

## Photochemical Behavior of Sitafloxacin, Fluoroquinolone Antibiotic, in an Aqueous Solution

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**Sitafloxacin (STFX) hydrate, an antimicrobial agent, is photo-labile in aqueous solutions. The photodegradation rates (*k*) in neutral solutions were higher than those observed in acidic and alkaline solutions and maximum at the maximum absorption wavelength of STFX. The structures of photodegradation products were elucidated as 7-[7-amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid and 1-(1-amino-2-[6-fluoro-1-(2-fluoro-1-cyclopropyl)-1,4-dihydro-4-oxo-3-quinolin-7-yl]-amino)ethyl)cyclopropanecarbaldehyde. This implies that dechlorination is the key step in the photodegradation of STFX. The effect of halide ions on the photodegradation of STFX was estimated by observing the increments in the photostability of STFX with the addition of chloride ions. In contrast, in the presence of bromide ions, instead of increased photostability of the STFX rate, a new photodegradation product in the presence of bromide ion was observed. The structure of this new photodegradation product was an 8-bromo form of STFX, which was substituted for chlorine at the 8-position, so the dissociation of C–Cl bond at the 8-position of STFX was the rate-limiting step in the initial process of the photodegradation. STFX generated  $\cdot\text{C}$  (carbon centered radical) and  $\cdot\text{OH}$  (hydroxyl radical) in the process of photodegradation in a pH 4.0 buffer. On the contrary, STFX did not generate  $\cdot\text{C}$  in the presence of chloride ion in a pH 4.0 buffer. The  $\cdot\text{C}$  was generated and then degraded into the above degradation products by photoirradiation in the absence of chloride ion, but the  $\cdot\text{C}$  immediately reacted with chloride when it was present. As a result, the C–Cl bond was recovered leading to a possible increase in the apparent photostability.**

**Key words** antimicrobial; fluoroquinolone; sitafloxacin; photodegradation

Sitafloxacin hydrate (STFX hydrate: (–)-7-[(7*S*)-7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid sesquihydrate) is a fluoroquinolone and its chemical structure is shown in Fig. 1.<sup>1)</sup> Fluoroquinolones are important synthetic antimicrobial agents and they have been widely used as therapeutic agents for general bacterial infectious diseases. However, some fluoroquinolones are known to induce phototoxicity as a side effect.<sup>2)</sup> A large number of studies have been reported to elucidate the mechanism of phototoxicity of fluoroquinolones. We reported that carbon centered radical ( $\cdot\text{C}$ ), hydroxyl radical ( $\cdot\text{OH}$ ), and singlet oxygen ( $^1\text{O}_2$ ) are generated during photodegradation of fluoroquinolones in neutral aqueous solutions.<sup>3)</sup> The fluoroquinolones substituted at the 8-position by fluorine generated a high degree of  $^1\text{O}_2$  and  $\cdot\text{OH}$  against photoirradiation. Such reactive species were related to DNA damage.<sup>4)</sup> Some fluoroquinolones are photo-labile compounds and the phototoxicity might arise from photodegradation products. This study was done based on such a background. This report describes the photochemical behavior of STFX in aqueous solution including the identification of major photodegradation products of STFX, the mechanistic consideration of photodegradation, and the effect of pH. Furthermore, the possibility improving the photostability of STFX was examined in the presence of chloride ion.

### Experimental

**Materials** STFX was synthesized at Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan.

**Structural Elucidation of Photodegradation Products** Ninety-four milligrams of STFX hydrate was dissolved in 1 l of purified water and irradiated with a D<sub>65</sub> fluorescent lamp (Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) at approximately 10000 lux for ca. 350000 lux·h. After irradiation,

the solution was loaded onto a preparative HPLC system and fractionated.

Preparative HPLC was carried out on a gradient system consisting of an LC 10AD pump (Shimadzu Co., Kyoto) equipped with a SPD-6A UV/vis detector (Shimadzu Co.). HPLC conditions were as follows: column, TSKgel ODS-80T<sub>M</sub> (21.5 mm i.d.×300 mm, Tosoh Co., Tokyo); eluent, 0.05 M phosphate buffer (pH 2.4): acetonitrile=82:18 (from 0 to 65 min) to 50:50 (from 65 to 100 min); flow rate, 5.0 ml/min (from 0 to 65 min) to 7.0 ml/min (from 65 to 100 min); injection, 2 ml; detection, 278 nm; column temperature, 40 °C.

