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Surface Modified Electrodes Used In Cyclic Voltammetric Profiling Of Quinine An Anti-Malarial Drug.

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Abstract: *In this paper electrochemical profiling of quinine, an effective anti- malarial drug administered to humans, was done using primarily the very versatile electrochemical technique- cyclic voltammetry. In the electro-analysis, the main supporting electrolyte used was sulphuric acid. The surface of the working electrode was modified using electronically conducting polymer- polyanailine and a clay montmorillonite- bentonite. Quinine and metal cation Cu^{2+}, Co^{2+}, Zn^{2+} and Sn^{2+} were also used to modify the electrode surface.The results obtained showed that quinine oxidation /reduction potential on bare carbon graphite electrode occured at 0.495V/0.300V and 0.015V (0.25M H_2SO_4 supporting electrolyte). Bentonite modified electrode gave 0.434V/0.480V (1M H_2SO_4 supporting electrolyte) and 0.360V/0.345V (1M HCl supporting electrolyte). A mechanistic pathway for the oxidation of quinine has also been proposed. It was also observed from the results obtained from studies on the effect of consumables such as tea, glycine and milk on quinine, that milk totally suppressed the redox process in quinine. Amino acids which are the building blocks in proteins and which is an important macromolecule in humans, does not affect significantly the redox process in quinine.*
Cyclic voltammetric profiling of quinine interaction with metal cations such as Cu^{2+}, Co^{2+}, Zn^{2+} and Sn^{2+} and drugs such as paracetamol, acetyl salicylic acid, hydrocortisone and ferrous fumarate revealed interactions between the redox centers.

Key Words: *Surface modified electrodes, cyclic voltammetry, polyaniline, bentonite and quinine*

I. Introduction:

Quinine has been a major asset in the fight against malaria, a disease caused by a one-celled parasite known as plasmodium thought to be transmitted to humans through the bite of a female Anopheles mosquito. The four distinct plasmodia that infect humans are : P.malariae, P. ovale, P. falciparum and P. vivax.

P. vivax and P. falciparum are the most common and P.falciparum the most deadly type of malaria infection . Extensive research has been conducted in an effort to contain malaria(1-17)

In this study we applied surface derivatised electrodes to study and assess the quality of anti-malarial drug quinine electrochemically.

In the analysis the oxidation-reduction profile of the quinine was analyzed using a versatile electrochemical tool- cyclic voltammetry. In addition, cyclic voltammetry was used to study redox interaction of quinine with consumables such as tea and milk, drugs such as acetylsalicylic acid, paracetamol, iso-nicotinic acid, hydrocortisone and ferrous fumarate. Quinine interaction with metal cations is also reported.

II. Experimental Section:

All chemical reagents were used as received without further purification, except the monomer liquid Aniline (Aldrich 99%) which was triply distilled until colorless liquid was obtained . It was then stored under nitrogen.

All solutions were prepared using de-ionized water. The clay montmorillonite, bentonite (sourced from Athi River Mining Company Ltd., Kenya) was purified as described by Bard(18-19). It has a mesh size ranging from 150 to 200 um, cation exchange capacity (CEC) 1.18-1.22 mM/g and a pH range of 8.4-9.6. The density of the bentonite is 1.25g/cm3 which are comparable to other clay minerals from different parts of the world (18). It has a solvent retention capacity of 22.5% and 4.8% for water and organic solvents respectively, while its moisture content is 8.5%. It swells by a factor of 1.7 and 1.4 in water and organic solvents respectively

In generating the cyclic potential scans, two sets of instruments were used. These comprised of a Princeton Applied Research (PAR) model 173 pontentiostat/galvanostat, a logarithmic current converter model 369 that controlled the current, a PAR model 175 universal programmer and a PAR RE 0089 X-Y recorder.

III. Results and Discussion

Electrochemical analysis of quinine:

The electrochemical response of quinine was carried out on bare carbon graphite and bentonite modified working electrode. 300mg of quinine was in a solution of 0.25 M sulphuric acid. The potential was cycled from -0.4 V to 0.90Vat a scan rate of 10mV/sec.

The resultant cyclic voltammetric response is shown in figure 1.

