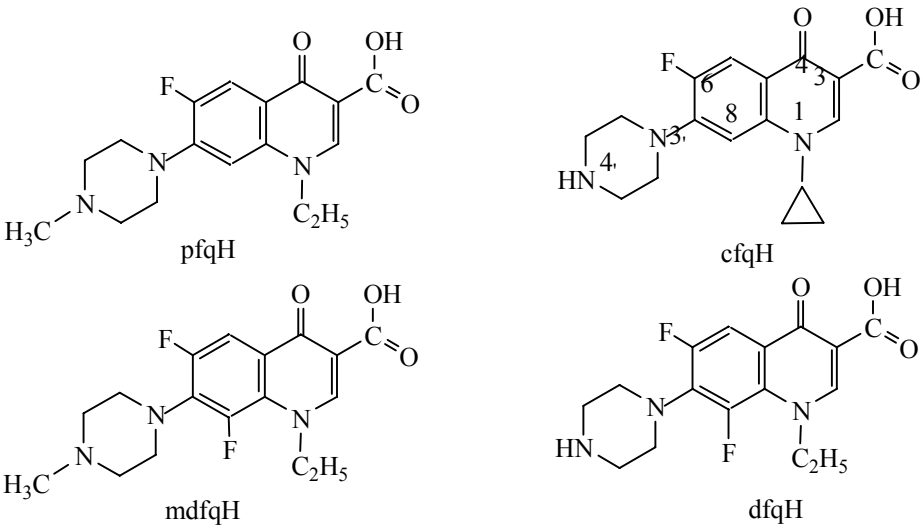
Molecules characterized by relatively strong donor–acceptor interaction through conjugated π-electron system are the subject of keen interest of researchers in the field of optoelectronics. Various photonic devices, such as light-emitting diodes, transistors, and biosensors, were designed on the basis of organic π-conjugated polymers [1–2].

Synthetic antimicrobial agents based on quinoline-3-carboxylic acid have found wide application in medical practice [3]. Photophysical and photochemical behavior of these compounds was described in [4–6]. Insofar as antibiotics of the quinolinone series consists of fragments including a dialkylamino group and quinolinone framework, intramolecular donor–acceptor interactions occur therein. According to the data of [7], dialkylamino group acts as electron donor, and 3-carboxy-1,4-dihydro-4-oxoquinoline fragment, as electron acceptor. Photoexcitation of such compounds could give rise to intramolecular charge transfer. Sortino et al. [8] presumed that intramolecular charge transfer upon excitation to the singlet state (S_1) is accompanied by some twisting of the piperazine ring about the $N^{3'}$–C bond with respect to the quinoline ring system (twisted intramolecular charge transfer, TICT). In keeping with the theoretical estimates reported in [9] for ofloxacin, the transition to the excited S_1 state is accompanied by rehybridization of the $N^{4'}$ atom in the piperazine ring from sp^3 to sp^2 (RICT).

The goal of the present study was to estimate the effect of some electron-donating and electron-withdrawing substituents on intramolecular charge transfer and spectral parameters of particular protolytic forms of fluoroquinolinones. As substrates we selected fluoroquinolinone having different numbers of fluorine atoms in their molecules: monofluoro derivatives: 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (ciprofloxacin cfqH), 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (norfloxacin, nfqH), and 1-ethyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (pefloxacin, pfqH); difluoro derivatives: 1-ethyl-6,8-difluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (mdfqH) and 1-ethyl-6,8-difluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (dfqH).

Samples (powders) of norfloxacin, ciprofloxacin, and pefloxacin of chemically pure grade (from Sigma–Aldrich) were used without additional purification. 1-Ethyl-6,8-difluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 1-ethyl-6,8-difluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid were synthesized according to the procedure reported in [10]. The concentrations of the compounds under study in water were 2×10^{-4} and 2×10^{-5} M. The pH values were measured using a



Thermo Orion 920A instrument. The electronic absorption spectra were recorded on an SF-256 UVI spectrophotometer (LOMO) using quartz cells (l = 1 cm). The luminescence spectra were measured on a Varian spectrometer (made in Australia). The lifetimes of excited states were determined with the aid of a FluoTime 200 instrument (PicoQuant). The results are collected in Table 1.