The collected fractions were concentrated and lyophilized. Then the sample was redissolved in water and loaded onto a desalting preparative HPLC. HPLC conditions were as follows: column, TSKgel ODS-80T<sub>M</sub> (21.5 mm i.d.×300 mm, Tosoh Co.); eluent, 0.1% acetic acid and acetonitrile=30:70; flow rate, 7.0 ml/min; injection, 2 ml; detection, 278 nm; column temperature, 40 °C. Isolated photodegradation products were elucidated by using a <sup>1</sup>H-NMR (JNM-GSX500 FT-NMR spectrometer (500 MHz), JEOL Co., Tokyo) and electron impact (EI), chemical ionization (CI), fast atom bombardment (FAB)-MS (JMS-HX110 mass spectrometer, JEOL Co.) spectra.

**Kinetics of Photodegradation** STFX was dissolved in Britton–Robinson buffer solutions of pH 2.0–11.0 and 0.1 mol/l sodium hydroxide (pH 13.0) (STFX, about 50 μg/ml). Each sample solution (2 ml) was poured into a glass container (internal diameter: ca. 20 mm), which was covered with clear polyvinylidene chloride film. Then, an exposure test was performed at 25 °C by irradiation with a D<sub>65</sub> fluorescent lamp; this is an artificial daylight fluorescent lamp that emits visible and ultraviolet lights. The illumination of the D<sub>65</sub> fluorescent lamp was adjusted to 4000 lux; at this illumination the near ultraviolet energy was about 120 μW/cm<sup>2</sup>. At appropriate time intervals, the sample solution was withdrawn, mixed with the HPLC mobile phase, and the resulting solution (ca. 5 μg/ml) was assayed by HPLC.

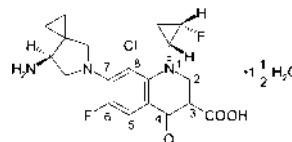


Fig. 1. Chemical structure of STFX hydrate.

**Wavelength Dependency of Photodegradation** Three milliliters of aqueous solution of STFX (50 mM, pH 7.4 phosphate buffer) in a quartz glass cell was irradiated for 0–10 J/cm<sup>2</sup> at various wavelengths (699, 649, 599, 499, 446, 419, 392, 365, 338, 311, 284, 257, 230 nm) by a grating monochromator apparatus, CRM-FA equipped with a Xe lamp (Japan Spectroscopic Co., Tokyo).

HPLC conditions were as follows: column, TSKgel ODS-80T<sub>M</sub> (4.6 mm i.d. × 150 mm, Tosoh Co.); eluent, 0.05 M phosphate buffer (pH 2.4) : acetonitrile = 80 : 20 (from 0 to 10 min), 36 : 64 (from 10 to 20 min), 80 : 20 (from 20 to 40 min); flow rate, 1.0 ml/min; injection, 20 μl; detection, 290 nm; column temperature, 40 °C.

**Liquid Chromatography (LC)-MS Analysis of a Photodegradation Product of STFX in the Presence of Bromide Ions** STFX was dissolved in 0.05 M citrate buffer (pH 4.0) containing 0.2 M of NaBr, and the resulting solution (about 2 mg/ml) was exposed to light from a D<sub>65</sub> fluorescent lamp, which had an overall illumination of ca. 368000 lux · h. After the reaction, the sample solution was mixed with the HPLC mobile phase and the resulting solution (ca. 50 μg/ml) was subjected to LC-MS, the conditions of which were as follows: column, YMC AM-302, 4.6 mm i.d. × 150 mm; eluent, trifluoroacetic acid (TFA) aqueous solution (pH 2.4)–acetonitrile (73 : 27, v/v); flow rate, 0.2 ml/min; detection, UV 294 nm; column temperature, 40 °C. Electrospray ionization (ESI)-MS conditions of which were as follows: ion mode, positive; spray kilovolts, 4.5 kV; heated capillary, 225 °C; sheath gas (N<sub>2</sub>), 80 psi; auxiliary gas (N<sub>2</sub>), 10 units.

