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ORIGINAL PAPER

Spectral-Luminescent Properties and Molecular Orbital Treatment of Some Mono- and Difluoroquinolones

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Abstract Electronic absorption and luminescent spectra of nonfluorinated nalidixic (nlqH) and pipemidic acid (pifqH), monofluoroquinolones – norfloxacin (nfqH) and pefloxacin (pfqH) as well as of their difluorinated analogs 1-ethyl-6,8-difluoro-1,4-dihydro-7-(1-(4-methylpiperazinyl) – 4-oxo-3-quinolinecarboxylic (mdfqH) acid and 1-ethyl-6,8-difluoro-1,4-dihydro-7-(1-piperazinyl) – 4-oxo-3-quinolinecarboxylic acid (dfqH) - were investigated. Quantum yields, lifetimes of excited states and rate constants of radiative and nonradiative transitions of the compounds were measured. The Mulliken charges of atoms from these compounds were calculated by quantum-chemical complex GAMESS. Differences in the electronic structures of these compounds and their spectral-luminescent characteristics were compared with the data of the phototoxicity degree of fluoroquinolones. Analysis of the Mulliken charges of the difluoroquinolones points to the changes of the redistribution of the electron density along π-conjugated system, and on the oxygen atoms of the carbonyl and carboxyl groups. The analysis of the molecular orbitals involved in the electronic transitions of the compounds revealed that both defluorination and piperazine photolysis are photodecomposition mechanisms which may take place in the excited states of these compounds. The relationship between the location order of the π-π* excited levels of the FQs and the degree of their phototoxicity has been determined

Keywords Fluoroquinolone · Luminescence · Quantum-chemical calculation · Electronic structure · Phototoxicity

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Introduction

Fluoroquinolones (FQs) are a class of compounds widely used as broad-spectrum antimicrobial agents [1]. FQs have evolved from nonfluorinated pipemidic and nalidixic acids, initially used as drugs against gram-negative bacteria. Further elaboration has shown that quinolones with 6-fluoro substituent possess better antibacterial activity and bioavailability (ciprofloxacin, norfloxacin, etc.) [2–5]. Moreover, it was found that the introduction of a second halogen atom at the position C8 of the aromatic system further expands the spectrum of antibacterial activity and improves the oral bioavailability [6].

From the photobiologic point of view, however, the position C8 turned out to be critical with respect to its phototoxicity [7–14]. It has been shown that the electron-withdrawing halogen substituent increases photodecomposition and the phototoxic effects of FQs by enhancing the internal charge-transfer character formed after photoexcitation [15, 16]. The photoreactivity (lomefloxacin > enoxacin > norfloxacin > ofloxacin) turned out to be directly related to the electronegativity of the substituent X at C8 (X = C-F > N > C-H > C-OMe) [17]. Due to this, a halogen atom has rarely been used as a substituent at C8 in the FQs. However, recent investigations conducted with a series of FQs have shown that

8- halogeno quinolones can be only mildly phototoxic if a proper substituent is placed at the position 1 (see Scheme 1 for numbering) of the aromatic system [18]. Thus, the photochemical behavior of FQs is strongly influenced by their structural characteristics.

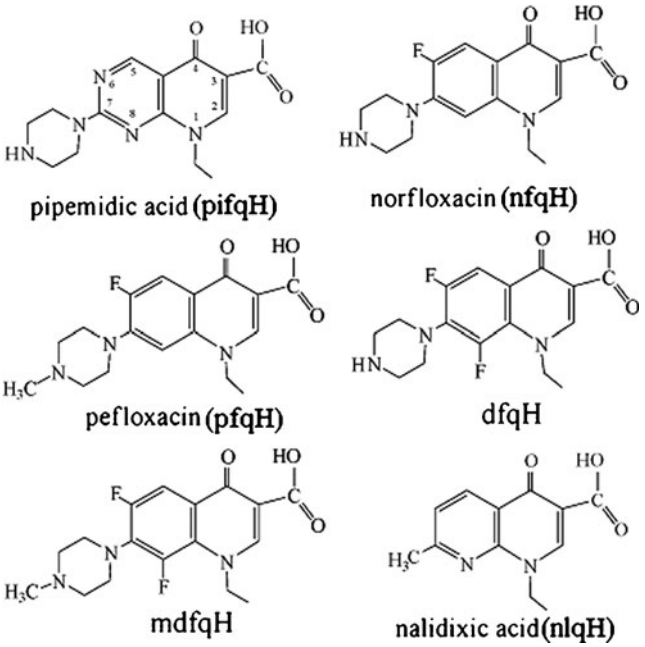
It has been shown that the photochemical behavior of fluoroquinolones also depends on pH [19]. Nanosecond flash photolysis experiments confirm that the yield of absorbing transients is at maximum at neutral pH while it decreases to zero at acid and alkaline pH [20]. For instance, the photodegradation quantum yield of enoxacin also is at maximum in neutral conditions (*ca* 0.04).