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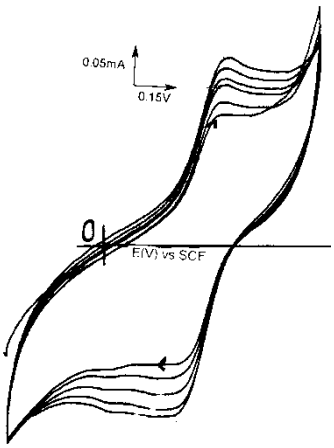


Fig. 1: Cyclic voltammetric response obtained when bare carbon working electrode potential was cycled within the potential range -0.4V to 0.90V in a solution containing 300mg of quinine and 0.25M H_2SO_4 solution

The redox process is quasi reversible with the oxidation peaks occurring at 0.495V and reduction peaks occurring at 0.300V and 0.015V respectively. It is notable that the reductive peak consists of several peaks, suggesting the presence of several redox centers. Quinine has a pyridine ring, therefore the presence of multiple peaks is not surprising given that, the pyridine ring has methoxy functional group. Attached as a side chain is also alcohol group.The redox potential observed occur at about the same potential as that, for quinine/imine derivatives observed during electrodegradation of polyaniline, a polymer electro generated from electro – polymerization of aniline. As the concentration of acid in the electrolyte media was increased, there was tremendous improvement in the redox profile of the quinine, yielding much better defined peaks (see figure 2).

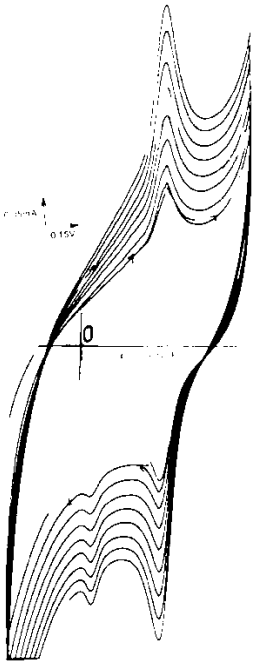


Fig. 2: Cyclic voltammetric response obtained when bare carbon working electrode potential was cycled within the potential range -0.4V to 0.90V in a solution containing 300mg of quinine and 2M H_2SO_4 solution.

It is worth noting that, in the case of 2M sulphuric acid solution, the reduction peak forms two clearly defined peaks. In the case of the oxidation peak, we have a single peak at 0.4425V and the reduction peaks occur at 0.4125V and 0.006V. It is apparent from this result that, the quinine redox process is strongly pH dependent. We observe a negative shift in the redox potentials with increasing pH. This observation can be attributed to the possibility of an e-c mechanism where we have electron transfer followed by a chemical reaction. In addition, the quinine/imine derivatives alluded to earlier have a strongly pH dependent redox process. This pH dependent redox activity of quinine is important given that, the pH is important in the gastro-intestinal tract of humans. This therefore means that the gastro intestinal system pH can impact on the absorption of quinine given that, there is always a Donnan potential developed across the membrane .

Scan rate dependence studies yielded linear plots, as in the case of anodic peak current versus square root of scan rate (See figure 3). This suggests that, the quinine redox process is a diffusion limited process.