**Effect of Chloride Ion on the Photodegradation Kinetics of STFX** STFX was dissolved in 0.05 M citrate buffer (pH 4.0) containing 0.2 M NaCl or 0.2 M of NaBr (STFX, about 50 μg/ml). Each solution (2 ml) was poured into a glass container (internal diameter: ca. 20 mm), which was covered with clear polyvinylidene chloride film. Then, an exposure test was performed at 25 °C by irradiating these sample solutions with Light-Tron LT-120. The illumination of the D<sub>65</sub> fluorescent lamp was adjusted to 4000 lux; at this illumination the near ultraviolet energy was about 120 μW/cm<sup>2</sup>. At appropriate time intervals, the sample solution was withdrawn, mixed with the HPLC mobile phase, and the resulting solution (ca. 5 μg/ml) was assayed by HPLC. The HPLC conditions were as follows: column, TSKgel ODS-80Ts (4.6 mm i.d. × 250 mm, Tosoh Co.); eluent, 0.05 M phosphate buffer (pH 2.4)–acetonitrile (70 : 30, v/v) containing 0.02 M ammonium acetate and 5 mM sodium 1-nonanesulfonate; flow rate, 0.8 ml/min; injection, 50 μl; detection, UV 294 nm; column temperature, 40 °C.

**Determination of Acid Dissociation Constants (pK<sub>a</sub>) of STFX** The acid dissociation constants of STFX were determined by the potentiometric titration method. The potentiometric titrator GT-05 (Mitsubishi Kagaku Co., Tokyo) was used. A 100 ml solution of STFX in 2 mol/l HCl was titrated with 0.1 mol/l KOH at 25 °C. The pK<sub>a</sub> values were calculated with the computer program, PKAS.<sup>5)</sup>

**Detection of Free Radical and Active Oxygen during Photodegradation by ESR Spin-Trapping** ESR measurements were recorded on a JEOL JES-FE2XG spectrometer (JEOL) with 100 kHz field modulation operating at 9.42 GHz and at room temperature. The following instrumental parameters were employed: modulation amplitude, 0.063 mT; microwave power, 8.0 mW; scan time, 2 min.

STFX solution (2.0 mg/ml pH 4, 50 mM citrate buffer solution) containing DMPO (ca. 1.80 M: 200 μl) in the presence or absence of 0.2 M NaCl was irradiated with D<sub>65</sub> fluorescent lamps at approximately 4000 lux for 20 min. The resultant solution was transferred to capillary tubes (Drummond MICROCAPS: 50 μl), sealed with TERUMOSEAL (Terumo, Tokyo), and measured by ESR.

## Results and Discussion

**Structural Elucidation of Photodegradation Products of STFX** STFX was decomposed rapidly in aqueous solution by photoirradiation. Figure 2 shows the HPLC chromatogram of STFX aqueous solution after being photoirradiated by fluorescent lamps for 350000 lux · h. Two major photodegradation products eluted around 22 and 24 min were observed in the chromatogram and designated P-1 and P-2, respectively. These products were isolated and identified by <sup>1</sup>H-NMR and MS spectra. The product P-1 was identified as 7-[7-amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid from the spectrum analy-

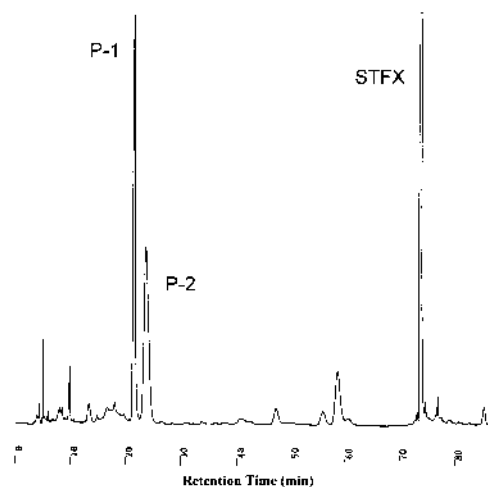


Fig. 2. High Performance Liquid Chromatogram of STFX Aqueous Solution Photoirradiated with Fluorescent Lamps for 350000 lux · h

