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Acid Decomposition of Omeprazole in the Absence of Thiol: A Differential Pulse Polarographic study at the Static Mercury Drop Electrode (SMDE)

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ABSTRACT: The reactions of omeprazole, a potent proton pump inhibitor (PPI), were investigated in the absence of a nucleophile. Reactions were monitored, using differential pulse polarography (DPP) at the static mercury drop electrode (SMDE), in solutions buffered to pH values ranging from 2.0 to 8.0. The fast, sensitive, and selective electrochemical technique facilitated to repeat recordings of successive voltammograms [peak current (nA) vs. peak potential (volts vs. Ag/AgCl saturated with 3.0 M KCl)]. The DPP signals of omeprazole and its degradation products, believed to be due to sulfur functional group (the principal site of electrode reaction), gave advantages over the previously employed UV detection technique. The latter primarily relied on pyridine and benzimidazole analytical signals, which are common reaction products of PPI in aqueous acidic solutions. After peak identification, the resulting current (nA)-time (s) profiles, demonstrated that omeprazole undergoes degradation to form two main stable compounds, the first is the cyclic sulfenamide (D^+), previously believed to be the active inhibitor of the H^+, K^+-ATPase, the second is omeprazole dimer. This degradation is highly dependant on pH. Unlike previous studies which reported that the lifetime of D^+ is few seconds, the cyclic sulfenamide (D^+) was found to be stable for up to 5–20 min. The results further indicated that omeprazole converts into the cyclic sulfenamide in an irreversible reaction, consequently, D^+ and sulfenic acid (an intermediate which rapidly converts into D^+) were not interconvertable. The present work suggested that the sulfenic acid is the active inhibitor *in vivo*. In addition, the omeprazole reactions, in the absence of the thiol, were not as complicated as were previously reported.
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Keywords: omeprazole; acid decomposition; differential pulse polarography; cyclic sulfenamide; sulfenic acid

INTRODUCTION

Omeprazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyrinylmethyl-sulfinyl)-1H-benzimidazol ($C_{17}H_{19}N_3O_3S$, f. wt. 345.42 g/mol) is a potent proton pump inhibitor (PPI), consisting of a substituted pyridine ring, connected to a substituted benzimidazole ring by a CH_2SO chain, as shown in the structure below. Omeprazole is amphoteric with pKa values of 3.98 for accepting a proton on the pyridine nitrogen atom, and 8.7 for releasing a proton from the NH group of the benzimidazole.[1]

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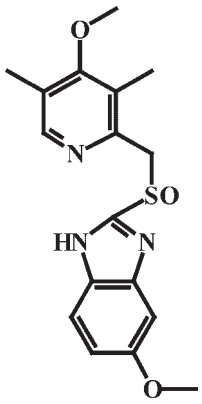
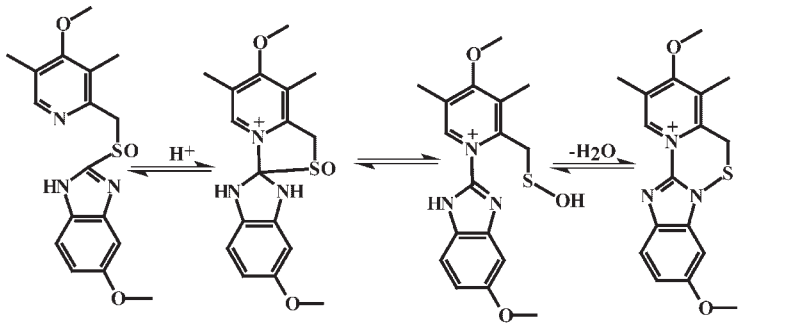


