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The unexpected photochemistry of marbofloxacin

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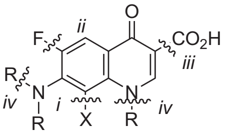
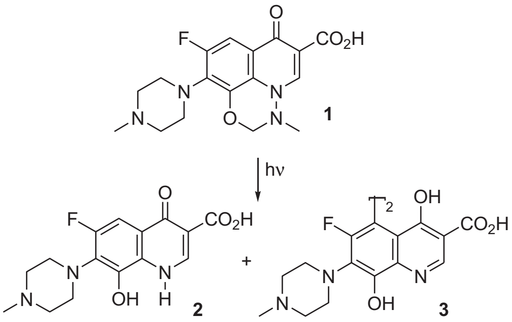
ABSTRACT

The veterinary antimicrobial Marbofloxacin undergoes none of the general photoreactions of fluoroquinolones. Irradiation rather leads to homolytic cleavage of the N–N bond and loss of a fragment to give a phenoxy radical. The final products result from the dimerization, the reduction, or the disproportionation of the radical.

The photochemistry of fluoroquinolones (FQs, the most common ones are 7-dialkylamino-6-fluoroquinol-4-one-3-carboxylic acids, see the formula below), a family of antibacterials largely used both for humans and for cattle is obtaining an increasing attention.[1] photochemical reactions of these drugs cause toxic effects on the skin and eyes, leading to mutagenesis and carcinogenesis in some cases.[2] Further, the high chemical stability of these compounds makes them persistent pollutants and solar irradiation may be one of the few effective paths for the decontamination of the surface water and soil.[3] Finally, studies on such compounds have revealed various—and in part novel—reactions in the photochemistry of heteroaromatics. Fifteen years of work have demonstrated that the reaction occurs via the triplet state and its course depends on the substituent X in position 8.[4] Thus, when X = F, Cl photoheterolytic cleavage takes place selectively from that position (an efficient S_N1 process, path i, Φ ca. 0.5);[5] when X = H the 6-fluoro is substituted (a S_N2 Ar process, path ii, Φ ca. 0.1);[5] when X = OR, SR the molecules are much less photolabile and only inefficient processes remain, viz. decarboxylation, path iii,[6] and degradation of the alkylamino side-chain (or of the N_1 side-chain, path iv, $\Phi \leqslant 0.01$).[5,7]

During our continuing study of the photochemistry of these drugs, we came across the case of marbofloxacin (**1**, see Scheme 1) recently emerging among the 'third generation' FQs and now being largely used in veterinary medicine. The oxygen substituent in 8 classed this compound in the third one of the above groups and a low reactivity was expected. The study reported below showed instead, that **1** was quite photoreactive, while following a wholly different mode of the reaction.[8]





Scheme 1.

Indeed, this compound was consumed in water with a quantum yield of 0.043, 40 times as much as ofloxacin (X = OMe, Φ 0.0012). The irradiation caused the formation of a precipitate that was filtered off and analyzed. It showed a molecular weight corresponding to twice as much as that of the starting material less that of the fragment C_2H_4N. The NMR spectrum was very simple, with a single aromatic C–H signal. A polar compound with molecular weight equal to the starting material less C_2H_2N remained in solution. Evaporation of the solution and treatment with diazomethane gave two compounds that were separated and analyzed, allowing the assignment of formulae **5** and **6** (methylated at the 8-OH and at the 1-NH respectively, see Supplementary data) to these derivatives and **2** to the photoproduct. Likewise, the structure of 5-biquinolinol **3** was assigned to the less soluble photoproduct, as supported by the functionalization with ethyl chloroformate/diazomethane to give product **8** (see Supplementary). The irradiated solution was further characterized by an intense blue color that was unaffected for several days independently on the presence of oxygen. The color disappeared in contact with silica gel, however, and we were unable to obtain a complete characterization. The visible spectrum (λ_{max} 650 nm, see Supplementary) can

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not be reconciled with any of the above photoproducts. However, calculations showed that this qualitatively corresponded to that calculated for quinolindione **4** (in vacuum, λ_{max} 720 nm, see Supplementary).

A further peculiarity that distinguished the photochemistry of **1** was the fact that it occurred at a comparable rate also in organic solvents (see Table 1), while most FQs react only sluggishly except in aqueous solution.

Preparative work thus demonstrated that the photoproducts from **1** resulted from the cleavage of the dihydroxadiazine moiety exclusively. As for the mechanism, examination of the luminescence characteristics showed that compound **1** exhibited both fluorescence (λ_{max} 405 nm) and phosphorescence, (λ_{max} 520 nm in a glassy matrix, onset 450 nm, triplet energy 63.5 kcal/mol) quite similar to those of other FQs, and particularly to those bearing an alkoxy group in **8**. This is consistent with the photochemical reaction proceeding, as with most of the other FQs, exclusively from the triplet state, otherwise a reduction in the phosphorescence intensity would be expected. The decrease of Φ in air equilibrated solution, 0.026 rather than 0.043, was equally consistent with this mechanism.

As for the chemistry occurring, compounds **2** and **3** are those expected from the reduction and respectively the dimerization of phenoxyl radical **9** or tautomeric **9**′, see Scheme 2. Compound **4** may result from the disproportionation of **9** along with **2** (see further below).