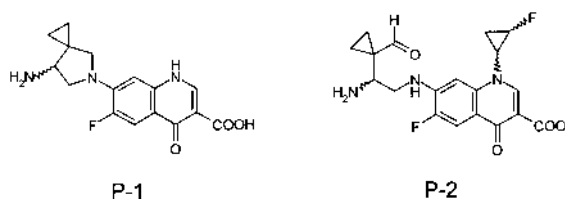


Fig. 3. Chemical Structures of Photodegradation Products

(M+H)<sup>+</sup>, <sup>1</sup>H-NMR (CD<sub>3</sub>COOD): 0.92, 1.19 (2H, m), 1.05 (2H, m), 3.37 (1H, d), 3.67 (1H, d), 4.12 (2H, m), 4.24 (1H, m), 6.80 (1H, d), 7.88 (1H, d), 8.74 (1H, s). The results showed that a chlorine at the 8-position and a cyclopropyl group at 1-position were eliminated. The product P-2 was identified as 1-(1-amino-2-[[6-fluoro-1-(2-fluoro-1-cyclopropyl)-1,4-dihydro-4-oxo-3-quinolin-7-yl]-amino]ethyl)cyclopropanecarbaldehyde: CI-MS *m/z*: 391 (M+H)<sup>+</sup>, FAB-MS *m/z*: 391 (M+H)<sup>+</sup>, <sup>1</sup>H-NMR (D<sub>2</sub>O+TFA): 0.14–0.33 (4H, m), 0.53, 0.58 (1H, m), 0.70 (1H, m), 2.14 (1H, m), 2.67 (1H, m), 2.77 (2H, m), 4.01, 4.14 (1H, m), 6.07 (1H, s), 7.24 (1H, s), 7.84 (1H, s). The P-2 product had the structure of STFX oxidized at the 7-position and with a chlorine eliminated at the 8-position. These structures of P-1 and P-2 are shown in Fig. 3. Both compounds contained a dissociated C–Cl bond at the 8-position.

**Effect of pH on the Photodegradation** In the case of ionizable compounds, the effect of pH on the photostability is significant.<sup>6)</sup> Figure 4 shows the first-order plots for the photodegradation reactions conducted at several pHs. The photodegradation of STFX followed an apparent first-order rate equation in the pH range of 2.0 to 12.9. The first-order plots exhibited good linear relationships with correlation coefficients of 0.99 or higher at all pHs examined. The apparent first-order rate constants (*k*) were obtained from the slopes of the plots (Table 1). The log *k*–pH profile for the photodegradation of STFX is shown in Fig. 5. The photodegradation rates in neutral solution were higher than those observed in acidic and alkaline solutions. STFX is an amphoteric compound with pK<sub>a</sub> values of 5.7 for the carboxylic group and 9.0 for the amine determined by potentiometric titration. This

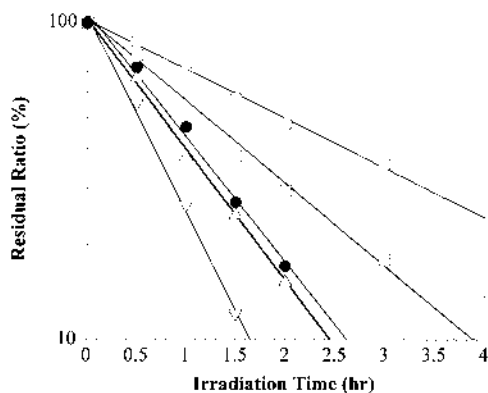


Fig. 4. Kinetics of STFX Photodegradation in Aqueous Solution at Several pHs

○, pH 2.0; □, pH 4.0; △, pH 6.0; ▽, pH 8.0; ●, pH 10.0.