Fluoroquinolones can exist in four possible forms: an acidic cation fqH_2^+, a neutral nonionized species fqH, an intermediate zwitterion $fqH^{\pm}$ and a basic anion fqH^-, depending on the pH of medium. At low pH values, both the 7- piperazinyl group and 3-carboxyl group are protonated, whereas at high pH values, neither is protonated. Although the ratio of the concentrations of the different forms appears to be very different in the various derivatives, at neutral pH the largely prevailing species is always the zwitterion [21]. However, the cationic form and the anionic form predominate in acidic and in basic solutions, respectively. Two macroscopic dissociation constants can be determined for fluoroquinolones. The first applies to the 3-carboxyl proton and the second to the 7-piperazinyl proton [22]. For example, pKa values for norfloxacin are pKa_1 ca. 6.22 and pKa_2 ca. 8.51; for pefloxacin they are 6.02 and 7.80 respectively [23]. The decrease in the acidity of the carboxylic group compared with benzoic acid (pKa 4.2) is explained by the intramolecular hydrogen bond to the keto oxygen resulting in a stabilization of the protonated species [22].

On the other hand, nalidixic acid, the first member of the family, has a single protonation constant (pKa≈6) in the pH range of 2–9. It is protonated in a strong acid solution to form a naphthyridinium cation with a pKa of −0.86. The drug exists in its undissociated form over a pH range of 1.6–3.6 [22].

Phototoxicity as well as the biological functionality of such agents is related to the geometry and the distribution of the charge density in these molecules, which are reflected in their electronic and fluorescence spectra [24]. Therefore, spectroscopic techniques, especially when they are supplemented by computational calculations, may be a useful tool for obtaining information about the compound structure - properties relationship [25].

In this study we employ spectroscopic techniques (steady state absorption and fluorescence) for the characterization of some structurally related (fluoro)quinolones, two of which are new difluoroderivatives (Scheme 1) designed to optimize the existing active agents. The experimental investigation and interpretation is aided by quantum mechanical calculations.



Scheme 1 Molecular structures of the investigated fluoroquinolones

To estimate the relationship between the phototoxicity degree and electronic structure, quinolones with different number of fluorine atoms in their structure were chosen for present study. These include: nonfluorinated nalidixic (nlqH) and pipemidic acid (piqH), monofluorinated compounds – norfloxacin (nfqH) and pefloxacin (pfqH) and their difluorinated analogs: 1-ethyl-6,8-difluoro-1,4-dihydro-7-(1-(4-methylpiperazinyl)–4-oxo-3-quinolinecarboxylic (mdfqH) acid and 1-ethyl-6,8-difluoro-1,4-dihydro-7-(1-piperazinyl)–4-oxo-3-quinolinecarboxylic acid (dfqH).

