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A Fluorine 1,2-Migration via Aryl Cation/Radical/Radical Anion/Radical Sequence

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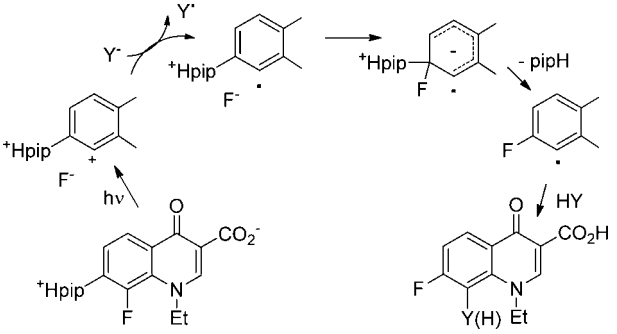
ABSTRACT



Irradiation of a 7-piperazino-8-fluoroquinolone causes formal 1,2-fluorine migration, piperazine loss and reduction, or nucleophile addition in 8. Product study, laser flash photolysis, and computational modeling support F^- detachment to yield a triplet 8-quinolyl cation that either inserts intramolecularly or is trapped by Cl^-, Br^-. However, iodide and pyrrole reduce it to the radical that continues the 'redox tour' (aryl cation→ radical→ radical anion→ radical and then again radical or radical anion) leading to the rearranged products.

The migration of iodine and bromine,[1a−k] as well as, to a limited extent, of chlorine,[1l−o] is frequently observed with aromatic and heterocyclic compounds in various reactions, from electrophilic substitution to the rearrangement of metalated derivatives. Fluorine migration is much less common, reasonably due to the strength of the carbon−fluorine bond (> 110 kcal/mol). The reported cases occur in high-energy intermediates such as carbocations (a process analoguous to the Wagner−Meerwein hydrogen migration),[2a−c] carbenes,[2d,e] and radicals,[2f−h] mostly in the gas phase, or as a secondary reaction after photocleavage.[2i−k] Reactions occurring under conditions closer to preparative application include intramolecular abstraction from a CF_3 group by phenyl cations formed from diazonium salts (via a three-centered transition state)[2a] and the rearrangement that accompanies the fluorination

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(1) For reviews, see (a)−(c): (a) Schnürch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046–1057. (b) Schnürch, M. *Top. Heterocycl. Chem.* **2012**, *27*, 185–218. (c) de Souza, N.; Vinicius, M. *Curr. Org. Chem.* **2007**, *11*, 637–646. (d) Mayers, B. T.; Fry, A. J. *Org. Lett.* **2006**, *8*, 411–414. (e) Schuisky, P.; Federsel, H. J.; Tian, W. *J. Org. Chem.* **2012**, *77*, 5503–5514. (f) Machara, A.; Pojarova, M.; Svoboda, J. *Collect. Czech. Chem. Commun.* **2007**, *72*, 952–964. (g) Wu, X.; Dube, M. A.; Fry, A. J. *Tetrahedron Lett.* **2006**, *47*, 7667–7669. (h) Proust, N.; Chellat, M. F.; Stambuli, J. P. *Synthesis* **2011**, 3083–3088. (i) Holzweber, M.; Schnürch, M.; Stanetty, P. *Synlett* **2007**, 3016–3018. (j) Cheng, D.; Croft, L.; Abdi, M.; Lightfoot, A.; Gallagher, T. *Org. Lett.* **2007**, *9*, 5175–8. (k) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373–376. (l) Ioffe, I. N.; Mazaleva, O. N.; Chen, C.; Yang, S.; Kemnitz, E.; Troyanov, S. I. *Dalton Trans.* **2011**, *40*, 11005–11011. (m) Mach, M. H.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 4660–4666. (n) de Bie, D. A.; van der Plas, H. C. *Tetrahedron Lett.* **1968**, *36*, 3905–3908. (o) Traynham, J. G. *Tetrahedron Lett.* **1976**, *26*, 2213–16.