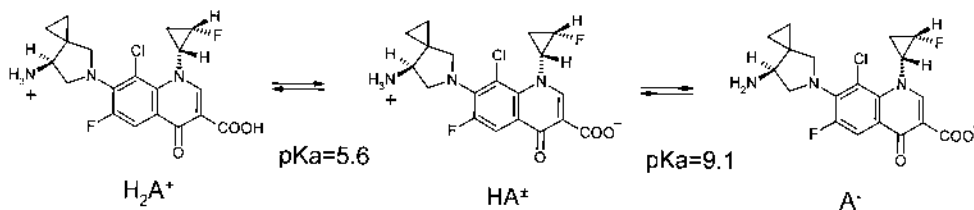


Chart 1

Table 1. Apparent First-Order Rate Constants ( $k$ ) for the Photodegradation of STFX at Several pHs

pH	$k$ ( $\text{h}^{-1}$ )
1.00	0.750
2.00	0.399
4.00	0.599
6.00	0.947
7.00	1.238
8.00	1.423
10.0	0.870
12.3	0.240

the zwitter ion at pH 7.4. STFX was the most sensitive to photodegradation in zwitter ionic form at slightly basic pHs. STFX was stable in the acidic region, where the carboxyl group was not ionized and the basic nitrogen was completely protonated.

**Wavelength Dependence of Photodegradation** Generally, so-called photo-labile compounds decompose under light of specific wavelengths and thereby contribute to photodegradation of the compounds.<sup>7)</sup> Figure 6a shows the photodegraded ratio of STFX after exposure to light of various wavelengths at the same energy ( $0.5 \text{ J/cm}^2$ ); it clearly shows that STFX was degraded wavelength dependently. The degradation rate and UV spectrum of STFX (Fig. 6b) correlated well. That is, STFX was the most labile at 284 nm, which was the maximum absorption wavelength.

**Mechanistic Consideration of Photodegradation of STFX** In some fluoroquinolones the structures of the photodegradation products have been already identified, such as levofloxacin (LVFX)<sup>8)</sup> and orbifloxacin (ORFX).<sup>9)</sup> These products are analogues altered at the piperazine moiety or

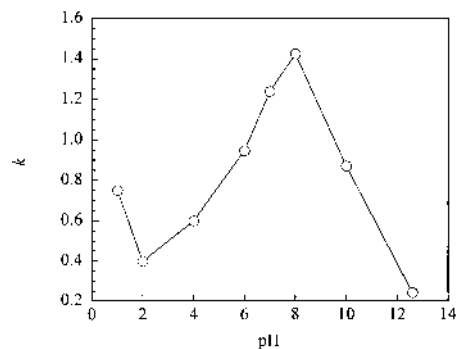


Fig. 5.  $k$ -pH Profile for the Photodegradation of STFX

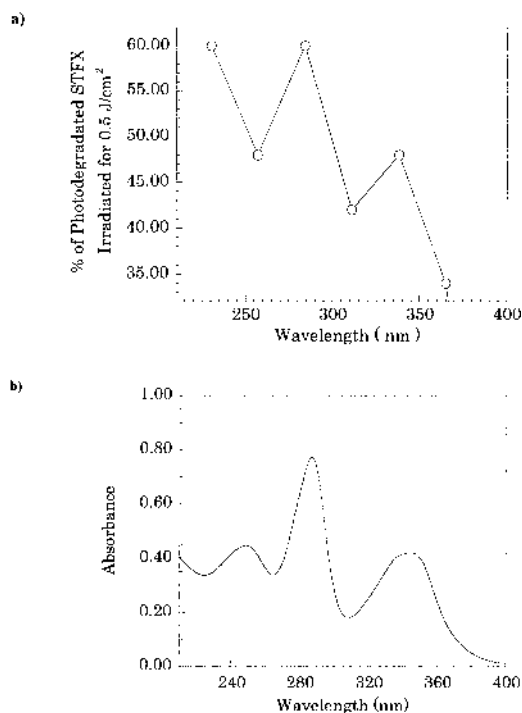


Fig. 6. Photodegraded Ratio of STFX in pH 7.4 Buffered Solution under Irradiation for  $0.5 \text{ J/cm}^2$  at Various Wavelengths (a) and UV Spectrum of STFX in pH 7.4 Buffered Solution (b)

quinolones. STFX was photodegraded in aqueous solution and gave two major products. The structures of the photodegradation products had in common the chlorine eliminated at the 8-position of STFX and in being subsequently degraded at the 1-position or 7-position of STFX. In general,