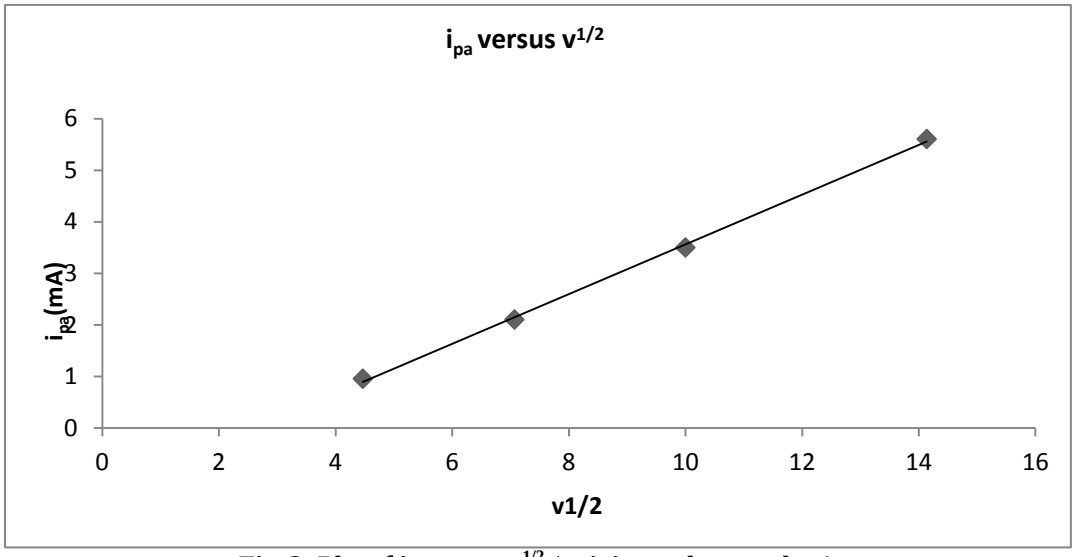


Fig. 3: Plot of i_{pa} versus $v^{1/2}$ (quinine on bare carbon)

Bentonite Modified Electrode:

Similar analysis was repeated, but on a bentonite modified electrode. The objective of this experiment was to study the effect of the host matrix on the redox behavior of quinine. The electrolyte media contained 300mg of quinine in 1M sulphuric acid solution and in another set 1M hydrochloric acid. The potential window ranged from -0.4V to 0.90 V. The resultant CV responses are shown in figures 4 and 5.

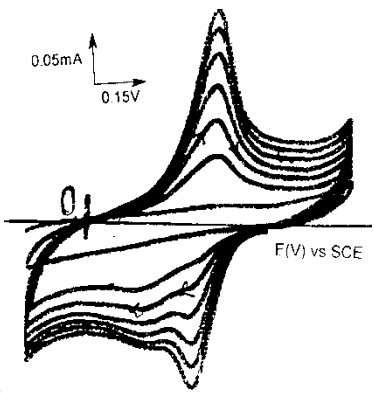


Fig. 4

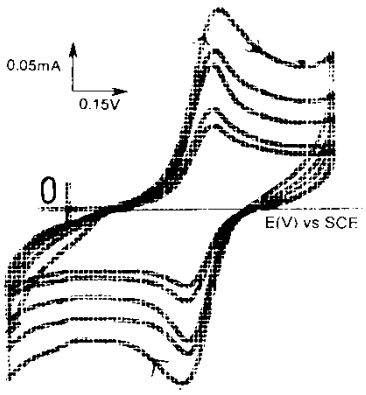


Fig. 5

Fig. 4: Cyclic voltammogram obtained when bentonite modified carbon working electrode was cycled within the potential range -0.4V to 0.90V in a solution containing 300mg of quinine and 1M H_2SO_4

Fig. 5: Cyclic voltammogram when bentonite modified carbon working electrode was cycled within the potential range -0.4V to 0.90V in a solution containing 300mg of quinine and 1MHCl

In all the cases the cyclic voltammograms in both acid media had well defined peaks with the oxidation and reduction peaks for the sulphuric acid and hydrochloric acid occurring at 0.435V/0.480 V and 0.360V/0.345V respectively. It is apparent from the results that the bentonite host matrix which is characterized by the presence of octahedral and tetrahedral plates (Bard et al) has probably suppressed/inhibited the follow-up chemical reaction observed in the bare carbon case. This improved redox response of quinine in the bentonite modified electrode can be attributed to the pre-concentration of the quinine molecules as a result of being trapped in the octahedral layers in the bentonite. This alignment of quinine in the clay montmorrilonite matrix decreases the overall entropy of the quinine molecules. It is also observed that, the redox potential is different. This differences can be attributed both to the nature of the host matrix and the type and size of anions in the supporting electrolyte i.e., chloride ions (Cl^-) in the case of hydrochloric acid and hydrogen sulphate/sulphate ions (HSO_4^-/ SO_4^{2-})in the case of sulphuric acid. The differences in the nature of the anions will affect their ingress profiles into the bentonite matrix subsequently affecting their redox potentials

To assess the behavior of quinine on the working electrode surface, scan rate dependence studies were conducted. A plot of anodic peak current versus square root of scan rate for quinine on bentonite modified electrode in hydrochloric acid, yielded a linear plot suggesting that the quinine is not a surface attached species and the redox process is diffusion limited (See figure 6). The fact that diffusion of quinine redox active moiety into the bentonite is the rate determining step is not surprising given that quinine is a bulky molecule.

