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Electro-oxidation of Atenolol at a Glassy Carbon Electrode

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The electro-oxidation of atenolol has been studied at a glassy carbon electrode in tetramethyl ammonium chloride in methanol media by using cyclic voltammetric technique. Effects of anodic peak potential (E_{pa}), anodic peak current (i_{pa}) and heterogeneous rate constant (k_o) have been discussed. Single irreversible voltammogram was observed. The effects of scan rate, concentration, dielectric constant and temperature were evaluated. The electro-oxidation product of atenolol has been identified as 2-[4-(3-isopropylamino-2-oxo-propoxy)-phenyl]-acetamide involving 2-electron oxidation. The electrode processes were shown to be diffusion controlled and irreversible involving adsorption effects.

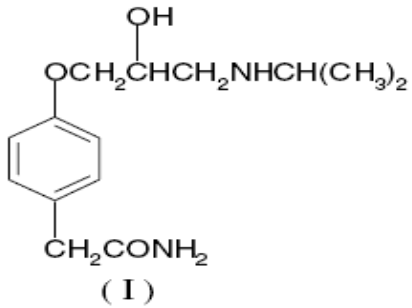
Keywords: Atenolol; Cyclic voltammetry; Glassy carbon electrode; Dielectric constant

1. INTRODUCTION

4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide, commercially known as atenolol (Scheme 1),a β-adrenoreceptor blocking agent,is used as a antihypertensive drug(1). It is also used for anti-angina treatment to relieve symptoms, improve tolerance and as an anti-arrhythmic to help regulate heartbeat and infections. It is also used in management of alcohol withdrawal, in anxiety states, migraine prophylaxis, hyperthyroidism and tremors (2,3). The derivative of oxidation product of atenolol finds its importance in biological systems such as plant growth hormones, herbicides, etc. β - Blockers are exceptionally toxic and have a narrow therapeutic range. The overdose of atenolol will lead to lethargy, disorder of respiratory drive, wheezing, sinus pause, bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia (4,5).

Investigations of the redox behavior of biologically occurring compounds by means of electrochemical techniques have the potential for providing valuable insights into the biological redox

reactions of these molecules. Due to their high sensitivity, voltammetric methods have been successfully used to study the redox behavior of various biological compounds (6-9). In this paper a simple and sensitive procedure to study the electro-oxidation of atenolol at glassy carbon electrode is presented and it undergoes electro-oxidation at tetra methyl ammonium chloride in methanol media and there is no oxidation in phosphate buffer as discussed by R.N.Goyal and his coworkers (10,11).



(I)

Scheme 1. Chemical Structure of atenolol.

2. EXPERIMENTAL PART

2.1. Reagents and Chemicals

Pure atenolol in powdered form was obtained as a gift sample from S.S.Antibiotics Pvt.Ltd, Aurangabad, India. Methanol (dry) and Tetramethylammoniumchloride (TMAC) are purchased from SD Fine-Chem Ltd. All other reagents used were of analytical grade. Double distilled water is used throughout the experiment. Pure N_2 (99.9%) is purged through the solution for 30 minutes.

2.2. Apparatus and Procedure

The electrochemical experiments were performed with CH Instruments, USA (Model 1110A,Version 4.01) Electrochemical Analyzer and were carried out in a 10ml single compartment three-electrode glass cell with a 3mm diameter glassy carbon electrode as the working electrode (Part No.CHI104), a platinum wire as counter electrode and Ag/AgCl electrode as reference electrode. All experiments were carried out at an ambient temperature of 25 ± 0.2^0C.

The GCE is polished using 0.3 micron Al_2O_3 before each experiment. After polishing, the electrode was rinsed thoroughly with methanol. After this mechanical treatement, the GCE was placed in 0.1M TMAC electrolyte and various voltammogramms were recorded until a steady state baseline voltammogram was obtained.

