CROATICA CHEMICA ACTA
CCACAA, ISSN 0011-1643, e-ISSN 1334-417X
Croat. Chem. Acta **86** (1) (2013) 49–56.
http://dx.doi.org/10.5562/cca2071

Original Scientific Article

Anaerobic Hydrolytic Degradation of Cefpodoxime Proxetil in the Presence of UV Irradiation and in Darkness: Kinetics and pH Effect

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RECEIVED MARCH 14, 2012; REVISED DECEMBER 6, 2012; ACCEPTED JANUARY 4, 2013

Abstract. In this study, the anaerobic hydrolytic degradation of cefpodoxime proxetil (CP) in the presence of UV-light irradiation and in darkness has been studied at Britton-Robinson (B-R) buffer solutions (pH 2.5–11) by cyclic and square-wave voltammetry techniques. By means of these electrochemical techniques, the hydrolytic degradation of CP was successfully followed. The pH effect on this degradation was also investigated. In darkness, the decrease in the peak current of CP was not practically observed at the acidic and physiological pHs (2.5, 5.0 and 7.4). But, in the basic medium (pH 9.0 and 11.0), a decrease in the peak current was detected. On the other hand, UV irradiation caused a decrease in the peak current of CP and a positive shift in its cathodic peak potential. Under the UV irradiation, the maximum stability of CP was observed in B-R buffer of pH 5. It has been determined that UV irradiation has a great effect on hydrolytic degradation of CP at basic medium. On the other hand, at pHs ≥ 7.4, a new peak has been also obtained at more positive potential than that of the first reduction peak of CP. The current of this peak increases by increasing UV irradiation time. This peak could be assigned to the reduction of a new electroactive product which was formed from the hydrolytic degradation of CP under UV irradiation. The hydrolytic degradation reaction of CP followed pseudo-first order kinetics.(doi: 10.5562/cca2071)

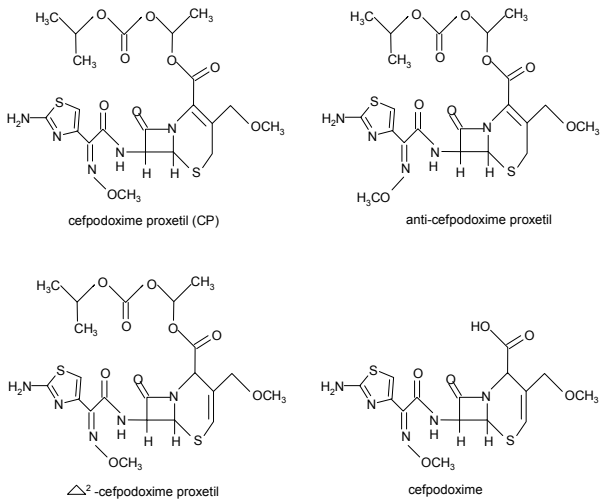
Keywords: cefpodoxime proxetil, hydrolytic degradation, pH effect, voltammetry, UV-irradiation, darkness

INTRODUCTION

The stability of drugs towards heat, moisture, oxidation and exposure to light is a topic of great practical interest owing to considerable complexity.[1,2] Since degradation products of pharmaceutical compounds can cause undesirable side effects in patients,[3] the information on the photodegradation of drugs is urgently needed for the safety of human beings. Also, the degradation of a pharmaceutical leads to increasing amounts of degradation products, therefore, the investigation of stability characteristics and degradation profile of a pharmaceutical is important.[3]

Cephalosporins are the second major group of β-lactam antibiotics.[4] CP (Scheme 1) is an orally absorbed broad spectrum third generation cephalosporin ester. This prodrug ester is deesterified *in vivo* into its active metabolite cefpodoxime.[5]

Stereo and structural isomers of CP (*e.g.* anti-CP and Δ^2-CP, see Scheme 1) can be present as possible as degradation products[6]. Isomerization from Δ^3-cephalosporin ester to its Δ^2-isomer can be catalyzed by general and specific bases.[6] Anti-cephalosporin ester yields from its syn-isomer as a function of photoisomerization under irradiation at 254 nm.[7]



Scheme 1. Structures of CP and its some related substances.