The electronic structures of the ground and excited states of fluoroquinolinones in different protolytic forms were calculated using GAMESS program [11]. Excited states are usually calculated in terms of the time-dependent density functional theory (TD-DFT) using 6-31G basis set and B3LYP functional for full geometry optimization. Analysis of the calculated data included localization of highest occupied and lowest unoccupied orbitals on particular fragments and determination of configurational composition of electron transitions. The nature of electron transition was identified by comparing orbital localizations in the initial and final states. In addition, electron density distribution over particular molecular fragments and its variation upon excitation were examined. The results were compared with variation of the Mulliken bond overlap populations (which are linearly related to the bond strengths), as well as with charge on atoms in the ground and excited states.

Table 1. Spectral parameters[a] of fluoroquinolinones in aqueous medium

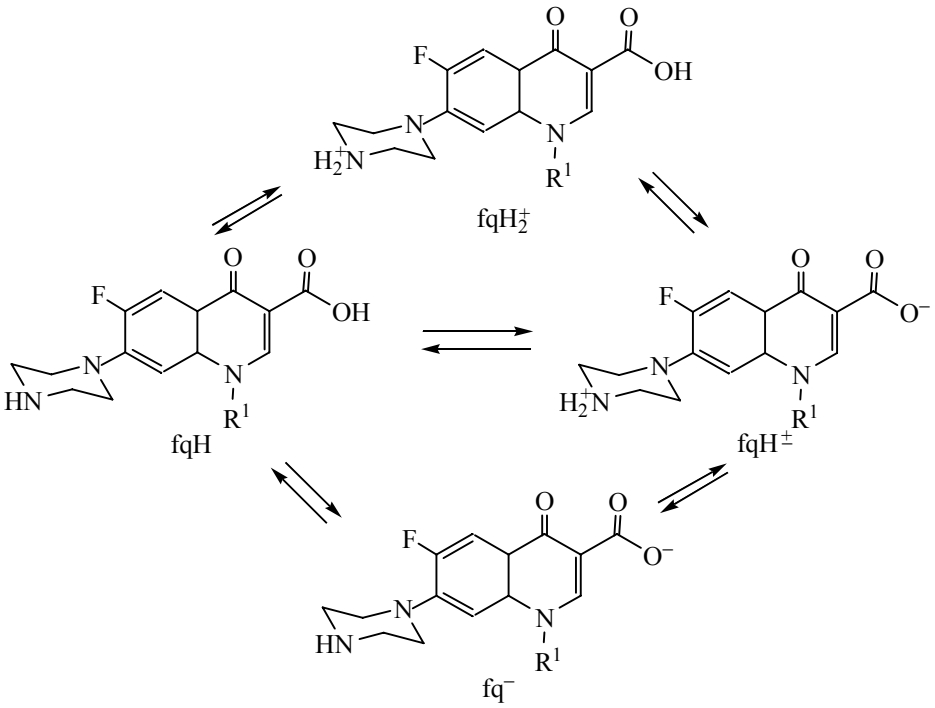
Compound	E_Ψ, eV	ν_{fl}, cm^{-1}	ν_{abs}, cm^{-1}	ν_{St}, cm^{-1}	τ, ns
nfq^-	2.95	22810	29851	6041	1.3
nfqH	3.01	24272	30303	6031	1.5
$nfqH_2^+$	2.76	22222	30769	8547	1.8
cfq^-	2.95	23810	30960	7150	–
cfqH	3.02	24390	31348	6958	4.0
$cfqH_2^+$	2.77	22321	31746	9425	1.5
pfq^-	2.90	23419	31949	8530	3.1
pfqH	2.83	22831	30303	7472	2.4
$pfqH_2^+$	2.84	22883	31847	8964	2.5
dfqH	2.74	22075	29940	7865	9.2
mdfqH	2.76	22222	29851	7629	2.6

[a] ν_{fl}, ν_{abs} are the fluorescence and absorption maxima, ν_{st} is the Stokes shift, E_Ψ is the energy of electron transition, and τ is the lifetime of the S_1 excited state.