The area of the electrode was calibrated using 10mM $K_4Fe(CN)_6$ in 0.1M K_2SO_4 by recording the current voltage curve. From the cyclic voltammetric peak current (17.3μA) the diffusion coefficient of $Fe(CN)_6^{4-}$, the area of the electrode was calculated [14,15] by using the equation

$$i_{pa} = (2.69x10^5)\, n^{3/2}\, A\, Do^{1/2}\, \nu^{1/2}\, Co^* \qquad (1)$$

where n=number of electrons transferred, A=area of the electrode, D=diffusion coefficient ($6.538x10^{-6}$ cm^2s^{-1}), ν=sweep rate ($0.05Vs^{-1}$) and Co*=concentration of electro active species (10mM).

The area of the electrode was found to be 0.058 cm^2. Equation (1) was used to calculate number of electrons transferred and found to be 2.

A stock solution of atenolol (10mM) and 0.1M TMAC was prepared in dry methanol. Required amount of the stock solution was added to 5ml of TMAC and total volume is made 10ml with methanol. The electrochemical measurements were then carried out.

3. RESULTS AND DISCUSSION

3.1. Electro-oxidation of atenolol

The oxidation of atenolol at a GCE was studied by cyclic voltammetry (CV) in 0.1M TMAC as supporting electrolyte in methanol media. In the studied potential range, the oxidation peak for methanol was not observed. The cyclic voltammogram obtained for 2mM atenolol solution at a scan rate $\nu=50mVs^{-1}$(Fig.1) shows one anodic peak that occur at E_{pa}= +1.097 V. On scanning in the negative direction, no reduction peak was observed, showing that the oxidation of atenolol is an irreversible process. A decrease of the oxidation current occurs with the number of successive scans and is due to the adsorption of atenolol oxidation products on the GCE surface (Fig.2).

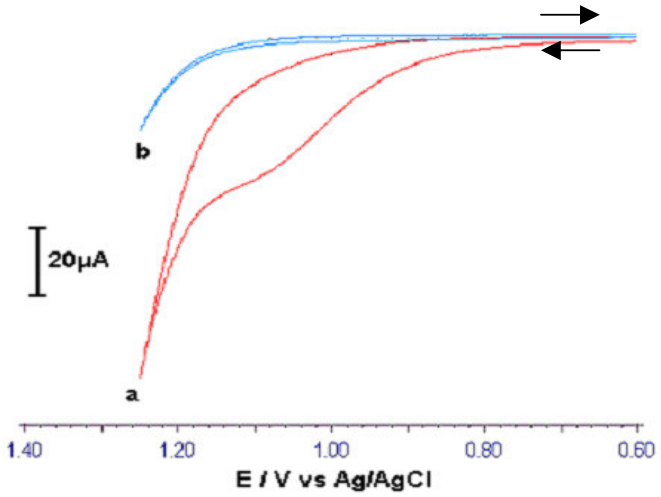


Figure 1. Cyclic voltammogram obtained for 2mM atenolol on GCE in 0.1M TMAC :(a) atenolol and (b) blank at $\nu=50mVs^{-1}$.

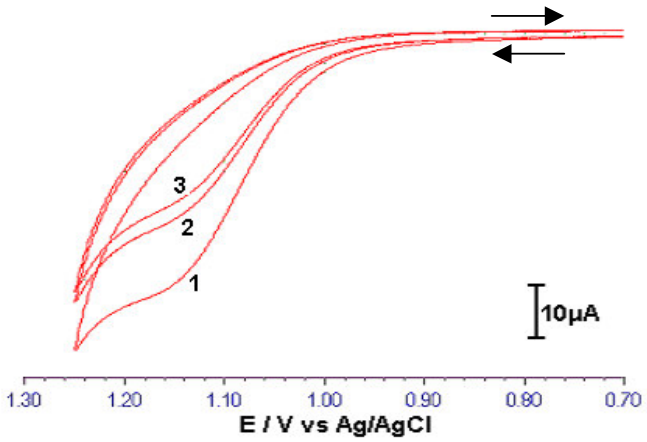


Figure 2. Successive cyclic voltammograms obtained for 3mM atenolol on GCE: (1) first, (2) second and (3) third scan at ν=50mVs^{-1}.