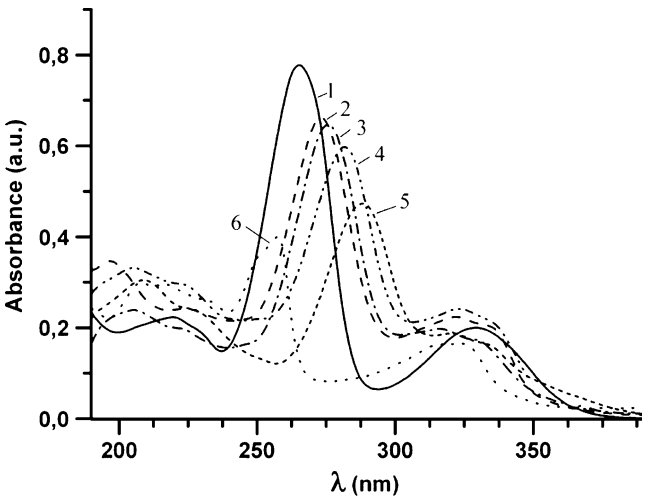


Fig. 1 Uv-vis spectra of the aqueous solutions of selected quinolones (c= 2×10^{-5} M): 1—piqH, 2—nfqH; 3—pfqH; 4—mdfqH, 5—dfqH, 6—nlqH

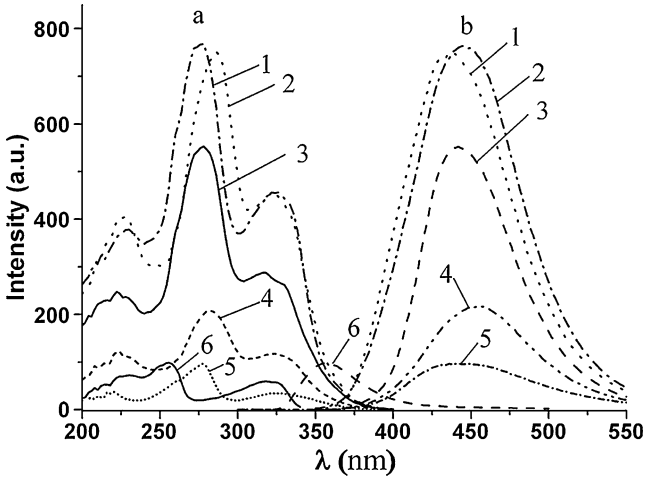


Fig. 2 Fluorescence excitation (**a**) and fluorescence (**b**) spectra of the aqueous solutions of selected quinolones ($c=2\times10^{-5}$ M): 1—nfqH, 2—mdfqH, 3—pfqH (diminished 1.3 times), 4—dfqH, 5—piqH, 6—nlqH

Experimental Section

Materials

Norfloxacin, nalidixic and pipemidic acid were purchased from Sigma Chemical Co. (St. Louis, U.S.A.) and were used without further purification. Pefloxacin and the difluorinated analogs (dfqH and mdfqH) were synthesized according to the method described in [26]. The other chemicals were of spectroscopy grade from Aldrich Chemical Co and were used as received. The aqueous solutions were prepared by using purified water, which was obtained by passing distilled water through a deionization system. The initial concentration of the compounds in water, 10^{-3} mol/l, was obtained by dissolving an accurately weighed sample of a substance in 100 ml of water. The concentration of the working solutions was 2×10^{-5} M, prepared by diluting the stock solution.

Methods

The pH measurements were performed with a Thermo Orion 920A plus pH-Meter having the Sensorex epoxy body combination electrode. The pH of the solutions was adjusted with NaOH or HCl after the addition of all other reagents. The absorption spectra were taken using a UV-vis spectrophotometer (SF-256 UVI (LOMO)) in 1 cm quartz cuvettes. Cary Eclipse Fluorescence Spectrophotometer (Varian, Australia) was employed to measure fluorescence and excitation spectra. All measurements were carried out at 300 K. Emission and excitation slit widths were 5 nm and rates of 600 nm/min were used. The lifetime was measured with a FluoTime 200 picosecond time-resolved spectrophotometer, using a Time-Correlated Single Photon Counting (TCSPC) PicoHarp 300. The data was fitted by a double - exponential function ($F(t) = a_1\exp(-t/\tau_1) + a_2\exp(-t/\tau_2)$). The quality of the fit was judged using statistical parameters and graphical tests. The data was fitted using nonlinear least squares method and the reduced chi-squared values obtained were close to 1. Luminescence quantum yield has been measured as described elsewhere [23]. The rate constants of radiative and nonradiative transitions were obtained by using equations $k_f = \varphi_f/\tau_f$ and $k_{nf} = (1/\tau_f) - k_f$, respectively.