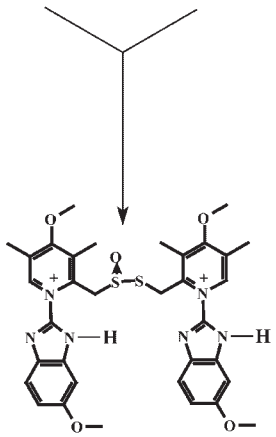
omeprazole

Omeprazole is a weak base, thus concentrates in the parietal cell (the most acidic cell in the body) containing the H^+, K^+-ATPase enzyme which is responsible for acid production.[2]

Several attempts have been made to understand the chemical conversions and the mechanism of action of omeprazole. Among others, these have included: isolation, structure elucidation, and characterization of both intermediates and decomposition products in the acidic media.[3–7] Reversed phase HPLC coupled with UV detection, and indirect UV spectrophotometry have been used to understand the degradation of omeprazole in acidic media; both in the absence and in the presence of 2-mercaptoethanol.[1–7] Previously employed analytical techniques suffered from at least two major drawbacks, which adversely affected an accurate prediction of omeprazole acid conversion scheme[1] and hindered the proper estimation of the rate of formation of the cyclic sulfenamide (D^+), believed to be the active inhibitor. The employed RP-HPLC technique was limited by (1) long-lag time from the moment when the reaction was stopped, to that at which compounds were eluted from the HPLC column (2) UV detection suffered from lack of specificity, since the core molecular structure of reactants, intermediates, and products contain essentially the same chromophoric species which exhibited similar UV spectra. In spite of these drawbacks, it also had limited sensitivity which hindered the detection of trace levels of intermediates. Following a kinetic study, a reaction mechanism have been proposed. Previous researchers suggested that all steps in the reaction scheme, except that which forms the dimer, were reversible as detailed in the reaction scheme below.[1]



omeprazole dihydrobenzimidazole sulfenic acid sulfenamide (D+)



omeprazole dimer

Previous studies on the electrochemical behavior of omeprazole primarily investigated the analytical potential of using electrochemical detection alone or coupled to a RP-HPLC system. An oxidative mode, relying on the amino group of the benzimidazole moiety have been utilized as the most easily oxidized in an adsorption controlled electrode reaction.[8] The reductive mode have also been suggested, since the appearance of omeprazole reduction peak was believed to be a four electron reduction process due to the sulfoxide reduction to sulfide followed by breakage of the CH_2-S bond.[9–12]

In spite of the limitations of previously employed methods and the reported advantages of electroanalytical techniques, no studies attempted to evaluate the current-time or concentration-time profiles of omeprazole and its conversion products at different pH values.

The present work utilized differential pulse polorography (DPP), at the static mercury drop electrode (SMDE), for monitoring simultaneously the current(s) of (1) omeprazole decay with time, and (2) the appearance of all degradation products in the absence of thiol. The fast, sensitive, and specific technique facilitated an accurate determination of a spectrum of compounds related to omeprazole decomposition products in buffered solutions covering a wide range of pH values between 2.0 and 8.0. Fast recording of each polarogram (153 s) facilitated the evaluation of current-time profiles of all species in situe.

EXPERIMENTAL

Chemicals and Reagents

Omeprazole working standard was kindly donated by Dar Al Dawa pharmaceuticals, Na'ur-Jordan. Methanol was HPLC grade from Merck (Darmstadt, Germany). Phosphoric acid, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, and trisodium phosphate were AR from Merck. The cyclic sulfenamide (D^+) was prepared at the pharmacutical Research Unit, Royal Scientific Society (Amman-Jordan) using a reported method.[7] Authentication of D^+ was concluded using ^{1}H-NMR, RP-HPLC coupled with a diode array detector, and polarographic techniques (DPP/SMDE).

All other reagents were used without further purification. Ultrapure water was obtained by initially passing through two reversed osmosis cycles before initiating a distillation followed by a deionization step. Oxygen free nitrogen was used for dearation, of each test solution, prior to initiating successive DPP cycles.