The stabilities of CP in 20 mmol dm^{-3} K_2HPO_4-methanol (55:45, *v*/*v*), 20 mmol dm^{-3} ammonium acetate-methanol (55:45, *v*/*v*), L-histidine solution (pH 2.5)-methanol (55:45, *v*/*v*) as well as water-methanol (55:45, *v*/*v*) were investigated by Wang *et al.*[6] at room

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temperature for about 22 h via HPLC analysis. They reported[6] that approximately 75 % of CP degraded in the phosphate solution, and about 4−6 % of CP in acetate and L-histidine solution, but no obvious degradation occurred in water-methanol (55:45, *v*/*v*) at room temperature after about 22 h.

CP has an asymmetric carbon at position 4 (Scheme 1) and is supplied racemic mixture of R- and S-enantiomers.[8] CP and other β-lactam antibiotic structures are known to degrade by hydrolysis in alkaline and acid solutions.[8,9] In the alkaline media, CP undergoes ester hydrolysis and is converted into cefpodoxime (see Scheme 1) to exhibit its antibiotic activity.[8,10–12] The degradation of CP in 0.01 mol dm^{-3} HCl, 0.01 mol dm^{-3} NaOH, 0.1 % H_2O_2 and 1.0 % hydroxylamine solutions was studied by Fukutsu *et al.*[12] and its degradation products were characterized by HPLC and MS analysis. They reported[12] that CP was relatively stable in both the 0.01 mol dm^{-3} HCl and 0.1 % H_2O_2 solutions. However, CP was completely degraded in 0.01 mol dm^{-3} NaOH.[12] For the 1.0 % hydroxylamine solution, CP was degraded rapidly.[12]

Hydrolysis of CP can proceed by a reversible base-catalyzed isomerization yielding the Δ^2-cephalosporin ester which is rapidly cleaved to give the biologically in active Δ^2-cephalosporin.[8] The degradation of CP in 0.6 mol dm^{-3} phosphate buffer (pH 7.4) at 37 °C over 24 h was studied using HPLC and NMR techniques by Stoeckel *et al.*[13] They reported[13] that in phosphate buffer, the major degradation product was the Δ^2-cephalosporin. The half-lives ($t_{1/2}$) for the diastereoisomers of CP were 2.5 and 2.2 h, respectively.[13]

The stability of CP was also investigated in buffers of pH values 1.2, 4.5, 5.4 and 6.8 for 24 h at 37 °C by Kakumanu *et al.*[14] According to this study, a strong influence of pH on the stability of CP was observed. The higher the pH of the buffer, lesser is the stability of CP, and buffer with pH 1.2 offered highest protection. There was a sudden increase in degradation of CP at pH 6.8. CP was stable for up to 12 h in all buffers except pH 6.8. Although the stability at pH 5.4 was less compared to those of pH 1.2 and 4.5, but the percentage of drug was maintained at 80 % till 24 h. At pH 6.8, about 55 % of its content was degraded within 8 h and complete degradation occurred in 24 h. The major degradation product was found to be cefpodoxime as analyzed by HPLC.[14]

The stability of CP in B-R buffers, at pH 2.0, 4.0, 6.0, 7.0, 8.0 and 10.0, was also studied at a temperature of 40 °C and its degradation products were determined by HPLC hyphenated techniques of LC-MS, LC-NMR and solvent-elimination LC-IR.[3] CP was not degraded under acidic to slightly acidic conditions, and no significant change of CP content was observed at pH 2.0 or 4.0. Under neutral to alkaline conditions, CP was slightly degraded at pH 6.0 but was degraded at pH 7.0 and 8.0. At pH 10.0, no detectable CP was observed after 2 h.[3]

The voltammetric behavior of CP was previously examined in pH range 2.0−12.0 by using DPV and CV techniques.[15] It was reported that CP gave two reduction peaks in the entire buffer system and these peaks were attributed to the reduction of azomethine group by two-electron process in two steps.[15] By means of cyclic voltammetry (CV) technique, no anodic peak was observed in the pH range for CP.[15] In addition, the peak potential of CP shifted towards a more negative potential along with an increase in the pH range.[15] The optimum pH for CP was selected as pH 2.0 where the first peak was sharp and reproducible and was preferred for the analysis.[15]