Ground state quantum chemical calculations of the electron structure were performed with the GAMESS program [37] by applying the Hartree-Fock method with the 6–31 G basis. Additionally, time dependent density functional theory (TDDFT) was employed for the investigation of the excited states above 250 nm. The B3LYP exchange-correlation functional with the TZVP basis set was used as implemented in the Turbomole computational software. IUPAC numeration of the atoms in quinolones is given in Scheme 1, while Fig. 3 presents the atom numbering used in theoretical calculations.

Results and Discussion

UV and Luminescent Spectroscopy

The absorption and fluorescence spectra of heterocycles depend both on the nature of the substituents and on their position. Hence, a detailed investigation of the relationship

Table 1 Photophysical properties and phototoxicity of fluoroquinolones (pH 3.5, $c=5\times10^{-5}$ M)

Compound	λ_{abs}/nm[a]	λ_{fl}/nm[b]	φ_f[c]	τ/ns[d]	$k_f/10^7$ s^{-1} [e]	$k_{nf}/10^8$ s^{-1} [f]	TD_{50}/(mg/kg)
$nfqH_2^+$	274	436 (98)	0.21	1.8	11	4.5	> 300
$pfqH_2^+$	277	441 (120)	0.26	2.6	9.9	2.8	265
$mdfqH_2^+$	283	446 (100)	0.22	3.9	5.7	2.0	–
$dfqH_2^+$	289	453 (28)	0.08	9.2	0.9	1.0	171
nlqH	254	356 (12)	0.02	0.2	10	49	> 300

[a] Absorption maxima. [b] Fluorescence band maxima and intensities (in arbitrary units), c) Quantum yield, [d] Lifetime of exited state. [e] Rate constant k_f for radiative transitions . [f] Rate constant k_{nf} for nonradiative transitions

Table 2 The numbering of the atoms in Table 2 follows that presented in Fig. 3 but is different from that shown in Scheme 1

Atom	dfqH	nfqH$^{\pm}$	pfqH	mdfqH
N(1)	−1.034	1.049	−1.059	−1.036
C(2)	0.301	0.215	0.365	0.302
C(3)	−0.350	−0.284	−0.352	−0.350
C(4)	0.559	0.531	0.537	0.561
O(5)	−0.667	−0.573	−0.655	−0.665
C(6)	−0.139	−0.153	−0.089	−0.138
C(7)	0.365	0.328	0.335	0.364
F(8)	−0.447	−0.479	−0.449	−0.447
C(9)	0.410	0.331	0.373	0.413
C(10)	0.283	−0.245	−0.208	0.283
C(11)	0.515	0.521	0.495	0.517
C(12)	−0.178	−0.220	−0.202	−0.175
C(13)	0.856	0.810	0.853	0.849
O(14)	−0.756	−0.687	−0.673	−0.756
O(15)	−0.579	−0.785	−0.624	−0.577
C(16)	−0.074	−0.071	−0.043	−0.075
C(17)	−0.453	−0.450	−0.411	−0.451
N(18)	−0.872	−0.838	−0.840	−0.874
C(19)	−0.011	−0.078	−0.045	−0.025
C(20)	−0.105	−0.145	−0.060	−0.088
N(21)	−0.766	−0.843	−0.664	−0.679
C(22)	−0.097	−0.146	−0.074	−0.078
C(23)	−0.082	−0.117	−0.073	−0.093
C(24)	–	–	−0.211	−0.229
…	...	...	...	...
F39	−0.458	–	–	−0.458
…		...	...	...

between optical (spectral) characteristics and structure of nonfluorinated, monofluorinated (C6 position) and difluorinated (C6, 8 positions) quinolones (Scheme 1) is important for both their practical applications as well as from a fundamental point of view.

