

FIRST ELECTROCHEMICAL DEFLUORINATION IN HETEROCYCLIC CHEMISTRY. MILD CATHODIC REDUCTION OF SOME FLUOROQUINOLONES

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Abstract - Some 7-piperazinoquinolones undergo smooth cathodic defluorination in aqueous buffer (pH 7.2) at -1.35 V vs Ag/AgCl *via* an ECE mechanism; a 6-fluoro derivative is reduced, a 6,8-difluoro analogue is selectively reduced at position 8.

There are very few examples of cathodic defluorination in aromatic chemistry^{1,2} and, to our knowledge, none in heterocyclic chemistry. Apparently, cleavage of the strong C-F bond is too slow and indeed in the electrochemical reduction of polysubstituted benzenes, other substituents are lost in preference to a fluoro atom (e. g. only the cyano group is eliminated in fluoro- and polyfluorobenzonitriles).^{3,4} Thus, reduction of the C-F bond is only possible under severe conditions, e.g. by using metals or hydrides, and this limits the application of such a method.

We have been involved in a study on the photoreactivity of fluoroquinolones, a largely prescribed class of antimicrobials, and observed that photolysis of these compounds in water caused loss of fluorine with formation of various substituted derivatives.^{5,6}

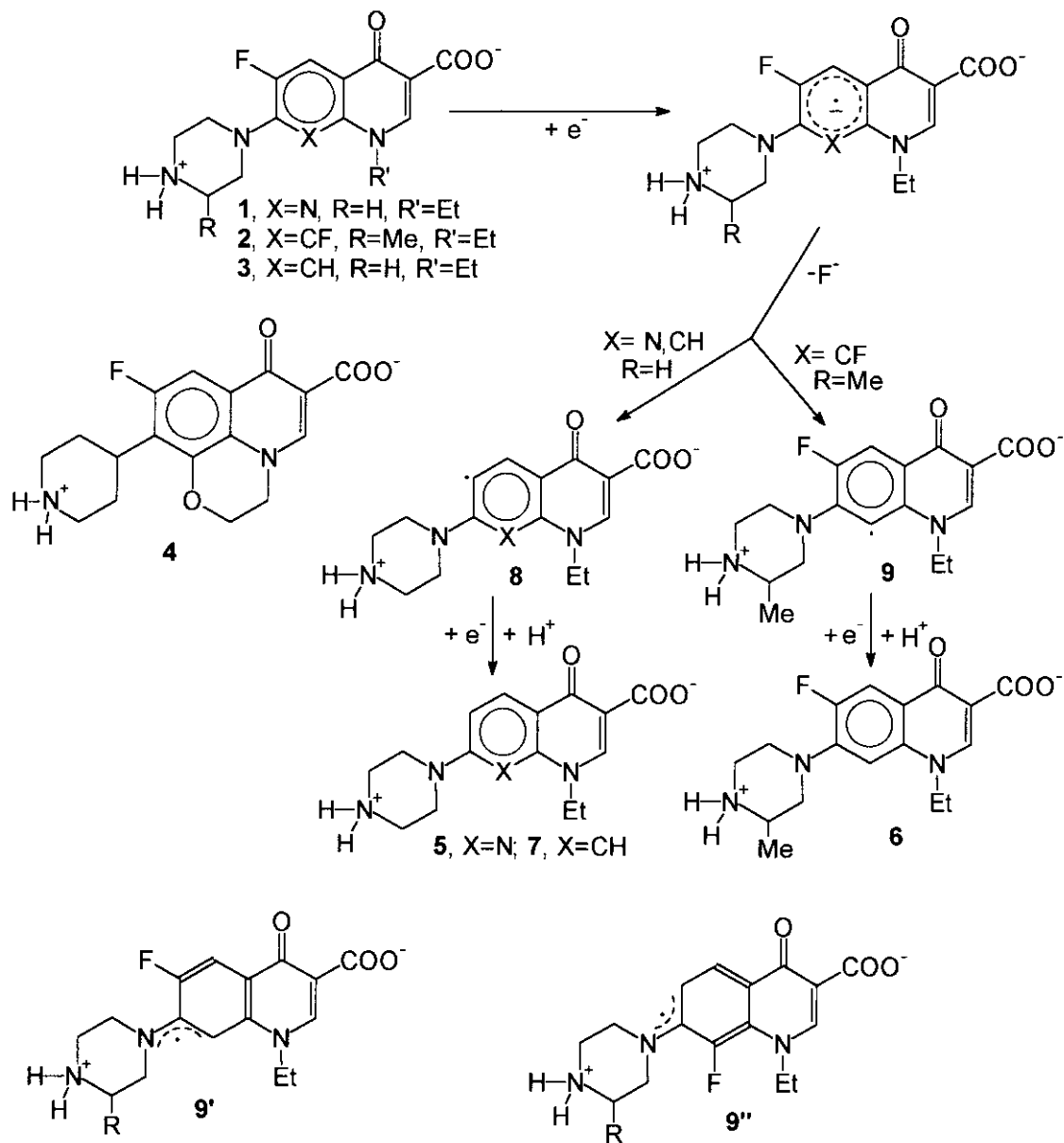
Recently, we observed that irradiation of some of these substrates in aqueous solution in the presence of 0.01 M sodium sulfite buffer at pH 7.0 led to mild defluorination. This led us to investigate the cathodic behavior of quinolones (1-4) (see Scheme 1). The electrochemical experiments detailed below were carried out in 0.1 M phosphate buffer at pH 7.2. The best results were obtained under the conditions, though a qualitatively similar behavior was observed in buffered solution with different electrolytes such as NaCl and KNO₃.