(2) (a) Ferraris, D.; Cox, C.; Anand, R.; Lectka, T. *J. Am. Chem. Soc.* **1997**, *119*, 4319–4320. (b) Shaler, T. A.; Morton, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9222–9226. (c) Nguyen, V.; Mayer, P. S.; Morton, T. H. *J. Org. Chem.* **2000**, *65*, 8032–8040. (d) Holmes, B. E.; Rakestraw, D. J. A. *J. Phys. Chem.* **1992**, *96*, 2210–2216. (e) So, S. P. *J. Phys. Chem.* **1993**, *97*, 11908–11911. (f) Kotaka, M.; Sato, S. *Chem. Commun.* **1986**, 1783. (g) Bell, A. N.; Fields, R.; Haszeldine, R. N.; Kamudaki *J. Chem. Commun.* **1975**, 866. (h) Yoon, Y. W.; Lee, S. W.; Lee, S. K. *Bull. Korean Chem. Soc.* **2010**, *31*, 2783–2785. (i) Yokoyama, A.; Yokoyama, K.; Takayanagi, T. *J. Phys. Chem. A* **1997**, *101*, 6647–6652. (j) Camaggi, G.; Gozzo, F. *J. Chem. Soc. C* **1971**, 925. (k) Kira, M.; Tokura, S. *Chem. Lett.* **1994**, 1459–1462. (l) Gakh, A. A.; Tuinman, A. A.; Adcock, J. L.; Sachleben, R. A.; Compton, R. N. *J. Am. Chem. Soc.* **1994**, *116*, 819–820. (m) Gakh, A. A.; Tuinman, A. A. *Tetrahedron Lett.* **2001**, *42*, 7137–7139.

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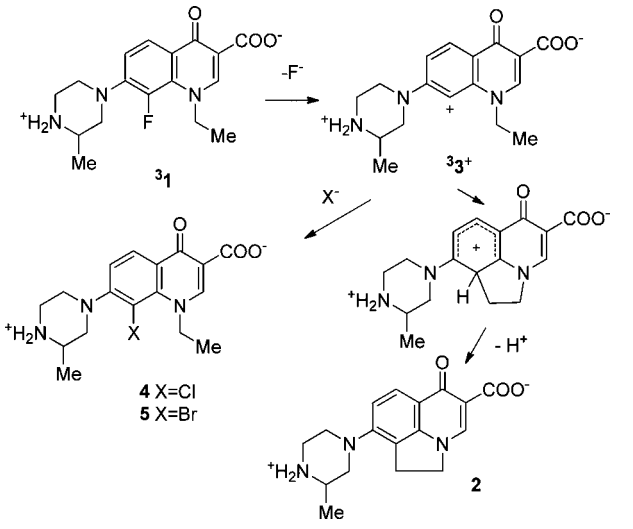
Scheme 1



of C_{60} by elemental fluorine and leads to only two over more than 10^7 potential $C_{60}F_{48}$ isomers at 240 °C.[2l,m]

We were thus surprised by the serendipitous finding of a formal 1,2 migration of a fluorine with formal substitution of an amino substituent upon irradiation in solution at rt. This puzzling result and the widespread interest for (hetero)aromatic fluorides, largely used as drugs,[3] prompted a mechanistic investigation based on an experimental and computational study.

The finding originated from the systematic study we are carrying out,[4] along with other laboratories,[5] on the photochemistry of fluoroquinolones (fluorinated-7-amino-4-quinolone-3-carboxylic acids, FQs), largely used antibacterials exhibiting varied photochemistry. The present investigation involved compound **1** (see Scheme 1), bearing a single fluorine in position 8, differently from previously considered FQs that were either 6-monofluoro or 6,8-difluoro derivatives.[4b–d] This compound was prepared through a variation of a known synthesis of FQs.[6] The irradiation of **1** in water cleanly gave the pyrroloquinolone **2** (see Scheme 1 and Table 1).