Stock standard solutions of omeprazole were freshly prepared by dissolving omeprazole (10.39 mg) in methanol to produce a final concentration of 3.0×10^{-3} M (stock solution). A 100 μL aliquot of each freshly prepared stock solution was spiked into a dearated buffer solution (10.0 mL; phosphate buffer 0.05 M) solution in a polarographic vessel to make up a final concentration of 3.0×10^{-5} M.

Instruments and Apparatus

A Metrohm 746 VA processor was used; it includes a potentiostat with a measuring amplifier, broad banded, and low noise with a piezoelectric keypad, in addition to a backlit LCD screen, which shows methods and routines. A Metrohm 747 VA stand with a multi-mode electrode (MME) comprising a SMDE as a working electrode, an auxiliary platinum electrode and a reference electrode (double junction type (Ag/AgCl saturated with a 3.0 M KCl solution)) completed the three-electrode cell.

Differential pulse polarograms (DPP) at the SMDE were scanned using the following experimental conditions: a mercury drop area of 0.90mm^2, t drop of 0.6 s, the voltage step was standardized at 13.33 mv/s sweep rate, and a pulse amplitude of 50 mV. A current potential range (ΔU) from 0.00 to −2.00 V versus Ag/AgCl was fixed for all measurement cycles. Unless otherwise specified, the temperature was adjusted using a thermostated polarographic vessel connected to a water bath equilibrated at 37°C.

Procedures

After adjusting the pH of individual phosphate buffer solutions (0.05 M) to the experimental value, a 10.0 mL aliquot was pipetted into the polarographic vessel. Dearation was started by passing nitrogen gas for 8 min, a background signal was measured prior to introducing omeprazole (100 μL, 3.0×10^{-3} M). This was immediately followed by initiating successive recordings of individual DPPs. Recordings were repeated until the omeprazole degraded completely and no analytical signal (current/nA) was detected. DPP profiles were scanned between 0.00 and −2.00 V versus Ag/AgCl. Nine cathodic

reduction cycles (each lasting for 153 s) were repeatedly recorded in each of the four measurement groups. Peak potential(s) (Volts vs. Ag/AgCl saturated with a 3.0 M KCl solution) and peak current(s) (nA) were recorded. This was followed by peak identification, based on each compound's peak potential, whenever possible; using a standard addition technique. The same procedures were followed using constant omeprazole concentrations (3.0×10^{-5} M) for each solution buffered to different pH values including: 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, and 8.0. Peak currents (nA), peak potentials (volts vs. Ag/AgCl), and time (minutes) were tabulated for all cycles in each group. Representative DPP are illustrated in Figure 1 for four groups covering the following time intervals: group (I) nine cycles measured between 0.00 and 19.00 min, group (II) between 26.59 and 71.58 min, group (III) 71.58 and 171.56 min, and group (IV) 291.58 min and 24.0 h.

RESULTS AND DISCUSSION

Identification of Polarographic Peaks

Omeprazole and D^+ peaks were identified using the standard addition technique. In order to achieve this, the cyclic sulfenamide (D^+) was prepared and isolated from a methanolic solution of omeprazole treated with perchloric acid. The yellow cyclic sulfenamide (D^+) was initially characterized using ^{1}H-NMR, IR, and UV spectroscopy. NMR results indicated that the chemical shift of the singlet proton on the pyridine ring of the D^+ was observed at 8.8 ppm, compared to 8.1 ppm for omeprazole. The chemical shifts of the two-methyl groups of the pyridine group of D^+ were observed at 2.4 and 2.6 ppm, compared to 2.1 and 2.2 ppm for omeprazole. The observed downfield shift of substituents on the pyridine ring of D^+ confirmed that the pyridine ring was indeed positively charged. Further evidence to characterize D^+ was the observed upfield chemical shift of CH_2-S of D^+ at 4.3 ppm, compared with 4.7 ppm in the case of $CH_2-S=O$ of the omeprazole. The results were consistent with the UV spectrum of a methanolic solution of D^+, which gave two peaks at 260 and 360 nm in methanol. IR spectra demonstrated that omeprazole and D^+ spectra were significantly different. The yellow crystalline product was subsequently used to confirm that peak (C) in Figure 1 corresponds