Electrochemical behavior of CP at dropping mercury electrode in the presence of some surfactants was also studied by Jain *et al.*[16] Reduction potential of CP shifted negatively and peak current was increased significantly in the presence of cetyltrimethylammonium bromide (CTAB). In addition, two well defined, cathodic and diffusion controlled waves were observed for CP in the presence of CTAB in entire pH range.[16] For the reduction of CP, the postulated mechanism by Jain *et al.*[16] was agreed with that by Reddy *et al.*[15] For the voltammetric determination of CP in CTAB (2.8×10^{-4} mol dm^{-3} – 0.14×10^{-6} mol dm^{-3}) and water (2.8×10^{-4} mol dm^{-3} – 0.71×10^{-6} mol dm^{-3}), the first reduction peak (wave I) was used by Jain *et al.*[16]

In fact, CP molecule has two electroactive sites (methoxyimino group and unsaturated C=C bond, see Scheme 1).[17,18] Zuman *et al.* reported the electroanalytical chemistry of cephalosporins and cefamycins.[18] The reduction of the unsaturated C=C bond occurs in two-electron process at potentials only slightly more positive than the reduction of H^+ ions from the supporting electrolyte used.[18]

The reduction of CP on the static mercury electrode in the pH range of 1.8−13.0 was also studied by Aleksic *et al.*[19] They reported[19] that the C=N–OCH_3 group was reducible in the whole pH range investigated (1.8−13.0). In acidic and neutral medium, pH<7, one well developed and sharp voltammetric peak (I) was present. In the pH range from 7 to 10.5, this peak splitted, and two peaks, II and III, were present.[19] The dependence of the DPV peak I current versus pH showed maximum at pH = 3.5, and both peak currents II and III reached the maximum at pH 9.0.[19] Besides these three peaks, two more peaks (IV and V) were present.[19] The former one was due to the reduction of methoxymino group at pH > 10, and the second one (at pH range of 1.8 – 6.5) was attributed to the two electron reduction of unsaturated C=C bond.[19]

Stabilities of CP and some cephalosporin antibiotics in solid state, drug formulation and solution were examined,[3,6–14,20–24] however, no specific findings on the electrochemical detection of the anaerobic hydrolytic degradation of CP and its degradation kinetics under UV-irradiation were reported. Therefore, for the first time, the kinetics on anaerobic hydrolytic degradation process of CP solutions, exposed to UV light or at darkness in vitro was examined by some voltammetric techniques.

EXPERIMENTAL

Reagents

CP was obtained from Fargem A.Ş. (Düzce/Turkey) and used as received. All other reagents used were of analytical reagent grade. For all voltammetric experiments, 0.04 mol dm^{-3} B-R buffer solutions were used as the supporting electrolyte. High-purity nitrogen gas was used for deaeration. The 1.0×10^{-3} mol dm^{-3} stock solution of CP was daily prepared by dissolving its appropriate amount in a mixture of water (triply distilled and deionized) and ethanol (40:60, % *v*/*v*).

Apparatus

The voltammetric measurements were carried out by using an EG&G PAR Model 384B polarographic analyzer connected to an EG&G PARC Model 303A SMDE polarographic cell (Princeton, NJ, USA) with three electrodes consisting of hanging mercury drop electrode (HMDE) as working electrode, an $Ag\,|\,AgCl\,|\,KCl_{sat.}$ reference electrode and a platinum counter electrode. Voltamograms were monitored by means of ECDSOFT[25] and Microsoft Excel package programs in a personal computer connected to the polarographic analyzer. The pH values of the buffer solution were measured with a Jenway 3010 pH meter.

For the electrochemical analysis, the CP sample (10 mL) is contained in a borosilicate glass. The borosilicate glass transmits UV light >310 nm.[26] Osram ultra-vitalux sun lamp (E27/ES) of 300 Watt was used as ultra-violet (UV) light source for UV-irradiation studies. Technical data for this light source: UVA (315−400 nm) radiated power is 13.6 W and UVB (280−315 nm) radiated power is 3.0 W.[27]

