J Fluoresc (2012) 22:373–379
DOI 10.1007/s10895-011-0969-1

ORIGINAL PAPER

Spectroscopic and Photophysical Properties of Protonated Forms of Some Fluoroquinolones in Solutions

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Received: 2 June 2011 / Accepted: 2 September 2011 / Published online: 16 September 2011

Abstract Electronic absorption and fluorescence spectra of ciprofloxacin, norfloxacin, enoxacin, pefloxacin and nalidixic acid in aqueous solutions were investigated. The time-resolved fluorescence spectra were measured and interpreted. The changes of the luminescence spectra and electron structure of the compounds under study are explained by different degrees of the spin-orbital interaction caused by nitrogen heteroatoms lone pairs effect. Possible ways of the protonation process for naphtyridine and quinolone rings with different substitutions are discussed. The photophysical behavior of FQs was studied using density functional theory (DFT) calculations.

Keywords Fluoroquinolones · Absorption · Fluorescence spectra · Quantum-chemical calculations · Electronic structure · Electron density redistribution · Protolytic form · Photophysical behavior

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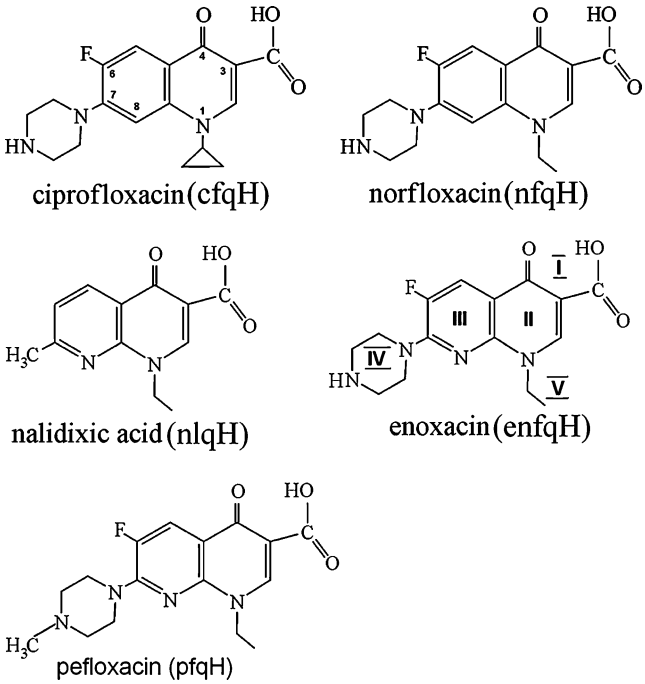
Introduction

Fluoroquinolone (FQ) antibiotics are widely prescribed synthetic agents with a broad spectrum of antibacterial action. FQs have evolved from nonfluorinated nalidixic and pipemidic acids, commonly denoted as the first-generation FQs, which were initially used as drugs against gram-negative bacteria. These are still chosen as first election drugs in the treatment of urinary-tract infections, gonorrhea and bacterial enteritis [1, 2]. Reactive groups, bearing nitrogen and oxygen atoms, are known to be essential to antibacterial activity. However, progressive modifications in their chemical structure have shown that quinolones with additional substituents possess better antibacterial activity and bioavailability [3, 4]. For example (Scheme 1), binding of a fluorine atom to C-6 and a piperazine or methyl piperazine to C-7 has produsedmore active agents such as ciprofloxacin, norfloxacin, enoxacin etc., which have been introduced as the second-generation FQs [5, 6]. Two major groups of compounds have been developed from the basic molecular structure of the nalidixic acid, namely fluoroquinolones and naphthyridones, whose currently used members represent major advances over the original nalidixic acid.