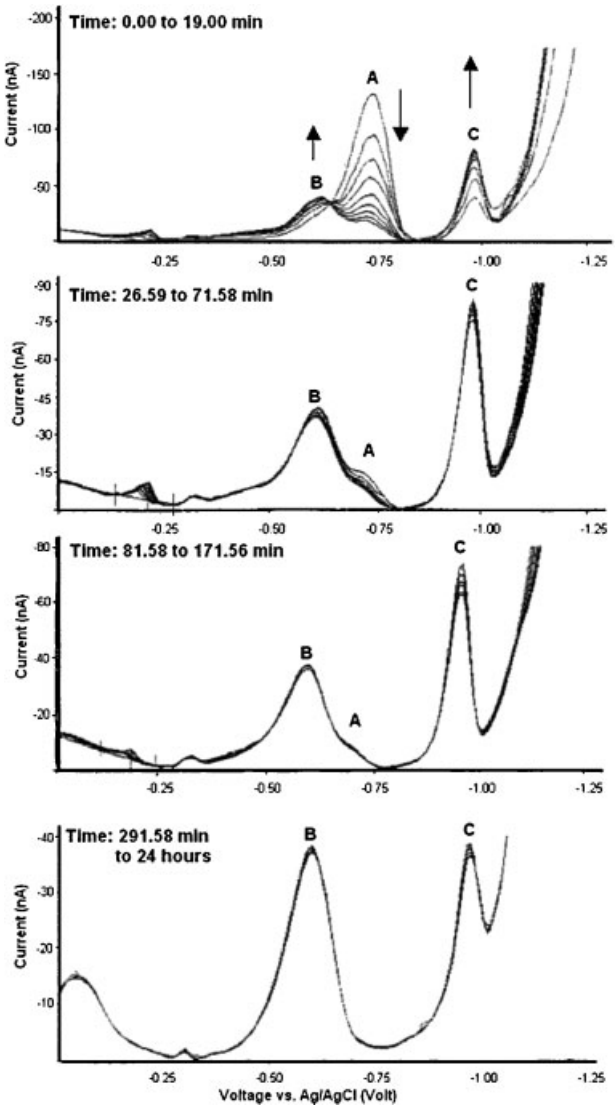


Figure 1. Representative differential pulse polarograms (DPP) at the static mercury drop electrode (SMDE) for omeprazole (3.00×10^{-5}) in a buffered solution (0.05 M, pH = 4) illustrating the decay curves of: omeprazole (A), the cyclic sulfenamide (D^+), (C) as well as omeprazole dimer (B). Group (I) scanned between 0.00 and 19.0 (min) group (II) scanned between 26.59 and 71.58 (min), group (III) scanned between 81.58 and 171.56 min, and group (IV) scanned between 291.58 min and 24.00 h.

to the cyclic sulfenamide (D^+). Peak A, appeared at −0.75 versus Ag/AgCl saturated with 3.0 M KCl solution was due to omeprazole.

Peak B (Fig. 1), was assigned to the dimer because it is the major product expected to result from the acid decomposition of omeprazole.[1]

A peak appeared between −1.3 and −1.4 mV versus (Ag/AgCl, 3.0 M KCl solution) (not shown)

was believed to be due to a reduction of product generated at the surface of the mercury electrode, and not due to the acid decomposition of omeprazole.[12]

Electrochemical Behavior of Omeprazole and its Related Acid Decomposition Products