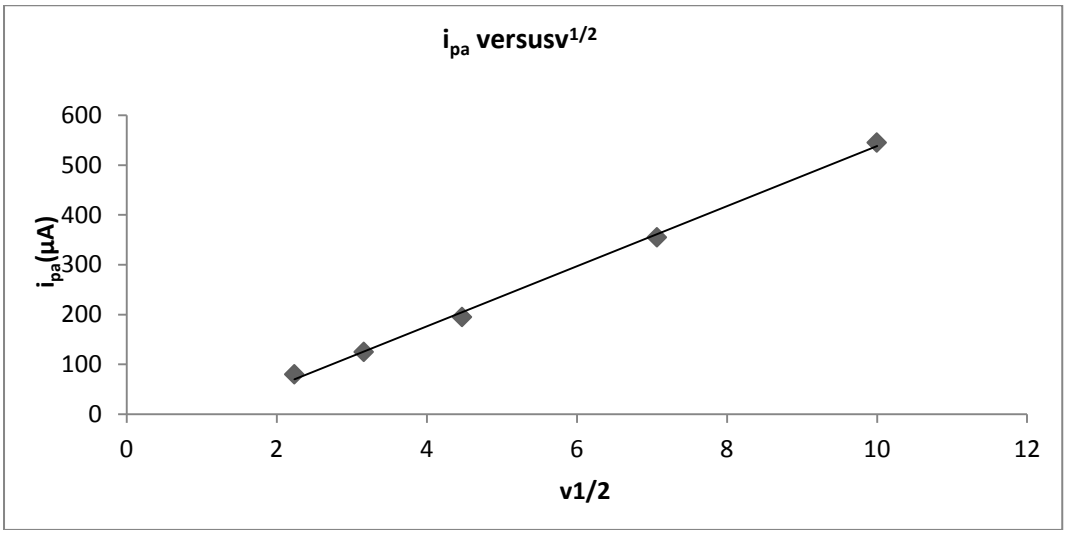


Fig. 6: i_{pa} versus $v^{1/2}$ in the case of quinine on bentonite modified electrode in 1M HCl

The pH dependence studies show that the redox peak attributed to quinine shifts towards positive potentials as the electrolyte pH is decreased. See figure 7.

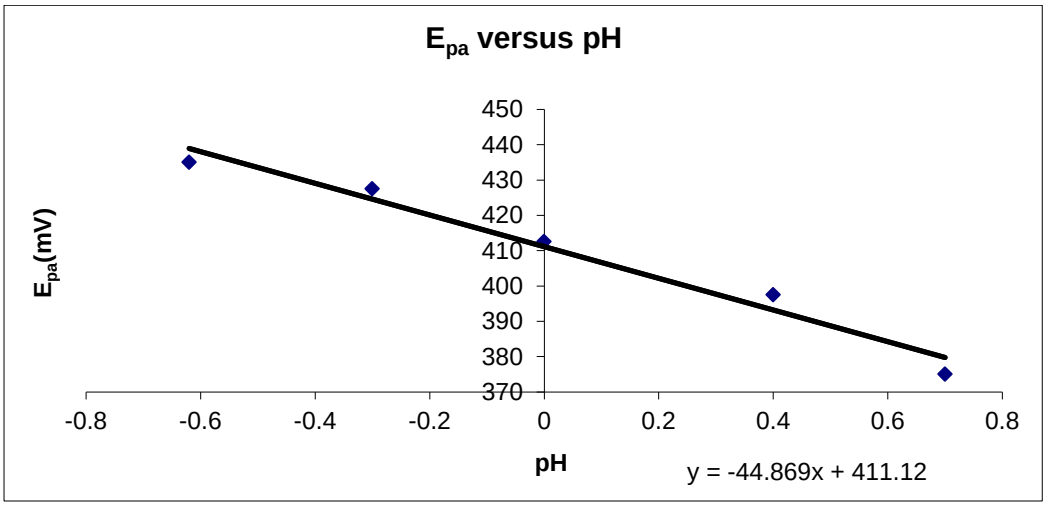


Fig. 7: Plot of E_{pa} versus pH for quinine on bentonite modified electrode in H2SO4 solutions (0.1M,0.5M,1.0M,1.5M and 2.0M).