Voltammetric measurements at a Standing Drop Mercury Electrode (SDME) with enoxacin (1) showed a cathodic wave at -1.31 V vs Ag/AgCl (see Fig. 1). The reduction wave was well distinguished, though close to the electrolyte discharge, and the process was irreversible. In the case of lomefloxacin (2) a similar wave was observed at -1.34 V. With norfloxacin (3) only a shoulder was detected at *ca.* -1.38 V and with ofloxacin (4) the blank discharge profile was barely altered by the addition of the drug (see Figure 1, Table 1). The shift of the reduction peak towards a more negative potential in the series (1) to (4) fitted with the decreasing electronegativity of the atom or group in position 8 (N, C-F, C-H, C-O-Alkyl respectively).

For the sake of comparison, measurements were also carried out in a reduction-resistant solvent such as DMF (see Table 1).⁷ Under the conditions, the reduction wave was well discernible for all compounds and it was confirmed that 1 was reduced at a less negative potential than the other quinolones.

Electrolysis (cathode potential, -1.36 V vs Ag/AgCl)⁸ of compound (1) led to release of fluoride (potentiometrically determined by means of an ion selective electrode) and formation of a single product as determined by HPLC.⁹ This was identical with the compound obtained by photolysis of 1 in sulfite

buffer, and was shown to be the defluorinated quinolone (**5**). Substrate consumption and fluoride liberation were identical within the detection limits and the current passed amounted to 2 ± 0.2 F per mole, corresponding to a two-electrons reduction.



Scheme 1

Similar experiments with the cathode potential at -1.5 V or with sodium chloride in the place of phosphate as the supporting electrolyte led to the same results.

The 6,8-difluoro derivative lomefloxacin (**2**) was also electroreduced at -1.36 V (the result was the same at -1.5 V). Similarly to the case of **1**, one equivalent of fluoride was liberated and a single product, 6-monofluoro quinolone (**6**), was formed. The same compound was obtained from the photoreduction of **2**.

In the case of norfloxacin (**3**) electrolysis at -1.5 V also led to release of a fluoride ion. However, the reduced quinolone (**7**) was only a minor product under the conditions, while **7** was the main product obtained by photolysis in the presence of sulfite.