The electrochemical behavior of omeprazole (3.00×10^{-5} M) in a 0.05 M phosphate buffer gave rise to well defined cathodic reduction peaks, these were identified in Figure 1 as omeprazole (peak A), cyclic sulfenamide (D^+) (peak C), and omeprazole dimer (peak B). Since the working electrode was a static mercury drop, the observed reduction peaks were believed due to sulfur adsorption prior to electrochemical reduction of each analyte. Adsorption is believed to be a prerequisite for the appearance of the observed reduction peaks. Such reduction peaks were not observed for compounds with limited adsorption properties.[11] Three other observations contributed to this conclusion, (1) other PPIs such as pantoprazole and lanzoprazole, which differed only in substituents on the pyridine and on benzimidazole, demonstrated similar reduction peaks (2) the 2-mercaptoethanol, which has no pyridine or benzimidazole moieties gave a well-defined reduction peak under the same experimental conditions (3), the cyclic voltammograms of freshly prepared omeprazole solutions in a phosphate buffer solution (1.23×10^{-3} M, pH = 8) demonstrated irreversibility, when measured at sweep rates: 24, 12, 6, 3, and 1.5 V/s (Fig. 2). It is worth observing that even though the electrode reactions are irreversible, carry over effects were not anticipated since the mercury drop electrode was automatically renewed prior to the recording of successive individual voltammograms.

Effect of pH on Peak Potential(s) for Omeprazole and its Related Acid Decomposition Products

The effect of pH on the reduction potentials of omeprazole and its degradation products is shown in Figure 3. It is clear that as the solution pH increases, the reduction potential(s) of omeprazole and its degradation products shift cathodically. This indicates that protonation of the electroactive site of the molecule affects the overall electrode reaction mechanism.

The sulfur atoms in the three main compounds namely: omeprazole, the D^+, and the dimer are in the sulfoxide, sulfenamide, and disulfide forms, respectively. However, Omeprazole and its degradation products demonstrated similar pH dependence (Fig. 3). It was therefore, concluded that the observed pH effect on the reduction potentials of omeprazole, and its degradation products was mainly due to an adsorption phenomena of the analytes at the surface of the mercury electrode and is the origin of the analytical signals (nA).

Omeprazole Decomposition at Different pH Values

At pH values of 2.0, 3.0 and 4.0, the degradation of omeprazole was fast, since peak currents (nA) of omeprazole reached approximately zero after 15–20 min. Degradation became slower as solution pH was increased from 2.0 to 8.0 (Fig. 4). This confirmed that omeprazole decomposition is acid catalyzed.

Effect of pH on the Appearance and Stability of the Cyclic Sulfenamide (D^+)

The appearance of D^+ is most prominent at a pH value of 2.0, it decreased as pH was increased from 2.0 to 5.0 (Fig. 5). Table 1 summarizes the maximum analytical signal and the time to reach this signal by D^+ evaluated at different pH values. A decrease in the maximum peak current was observed as pH increased from 2.0 to 5.0. No currents were observed for D^+ at pH values 6.0, 7.5, and 8.0, since omeprazole degradation was too slow, with some degradation occuring after 48 h. This confirms that omeprazole is essentially stable in solutions having neutral or basic pH values.

After reaching a maximum peak current (nA), depending on solution pH, the cyclic sulfenamide (D^+) may react with the sulfenic acid intermediate to form a dimer (see reaction scheme above). Table (1) clearly indicates that the lifetime of D^+ is relatively large contrary to previous reports which pointed out that the lifetime of D^+ is only few seconds. This observation becomes significant for predicting the mechanism of proton pump inhibition.