Figure 1 shows the electronic absorption spectra of fluoroquinolinones in the UV region. The π–π*-transition maxima are sensitive to both replacement of hydrogen by an electron-donating group (CH_3) and change in the number of fluorine atoms acting as electron acceptors toward π-conjugated systems. As the number of fluorine atoms increases, maxima of the π–π*-transition bands shift to longer wavelengths.

Some parameters of the electronic absorption and luminescence spectra of anionic, neutral, and cationic forms of mono- and difluoroquinolinones are given in Table 1. The large Stokes shift (ν_{St}) suggests transformations of molecules in the excited state, which correspond to new electron density distribution. The lifetimes of the S_1 excited state fall into nanosecond range.

Depending on the acidity of the medium, fluoroquinolinone molecules can exist in four different protolytic forms: neutral, anionic, cationic, and zwitterionic. According to [12], the behavior of fluoroquinolinones in neutral, basic, and acidic media can be described by the following scheme.



The results of studying protolytic transformations of quinolinones in the physiological pH range were reviewed in [9]. Acid properties of these compounds are determined by the presence of carboxy group. 7-(Piperazin-1-yl)-substituted quinolinones possess an additional amino group which is responsible for their basic properties. Therefore, 7-(piperazin-1-yl)quinolinones in aqueous solution generally exist in three protolytic forms: anionic, cationic, and zwitterionic. Quinolinones having no piperazinyl substituent give rise to only neutral or anionic species. As shown in [13], equilibrium mixtures of the above protolytic forms at different ratios exist in the pH range from 4 to 8, which is typical of mammalian gastrointestinal tract. The spectral parameters of particular protolytic forms are given in Table 1, and Fig. 2 shows the energy gaps between the S_1 states for cfqH as an example. These gaps fall into a fairly narrow range, 1.5–5.0 kcal/mol. In this case, activation barriers separating one protolytic form from another are not high. Therefore, the energy profiles along the reaction paths shown in the above scheme could be run by applying a weak physical impact ($h\nu$, T). Proton transfer through hydrogen bond system between two heteroatoms occurs in the ground and excited states with low energies of activation and very high rate constants (10^{10}–10^{11} l mol^{-1} s^{-1}) [14].

Quantum-chemical calculations of the Mulliken charges on atoms allowed us to trace electron density redistribution over particular molecular fragments of fluoroquinolinones upon excitation to the S_1^* state. Analysis of configuration interaction for all com-

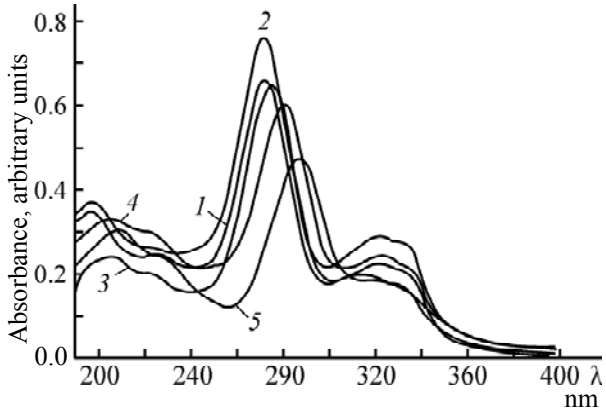


Fig. 1. UV spectra of aqueous solutions ($c = 2 \times 10^{-5}$ M) of (*1*) nfqH, (*2*) cfqH, (*3*) pfqH, (*4*) mdfqH, and (*5*) dfqH.

pounds showed that all transitions indicated above may be regarded as one-electron transitions. Redistribution of charges in a π-conjugated system leads to appreciable change of dipole moment of the molecule. On the other hand, the direction of dipole moment of neutral species almost does not change upon photoexcitation. Protonation induces reorientation of the dipole moment vector relative to the initial structure, and its absolute value appreciably increases (Fig. 3).