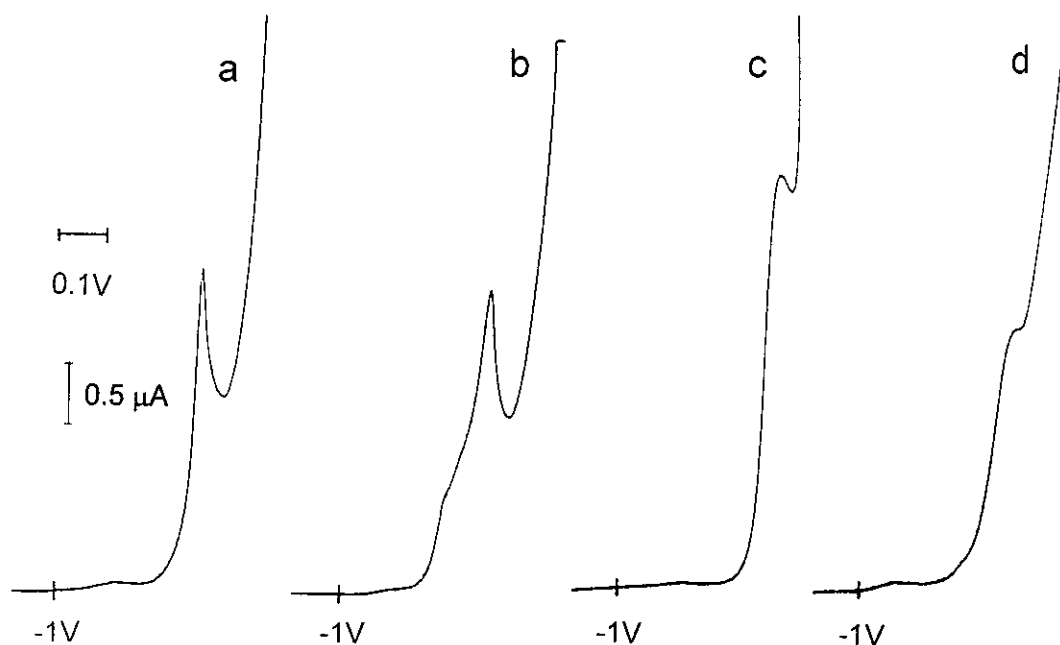


Figure 1. Differential pulse voltammetry (DPV) of fluoroquinolones (**1**) to (**4**) 1.5×10^{-5} M in 0.1 M phosphate buffer at pH 7.2 (three electrode cell, Standing Drop Mercury working electrode, Pt wire counter electrode, Ag/AgCl reference electrode, scan rate 20 mV s^{-1} , pulse height 50 mV).

Table 1. Electrolysis of fluoroquinolones in 0.1 M phosphate buffer at pH 7.2.

Compound	E_{red} , V vs Ag/AgCl		Product (cathode)	Product (hv, 0.01M sulfite buffer)
	H ₂ O	DMF		
1	-1.31	-2.24	5 , quantitative	5 , 80%
2	-1.34	-2.56	6 , quantitative	6 , 40%
3	ca. -1.39	-2.43	7 , ca. 10%	7 , 65%
4	ca. -1.4	-2.48		

Comparison of the electrochemical results with the voltammetric data shows that compounds (**1**) and (**2**), for which a reduction wave in water is well discernible, undergo clean reductive defluorination, while with compound (**3**), where the cathodic wave is close to the electrolyte discharge, the chemistry is less simple.

The clean cathodic reduction of compound (**1**) and (**2**) to **5** and **6** respectively is interesting from the mechanistic point of view. As mentioned in the introduction, cathodic defluorination of aromatic

compounds has little precedent, and when observed (in DMF) apparently involves a specific role of the electrode metal (aluminium or mercury in the two reported cases).^{1,2} Indeed, cleavage of the strong C-F bond of the radical anion intermediate is usually slow, as shown e.g. by the fact that the 2-fluoropyridine radical anion lives long enough that the ESR spectrum can be registered.¹⁰ In the present case, the fact that the cathodic wave is close to the attainable limit precludes a detailed electrochemical investigation. However, the fact that the same products are obtained both by cathodic reduction in water and photochemically gives an indication. In fact, in the latter case the radical anion of the substrate is necessarily formed by single electron transfer from sulfite to the excited state and double electron transfer is unlikely. This leaves no doubt that also in the electrochemistry an ECE (electron transfer-cleavage-electron transfer) mechanism (Scheme 1) operates and gives radicals (8) and (9) respectively.

We suggest that the presence of a vicinal amino group stabilizes the intermediate radical and this makes fluoride loss from the radical anion sufficiently fast. The similarity is noticeable in particular in the selective monodefluorination in position 8 from 2 observed in both photo- and electrochemical reduction. In this case, the stabilization is larger for the radical in position 8, since there a mesomeric formula with the radical localised on the amino nitrogen and conserving the aromaticity of the pyridone moiety is possible (formula 9'), whereas this is not the case for a radical in position 6 (formula 9''), where the pyridone ring is no more aromatic).

Even with the less easily reduced fluoroquinolone (3), defluorination to 7 occurs though in a low yield due to side-reactions introduced by reactive species formed in the concomitant discharge of the supporting electrolyte.

In conclusion, it appears that cathodic reduction of (hetero)aromatic fluoro derivatives is viable provided that the intermediate aryl radical is sufficiently stabilized. This may be a convenient procedure for obtaining defluorination under mild conditions.

ACKNOWLEDGEMENT

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- 7 The experiments were performed in DMF containing 0.1 M tetrabutylammonium tetrafluoroborate in a three electrode cell (20 mL). Working electrode a mercury film (deposited at -1 V on a glassy capillary electrode from 10⁻⁵ M Hg(NO₃)₂ for 1 min). Reference electrode, Saturated Calomel Electrode, counter electrode, Pt wire.
- 8 The electrolysis was carried out in a three electrode cell equipped with a mercury pool working electrode (area 8 cm²), Ag/AgCl counter electrode and Ag/AgCl reference electrode. Substrate concentration was 2x10⁻⁴ M, the volume 50 mL.
- 9 HPLC analyses were performed by using a Purosphere RP-18 (3x125 mm) column and eluting with a 85/15 MeCN/pH 3 phosphate buffer (prepared by adding phosphoric acid to a 0.75% triethylamine solution)
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