3.2. Effect of scan rate

The effect of scan rate on the anodic oxidation of atenolol was studied at a concentration of 2x10^{-3}M in 0.1 M TMAC in methanol media. In all cases the anodic peak current was proportional to the square root of the scan rate. Under these conditions, the process was diffusion-controlled (14). A linear relationship was observed between log i_p and log ν (Fig.3) corresponding to the equation: log i_{pa} (μA)=0.428 log ν +0.2517,where ν is in mVs^{-1}. The slope of 0.43 is close to the theoretically expected value of 0.5 for a purely diffusion-controlled current (15). The plot of $i_{pa}/\nu^{1/2}$ v/s log ν indicated an increase in peak current with an increase in sweep rate (Fig.4) confirming that the electrode surface has some adsorption complications (16-18).

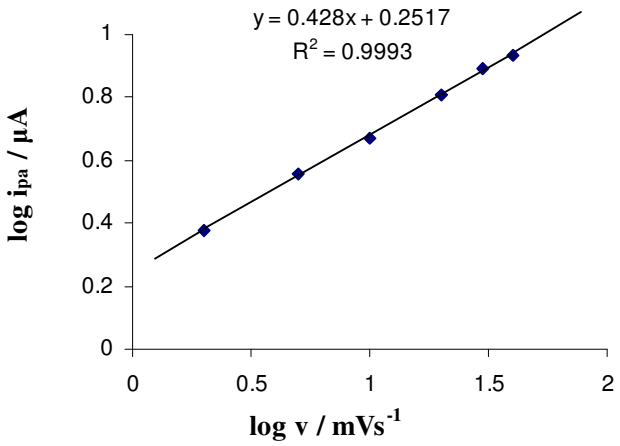


Figure 3. Variation of the logarithm of peak current with the logarithm of the sweep rate for 2mM atenolol.

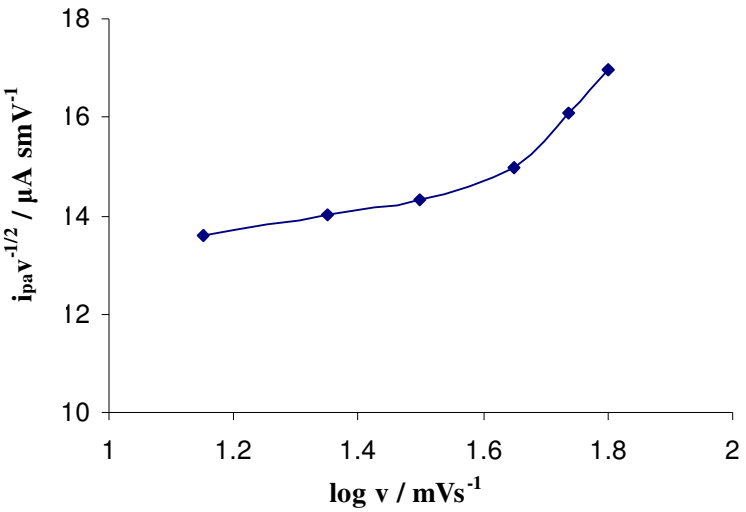


Figure 4. Dependence of $i_p/\upsilon^{1/2}$ on log υ for 2mM atenolol at glassy carbon electrode.

The E_{pa} of the oxidation peak was also dependent on scan rate. The plot of E_{pa} v/s log ν was linear having a correlation coefficient of 0.995(Fig.5) and this behavior was consistent with the EC nature of the reaction in which the electrode reaction is coupled with an irreversible follow-up chemical step (19). The relation between E_{pa} and ν can be expressed by the equation E_{pa} (V)=0.0743logν +1.0467.

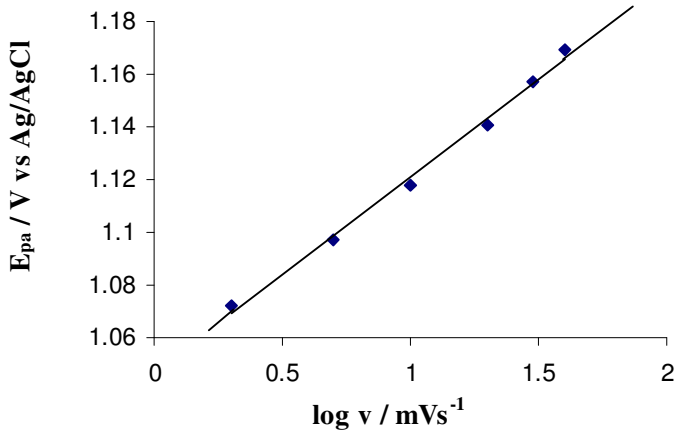


Figure 5. Dependence of E_p on log v for 2mM atenolol.