All of the fluoroquinolones under investigation (nlqH, piqH, nfqH, pfqH, dfqH and mdfqH) have uniform UV absorbance spectra as illustrated in Fig. 1. The UV-vis spectra of the studied FQs have characteristic absorption bands. The first one is in the region 200–230 nm. The second maximum is observed between 240 and 300 nm, which is due to π→π* electronic transition of the delocalize electrons in the aromatic ring; the longest wavelength maximum (between 300 and 380 nm) is due to an n→π* electronic transition [27, 28]. According to [28] two subpeaks of the n→π* electronic transition are caused by an equilibrium of the FQs molecules forming an intermolecular hydrogen bond with the solvent and FQs forming an intramolecular hydrogen bond of the 4-keto and the 3-carboxylic acid group. Displaying of these subpeaks depends both on the molecular structure of the compound and pH of solution.

However, as seen by examining the spectra in Fig. 1, by introducing a methyl substituent in the piperazinyl ring (pfqH) and/or an additional fluorine atom at the position C8 (dfqH, mdfqH) the band of the π→π* electronic transition undergoes red shift (Figs. 1 and 2). The maxima of the π-π* transitions are sensitive to the number of fluorine atoms in the molecule, since the F atoms serve as electron-withdrawing substituents of the conjugated π-systems. Consequently, a gradual red-shift of the π-π* transitions is observed with increasing amount of fluorine substitutions in the quinolone nucleus. On the contrary, the two subpeaks of the band of n-π* transition in the 320 nm region, caused by the conjugated system of carbonyl and carboxylic

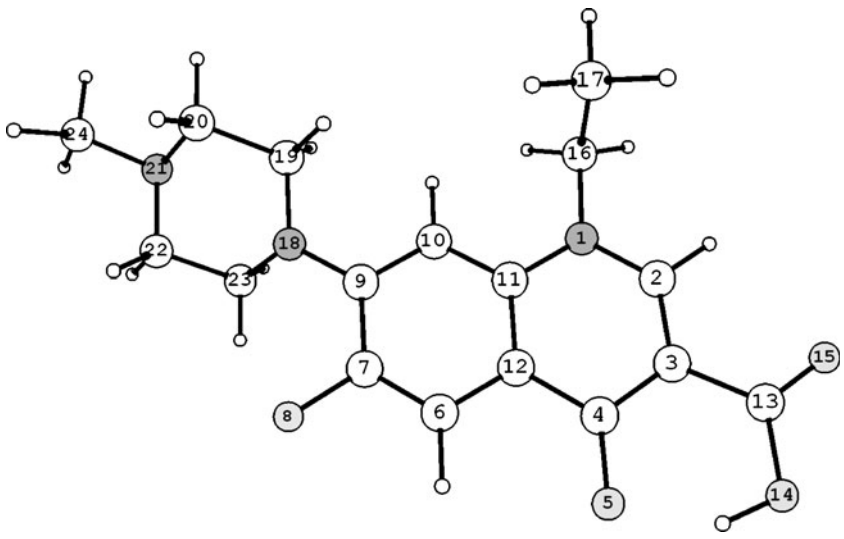


Fig. 3 Structure of the pefloxacin [32]

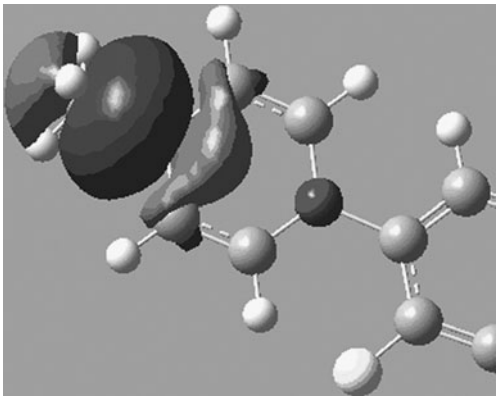


Fig. 4 σ-bonding MO shapes providing the N-CH_3 covalent bond

groups, are less sensitive to the introduction of additional fluorine atoms. Consequently, the above mentioned substituents change the position of the $^1(\pi\pi^*)$-levels of organic molecules.

Fluorescence spectra of the compounds are independent of the excitation wavelength, and the excitation spectra agree reasonably well with their absorption spectra (see Fig. 2). Therefore, similar influence of the substituents on the fluorescence and excitation spectra of the compounds is seen as in the case of absorption.