Procedure

At the voltammetric method, ten milliliters solution containing 0.04 mol dm^{-3} B-R buffer with different pHs was transferred into an electrochemical cell. And then, the solution was deoxygenated, by bubbling with highly purified nitrogen gas. The voltamogram of the supporting electrolyte was recorded from 0.00 to –2.00 V. After the background voltamogram was obtained, an aliquot amount of solution of CP was added into the cell while maintaining the nitrogen atmosphere. Thus, the voltamograms of 2.91×10^{-5} mol dm^{-3} CP were recorded if not stated otherwise. And then, the CP solution in B-R buffer (pH 2.50−11.00) was irradiated with UV-light at a distance of 30 cm for different times. The voltamograms of the CP solutions, irradiated were also recorded at different pH values. In addition, hydrolysis experiments were conducted in the CP solutions, kept in the dark. To evaluate the influence of pH on the hydrolysis of CP in the darkness, voltamograms were taken at different values of pH (2.5, 5.0, 7.4, 9.0 and 11.0) for different waiting times. The conditions of square-wave voltammetric measurements were usually as follows; a scan increment of 2 mV, a pulse height of 20 mV, a medium mercury drop size (surface area of 0.0154 cm^2), equilibrium time of 5 s, frequency of 100 Hz and a scan rate of 200 mV s^{-1}. The cyclic voltammetric measurement was performed using a HMDE, an equilibrium time of 5 s, and a scan rate of 500 mV s^{-1} unless stated otherwise.

All experiments were carried out at the ambient temperature of the laboratory (≈ 25 °C).

RESULTS AND DISCUSSION

The Voltammetric Behavior of CP

The voltammetric behavior of CP was studied in B-R buffer solutions (in the pH range of 2.5–11). In Figure 1, typical square-wave voltamograms (SWVs) of CP at different pH values are shown. CP exhibits two well-defined peaks at very negative potentials in the entire buffer system. As can be also seen in Figure 1, these peaks are shifted towards more negative potentials as the pH increased.

Owing to no anodic peaks observed for CP (Figure 2A), the nature of the electrode process of these peaks was determined to be irreversible. The first one can be attributed to the reduction of >C=N–OCH_3 group, but the second one at more negative potential (E_p = –1.3 V, pH 5) is more likely due to the two electron reduction of unsaturated C=C bond.[15–19] The second reduction process is well known to take place at high negative potentials.[18] At pH 11, the additional peaks were observed at more positive potentials from that of the first reduction peak of CP (Figure 2C). One of the additional peaks was obtained at –0.780 V. At pH 11, the amino group of CP is probably unprotonated. For CP, the dissociation equilibrium (due to the amino group of the thiazole ring) with a dissociation constant of 3.20 ± 0.13 was obtained from UV spectra in buffer solutions with the various pH values.[28] Therefore, it can be said that Hg(I)NH-R formed according to the sugges-

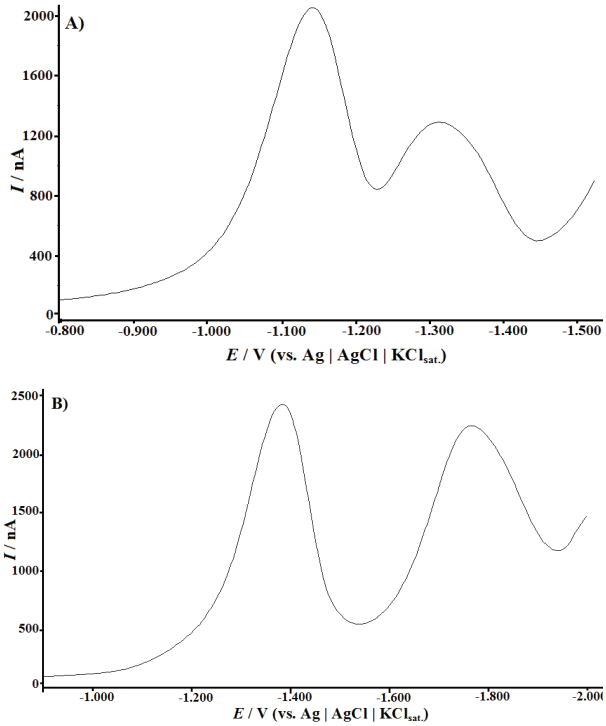

Figure 1. SWVs of CP at daylight in B-R buffer solutions. (A) pH = 5, (B) pH = 9 and [CP] = 9.90×10^{-6} mol dm^{-3}.