3.3. Effect of concentration

A plot of i_{pa} v/s the concentration of atenolol shows linearity (Fig.6), indicating further that the electrode process is diffusion-controlled (20,21), with correlation coefficient 0.989. The linear relation expressing dependence of i_{pa} on concentration in the range 2.0-10.0 mM can be described as

i_{pa} (µA)=1.1747C, where C is in mM/L.

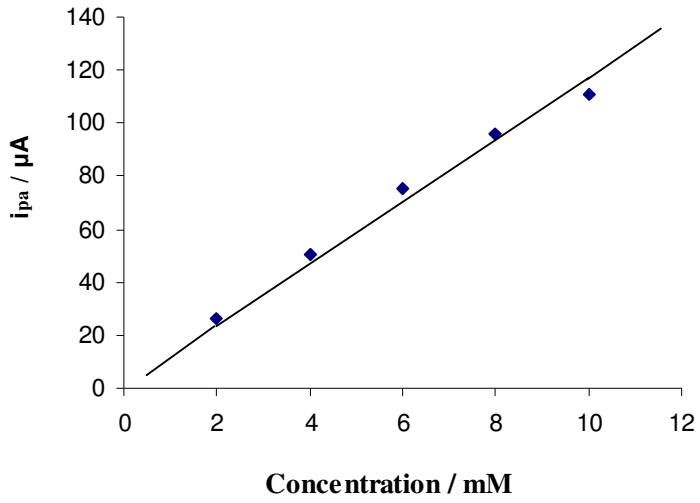


Figure 6. Effect of concentration of atenolol on peak current at glassy carbon electrode. Sweep rate: $50mVs^{-1}$.

3.4. Effect of temperature

The electro-oxidation of atenolol was carried out at different temperatures (298-313 K). Cyclic voltammograms of mixture of atenolol (2mM) and TMAC (0.1M) were recoded at different temperatures. The anodic peak current increased linearly (Fig.7) with correlation coefficient 0.9899. The heterogeneous rate constants (k_o) were calculated at different temperatures by using the equation (14):

$$i_{pa}=k_o\ (0.227)\ n\ F\ A\ Co\ \exp\ \{-\alpha_{na}\ (Ep-E)\} \qquad (2)$$

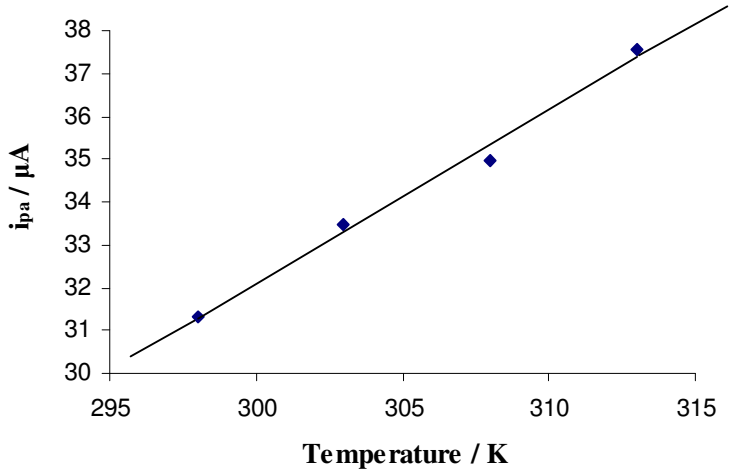


Figure 7. Observed dependence of i_{pa} on temperature for 2mM atenolol at GCE.

Table 1A. Calculated heterogeneous rate constants at different temperatures for 2mM atenolol with scan rate 50 mVs^{-1} at GCE.