The absorption and fluorescence characteristics found for the quinolones in the present study are described in Table 1. The table also includes the median toxic dose (TD_{50}) of a drug needed for inducing phototoxical effects in 50% of the mice population [29]. As seen from Table 1, the longer the excited state lifetime of fluoroquinolones is, the higher is the probability of their photodegradation and possible formation of toxic photoproducts.

Since the rate constant $k_{nf} \geq 10^9\ s^{-1}$ for nlqH, it can be assumed that an effective intercombinational transition from the singlet exited level to the triplet exited level takes place in the molecule. Indeed, according to [19] the lifetime of triplet exited state τ_T of nlqH is two orders of magnitude

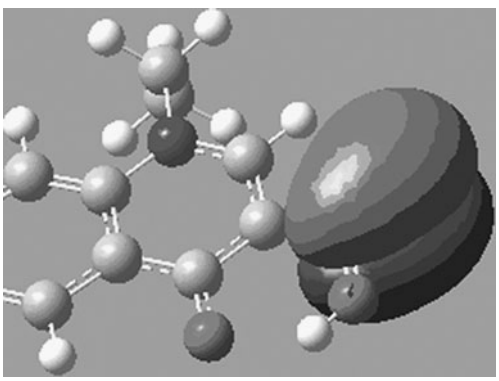


Fig. 5 π-bonding MO shapes providing the C-O covalent bond

larger than that of nfqH. Violation of the exclusion of interconversion occurs as a consequence of the n-π* transitions having a strong spin-orbital disturbance. The magnitude of the spin-orbit interaction is inversely proportional to the difference of the energies of the exited singlet and triplet levels of the molecule [30, 31].

In addition to the changes induced by structural characteristics, the absorption and emission properties of FQs are strongly affected by pH. In the representative examples, three main maxima are observed, which are all shifted at different pH values. Especially the long wavelength absorption band is sensitive to pH changes. The changes can be attributed to the extent of ionization of the carboxylic group [22]. Upon increasing the pH value of the solution a bathochromic shift of the absorption maximum is observed; opposite shift happens in acid medium (spectra are not shown).

Quantum-Chemical Calculations

Quantum-chemical calculations have been made with the consideration of X-ray data (interatomic distances and valence angles) [22, 32]. The Mulliken charges magnitudes of the mono- and difluoroquinolones are presented in Table 2. Substitution of the hydrogen atom by the fluorine one at the C8 position results in the changing of the Mulliken charges on the atoms conjugated with fluorine atom (C6, C7, C10, C12). The analysis has been conducted for the compounds pair dfqH and mdfqH, where the hydrogen atom at position N21 was substituted by the electron-donating CH_3- group, as well as for pair pfqH and mdfqH, where the hydrogen atom at position C24 in Fig. 3 (C8 in Fig. 1) was substituted by the fluorine atom [33]. Calculations of the dipole moments pfqH (12.27) and nfqH (11.67) give evidence of increasing of the polarization degree of the pfqH due to presence of electron-donating CH_3 group. Moreover, the calculations revealed that with pfqH and mdfqH the charges on the oxygen atoms of the carbonyl and carboxyl groups change.

Quantum-chemical calculations of the mono- and difluoroquinolones demonstrate that in all compounds the LUMO orbital (lowest unoccupied molecular orbital) is a π-orbital with C-N antibonding character. The character of the HOMO orbital (highest occupied molecular orbital) is also similar for all compounds mentioned above. It is formed by the electron density of the carbon atom accompanied by a small negative π-contribution from the surrounding atoms. Relative location and composition of the valence MOs of the compounds in neutral form (pfqH, dfqH, mdfqH) are very similar.

Both in pfqH and mdfqH there is a σ-bonding MO at a depth of −0.9 a.u. from the HOMO level that provides

Table 3 Molecular orbital energies obtained by DFT/B3LYP/TZVP calculations. The energies are given in eV

	nfqH	pfqH	dfqH	mdfqH
LUMO+1	−1.45	−1.46	−1.64	−1.66
LUMO	−1.97	−1.97	−2.07	−2.08
HOMO	−6.27	−6.28	−6.27	−6.27
HOMO-1	−6.52	−6.52	−6.59	−6.51
HOMO-2	−6.88	−6.57	−6.82	−6.60
HOMO-3	−7.05	−7.05	−7.16	−7.17
HOMO-4	−7.32	−7.33	−7.46	−7.47

covalent bonding of N atom with the CH_3 group (Fig. 4). In nfqH and dfqH, which do not have an electron-donating CH_3 group in the piperazinyl ring one can see a MO possessing N-H bonding character instead of a σ(N-CH_3) one.