The chemical structure of FQs contains several proton-binding sites with similar acid–base behavior, namely the carboxyl, carbonyl and amino groups. The above groups are protonated in a competitive fashion. Due to this fact, the properties of FQs are influenced by the physicochemical characteristics of the solvent [7] and, thus, their antibacterial activity is strongly pH-dependent [8, 9]. The importance of the protonation of FQ molecules in the interaction with DNA has been shown by Son and coworkers who



Scheme 1 Chemical structures of selected quinolones

evidenced the fact that protons can promote norfloxacin binding to DNA at a neutral pH by neutralizing the negative charge on the carboxyl group of the bound drug [10]. Moreover, the interaction with ct-DNA seems to involve mainly cationic species of FQs [11]. In addition, it was revealed by several studies that even slight and subtle structural modifications could result in significant changes of the antibacterial activity. Thus, the antibacterial response of (fluoro)quinolone antibiotics is influenced by their structural details and physical chemical properties of the environment. For example, fluoroquinolones and naphthyridones show completely different antibacterial responses and chemical properties as the physicochemical properties of solvents are changed [7, 12]. These observations suggest that there is a major difference between these two groups of drugs with respect either to their mode of action or their mechanism of penetration into bacteria.

In the present work we have studied, in addition to the original quinolone—nalidixic acid, members of both classes of compounds, i.e. fluoroquinolones, whose structures are depicted in Scheme 1. Enoxacin has, like nalidixic acid, a naphthyridine nucleus with nitrogens at positions 1 and 8 and an additional fluorine atom at position 6. Ciprofloxacin, pefloxacin and norfloxacin are based on a nucleus with only one nitrogen in position 1 generally denoted as quinoline ring (see Scheme 1).

We explain the interfragmental charge transfer and spectroscopic characterization of the compounds as a function of the solution pH and quantity and position of nitrogen heteroatoms. The experimental results are supplemented by theoretical calculations of the FQs.

Experimental Section

Ciprofloxacin, norfloxacin, enoxacin and nalidixic acid were purchased from Sigma Chemical Co. (St.Louis, U.S.A.) and used without further purification. Other chemicals used in the study were of spectroscopy grade from Aldrich Chemical Co. and used as received. The aqueous solutions of FQs were prepared with distilled water passed through a deionization system. The initial concentration of the compounds in aqueous solution, 10^{-3} mol/l, was created via dissolving an accurately weighted sample of a substance in 100 ml of distilled water. Working solutions were prepared by an appropriate dilution with water and HCl. The concentration of the working solutions was 2×10^{-5} M (diluted from the stock solution 2×10^{-4} M).

Apparatus

The pH measurements were performed with a Thermo Orion 920A plus pH meter model with the Sensorex epoxy body combination electrode. The pH was adjusted by addition of NaOH or HCl after all other reagents were added.

The absorption spectra were measured using a UV–vis spectrophotometer (SF-256 UVI (LOMO)) in 1 cm quartz cuvettes. Cary Eclipse Fluorescence Spectrophotometer (Varian, Australia) was applied to measure fluorescence and excitation spectra. All measurements were carried out at room temperature. The fluorescence excitations and emissions were recorded by monitoring the emission and excitation, respectively, at the maximum wavelengths for each solution. The lifetime was measured with a FluoTime 200 ps time-resolved spectrophotometer. The fluorescence lifetimes of the fluoroquinolone derivatives were measured at room temperature using a Time-Correlated Single Photon Counting (TCSPC) PicoHarp 300. The data were fitted by a double–exponential function ($F(t)=a_1\exp(-t/\tau_1)+a_2\exp(-t/\tau_2)$). The quality of the data fit was judged using statistical parameters and graphical tests. The data were fitted using the nonlinear least squares method. The reduced chi-squared values were close to 1. The calculations of rate constants of radiative and nonradiative transitions were made using $k_f=\varphi_f/\tau_f$ and $k_{nf}=(1/\tau_f)—k_f$, respectively. As the nonlinear fitting method we used the built-in analysis software that came with the instrument. For the decay curve tail region we used the kinetic model of stretched exponentials (Tailfit).

In order to understand the origin of different photophysical behavior of the studied compounds, we employed density functional theory (DFT) calculations to investigate of fluoroquinolones and naphthyridones.