The oxidation potential versus pH curve had a slope of -44mV/pH unit. This suggests that, the quinine redox process is a $1H^+/1e^-$ process. This observation suggests that, the central redox activity in quinine is as a result of redox activity of the pyridine derivative in the molecule..

Polyaniline Modified electrode:

The surface of the working electrode was modified with polyaniline. The polyaniline film was electrodeposited on the electrode surface by cycling the potential of a solution containing 0.1M aniline in 1M sulphuric acid and cycling the potential from – 0.2V to 0.80V at a scan rate of 20mV/sec. A thin film of polyaniline, having an oxidative peak current of 2.05mA on the cyclic voltammogram was used as the host matrix. the polyaniline modified electrode was then transferred to a solution containing 0.1g quinine in 1M sulphuric acid. The resultant cyclic voltammograms are shown in figures 8a and 8b.
responses are shown in figures 10a and 10b.

Fig. 8a

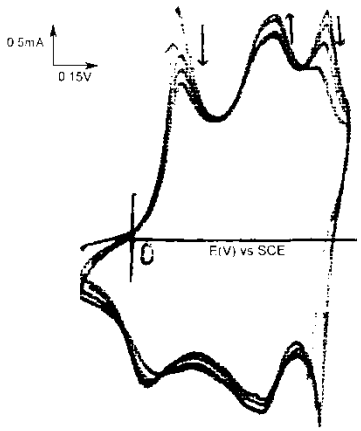


Fig. 8b

Fig. 8a: CV response of PAN electrodeposited on bare carbon graphite electrode in a solution containing1M H_2SO_4 and 0.1M aniline. Potential window: -0.2V to 0.80V. Scan rate 20mV/sec.
Fig. 8b: Cyclic voltammogram when polyaniline modified carbon working electrode was cycled from -0.4V to 0.90V in a solution containing 300mg of quinine and 1M H_2SO_4

We observed that the oxidative peak potential for the quinine overlaps with the quinine/imine redox peaks at the potentials 0.540V/0.501V. This confirms our earlier assertion that oxidation of quinine leads to the formation of quinine/imine derivatives. It is also apparent that the oxidation potential of quinine is significantly altered positively on a polyaniline modified electrode. This is not surprising in that the orientation of quinine molecules on the polyaniline host matrix is affected by the fact that, there will be a tendency of the heterocyclic nitrogen in the quinine ring and that in the polyaniline polymeric structure to cluster together. The net effect of this is a decrease in the entropy of the quinine on the polyaniline host matrix leading to an increased oxidation potential.

Quinine Modified Electrode:

In this experiment, the surface of the carbon graphite working electrode was modified with quinine. The potential of the quinine modified electrode was cycled from -0.4 V to 0.90 V in 1M sulphuric acid. The scan rate was 20mV/sec. The resultant cyclic voltammogram is shown in figure 9. The redox activity is reversible and the rate of change of anodic peak current with time is linear.

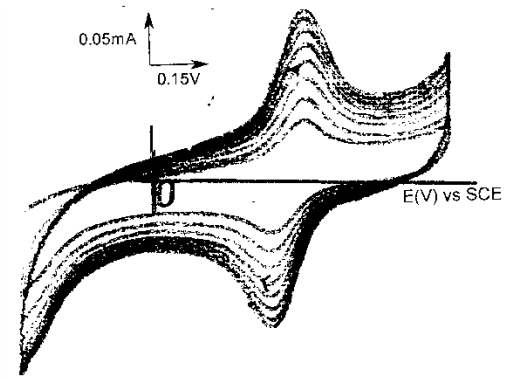


Fig. 9: Cyclic voltammogram when quinine modified carbon working electrode was cycled within the potential range -0.4V to 0.90V in 1M H_2SO_4 at a scan rate of 20mV/sec

The redox response is reproducible therefore pointing at a memory effect or factor in relation to the redox process. Such a memory effect has been observed in polymeric system such as polyaniline, where the film is stable even after nearly a million potential cycles. This property of quinine is a pointer to the prominent role of the pyridine group leading to a form of di/poly-merization of quinine involving the nitrogen group in the pyridine ring.

The deposition rate is proportional to the change in peak current since the anodic peak current is proportional to oxidative charge. This in turn can be related to the surface coverage by the equation

$$\Gamma_T = \frac{Q_{ox}}{nFA} \quad \text{…….. ……}$$

Where Q_{ox} is the oxidative charge, Γ_T is the surface coverage, n is the number of electrons, A is the surface area of the electrode and F, the Faraday constant.