Like many biologically active molecules which could be fully or partially ionized at a physiological pH, the antibacterial activity of quinolones is pH-dependent. [22, 33]. For instance, penetration of the ofloxacin molecule through bacterial membrane depends on the protonation degree of the molecule and the intramolecular charge redistribution (zwitterionic form) [33]. According to our calculations, the electronic structure of $nfqH^{\pm}$ and $pfqH^{\pm}$ zwitterions (see Table 2, numbers for these compounds are similar and given only for $nfqH^{\pm}$) undergoes considerable changes in comparison with neutral forms (with the exception of LUMO and HOMO). It is characterized by its close location to the HOMO, which is formed by the lone pair of the carbonyl oxygen. It leads to the lowering of the energy of the antibonding orbitals.

As shown in Fig. 5, two MOs are responsible for the covalent bonding of the carbon atom C9 to the oxygen atoms in neutral molecules, whereas in the zwitterionic forms a MO appears which has a lone pair character at O (11) rather than one σ^+ MO. This results in the weakening of the C-O(11) bond in $nfqH^{\pm}$ and $pfqH^{\pm}$. However, in these cases the mobility of the zwitterion should increase.

Consequently, the lack of two bonding MOs [σ(C-N) and π(C-O)] in the zwitterionic form decreases their stability and increases the chemical activity. These results are in line with the data [22, 33] that zwitterions of fluoroquinolones are passing more easily through the bacterial membrane, and thus possess higher antibacterial activity.

In addition to their antibacterial activity, fluoroquinolones are known to undergo a variety of photochemical processes which are associated with their phototoxicity. Photolysis leading to breakdown of piperazine ring and defluorination have been identified as contributing significantly to the side effects of fluoroquinolones [34–36]. These processes are evidenced by our TDDFT calculations and by the analysis of the LUMO orbitals involved in the calculated excitations. The calculated excitation energies correspond reasonably well with the experimental absorption spectra having for all fluoroquinolones two transitions with high oscillator strengths in the intervals 320–340 nm and 270–290 nm. Moreover, the red shift of the absorption peaks which is observed experimentally when comparing mono- and difluorinated quinolones is also reproduced by the calculations. As such pefloxacin exhibits two peaks at 326 and 273 nm as compared to mdfqH for which the first peak is at 336 nm and the second one is formed by three excitations at 290, 283 and 279. Similarly the norfloxacin has two peaks at 326 and 271 nm while dfqH has the first