Quantum-chemical calculations of FQs ground and exited states were carried out by the B3LYP functional and 6–31 G basis set using the GAMESS (2010) computational package [13, 14].

The IUPAC numeration of quinolone atoms is given at the Scheme 1 (left), the same Scheme presents the fragments numbering used in theoretical calculations (right).

Results and Discussion

UV and Luminescent Spectroscopy

The absorption, fluorescence and fluorescence excitation spectra of heterocycles depend on the lenghth of the system of π-conjugation of aromatic rings. The luminescence intensity is greatly affected by the spin-orbital interaction of the heteroatom n-electrons. Hence a detailed investigation of the relationship between the spectral characteristics and the degree of electron transfer from heteroatoms to the π-system of FQs aromatic rings is fundamentally important.

In addition, as was said above, the interfragmental charge transfer and spectroscopic characterization of the compounds depend on the quantity and position of protons, notably the solution pH.

The pH-dependence of absorption and emission behavior of different FQs has been the topic of numerous previous publications. In particular, the authors of [9, 16] study FQs fluorescence as the function of solutions pH. (приводят зависимость флюоресценции фторхинолонов от pH растворов.) M.C. Cuquerella and coauthors provide a clear evidence of the singlet excited-state deactivation of nfqH and its methyl derivative pfqH via intramolecular electron transfer from the piperazinyl ring to the fluoroquinolone main system. Acetylation of the piperazinyl ring (as in pfqH) decreases the availability of the lone pair, making observable its fluorescence and the transient absorption spectrum of its triplet excited state even at high pH.

Our investigations continue the above researches. In this work we present both the spectral results and the attempt to explain theoretically (using the quantum chemistry methods) the peculiarities of the photochemical behavior of the compounds with the different numbers of nitrogen atoms in terms of the spin-orbital interaction and nitrogen lone pairs influence.

The UV/vis spectra of quinolone and quinolone-like molecules have three characteristic absorption bands. The maximum observed in the range 200–230 nm is results from the absorption of the C2–C3 double bond. The second maximum is observed between 240 and 300 nm which appears due to the π→π* electronic transition in the aromatic ring. The longest wavelength maximum (between 300 and 380 nm) results from the n→π* electronic transition [15] and consists of two subpeaks caused by an equilibrium of the quinolone molecules forming an intermolecular hydrogen bond with the solvent and quinolones forming an intramolecular hydrogen bond between the 4-keto and the 3-carboxylic acid group [16].

As was reported in previous studies [15, 17], both the absorption and emission properties are strongly affected by pH. This is evidenced by the fact that all characteristic maxima of the FQs spectra undergo a visible shift at different pH values.

In order to investigate the effect of protonation of the compounds based on quinolone and naphtyridine nucleus, having different numbers of nitrogen atoms, the absorption spectra of FQs were recorded.

As an example, Fig. 1 shows the absorption spectra of cfqH in water solutions at different acidity values (from 1 to 10 M HCl). One can see that the bands corresponding to the π→π* and n→π* transitions are very sensitive to pH changes. As pH decreases, the short-wavelength band increases in intensity, whereas the long-wavelength band decreases.

In order to explain the peculiarity of the changes in the fluoroquinolones absorption and luminescence spectra in terms of their geometrical and electronic structure, the X-ray analysis results of the FQs crystals, synthesized from strong acid solutions, have been taken into account. The compounds $cfqH_2^+$ and $cfqH_3^{2+}$ with atomic labeling are