tion of other authors in the literature.[15,29,30] Finally, this peak can be interpreted as a reduction of mercury salt of CP on the mercury surface under these conditions. Similarly, cefaclor exhibited a peak at –0.67 V in B-R buffer pH 10.[31]

Other additional peak which corresponds to the reduction of the alkaline degradation product of CP can be seen at –0.904 V (Figure 2C, a). A similar peak was obtained by the alkaline hydrolysis of cefaclor.[32]

The Voltammetric Monitoring of Hydrolytic Degradation of CP under UV Irradiation

To follow the kinetics of hydrolytic degradation of CP under UV radiation, its first peak was selected. CVs of CP after UV irradiation are also presented in Figure 2. As can be seen in Figures 2 and 3, with increasing irradiation time, the cathodic peak currents of CP significantly decreased and their potentials shifted to more positive potentials. The similar electrochemical results were also observed for the photolysis of some drugs under UV-irradiation.[33–36] And also, a new peak, dependent on pH (Figure 2B, Inset), appears at different potential from those of reduction peaks of CP. The formation of a new peak indicates the electroactivity of the degradation product of CP. At pH 7.4, a small reduction peak could be detected at –0.746 V which may be attributed to the formation of a new electroactive degrada-

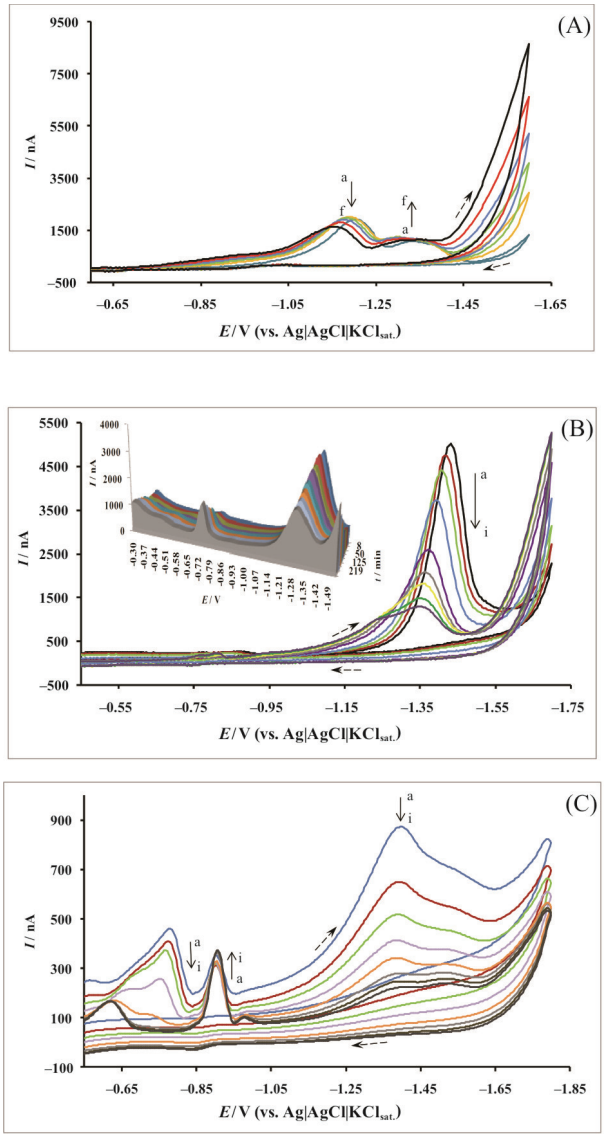

Figure 2. CVs of CP solutions, exposed to UV irradiation at different pHs. (A) pH 5; (a) 0, (b) 23, (c) 40, (d) 60, (e) 85, (f) 115 min. (B) pH 7.4; (a) 0, (b) 8, (c) 15, (d) 30, (e) 60, (f) 80, (g) 100, (h) 120, (i) 130 min. (C) pH 11; (a) 0 (day light), (b) 5, (c) 12, (d) 20, (e) 30, (f) 32, (g) 37, (h) 42, (i) 47 min. The inset at Figure 2B shows 3 D square-wave voltamograms of CP solution at different UV-irradiation times (t); (a) 8, (b) 24, (c) 50, (d) 67, (e) 125, (f) 163, (g) 219, (h) 279 min.