The maximum oxidative charge occurred after 15 min. This charge corresponds to the surface coverage of 8.39×10^{-9} mol/cm^2.

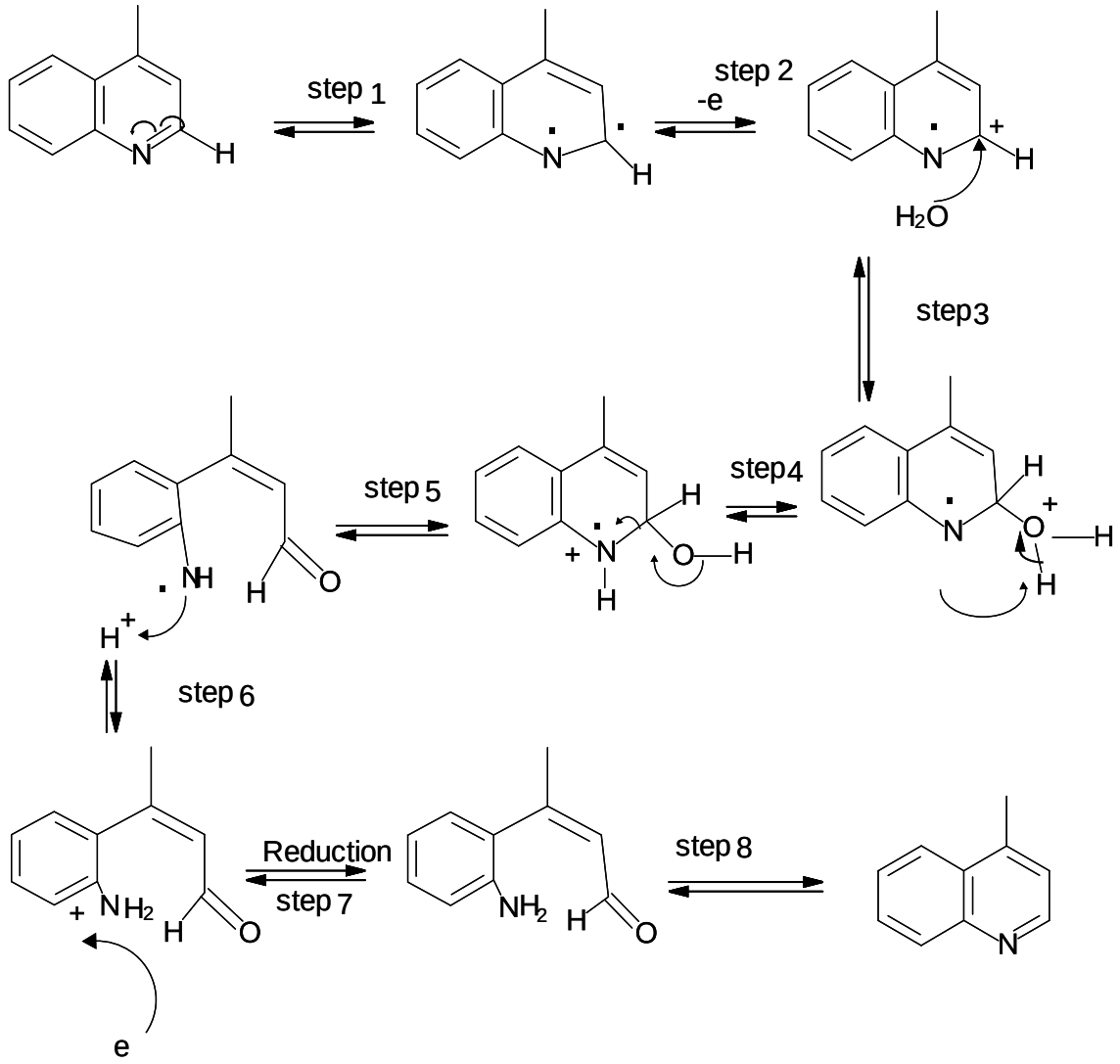
This value corresponds to 0.03g of quinine which based on the molecular weight of quinine gives a surface coverage of 7.62×10^{-5} mol/cm^2. The concentration of redox active drug species deliberately attached at the working electrode surface was computed using the limiting oxidative charge for quinine. The percentage of electro active species is 0.011%.