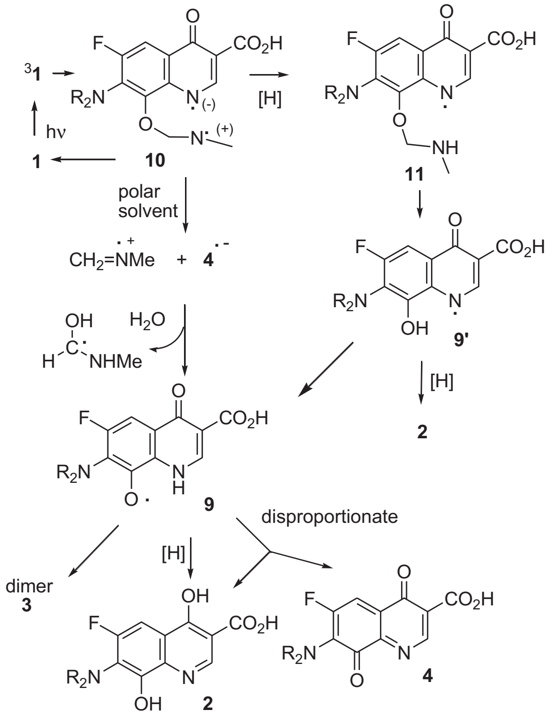
An economic rationalization can be offered that accounts for the observed medium dependence of efficiency and product distribution (see Table 1). This assumes that the primary process is cleavage of the N–N bond in triplet ^{3}**1** to give biradical **10** and that this step is reversible, so that the process is efficient only when a subsequent reaction takes place before recombination (see Scheme 2). This occurs under either of the two conditions, viz. (i) stabilization of the polar biradical by solvents of high dielectric constant such as water or, to a lesser degree, less polar trifluoroethanol, or (ii) trapping by the solvent via hydrogen transfer.

In water intermediate **10** reasonably has some zwitterionic character. Fragmentation to give the radical anion $4^{\cdot -}$ and proton transfer lead to radical **9** (releasing the emiacetal radical that then evolves to *N*-methylformamide).[9] Radical **9** dimerizes to **3** or disproportionates to **2**+**4**. The dione is a significant product, as indicated by the deep blue color of the solution.

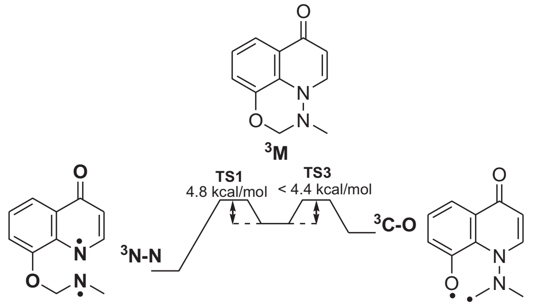
In hydrogen-donating solvents, on the other hand, **4** is not formed and the radical is mainly reduced to **2**. This becomes the main product, whereas in the previous case the ratio **2**/**3** was ca. 1. Noteworthy, the reaction is more efficient in solvents containing electrophilic C–H bonds such as chloroform, DMSO or even acetone than in those containing nucleophilic hydrogens, such as alcohols and ethers. This is what was expected for a reaction of an aminyl $R_2N^{\cdot}$ radical[10] and thus consistent with a preferential reaction of biradical **10** at the aggressive aminyl site rather than to the quinolone site. This leads to the stabilized radical **11** and, upon hydrolytic loss of the side-chain, to radicals **9**, **9**′. B3LYP calculations suggest that the first form is the most stable (by 15 kcal/mol, Scheme 3) and is characterized by a high spin density at position 5 facilitating dimerization, an example of the well known naphthalenoxy radical dimerization.[11]

Table 1
Photochemical reaction of marbofloxacin **1** in various solvents

Solvent	Relative reaction rate	Ratio **2**/**3**	Color
Water	1	1.7	Deep blue
$CHCl_3$	0.4	10	Colorless
DMSO	0.25	4	Colorless
Me_2CO	0.16	4.5	Colorless
CF_2CH_2OH	0.13	0.8	Blue
iso-PrOH	0.1	4	Colorless
MeOH	0.08	1	Light blue
THF	0.06	5	Colorless



Scheme 2.



Scheme 3.

This finding supports that the robust structure of quinolones inevitably ‘shutters’ any compound of this class to the ππ* triplet. At this point different processes not altering the aromaticity (or doing it transiently) occur. Previous work had evidenced under conditions that the heterolysis of a strong, polar bond such as C-F occurs via a S_N1 or a S_N2 process.[4] Consistent with the above generalization, neither of these processes occurs with marbofloxacin, whereas, however a different efficient reaction has been revealed, homolysis of the N–N bond.

Being different from the above ionic reactions that are efficient only from the zwitterionic state in water, the present reaction has a larger scope, although with limitations that are rationalized by taking into account the nature of the radicals involved. More generally, these findings suggest that one may attach a fragmentable moiety, as here the N–N bond, to a stabilized excited state, such as a six-membered heteroaromatics, and obtain that fragmentation smoothly with no competing degradation. The photochemistry of heteroaromatics may be more diverse than commonly thought and probably deserve more attention. The advancement in the understanding of these reactions may be the basis for preparing tailored molecules, for instance for photoremovable protecting groups, drug photorelease, and polymerization initiators.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.137.

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