This is rationalized as involving heterolysis of the C–F bond from triplet ^{3}**1** that yields aryl cation ^{3}**3**$^+$, likewise in the triplet state. It has been previously demonstrated that quinolyl cations, just as simpler models such as phenyl cations, have radical (one electron in the planar σ orbital)/radical cation (the other unpaired electron delocalized on the π system) character in the triplet state.[4b] This explains the cation insertion into the accessible C–H bond of the *N*-ethyl side chain rather than undergoing solvolysis. Positive evidence for this intermediate was obtained from nanosecond laser flash photolysis. The end-of-pulse absorption spectrum showed a peak at 350 nm (15 ns lifetime, assigned to triplet ^{3}**1**) that evolved into a peak at 470 nm (400 ns lifetime; see Figure 1), assigned to triplet cation ^{3}**3**$^+$, similar in shape and lifetime to the corresponding cation from 6,8-difluoroquinolone **1′** (the drug lomefloxacin), which selectively cleaves the fluorine in position 8.[4b,d]

Table 1. Products Formed by Preparative Photolysis of Compound **1** in Aqueous Solution (see Schemes *1*, *2*)

		products formed, %						
additive (0.1 M)	converted **1**, %	**2**	**6**	**4**	**5**	**7**	**8**	**9**
none	96	66	13					
$NaHSO_3$	62		68					
KCl	90	29	42	20				
NaBr	82	8	14		78			
KI	81	10	9			52	7	18
pyrrole	53	24	16					58

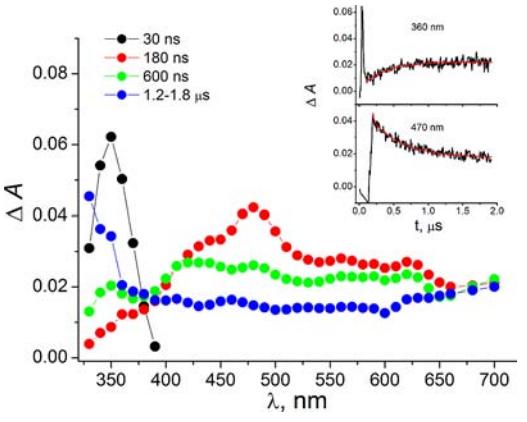
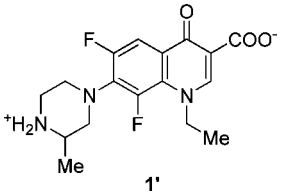


Figure 1. Transient absorption spectra upon excitation at 355 nm of a 1.4×10^{-4} M aqueous solution of compound **1** of pH 6.9 at 25 °C at various delays from pulse end. Inset: absorption time profiles at 360 and 470 nm.



(3) (a) Gakh, A. A.; Kirk, K. L. *Fluorinated Heterocycles*; American Chemical Society: Washington, DC, 2009. (b) Gakh, A. A; Burnett, M. *J. Fluor. Chem.* **2011**, *1322*, 88–93.

(4) (a) Albini, A.; Monti, S. *Chem. Soc. Rev.* **2003**, *32*, 238–250. (b) Freccero, M.; Fasani, E.; Mella, M.; Manet, I.; Monti, S.; Albini, A. *Chem.—Eur. J.* **2008**, *14*, 653–663. (c) Fasani, E.; Monti, S.; Manet, I.; Tilocca, F.; Pretali, L.; Mella, M.; Albini, A. *Org. Lett.* **2009**, *11*, 1875–1878. (d) Monti, S.; Sortino, S.; Fasani, E.; Albini, A. *Chem.—Eur. J.* **2001**, *7*, 2185–2196. (e) Fasani, E.; Barberis Negra, F. F.; Mella, M.; Monti, S.; Albini, A. *J. Org. Chem.* **1999**, *64*, 5388–5395.