Temperature/ K	$i_{pa}/\mu A$	$k_o \times 10^{5}$/ cm s^{-1}
298	31.32	6.16
303	33.48	6.59
308	34.96	6.88
313	37.56	7.39

The calculated rate constants were tabulated in Table.1A. The energy of activation (Ea) was evaluated from the Arrhenius plot of log k_o versus 1/T, which was linear with the slope= -478.04. (Fig.8). The other activation parameters were obtained from this Ea value and are tabulated in Table.1B.The less value of $\Delta H^{\#}$ indicates the electro-oxidation of atenolol might be taking place through physical adsorption. The more –ve $\Delta S^{\#}$ value indicates the electro-oxidation of atenolol might be taking place via the formation of an activated adsorbed complex (22) before the products are formed. Such adsorbed intermediate complex is more ordered than reactant molecules itself.

Table 1B. Calculated thermodynamic activation parameters for the electro-oxidation of 2mM atenolol at GCE.

Activation parameters	Values
Ea (kJ mol^{-1})	9.1
$\Delta H^{\#}$ (kJ mol^{-1})	6.6
$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-311
$\Delta G^{\#}$ (kJ mol^{-1})	97

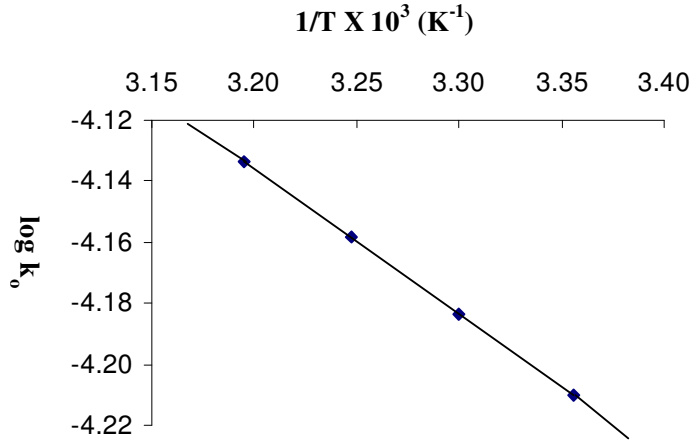


Figure 8. Effect of temperature on the electro-oxidation of 2mM atenolol with scan rate 50 mVs^{-1} on GCE: Plot of log k_o versus 1/T.

3.5. Effect of solvent

The solvent effect was also studied using the above system. Cyclic voltammograms of mixture of atenolol (2mM), TMAC (0.1M),methanol and water were recorded at 298 K at a sweep rate of 50 mVs^{-1}. Taking the fixed amount of atenolol and TMAC, the amount of water-methanol (%v/v) content was varied. The anodic peak potential and anodic peak current decreased on increasing the amount of water (Fig.9&10). But well resolved anodic peaks were obtained at 50% water-methanol media (Fig.11). The balance between the solubility and conductivity was achieved by using this system. The heterogeneous rate constants were calculated for this system by using Equation (2) and are tabulated in Table.2. The dielectric constants are calculated by using the equation:

$$D=D_1V_1+D_2V_2 \quad (3)$$

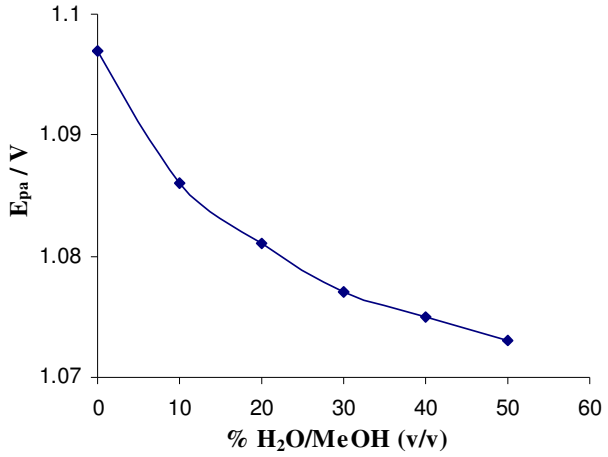


Figure 9. Dependence of peak potential on % of solvent for 2mM atenolol at scan rate 50mVs^{-1} at GCE.