We observe that, the quinine oxidative peak potential overlaps with the quinine/imine redox peaks at 0.540V/0.510V. This is in agreement with our earlier assertion that, oxidation of quinine leads to formation of quinone derivatives. It is also apparent that, on the polyaniline host matrix, we have a significant positive potential of quinine.This implies that, the polyaniline host matrix influences the redox potential of quinine, in this case increasing its oxidation potential. This is not surprising given that, the orientation of quinine molecules in the polyaniline host matrix will probably be characterized by the tendency of the heterocyclic nitrogen in quinine aligning itself with nitrogen s in the polyaniline polymeric structure, leading to a decrease in the entropy leading to an increase in the oxidation potential.

Proposed Mechanistic Pathway for the Oxidation of Quinine:

We propose that the mechanistic pathway for quinine oxidation is the one shown in Scheme 1. The oxidation (steps 1 to 6) shows the removal of one electron and one proton. This is in agreement with our observation where the shift in oxidation potential versus pH is 58mV/pH. On continued oxidation /electrode gradation, we note quinine/imine peaks reminiscent of electro-degradation of polyaniline where quinine imine derivatives were formed. We propose therefore propose that, the steps associated with this quinine oxidation process are in steps 1to 5.

formed.



Scheme 1: Proposed mechanistic pathway for the quinine redox process

Interaction of Quinine with Various Substances:

The carbon graphite working electrode was modified with quinine as already described. The quinine modified electrode was then transferred to various electrolyte media containing 4000ppm tyrosine, 4000ppm cholesterol, 4000ppm leucine, 4000ppm iso-nicotinic acid and 4000ppm acetylsalicylic acid. The supporting electrolyte in all the cases was 1M sulphuric acid. The potential was cycled from -0.2 V to 0.9V at a scan rate of 20mV/sec. The choice of the interactive substance was based on the fact that, proteins are important in human physiology. Salicylic acid and nicotinic acid are drugs which regularly interact with the human system when deliberately ingested orally or injected into the human physiological system. The resultant cyclic voltammetric responses are shown in figures 11a to 11d.

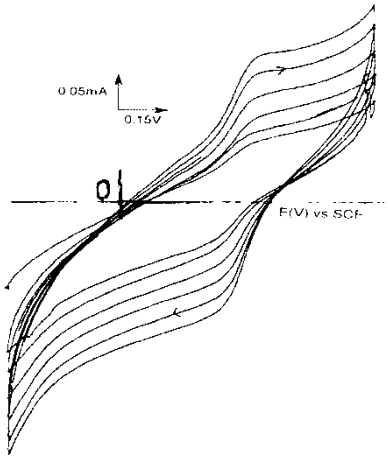


Fig. 11a

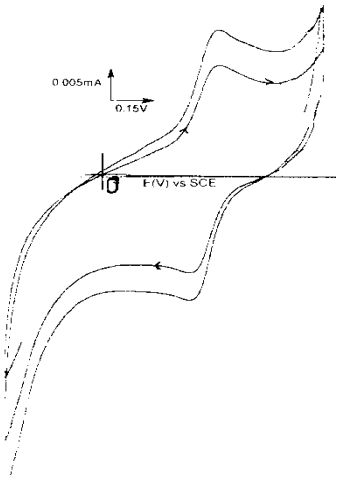


Fig. 11b

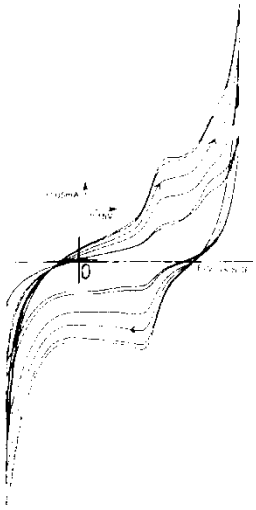


Fig. 11c

Fig. 11a, 11b, and 11c: CV responses obtained when quinine modified electrode(QME) was cycled in 1M H_2SO_4 and 4000ppm tyrosine; 1M H_2SO_4 and 4000ppm leucine; 1M H_2SO_4 and 4000ppm cholesterol. Potential range: –0.2Vto 0.9V. Scan rate of 20mV/sec

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