Piperazine ring in neutral and protonated forms acts as electron donor. Photoexcitation of anionic and zwitterionic forms involves oxygen atoms in the carboxy group as electron donor and protons in the piperazine ring and CH_3 group as acceptor. The data in Table 2 show variations of charges as a result of electron density transfer between molecular fragments. All compounds are characterized by strong donor–acceptor interaction. In all cases fluorine atoms and fragment *V* are weak acceptors of electron density (an exception is zwitterionic form). In neutral or protonated molecules, donors of electron density upon excitation are the CH_3 group and ring IV. The amount of transferred electron density depends on the substituent: the maximal electron density transfer is observed for pefloxacin (0.69 *e*), and the minimal, for ciprofloxacin (0.56 *e*). Such an appreciable charge transfer increases the dipole moments of their molecules, the maximal increase being also observed for pefloxacin (Δμ = 23.7 D). It is known [3] that dipolar structure favors fast transport of a drug molecule through outer cell membrane.

The opposite pattern is typical of compounds existing in anionic or zwitterionic form. In this case, rings I–III act as electron donors, and the CH_3 group and ring IV, as acceptors. According to the calculations, the maximal electron density transfer is observed for zwitterionic form of pefloxacin (0.8 *e*). This charge transfer strongly reduces the dipole moment (Δμ = –37.7 D). All the examined compounds in the ground and first excited states are characterized by a large dipole moment oriented approximately along the conjugation chain as shown in Fig. 3 (Table 2).

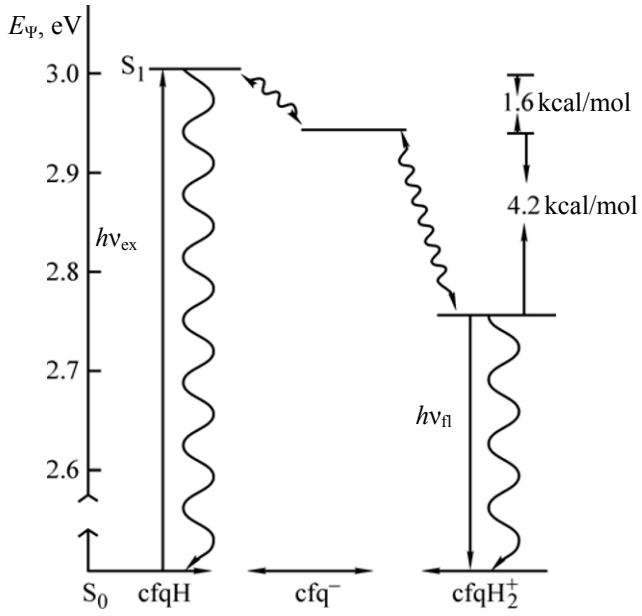


Fig. 2. Energy levels of $S_0 \rightarrow S_1$*-transitions in different protolytic forms of ciprofloxacin (cfqH) in aqueous solution.

Analysis of the orbital structure showed that all frontier molecular orbitals are localized mainly on particular molecular fragments. Figure 4 shows the structure of frontier molecular orbitals for different protolytic forms of pfqH. Some conclusions concerning participation of each molecular fragment in electron transitions and charge transfer can be drawn.