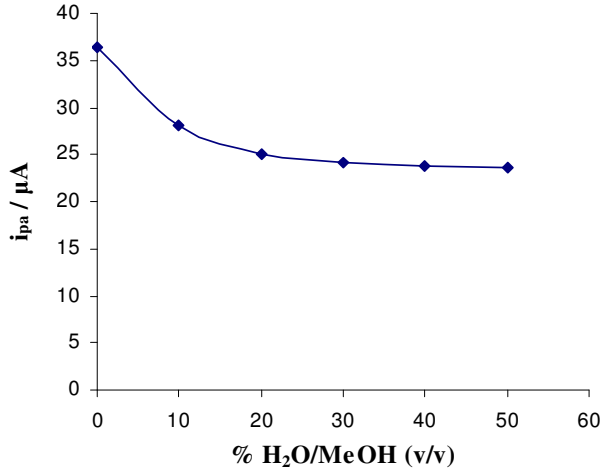


Figure 10. Dependence of peak current on % of solvent for 2mM atenolol at scan rate 50mVs^{-1} at GCE.

Where V_1 and V_2 are volume fractions and D_1 and D_2 are dielectric constants of water and methanol as 78.5 and 32.7 at 298 K respectively. A plot of log k_o versus 1/D was linear with positive slope (Fig.12).

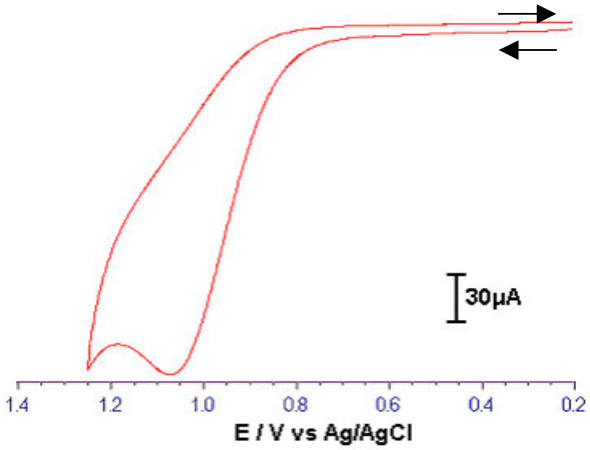


Figure 11. Cyclic voltammogram of 2mM atenolol for 50% v/v MeOH/H_2O system on GCE with ν=50mVs^{-1}.