(5) (a) Lhiaubet-Vallet, V.; Cuquerella, M. C.; Castell, J. V.; Boscà, F.; Miranda, M. A. *J. Phys. Chem. B* **2007**, *111*, 7409–7414. (b) Cuquerella, M. C.; Miranda, M. A.; Boscà, F. *J. Phys. Chem. B* **2006**, *110*, 6441–6443. (c) Cuquerella, M. C.; Boscà, F.; Miranda, M. A.; Belvedere, A.; Catalfo, A.; de Guidi, G. *Chem. Res. Toxicol.* **2003**, *16*, 562–570. (d) Martinez, L. J.; Sik, R. H.; Chignell, C. F. *Photochem. Photobiol.* **1998**, *67*, 399–404. (e) Lorenzo, F.; Navaratnam, S.; Allen, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 12238–12241. (f) Musa, K. A.; Eriksson, L. A. *J. Phys. Chem. A* **2009**, *113*, 10803–10810.

(6) (a) Leyva, S.; Leyva, E. *Tetrahedron* **2007**, *63*, 2093–2097. (b) Domagala, J. M.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Nichols, J. B.; Solomon, M.; Worth, D. F. *J. Med. Chem.* **1988**, *31*, 991–1001.

The reaction was rather efficient, with a defluorination quantum yield Φ_{-F} of 0.26 (for **1′**, $\Phi_{-F} = 0.55$).[4b,d] DFT computations were carried out and showed that heterolysis of C_8−F in the case of **1** involved a sizable barrier (18.5 kcal/mol) in the gas phase, while with **1′** barriers of 8.3 and 24 kcal/mol for the reactive C_8−F and for the nonreactive C_6−F bond, respectively, were found.[4b,d] The effect of various nucleophiles on the photochemistry of **1** was next investigated. Differently from water, charged nucleophiles attacked the triplet aryl cation, reasonably because of the Coulombic interaction. Thus, in the presence of 0.1 M chloride and bromide the respective 8-halo derivatives were formed (compounds **4** and **5** in Scheme 1, the former in a poor yield; see below). In the presence of 0.1 M sulfite, neat reductive dehalogenation gave compound **6** (see Scheme 2, formed also by prolonged irradiation with Cl^-, through a secondary dechlorination of primarily formed compound **4**,[7] as well as a minor product in neat water; see Table 1).

In the presence of 0.1 M iodide a certain amount of compounds **2** and **6** was formed, but the main products obtained had a completely unexpected structure, **7**–**9**. These were positively identified by spectroscopic analysis and by single crystal structure determination (see Supporting Information (SI)).

As shown in Scheme 2, in every case the piperazino group had been eliminated and the fluorine atom had migrated into position 7. In the presence of pyrrole, no pyrrole-containing product was isolated, but a fluorine-rearranged compound (**9**) was the main product.

Kinetics analysis on the μs time scale showed that sulfite quenched cation $^3\mathbf{3}^+$ while an absorption at 360 nm with a tail in the visible grew in with a rate constant of 6.9×10^9 M^{-1} s^{-1}, compatible with electron transfer (ET; see Table 2 and Figures S1and S2). Analysis at 470 nm gave poor results, due to the overlapping of further species, reasonably including $\mathbf{1}^{\bullet-}$, previously found as a chemically unproductive path for **1′**.[4b,c,e] Iodide and pyrrole quenched similarly and generated the same 360 nm band (see Figure 2), which is thus confidently attributed to radical **3**$^\bullet$. A clean reaction occurred with I^- indicating that formation of aryl cation $^3\mathbf{3}^+$ was the only photochemical process and was followed by monoelectronic reduction to the radical. Examination at $\lambda \geq 580$ nm at longer times showed that in turn **3**$^\bullet$ decayed by first-order kinetics with a ca. 700 ns time constant (see Figure S3).

This evidence explained the clean formation of **6** with sulfite via further reduction of **3**$^\bullet$ to **3**$^-$ and protonation, but this was a minor process with I^- and pyrrole.