tion product of CP on mercury electrode. On CV at pH 7.4, this small peak is well defined by square-wave voltammetry (Figure 2B, inset). As can be seen in Figure 2B, the current of the peak at –0.746 V increased by increasing UV-irradiation time. In a basic medium (*i.e.* pH 11), this new peak was also observed at more negative potential (–0.904 V) in the absence of UV-irradiation (Figure 2C, a). Probably, day light is sufficient for the formation of this peak at alkaline medium. At this basic medium, the current of this peak also

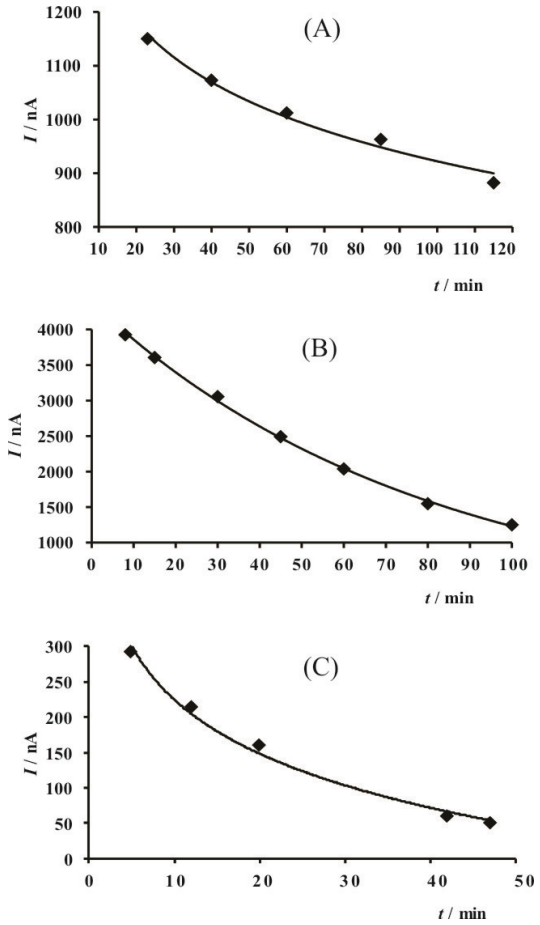

Figure 3. The effect of irradiation time on CV response of CP solution at different pHs: (A) 5, (B) 7.4 and (C) 11.

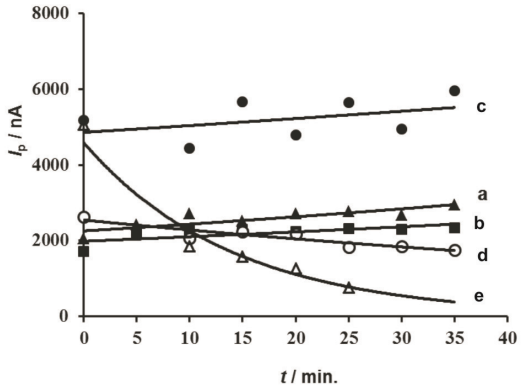

Figure 4. Kinetics of CP solution following a 35-min exposure to darkness at room temperature in B-R buffers with different pHs: a) 2.50 (▲), b) 5.00 (■), c) 7.40 (●), d) 9.00 (○), e) 11.00 (Δ).

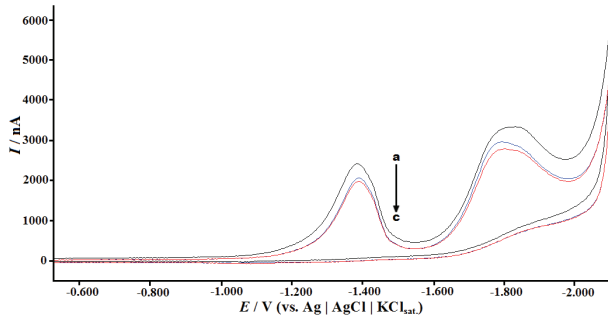

Figure 5. CVs of 9.90×10^{-6} mol dm^{-3} CP solution, exposing to darkness at room temperature in B-R buffer (pH = 9). a) 10, b) 25, c) 35 min.