Effect of pH on the Appearance of Omeprazole Dimer

The appearance of omeprazole dimer was faster at pH = 2.0, it slowed down as the solution pH was increased from 2.0 to 5.0. Peak currents (nA) of the dimer were not observed in solutions having pH values of 6.0, 7.5, and 8.0 (Fig. 5). Consequently, the degradation of omeprazole and the appear-

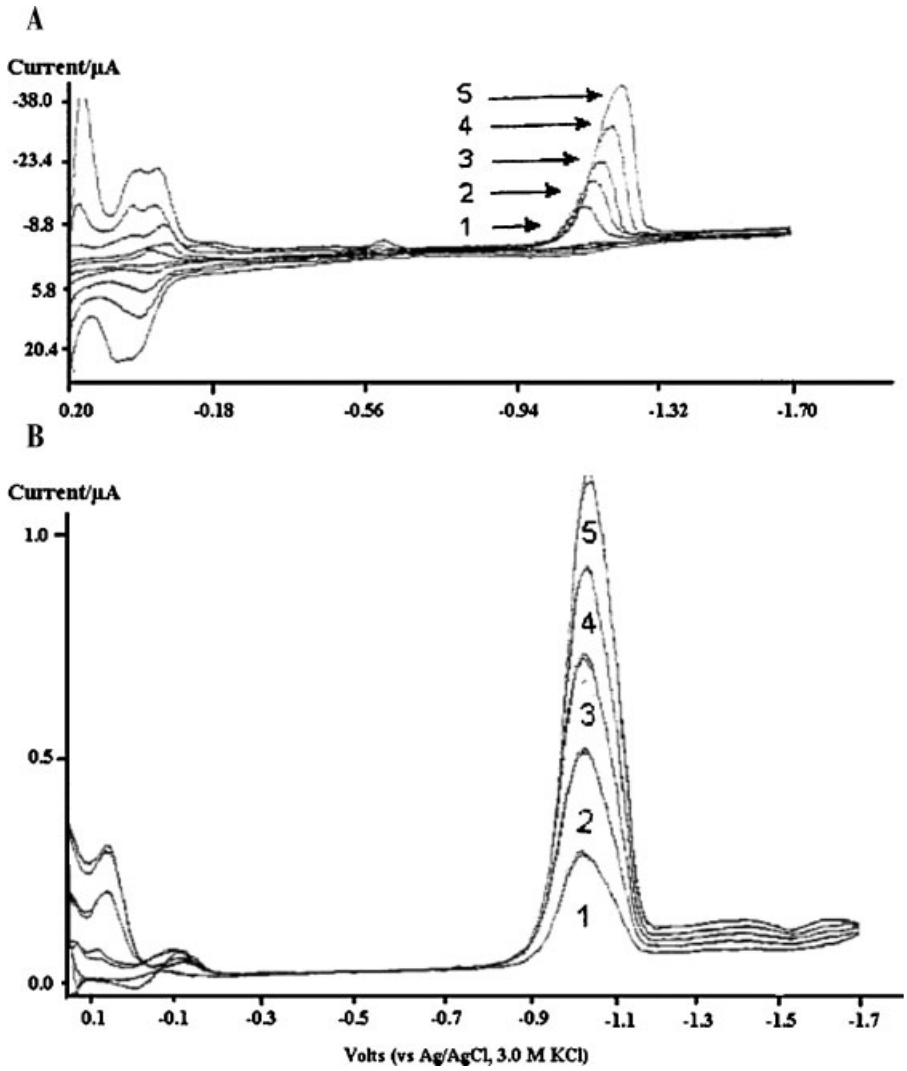


Figure 2. (A) Cyclic voltammograms for omeprazole; recorded at different sweep rates of (1) 24 (2) 12 (3) 6 (4) 3 (5) 1.5 (V/s). (B) Standard addition of 100 μL, 200 μL, 300 μL, 400 μL, and 500 μL (1–5), respectively of 0.0492 M omeprazole solution in methanol to a 10.00 mL buffered solution (0.05 M, pH 8).