Reasoning backward from the structure of products **7**–**9**, the only viable precursor appeared to be radical **10**$^\bullet$. This would undergo nucleophilic addition of either iodide or fluoride yielding the corresponding radical anions and products **8** and **9**, respectively, from them (see Scheme 2) or alternatively undergo intramolecular hydrogen abstraction from the *N*-ethyl group leading to radical **11**$^\bullet$ and to product **7** from it. Apparently, pyrrole was a sufficiently good donor for causing the ET step, but not a sufficient nucleophile for the following reactions, so that only fluoride acted in this role and the 7,8-difluoro derivative **9** was the exclusive product through this path.[8a]

How radical **10**$^\bullet$ was produced remained to be clarified. A conceivable way, supported by the first-order decay kinetics of radical **3**$^\bullet$, was by addition of fluoride (reasonably remaining coupled to the ammonium group). This would yield radical anion **13**$^{\bullet-}$ and **10**$^\bullet$ by loss of neutral piperazine and protonation (Scheme 2). The viability of such a mechanism was tested by means of DFT calculations at the unrestricted B3LYP level of theory with Pople's basis set 6-31+G(d,p) (see SI). Some trouble was encountered because the fluoride anion tended to combine with a proton from the ammonium group,[8b] but the path available and the preferred alternative were reproduced.

The comparison with compound **1′** was useful since in the presence of iodide this gave a *N*-(*β*-iodoethyl)-quinolone resulting from intramolecular H-abstraction by intact radical **3′**$^\bullet$ (to give radical **14**$^\bullet$; see Scheme 3).[4b] All the steps from **1**, **1′** to the radicals **3**$^\bullet$ and **3′**$^\bullet$ could be detected and proven to be identical (in particular flash photolysis revealed the analogue of **3**$^\bullet$ from **1′** with I^-).

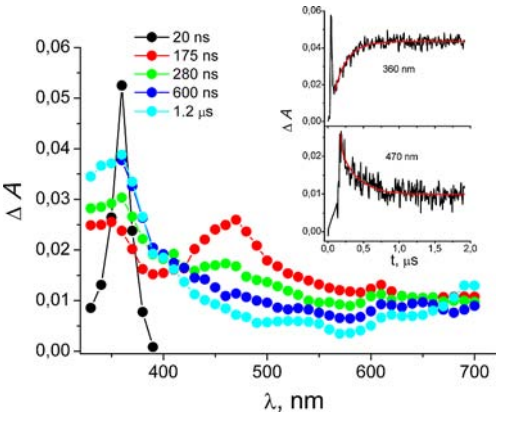


Figure 2. Transient absorption spectra upon excitation at 355 nm of a 1.4×10^{-4} M aqueous solution of **1** of pH 6.9 with 5 mM NaI at 25 °C at various delays from pulse end. Inset: kinetics at 360 and 470 nm.

Table 2. Rate Constants, k, 10^9 M^{-1} s^{-1}

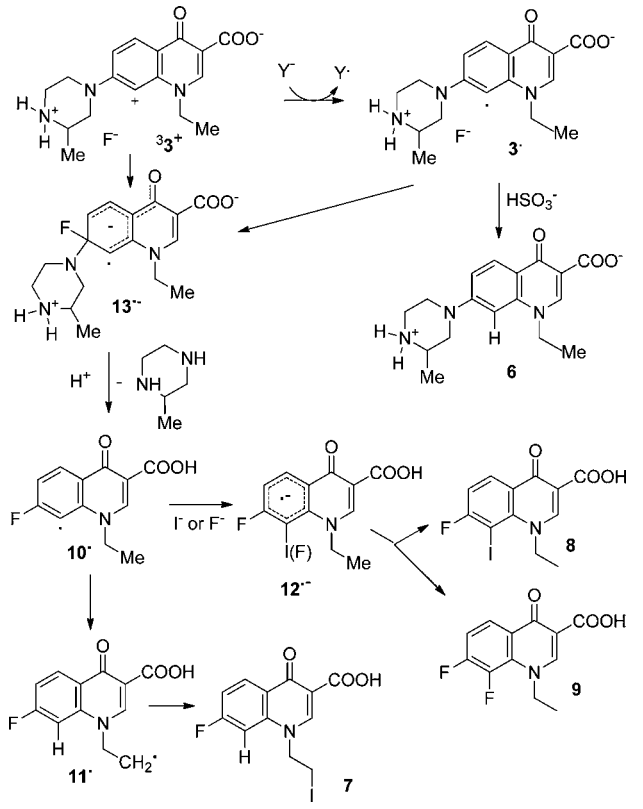
I^-	8.4 ± 0.2^a	8.6 ± 0.4^b
pyrrole	1.3 ± 0.1	–
HSO_3^-	1.8 ± 0.1^a	6.9 ± 0.4^b

[a] Monitoring the decay of cation $^3\mathbf{3}^+$ at 470 nm. [b] The grow-in of the absorption at 360 nm.