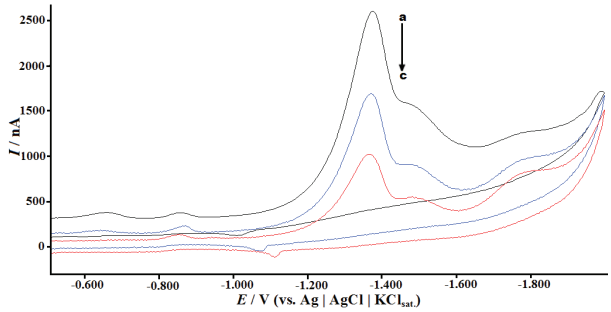

Figure 6. CVs of CP solution, exposing to darkness at room temperature in B-R buffer (pH = 11). a) 10, b) 20, c) 30 min.

increased by increasing UV irradiation time (Figure 2C, b-i).

On the other hand, the peak (at –0.780 V) , attributed to the reduction of mercury salt of CP on the mercury electrode surface at pH 11 decreased and its potential shifted to more positive potentials by increasing UV-irradiation time (Figure 2C).

The Voltammetric Monitoring of Hydrolytic Degradation of CP in Darkness

To understand the effect of UV irradiation on the hydrolytic degradation of CP, the voltamograms of CP solution in darkness have been also recorded with time for different pH values. At acidic pHs (2.5 and 5.0) and physiological pH (7.4), the peak currents of CP have not nearly changed (Figure 4). As regards to the obtained results, it can be concluded that CP is more stable under these circumstances. However, in the basic medium (pHs 9 and 11), the peak currents of CP decrease in a similar manner to the presence of UV irradiation (Figures 5 and 6). Moreover, according to the literature[8,12], CP is degraded to cefpodoxime, leaving >C=N–OCH_3 group "untouched", while the C=C bond is shifted in the alkaline media. Therefore, the reduction peak of C=C bond should be much more affected from that of methoxyimino group. As can be seen in Figure 5, its peak potential versus waiting time is shifted to more positive potentials while the peak potential of first peak shows no shift at darkness. The kinetic data on the hydrolytic degradation of CP in darkness and basic medium are given in Table 1.

Table 1. The pseudo first-order kinetic constants and half-life time for hydrolytic degradation of CP solutions under UV-irradiation or in darkness at different pHs

pH	*UV-irradiation*			*darkness*		
	k / min^{-1}	$t_{1/2}$ / min	r^2	k / min^{-1}	$t_{1/2}$ / min	r^2
2.5	0.007	99.00	0.987	-	-	-
5.0	0.003	231.00	0.988	-	-	-
7.4	0.013	53.30	0.998	-	-	-
9.0	0.017	40.76	0.996	0.006	115.50	0.978
11.0	0.042	16.50	0.999	0.017	40.76	0.990

The first order kinetic constant and half-life time

The kinetic data for hydrolytic degradation of CP have been observed to obey a pseudo first-order rate equation as follows:

$$\ln I_{pt} = \ln I_{p0} - k \times t \quad (1)$$

where, I_{p0} and I_{pt} are currents of CP at time 0 and t (min), respectively. Also, k (min^{-1}) is the first-order rate constant. k can be obtained through a linear least-square fit of the ln I_p data *versus* time. In above equation, it was thought that peak current was related to the bulk concentration of CP. The half-life ($t_{1/2}$) is the time required to decrease the main peak current of CP to half of its initial value. It was calculated according to the following equation:

$$t_{1/2} = 0.693 / k \quad (2)$$

In the presence of UV irradiation and in darkness, the values of the first order kinetic constants, determined from the plot of ln I_{pt} *versus* t, are given in Table 1. The values of half-life are also presented in Table 1.

As can be seen in Table 1, the pH and light had a significant effect on hydrolysis of CP. The hydrolysis rate constant increased as pH increased from 5.0 to 11, indicating that pH played an important role in hydrolysis of CP under UV light irradiation.

In darkness, it is very interesting that the hydrolysis of CP is only observed at basic pH values (9.0 and 11.0). In this case, the acidic and physiological conditions favoured the stability of CP, and alkaline conditions increased the hydrolytic degradation rate of CP; half-life time of CP decreased from 115.50 min. to 40.76 min. when pH increased from 9.0 to 11.0 (Table 1).