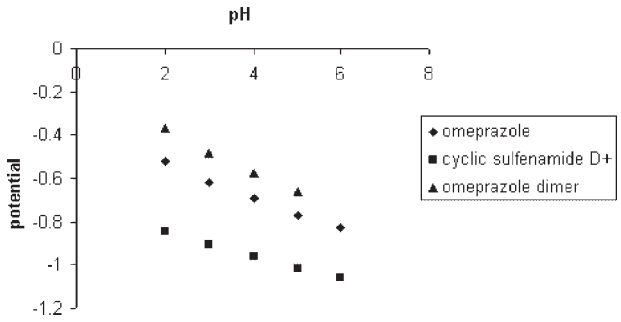


Figure 3. Dependence of peak potentials of omeprazole, cyclic sulfenamide (D^+), and omeprazole dimer on pH.

ance of D^+ were not significant at pH values higher than 5.0, formation of omeprazole dimer was, therefore, similar to that of D^+. Once formed, the dimer was stable, as depicted in Figure 5, which showed a plateau of the analytical signal with time, this confirmed further that the dimer is the final product of the investigated reaction.

Reversibility of Omeprazole Reaction to Form the Cyclic Sulfenamide (D+)

To test reversibility of the reaction omeprazole ↔ D^+, a methanolic solution of a perchlorate salt of D^+ (3.0×10^{-3}) was spiked into a dearated phosphate buffer solution (0.05 M, pH 4.0) to

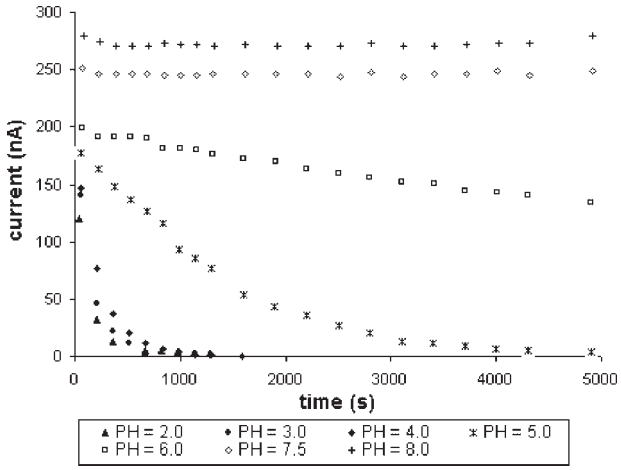


Figure 4. Current-time decay curves of omeprazole (3.00×10^{-3}) in solutions, individually buffered to pH values of 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, and 8.0.

make up a final concentration of 3.00×10^{-5} M. Successive polarograms were scanned with time (Fig. 6). Contrary to previous reports,[7] peak currents pertaining to D^+ remained constant for 172.9 min. No reversible generation of omeprazole was observed. This observation confirmed that the degradation of omeprazole to D^+ is irreversible.

Similar experiments in solutions having pH values of 2.0 and 6.0 demonstrated that D^+ degraded to half of its initial signal after about 20 and 40 min, respectively. This degradation of D^+ was not accompanied by an increase in any of the signals due to species in the investigated potential window. This indicates that D^+ may have degraded to form an electrochemically inactive product. The weak analytical signal of omeprazole dimer which appeared with the D^+ signal did not show significant increase during the degradation of D^+.

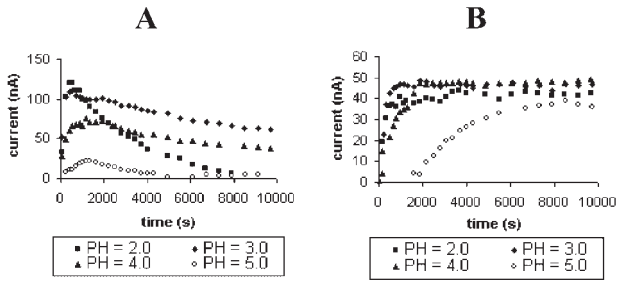


Figure 5. Current-time profiles of (a) the cyclic sulfenamide (D^+) and (b) omeprazole dimer in omeprazole solutions (3.00×10^{-3}) individually buffered to pH values of: 2.0, 3.0, 4.0, and 5.0.