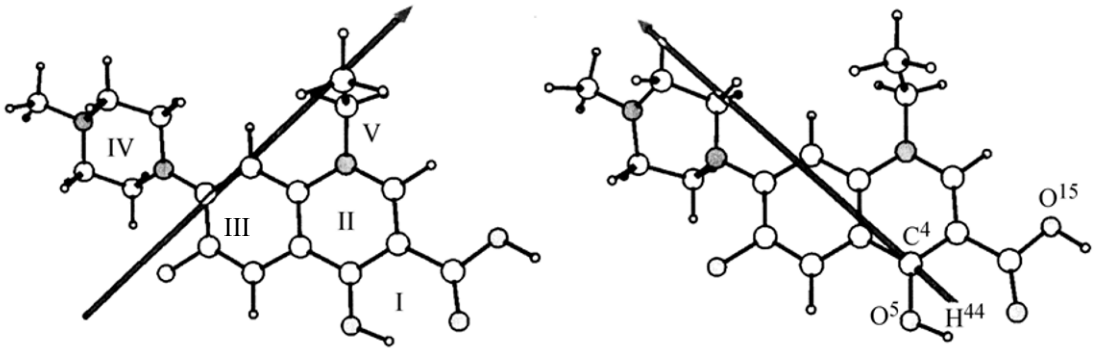


Fig. 3. Structure of protonated pefloxacin molecule ($pfqH_2^+$) and reorientation of its dipole moment upon excitation $S_0 \rightarrow S_1$; I–V denote particular molecular fragments: I–III correspond to the quinolinone framework, IV to piperazine ring, and V to the substituent on N^1.

The transition $S_0 \rightarrow S_1$ for all compounds is the transition between the HOMO and LUMO. It is seen that (Fig. 4) that molecular orbitals of compounds in neutral or protonated form strongly differ from those of compounds in anionic or zwitterionic form. The HOMO in neutral or protonated molecules is localized on ring IV, and the LUMO, on rings I–III. This is consistent with electron density transfer from ring IV to rings I–III. The structure of frontier MOs and electron density transfer in structurally related compounds cfqH, dfqH, and mdfqH are similar.

Localization of the HOMO changes in going to anionic form: it appears on the COO^- group, whereas the LUMO remains almost the same as in the neutral form. Therefore, the COO^- group in pfq^- acts as electron donor, and rings III and IV and fragment V are electron acceptors.

Proton addition to the $N^{4'}$ atom (Fig. 3) upon transformation into zwitterionic structure considerably changes electron density distribution pattern. The HOMO in zwitterion is localized on the COO^- group, and the LOMO, mainly on the hydrogen atom in the piperazine ring. Therefore, excitation of $pfqH^{\pm}$ is accompanied by electron density transfer to that hydrogen atom, and the latter acquires a negative charge. Here, the molecular fragment including ring I and COO^- group is electron donor, while the CH_3 group and piperazine hydrogen atom are electron acceptors.

Electron density transfer also induces variation of bond strengths and hence their lengths. As follows from the results of calculations, the strength and length of a bond between molecular fragments change insignificantly if charge transfer in the corresponding fragments is not large. If charge transfer is significant, variations of the bond strengths and lengths in the corresponding fragments are appreciable. For example, the C^4–O^5 bond in neutral and protonated species weakens (Fig. 3), and its length increases. Electron density transfer from ring IV to the quinolinone fragment in neutral and protonated molecules leads to weakening and extension of the bond between rings III and IV and increase of the relative mobility of the piperazine ring. Neutral compounds are also characterized by considerably increased overlap population of bonds in ring I; in particular, the $O^5 \cdots H^{44}$ hydrogen bond becomes so strong that it may be regarded as almost covalent, and ring I tends to be closed.

Table 2. Variation of charges on molecular fragments (Δq, e) and dipole moments ($\Delta\mu$, D) of fluoroquinolinones upon transition from the ground (S_0) to the excited (S_1) state

Fragment	pfq^-	pfqH	$PfqH^{\pm}$	$pfqH_2^+$	cfqH	mdfqH	dfqH
I	0.14	–0.19	0.40	–0.13	–0.13	–0.37	–0.18
II	0.03	–0.13	0.05	–0.13	–0.12	–0.14	0.10
III	–0.02	–0.35	0.08	–0.09	–0.19	–0.31	–0.26
IV	–0.06	0.47	0.03	0.41	0.56	0.47	0.62
V	–0.03	–0.08	0.06	0.07	–0.07	–0.04	–0.06
CH_3	0.00	0.22	–0.26	0.23	–	0.12	–
O^{15}	0.16	0.03	0.16	0.00	–0.03	–0.04	–0.04
F	–0.02	–0.05	0.00	–0.04	–0.04	–0.04	–0.04
$\Delta\mu$, D	–11.35	23.75	–37.76	12.41	18.02	23.30	20.73

Unlike neutral species, donors of electron density in zwitterionic form are rings I, II, and III, while ring IV and the CH_3 group act as electron acceptor. The bond between rings III and IV in $pfqH^{\pm}$ strengthens and shortens. In addition, overlap population of the bond between ring II and COO^- group considerably increases ($\Delta Q = 0.23$), and this bond shortens by 0.05 Å.