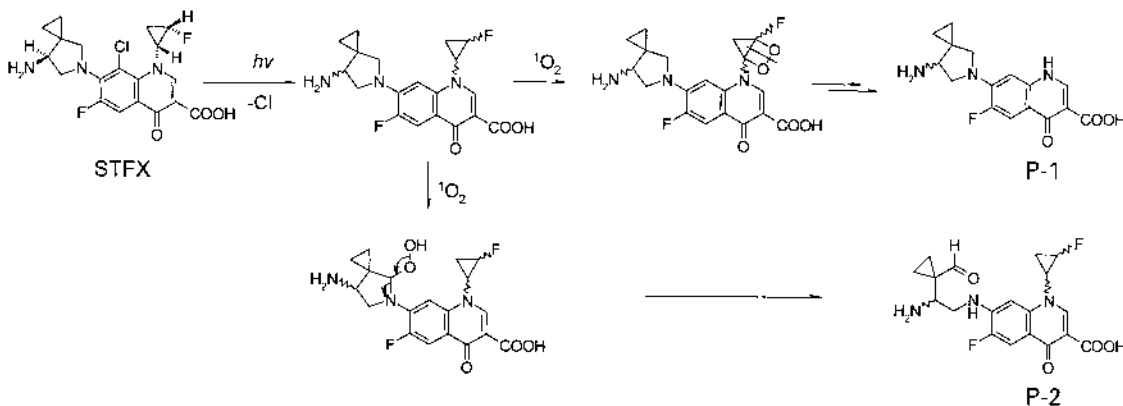


Chart 2

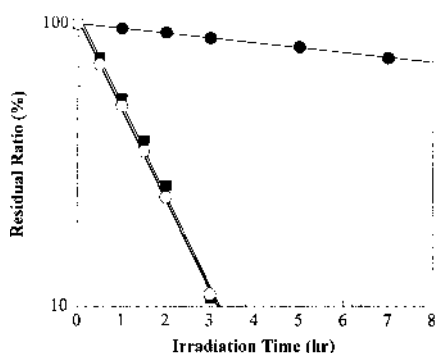


Fig. 7. Photodegradation Kinetics of STFX in pH 4.0 Citrate Buffer in the Presence of Chloride Ion, Bromide Ion, and in the Absence of Halide Ion (Control)

●, 0.2 M NaCl; ○, 0.2 M NaBr; ■, control.

may occur are classified as follows. The Type I mechanism is a free radical chain process and is generally termed autoxidation. The Type II mechanism involves the excited  $^1\text{O}_2$  and is termed oxygenation. It is well known that heterocyclic compounds such as pyrrole and furan undergo photooxidation by a Type II mechanism. We demonstrated that STFX and the other fluoroquinolones generated  $^1\text{O}_2$  in response to photoirradiation.<sup>3)</sup> We concluded from these that  $^1\text{O}_2$  production by irradiated STFX was responsible for photodegradation. STFX reacts with  $^1\text{O}_2$  to form a dioxetan intermediate, and then undergoes hydrolysis to afford the photodegradation products P-1 and P-2, as presented in Chart 2 according to the Type II mechanism. However, details of the mechanism of the photochemical reaction of STFX are not as clear.

**Effect of Halide Ion on the Photodegradation** ORFX, a fluoroquinolone having a fluorine at the 8-position, was converted into a photoproduct substituted by chlorine at the 8-position in an aqueous solution containing chloride ions.<sup>10)</sup> Since STFX has a chloride at the 8-position, if photodegradation of STFX were done in aqueous solution containing chloride ion, its apparent stability might be improved. Therefore, we demonstrated the photodegradation studies of STFX at several pHs in the presence and absence of chloride ion. Figure 7 shows the first-order plots for the photodegradation of STFX in pH 4.0 citrate buffer solutions containing chloride ion, bromide ion, or without halogen ion (control). The photodegradation of STFX followed an apparent first-order rate equation in each buffer. The first-order plots exhibited

Table 2. Apparent First-Order Rate Constants ( $k$ ) for the Photodegradation of STFX in pH 4.0 Citrate Buffer in the Presence of Chloride Ion, Bromide Ion, and in the Absence of Halide Ion (Control)

	$k$ ( $\text{h}^{-1}$ )	Ratio <sup>a)</sup>
Without halide ion (control)	0.733	1.00
With 0.2 M NaCl	0.040	18.4
With 0.2 M NaBr	0.739	0.99

a)  $k$  of control as 1.00.