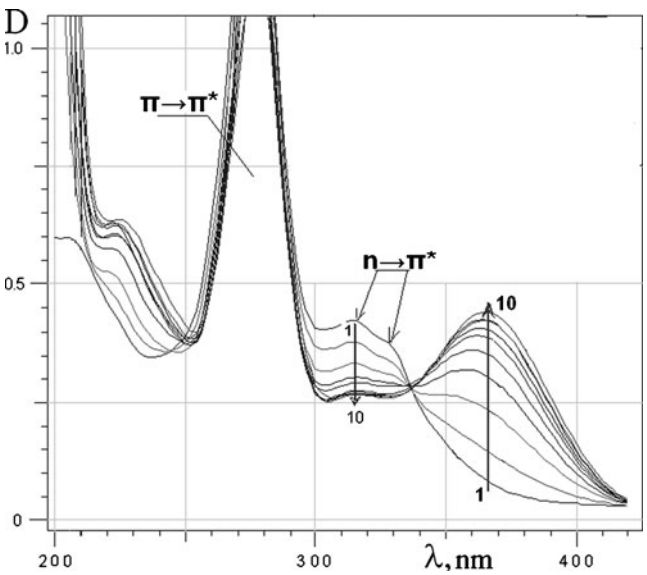


Fig. 1 Absorption spectra of cfqH recorded at different concentrations of HCl: 1 M–10 M. ($c=5\times10^{-5}$ M)

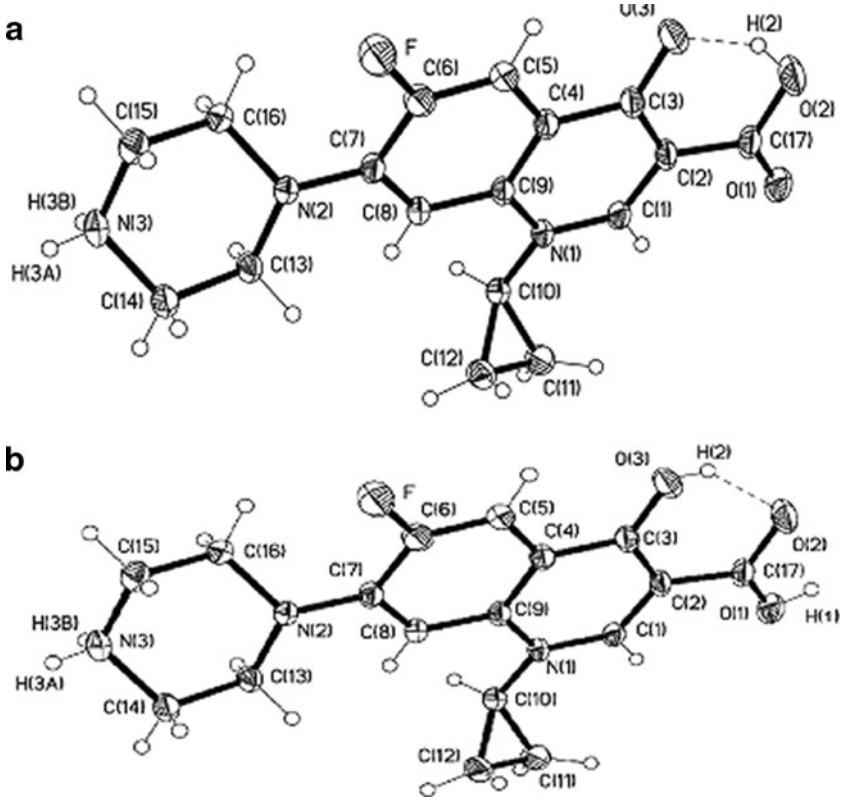


Fig. 2 Structure of $cfqH_2^+$ **a** [18] and $cfqH_3^{2+}$ **b** [19]

shown in Fig. 1. As follows from the results of the X-ray analysis of the compound $cfqH_2^+[AuCl_4]H_2O$ [18], the monoprotonated form $cfqH_2^+$ is formed by the coordination of H^+ to the oxygen atom of –COOH group. The hydroxylic hydrogen of the –COOH group is that hydrogen bonded to the 4-keto oxygen, thus forming a six-membered pseudo-ring.

As seen from the $cfqH_3^{2+}$ structure [19] presented in Fig. 1b, the carbonyl oxygen O(3) is protonated. The latter is supported by the value of the interatomic distance C(3)-O(3)=1.329 Å. This hydrogen atom H(2) forms the intramolecular H-bond 2.536 Å with the carboxyl group oxygen. C(17) atom is double-bonded with the O(2) atom (1.234 Å), whereas O(1) is bonded with C(17) by a single bond.