Thus transition of different protolytic forms of fluoroquinolinones to the S_1 excited state is accompanied by electron density redistribution over particular molecular fragments, which leads as a rule to additional polarization of their molecules. In the series of fluoroquinolinones with electron-donating and electron-withdrawing substituents the overall charge on atoms in the piperazine ring (ring IV) is negative, the overall charge on atoms in ring III is always positive, and the overall charge on ring II upon photoexcitation may be either negative or positive, depending on the degree of protonation. Substituents in positions *1*, *7*, and *8* weakly affect localization of frontier molecular orbitals of fluoroquinolinones.

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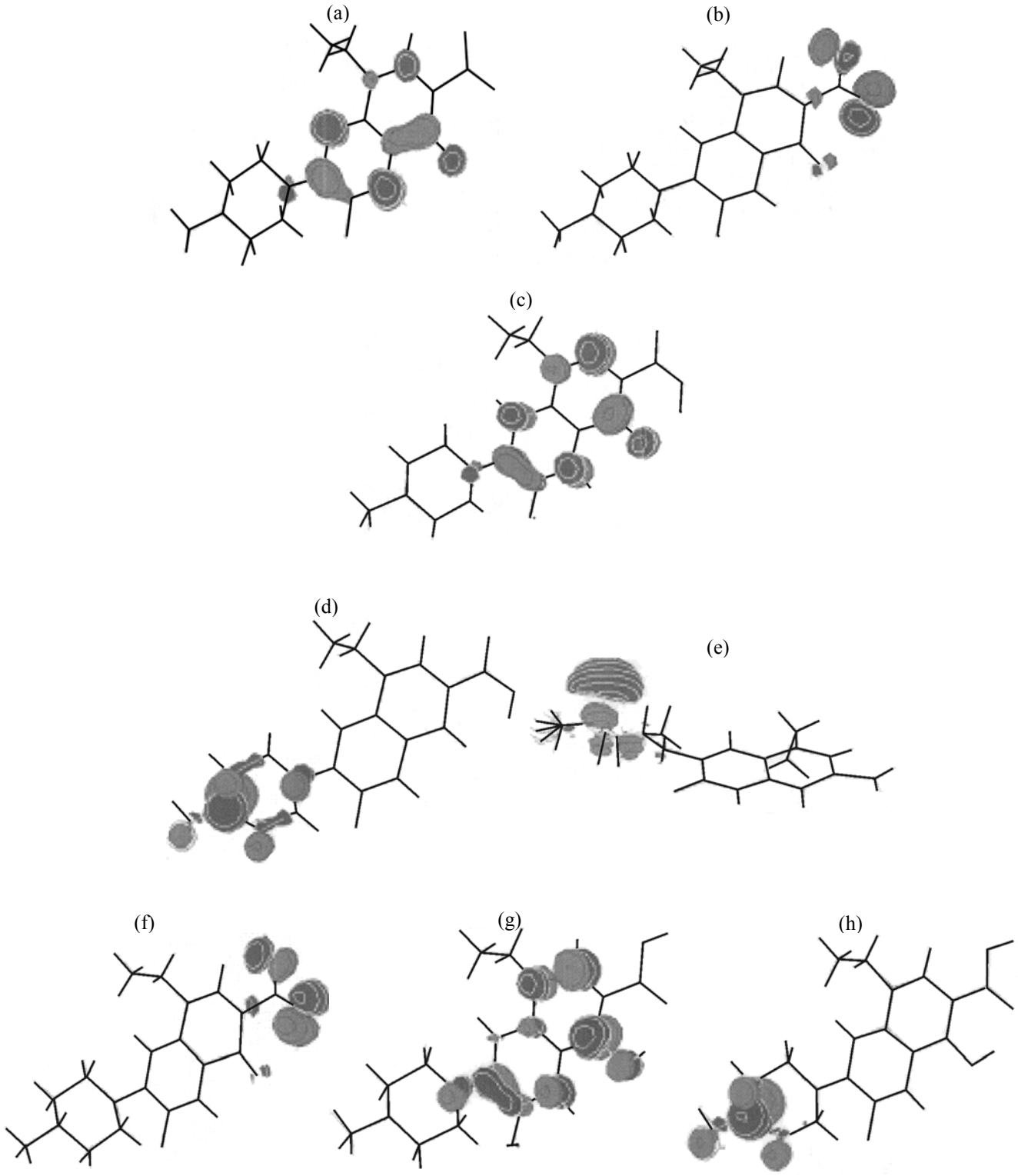