Photocatalytic effect was estimated by comparing the hydrolytic degradation of CP in UV light exposure and in darkness. Although the hydrolysis of CP was not seen in darkness at pH range 2.5–7.4, UV light exposure caused the considerable hydrolytic degradation of CP in this pH range. Also, UV light exposure increased hydrolytic degradation of CP, exhibiting the higher degradation rates than those under darkness at pHs 9 and 11 (Table 1).

As can be seen in the presence of UV irradiation, the lowest k was observed at pH 5.0. At pH range 5−11, k increased by increasing pH value. At pH 11, k is 14 times higher than that of pH 5. The catalysis of OH^- ions in the hydrolysis of CP under UV-light irradiation was verified by the increase in hydrolysis rate constant as buffer pH increased from 7.4 to 11.0. Since OH^- ions have much higher nucleophilicity than water molecules,[37] its effect in the hydrolysis reaction of CP becomes more significant as the buffer solution pH increases. However, the degradation rate at pH 2.5 may be increased from the acid catalysis under UV irradiation.

Cephalosporins were previously reported to produce sulfide ions upon alkaline degradation and it was found to be one of their major degradation products.[24,38] Also, Gouda *et al.*[39] reported that Cefdinir, third-generation cephalosporin produced sulfide ions in the basic experimental conditions (in 0.5 mol dm^{-3} NaOH, 100 °C and 30 min.). On the other hand, the anodic depolarization of the mercury electrode by sulfide is well known.[40] In the present study, the peak at −0.746 V (Figure 2B, Inset) may be probably assigned to the mercury electrode reaction of sulphide species, formed from the hydrolytic degradation of CP in basic medium under UV irradiation. It is well known that the thiol products may be form by alkaline hydrolysis of the thioethers.[41] Probably, UV-light accelerates the hydrolytic degradation of CP and also the formation of the sulphide species by means of basic medium.

Under UV-irradiation or in darkness, the positive shifting of the main peak potential and the decrease in the peak current of CP can be explained by the conversion of CP to cefpodoxime by means of hydrolysis. Cefpodoxime is electroactive and can be also reduced by >C=N–OCH_3 group and also unsaturated C=C bond as like in the CP molecule.

Although the borosilicate glass used in the experiments may partially absorb ultraviolet (UV) radiation,[42]

it is presumed that UV radiation has little direct influence on the hydrolysis based on photolysis reactions.[43] The similar results have been also obtained in this study.

CONCLUSION

The hydrolytic degradation of CP in the presence of UV-irradiation and in darkness was followed at pH range 2.5–11.0 by cyclic and square-wave voltammetry techniques. While the hydrolysis of CP in darkness is only observed at basic pH values (9.0 and 11.0), the CP solutions are stable in the pH range 2.5–7.4. When compared to the results observed in darkness, it can be said that the rate of hydrolytic degradation of CP is increased by UV irradiation of its solutions. The results demonstrate that CP is a photo-labile drug. Owing to the decreases in the main peak current of CP and positive shifts in its potential, it can be postulated that CP undergoes hydrolysis to form cefpodoxime. Under UV-irradiation, CP has the maximum resistance ($t_{1/2}$ = 231 min) for hydrolysis at pH 5. Also, the rate of hydrolytic degradation of CP is increased by increasing pH in the pH range of 5.0–11.0. In addition, the hydrolysis kinetics of CP fitted well with a pseudo first-order reaction at the studied pH range (2.5–11.0). In basic medium (pH 7.4–11.0), the hydrolysis of CP leads to a new electroactive product. These results will aid in the understanding of the anaerobic degradation of CP in the case of the aqueous environment conditions in the presence of UV-irradiation and in darkness. We have established the best pH storage conditions for CP, which are the following: a medium with a pH of 5 under UV light irradiation or a medium with a pH of 2.5 to 7.4 under darkness.

Acknowledgements. This work was supported by Ondokuz Mayıs University Research Fund for financial support through project number PYO.FEN.1901.11.004. The authors are thankful to Fargem A.Ş. (Düzce/Turkey) for providing CP sample used in this study.

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