In the cfqH absorption spectra the formation of the different polymorph forms of quinolones is reflected in the

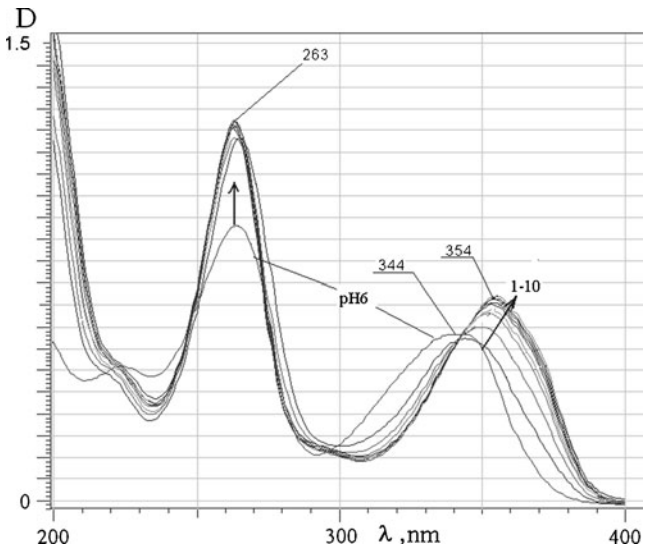


Fig. 3 Absorption spectra of enfqH recorded at different concentrations of HCl: 1 M–10 M. ($c=5\times10^{-5}$ M)

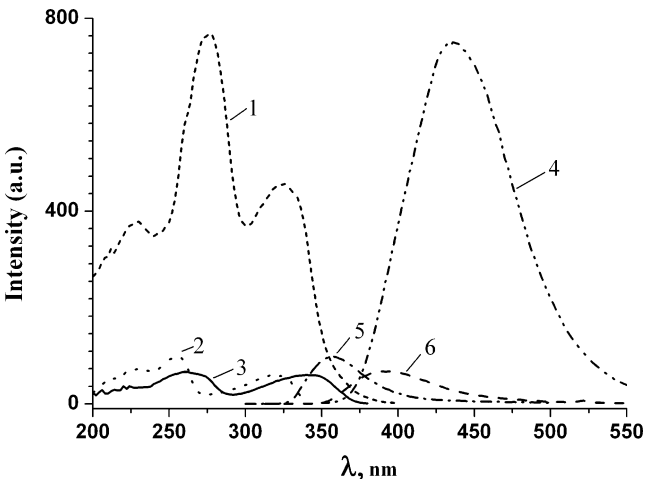


Fig. 4 Fluorescence excitation and fluorescence spectra of nfqH (1,4), nlqH (2,5), enfqH (3,6) aqueous solutions ($c=5\times10^{-5}$ M, pH 6,1)

Table 1 Photophysical properties of neutral and protonation forms of fluoroquinolones ($C=5\times10^{-5}$ M)*

Compound	λ_{abs}, nm	λ_{fl}, nm	φ_{fl}	τ, ns	$k_{fl}10^{-7}$	$\kappa_{nf}10^{-8}$
nfqH	272	412	0.10	2.0	5.0	45
cfqH	273	417	0.12	1.5	8.0	5.8
enfqH	263	385	0.05	0.8	6.0	9.4
nlqH	254	356	0.02	0.2	10	49
$nfqH_2^+$	274	436	0.21	1.8	11.0	4.5
$cfqH_2^+$	277	445	0.18	1.5	12.0	5.5
$enfqH_2^+$	263	400	0.01	0.8	1.3	12.0
$nlqH_2^+$	254	414	0.08	0.2	4.0	50
$cfqH_3^{2+}$	277	430	0.09	0.7	13.0	13.0

[a]All measurements are done at appropriate acid concentrations of aqueous solutions

redistribution of the intensity of the doublet components of the n→π* transition band (Fig. 1).