Fig. 4. Structures of the highest occupied (HOMO) and lowest unoccupied molecular orbitals (LUMO) in different protopytic forms of pefloxacin: (a, b) pfq^-, (c, d) pfqH, (e, f) $pfqH^{\pm}$, (g, h) $pfqH_2^+$; (a, c, e, g) LUMO, (b, d, f, h) (HOMO). The energies of the $S_0 \rightarrow S_1$ transition for $pfqH^{\pm}$ and $pfqH_2^+$ are 0.069 and 0.508 eV, respectively.

REFERENCES

1. Halls, J.J.M., Walsh, C.A., Greenham, N.C., Marseglia, E.A., Friend, R.H., Moratti, S.C., and Holmes, A.B., *Nature*, 1995, vol. 376, p. 498.
2. Shen, Z.L., Burrows, P.E., Bulovi, V., Forrest, S.R., and Thompson, M.E., *Science*, 1997, vol. 276, p. 2009.
3. Mokrushina, G.A., Charushin, V.N., and Chupakhin, O.N., *Khim.-Farm. Zh*., 1999, vol. 29, no. 9, p. 5.
4. Monti, S., Sortino, S., Fasani, E., and Albini, A., *Chem. Eur. J*., 2001, vol. 7, no. 10, p. 2185.
5. Albini, A. and Monti, S., *Chem. Soc. Rev*., 2003, vol. 32, no. 4, p. 238.
6. Polishchuk, A.V., Kazachek, M.V., Karaseva, E.T., and Karasev, V.E., *Zh. Fiz. Khim*., 2008, vol. 82, no. 4, p. 754.
7. Cuquerella, M.C., Mirand, M.A., and Bosca, F., *J. Phys. Chem. A*, 2006, vol. 110, p. 2607.
8. Sortino, S., Marconi, G., Giuffrida, S. De Guidi, G., and Monti, S., *Photochem. Photobiol*., 1999, vol. 70, no. 7, p. 731.
9. Park H.R., Kim T.H., Bark K.M., *Eur. J. Med. Chem.,* 2002, vol. 37, p. 443.
10. Aizikovich, A.Ya., Charushin, V.N., and Chupakhin, O.N., *Khim.-Farm. Zh*., 1996, vol. 30, no. 8, p. 43.
11. Schmidt, M.W., Baldridge, K.K., Boatz, J.A., Elbert, S.T., Gordon, M.S., Jensen, J.H., Koseki, S., Matsunaga, N., Nguyen, K.A., Su, S., Windus, T.L., Dupuis, M., and Montgomery, J.A., *J. Comput. Chem*., 1993, vol. 14, no. 11, p. 1347.
12. Tyrel, I., *Coord. Chem. Rev*., 2002, vol. 232, p. 27.
13. Sun, J., Sakai, S., Tauchi, Y., Deguchi, Y., Chen, J., Zhang, R., and Morimoto, K., *Eur. J. Pharm. Biopharm*., 2002, vol. 54, no. 1, p. 51.
14. Kalnin'sh, K.K. and Panarin, E.F., *Vozbuzhdennye sostoyaniya v khimii polimerov* (Excited States in the Chemistry of Polymers), St. Petersburg: Sankt-Peterb. Gos. Univ. Tekhnol. i Dizaina, 2007.