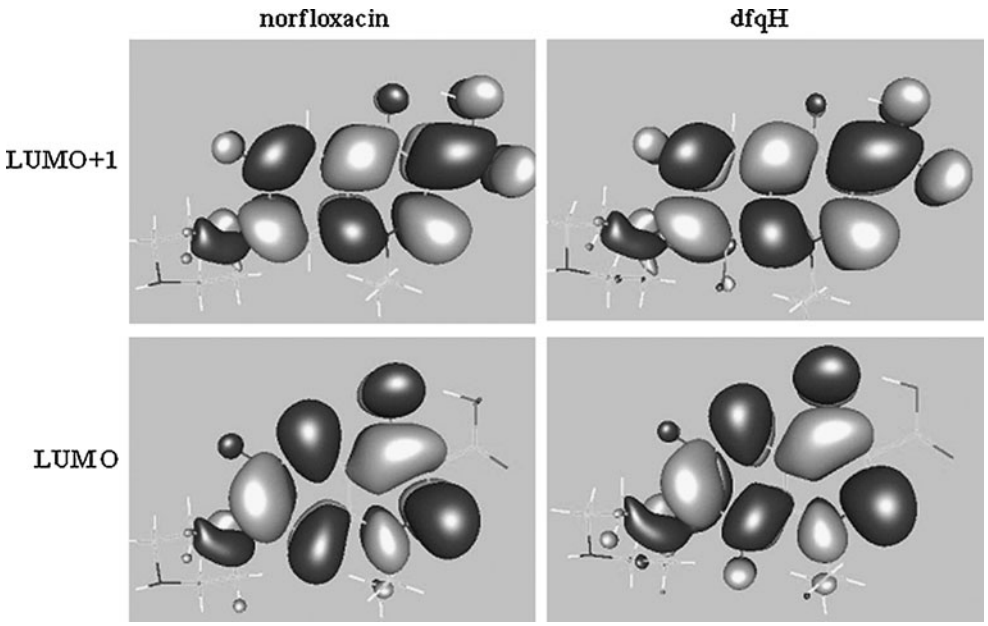


Fig. 6 Isosurfaces of LUMO and LUMO+1 of norfloxacin and dfqH plotted by using the same isosurface value

peak at 337 nm and the second one formed by three transitions at 288, 281 and 273 nm.

Analysis of the molecular orbitals of the electronic transitions contributing to the absorption of the fluoroquinolones above 250 nm reveals that for all studied fluoroquinolones LUMO and LUMO+1 orbitals are the only unoccupied orbitals involved. On the other hand the contribution of the occupied orbitals goes down to HOMO-4. The energies of the molecular orbitals involved in the calculated transitions are given in Table 3.

In order to get some insight into the possible photochemical processes of the fluoroquinolones in excited states we have plotted the isosurfaces of the unoccupied orbitals involved in the transitions. The same isosurface value was used for all plots. Isosurfaces of the LUMO and LUMO+1 orbitals for the mono- and di-fluorinated quinolones are exemplified for the case of norfloxacin and dfqH in Fig. 6. Only small differences have been observed when comparing the isosurface plots of the LUMO and LUMO+1 orbitals of pefloxacin and norfloxacin or dfqH and mdfqH.

As can be seen from Fig. 6 both mono- and di-fluorinated quinolones exhibit significant amplitudes of the LUMO on the 8-fluoro substituent and on the N-C bond of the piperazine ring. This is an indication that both defluorination and piperazine photolysis are mechanisms which can take place in the excited states of these compounds. In addition, LUMO of dfqH exhibits high amplitudes also on the second fluorine atom. Thus, in the case of di-fluorinated quinolones one can expect both defluorination of one or two fluorines and also piperazine photolysis. As revealed by the investigations in reference [34] the environment can play a role in favoring either the loss of two fluorine substituents or defluorination followed by piperazine photolysis. Moreover, also for mono-fluorinated quinolones experimental observations have shown that their photochemistry is pH and medium dependent [19, 20].

The introduction of the electron-withdrawing substituent at the position C8 in mdfqH and dfqH molecules decreases the HOMO-LUMO gap as compared to their corresponding mono-fluorinated quinolones (see Table 3). Thus, one may expect that low-located electronic states in di-fluorinated quinolones can be more effectively populated by the photoexcitation by lower energy light. The order of the decrease of energy of the excited π-π^* levels nlqH > nfqH > pfqH > mdfqH > dfqH is identical with the order of the photoreactivity of the drugs nlqH < nfqH < pfqH < dfqH.

Conclusions

Comparative analysis of the photophysical properties of the non-, mono- and difluoroquinolones has been made. It was shown that pfqH has the highest quantum yield of luminescence and the highest polarization degree among the investigated compounds. Absence of two bonding MO (σ(C+N) and π(C+O)) in the compounds in zwitterionic form decreases their stability and improves chemical activity. Analysis of the Mulliken charges of the difluoroquinolones points to the changes of the electron density redistribution both along π-conjugated system and on the oxygen atoms of the carbonyl and carboxyl groups. The analysis of the molecular orbitals involved in the electronic transitions of the compounds revealed that both defluorination and piperazine photolysis are photodecomposition mechanisms which may take place in the excited states of these compounds. The relationship between the location order of the π-π^* excited levels of the FQs and the degree of their phototoxicity has been determined.

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