The spectroscopic properties of enfqH in acid solutions differ significantly from those described above for cfqH. The absorption spectra of acid solutions of enfqH in the range of H_0 −0.2 to −3.68 are presented in Figs. 2 and 3. In the case of enfqH, the increase in acid concentration is gradually shifting the n→π* electronic transition band, having a maximum at 340 nm, towards longer wavelengths (red shift) and reaches 355 nm at H_0 −3.68. This is accompanied by an increase in optical density. The band of the π→π* transition (located at 265 nm) does not appear to be strongly influenced by the pH. Its maximum located at 265 nm does not shift and only a slight increase of the optical density is observed.

In addition, different ratios of the integral intensities of the bands corresponding to the π→π* and n→π* electronic transitions in the absorption spectra of FQs can be attributed to the specific features of the compounds. For instance, for nfqH and cfqH this value is 4:1, whereas for enfqH it equals to 1:1. Increase of the optical density in the region of the n→π* electronic transition band of enfqH, on the one hand, and decrease of that of π→π* electronic transition band, on the other hand, is a result of larger amount of nitrogen heteroatoms possessing lone pairs of electrons (see Scheme 1).

Fluorescence Spectra

The fluorescence and fluorescence excitation spectra of nfqH, nlqH and enfqH in aqueous solutions at pH6 and pH1 are presented in Fig. 4. The fluorescence spectral data of all compounds are listed in Table 1.

Figure 4 reveals that the fluorescence spectra of the studied compounds have broad and structureless bands with large Stokes shifts, which indicate to significant changes in the geometry of the emitting state with respect to the ground state.

The presence of two nitrogen heteroatoms in the naphtyridine nucleus of nlqH and enfqH intensifies the pseudoaromaticity of the ring and results in both low fluorescence intensity (Fig. 4) and short lifetime of the singlet exited state (0.2–0.8 ns) (Table 1). Additional substituents (F6 and piperazinyl (pip) at position 7) in enfqH, as compared to nlqH, lead to a red shift of the spectrum. Consequently, when comparing the fluorescence properties of nlqH to those of cfqH, pfqH and nfqH, both a strong increase in intensity and a red shift of the spectrum are observed due to the additional substituents and the deficiency of one nitrogen heteroatom in the aromatic nucleus. In addition, one can see an extension of the excited state lifetime for cfqH and nfqH (Table 1) as compared to nlqH and enfqH. Moreover, on the one hand, enfqH belongs to the 1,8-naphtyridine compounds like nlqH, but, on the other hand, it is a close analog of nfqH. As a result, luminescent properties of enfqH are intermediate between nlqH and nfqH (Table 1).

The comparative analysis of the nlqH, nfqH, pfqH and enfqH luminescent spectra indicates to the presence of fluorescence in all protolytic forms: anionic, neutral and cationic [9, 16]. In the latter works there are the fluorescent

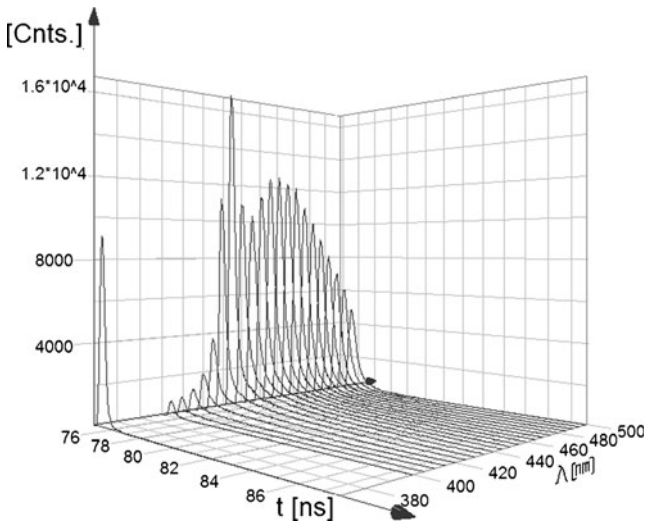


Fig. 5 Time-resolved fluorescence spectrum of ciprofloxacin (1 M HCl, 10^{-5} M)