(7) At 30% conversion compound **4** was more abundant than compound **6**, but did not increase further.

(8) (a) Incorporation of pyrrole has been observed in the case of a related fuoroquinolone, fleroxacin; see ref 4c. (b) This supports that F^- remained close to the ammonium site and its addition to **3**· involved no kinetic barrier.

Scheme 2

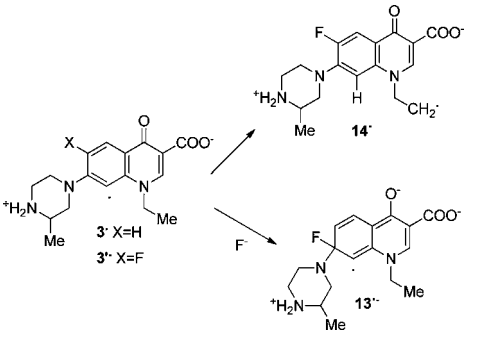


DFT analysis of the conformation of such radicals offered a clue. Thus, in the case of **3**$^{\bullet}$ two low-lying conformers were located, the absolute minimum **3a**$^{\bullet}$, with the piperazino group tilted out of plane (see Figure S4), and a roughly planar conformer **3b**$^{\bullet}$ only +2 kcal/mol above it. Fluoride insertion in **7** was possible only for conformer **3b**$^{\bullet}$, although only a rough estimate of $\Delta G(\mathbf{3}^{\bullet} \rightarrow \mathbf{13}^{\bullet-}) = +20 \pm 5$ kcal/mol was obtained due to the uncertainty of the calculated solvation energy of F^- (see Figure S5).

As for H-abstraction, this required first the rotation of the *N*-ethyl group, which in both stable conformers pointed away from C_8 (12 kcal/mol for **3b**$^{\bullet}$, a steeper rise for **3a**$^{\bullet}$). Thus, though we were unable to find a transition state for H-transfer, the sum of the two steps reasonably exceeded the energy for fluoride addition, in accord with experiments. The ensuing detachment of the piperazine molecule was markedly exergonic [$\Delta G(\mathbf{13}^{\bullet-} \rightarrow \mathbf{10}^{\bullet}) = -12$ kcal/mol].

In contrast, the 6-F made tilted conformer **3′a**$^{\bullet}$ the only minimum in the case of radical **3′**$^{\bullet}$ and H-abstraction the sole available path, despite the marked barrier to rotation mentioned above. Thus, a path leading to unusual products **7**–**9** and a conformation based justification for the different path followed by **1** and **1′** could be proposed.

Scheme 3



In summary, we have individuated a peculiar fluorine migration in the 8-fluoro quinolone **1** initiated by C–F heterolysis, a photochemical process also known with simple models, such as haloanilines, and favored with F or Cl, but not with bromides or iodides (where homolysis may rather occur).[9] The triplet aryl cation exhibits the reactivity of such species, including reduction to an aryl radical. Addition of fluoride, substitution of the amino group originally present, and reduction or introduction of a halide at the starting position follow. Such a formal fluorine migration under photochemical conditions in an aqueous environment may be of interest for applications.

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Supporting Information Available. Synthesis and characterization of compound **1**, photoreactions and product characterization, including NMR and X-ray data, computational data of the intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) (a) Guizzardi, B.; Mella, M.; Fagnoni, M.; Freccero, M.; Albini, A. *J. Org. Chem.* **2001**, *66*, 6353–63. (b) Freccero, M.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2003**, *125*, 13182–13190.

The authors declare no competing financial interest.