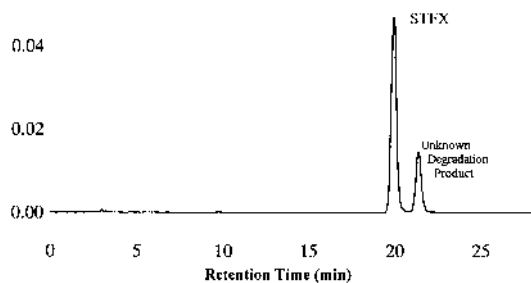


Fig. 8. High Performance Liquid Chromatogram of STFX Photoirradiated in pH 4.0 Citrate Buffer Containing Bromide Ion with a  $D_{65}$  Fluorescent Lamp for 0.5 h

or higher. The apparent first-order rate constants ( $k$ ) were obtained from the slopes of the plots. Table 2 shows the  $k$  for the photodegradation of STFX in the pH 4.0 citrate buffer solutions containing chloride ion, bromide ion or without halogen ion (control). The photostability of STFX was improved approximately 18 fold in the presence of chloride ion, while it was not affected in the presence of bromide ion.

**LC-MS Analysis of Photodegradation Product in the Presence of Bromide Ion** Figure 8 shows a high-performance liquid chromatogram of STFX in a pH 4.0 buffer containing 0.2 M NaBr following irradiation with a  $D_{65}$  fluorescent lamp. Even though the photostability was not affected in the presence of bromide ion, an unknown photodegradation product was newly observed. Quasi-molecular ions at  $m/z=454$  and  $m/z=456$  were present in the LC-ESI mass spectrum. Therefore, the structure of the newly observed photodegradation product of STFX in the presence of bromide is the 8-bromo form of STFX, which is substituted for chlorine as shown in Chart 3.

**Kinetics of the Photodegradation in the Presence of Chloride Ion at Several pHs** Figure 9 shows the first-

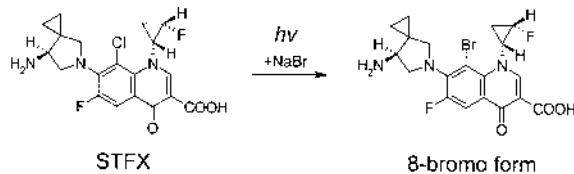


Chart 3

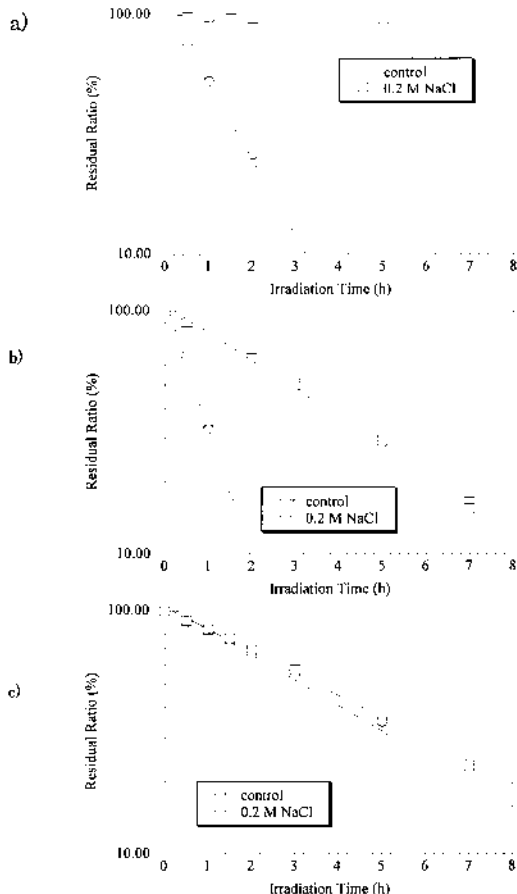


Fig. 9. Photodegradation Kinetics of STFX in the Presence or Absence of Chloride Ions in Aqueous Solutions at Several Different pHs

a) 0.1 M HCl, b) phosphate buffer (pH 7.0), c) 0.1 M NaOH.  
 ○, control (without chloride ion); □, with 0.2 M NaCl.