Table 2 Pre-exponential factors and lifetimes (τ, ns) of the exited states of ciprofloxacin in neutral and acid aqueous solutions

Characteristic	pH 7.4	pH 0		H_0=−0.2	
	430 nm	430 nm	455 nm	430 nm	455 nm
A_1	781	630	260	417	215
τ_1, ns	1.2	1.0	1.0	7.8	10.1
A_2	–	88	143	736	734
τ_2, ns	–	13.9	8.9	2.4	3.1
A_3	–	475	294	2204	1826
τ_3	–	3.5	4.0	0.3	0.4

spectra of norfloxacin and enoxacin at different pH are presented. One can see that in the case of norfloxacin the maximal intensity of fluorescence is observed at pH 3.4 (monoprotonated form). In the case of enoxacin the maximal fluorescence intensity is at pH 7.2 (neutral form). In an alkaline solution the fluorescence is weak for all the compounds under study.

In most cases the fluorescence strength of anionic forms is lower than that of neutral and protonated compounds. The luminescence strength for each of the related compound rises at pH<2 in the following way: the luminescence is maximal for enfqH and nlqH in a neutral form, but for nfqH, cfqH and pfqH in a monoprotonated form. The reason of such a behavior is a different degree of spin-orbital interaction of heteroatom lone pair electrons with the π-system of aromatic rings that affects the molecular intercombinatory transitions. The probability of intercombinatory transitions sharply increases for molecules with the high spin-orbit interaction (π*→n transitions), so that their fluorescence decreases while the phosphorescence intensity increases. It is evident for anionic $enfq^-$ and nlq^- with two N heteroatoms in aromatic ring.

The quantum chemistry calculations (Fig. 6) show that for such compounds the π*→n transition is typical. The acidification of solution by the HCl results in the appearance of electron acceptor in quinolone molecule and higher degree of n-electron localization on the heteroatom N(3) of piperazine group (Fig. 2). At the same time, spin-orbital interaction of n-electrons with the π-system of aromatic rings decreases which facilitates the π-electron conjugacy degree and luminescence intensity.

Time-Resolved Fluorescence Spectra and Quantum-Chemistry Calculations

As an example, the time-resolved spectrum of $cfqH_2^+$ recorded in 1 M HCl solution is shown in Fig. 5. Analysis of the results of the time-resolved fluorescence spectroscopy indicates to the simultaneous presence of two different photolytic forms $cfqH_2^+$ and $cfqH_3^{2+}$ in acid solutions. The first luminescent maxima (λ=417 nm) is up to the neutral form of cfqH, and the second luminescent maxima (λ=445 nm), which is wider, is up to the monoprotonated form $cfqH_2^+$.

In Table 2 the luminescence lifetimes of the neutral form cfqH (pH 7.4), monoprotonated form $cfqH_2^+$ (pH 0) and diprotonated form $cfqH_3^{2+}$ (H_0=−0.2) of ciprofloxacin are compared. In the case of cfqH it is monoexponential