Table 1. Maximum Peak Current (nA) of D^+ Reached and With Time (min) to Reach Maximum Current for a Constant Omeprazole Concentration (3.00×10^{-5}) in Individually Buffered Solutions With pH Values (2.0–5.0)

pH	Maximum Current (nA)	Time to Reach Maximum Signal (min)
2.0	120	6
3.0	110	9
4.0	76	20
5.0	22	22

Effect of Temperature

Omeprazole conversions were monitored in buffered solutions previously equilibrated to either 23 or 37°C. The rate of disappearance of omeprazole was obviously faster at 37°C, as a result; the rate of appearance of the cyclic sulfenamide (D^+) and omeprazole dimer were consequently faster. This indicates that the degradation of omeprazole is endothermic and is entropy driven.

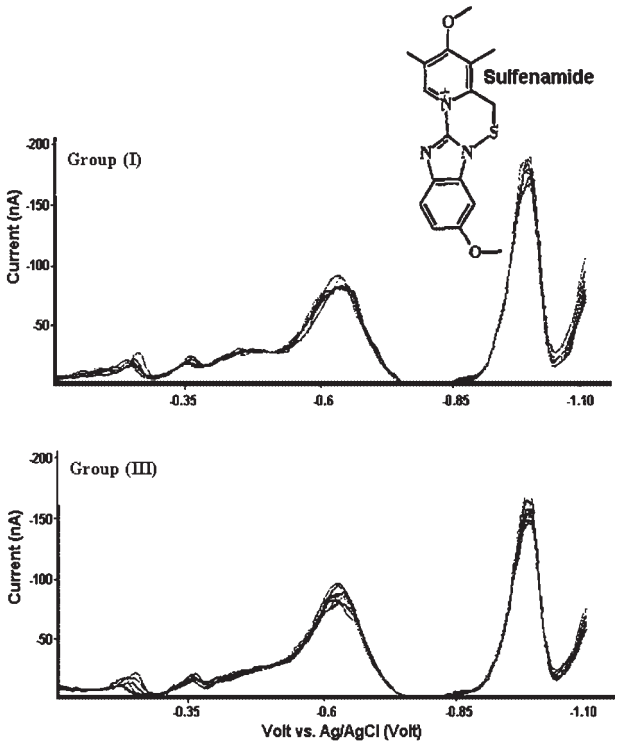


Figure 6. Representative voltammograms for the cyclic sulfenamide (D^+) and omeprazole dimer: Group (I) scanned between 0.00 and 19.00 (min), group (III) scanned between 82.5 and 172.92 (min).

Effect of Day Light

The cyclic sulfenamide was found to be slightly less stable in day light compared to its stability when kept in the dark.

OVERALL CONCLUSIONS ON THE ACID DECOMPOSITION OF OMEPRAZOLE IN THE ABSENCE OF AN ADDED THIOL

Using the fast, sensitive, specific and selective electroanalytical method, the authors investigated omeprazole under different reaction conditions. The cyclic sulfenamide (D^+), previously believed to be the active inhibitor of H^+, K^+-ATPase enzyme, was found to be a relatively stable main degradation product of omeprazole. The authors concluded that, as a result of omeprazole degradation, D^+ converts into the dimer and/or other electrochemically inactive products.

The presence of sulfenic acid as an intermediate is believed to be necessary for the formation of the dimer. If one starts from a perchlorate salt of D^+ solution, no measurable conversion of D^+ into omeprazole or dimer is observed. It was thus concluded that the reaction of omeprazole to the cyclic sulfenamide D^+ was irreversible; no sulfenic acid intermediate forms. Due to this irreversibility, D^+ and sulfenic acid were not rapidly interconvertable, as previously reported. Sulfenic acid, therefore, should be further investigated as the active inhibitor *in vivo*.

Based on these observations, acid decomposition of omeprazole in the presence of a thiol should be extensively investigated to confirm the mechanism of action of PPIs.

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