HClO<sub>4</sub>, pH 7.0 phosphate buffer, and 0.1 M NaOH in the presence and absence of chloride ion. Table 3 and Fig. 10 show  $k$  for the photodegradation of STFX in the presence and absence of chloride ion in the above solutions. The photostability of STFX was improved approximately 31 fold in the presence of chloride ion in 0.1 M HClO<sub>4</sub>. Conversely, it was not affected in the presence of chloride ion in 0.1 M NaOH. Furthermore, the photodegradation rate in a neutral solution was almost equal to that in an alkaline solution in the presence of chloride ion.

Fluoroquinolones generated  $\cdot\text{C}$  and  $\cdot\text{OH}$  in the process of photodegradation in pH 7.0 buffer by means of the 5,5-dimethylpyrroline-1-oxide (DMPO) spin trapping method.<sup>3)</sup> The 8-fluorine-substituted fluoroquinolones such as lomefloxacin and sparfloxacin produced  $\cdot\text{C}$ ; however, STFX did not produce the  $\cdot\text{C}$  in pH 7.0 buffer. Figure 11a shows the ESR spectrum of photoirradiated STFX in pH 4.0, and Fig.

Table 3. Apparent First-Order Rate Constants ( $k$ ) for the Photodegradation of STFX in the Presence and in the Absence of Chloride Ion in Aqueous Solution at Several pHs

	$k$ (h <sup>-1</sup> )		Ratio A/B
	Without Cl <sup>-</sup> (A)	With 0.2 M NaCl (B)	
0.1 M HClO <sub>4</sub>	0.750	0.025	30.6
pH 4.0 citrate buffer	0.733	0.040	18.4
pH 7.0 phosphate buffer	1.238	0.264	4.7
0.1 M NaOH	0.240	0.209	1.1

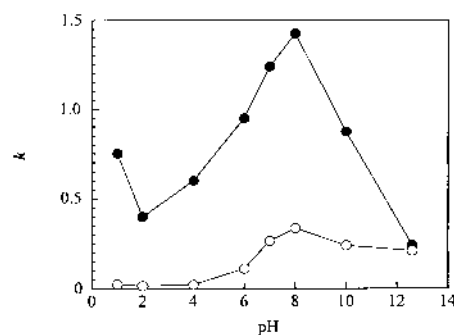


Fig. 10. Apparent First-Order Rate Constants ( $k$ ) of the Photodegradation of STFX in the Presence or Absence of Chloride Ions in Aqueous Solutions at Several pHs

○, control (without chloride ion); ●, with 0.2 M NaCl.

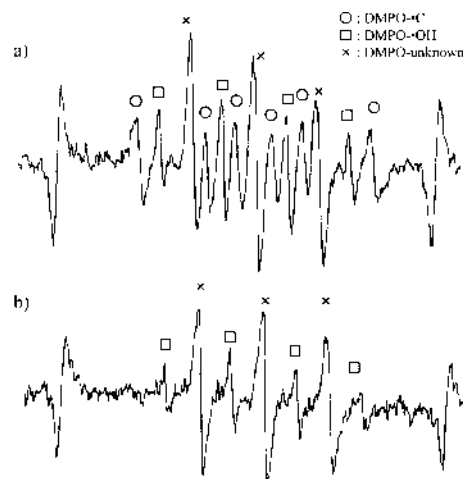


Fig. 11. ESR Spectra of Photoirradiated STFX Solution in the Presence of DMPO

a) STFX in pH 4.0 citrate buffer in the absence of chloride ion was irradiated with D<sub>65</sub> lamps (approximately 4000 lux) for 20 min. b) STFX in pH 4.0 citrate buffer in the presence of 0.2 M NaCl was irradiated with D<sub>65</sub> lamps (approximately 4000 lux) for 20 min.

4.0 in the presence of 0.2 M NaCl. Figure 11a shows that STFX generated  $\cdot\text{C}$  and  $\cdot\text{OH}$  in the process of photodegradation in pH 4.0 buffer. Therefore, the homolytic bond scission of the C–Cl took place in the absence of chloride ion in pH 4.0 buffer solution. On the contrary, STFX did not generate the  $\cdot\text{C}$  in the presence of 0.2 M NaCl in pH 4.0 buffer (Fig. 11b). These results suggest that the chloride ion competes with DMPO in reacting with the generated  $\cdot\text{C}$ .

**The Mechanism of the Increments in Photostability in**



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