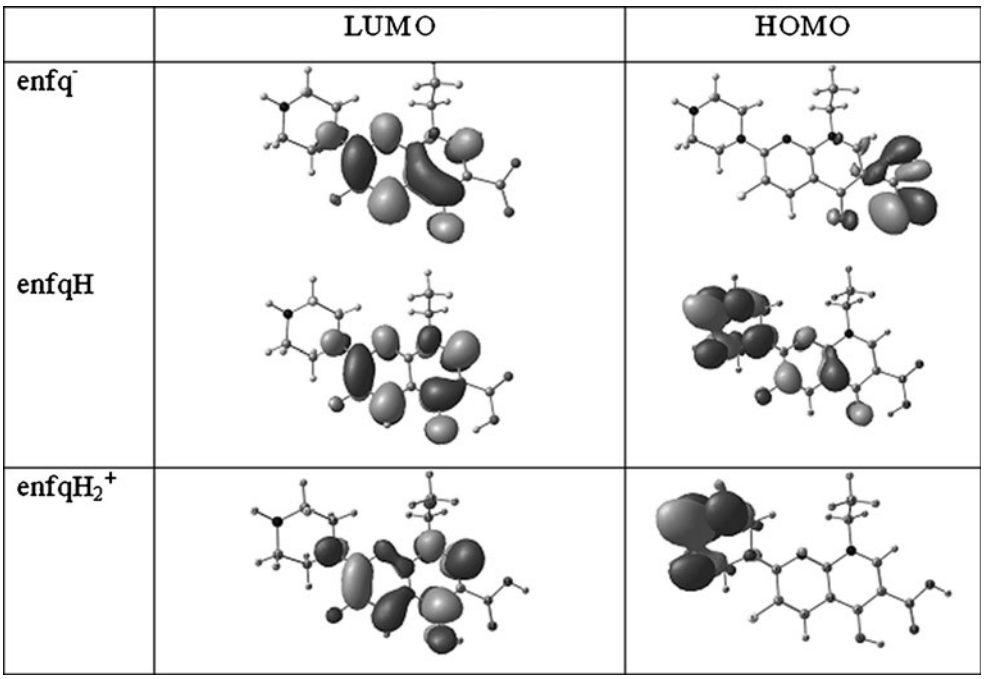


Fig. 6 HOMO and LUMO structure of enfqH in different protolytic forms

whereas then for $cfqH_2^+$ and $cfqH_2^{2+}$ the fluorescence decay curve is of a complex nature and can be only described by the decomposition to three components. At the same time, there are two maxima of fluorescence in the wavelength scale (Fig. 5) that indicates to the fact that the protonation processes of fluoroquinolones can be accompanied by the molecules association [17].

Indeed, the electron density shift of the heteroatom lone pairs in the opposite direction depending on the proton presence and its connecting place with reaction centers of the antibiotics is observed in accordance with the results of quantum chemistry calculations of FQs (Fig. 6).

The results of the boundary MO calculations for different protolytic forms of FQs demonstrate that all of them have general and specific features. As an example, Fig. 6 shows the HOMO and LUMO structure of enfqH in different protolytic forms. The electron density on LUMO for all protolytic forms of the compound is distributed over the naphtyridine ring. This indicates to the preferential occupation of the π^*-excited state. In its turn, the HOMO analysis allows combining the anion forms of FQs in one group, and neutral and monoprotonated forms in another one. For the former compounds, the HOMO electron densities are localized generally on the carboxyl group, and for the latter ones the HOMO electron densities are localized on the pip ring and the CH_3-group. This means that the $\pi^* \rightarrow n$ electron transition is characteristic for the anion forms of FQs, whereas the $\pi^* \rightarrow \pi_{pip}$ transition is characteristic for other protolytic forms of FQs. These peculiarities allow explaining the dependencies of luminescence band intensities of different compounds from the pH solution.

Conclusion

The experimental and quantum chemistry methods were used for studying of the photochemical behavior fluoroquinolones as the function of their protonation degree and the number of nitrogen atoms in quinolone rings. It was revealed that naphtyridine and quinolone rings had different degrees of nitrogen lone pairs spin-orbital interaction with the π-system of aromatic rings.

The results of quantum chemical calculations demonstrate that photoexcitation of FQs leads to the intramolecular electron density transfer. Its direction depends on the number of protons and their position in the reaction centers of antibiotics. The protonation degree has an impact on the nitrogen lone pair localization, which results in the decrease of the spin-orbital interaction of n-electrons with the π-conjugacy of aromatic rings. According to our calculations, the anion and zwitter-ion forms of FQs are characterized by the typical $\pi^* \rightarrow n$ electron transition, whereas for all other protolytic forms the $\pi^* \rightarrow \pi$ transition is typical. Such a conclusion enables one to explain the dependencies of luminescence bands intensities of different compounds from the solutions pH.

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