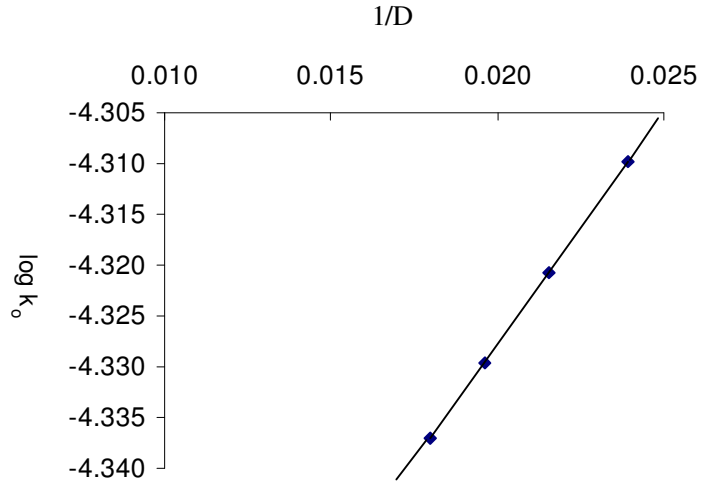


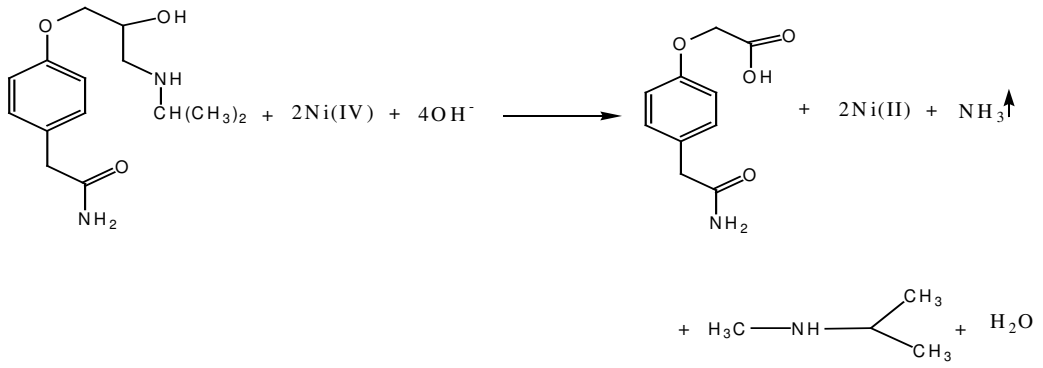
Figure 12. Effect of dielectric constant on the electro-oxidation of 2mM atenolol with scan rate 50 mVs^{-1} on GCE: Plot of log k_o versus 1/D.

Table 2. Effect of dielectric constant (D) on the heterogeneous rate constant, for the electro-oxidation of 2mM atenolol with scan rate 50mVs^{-1} at GCE.

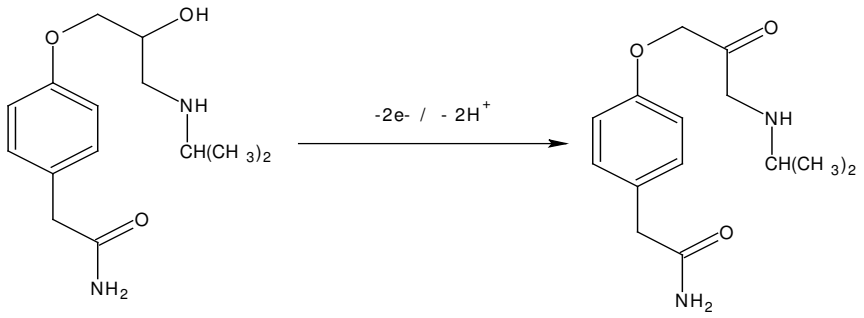
% H_2O-MeOH (v/v)	D	k_ox10 ^{5}/cm s^{-1}
20.00	41.83	4.93
30.00	46.41	4.75
40.00	50.99	4.66
50.00	55.58	4.63

3.6. Mechanism

In a separate study we found that chemical oxidation of atenolol by a moderate oxidant diperiodatonickelate (IV) gave the main product as 4-carboxy methoxy phenyl acetic acid. Based on the kinetic data (23) the mechanism has been proposed as shown in Scheme. 2. But based on the cyclic voltammetric experiments the product was identified as 2-[4-(3-isopropylamino-2-oxo-propoxy)-phenyl]-acetamide, and the number of electrons transferred for electro-oxidation of atenolol was 2. Hence the proposed mechanism is shown in Scheme .3. These studies show that oxidative pathways of electrochemical and chemical processes are different.



Scheme 2. Mechanism for oxidation of atenolol based on kinetic data.



Scheme 3. Proposed mechanism for electro-oxidation of atenolol at GCE.

3.7. Identification of products of electrolysis

Controlled potential electrolysis was carried out using H type cell separating the anode and cathodic compartments by a fine glass sinter. The rate of electrolysis was enhanced by using a glassy carbon electrode with a larger surface area, as the working electrode in the cathodic compartment and applying a potential of 1.2V using Ag/AgCl electrode as reference electrode. The potential is usually fixed slightly higher than that obtained in CV experiments. Platinum gauze acted as anode in the other compartment. Ag/AgCl electrode used as a reference electrode was placed in the same compartment

along with GCE. The electrolysis was carried out for 12 hrs for complete oxidation using 2 x 10^{-3} M atenolol and TMAC as supporting electrolyte under hydrodynamic conditions in order to speed up the mass transport. All measurements were carried out at laboratory ambient temperature controlled at 25 ± 0.2^0C. Oxidized products were isolated and separated in a column. The oxidized product was identified as 2-[4-(3-isopropylamino-2-oxo-propoxy)-phenyl]-acetamide and characterized by ^{1}HNMR.

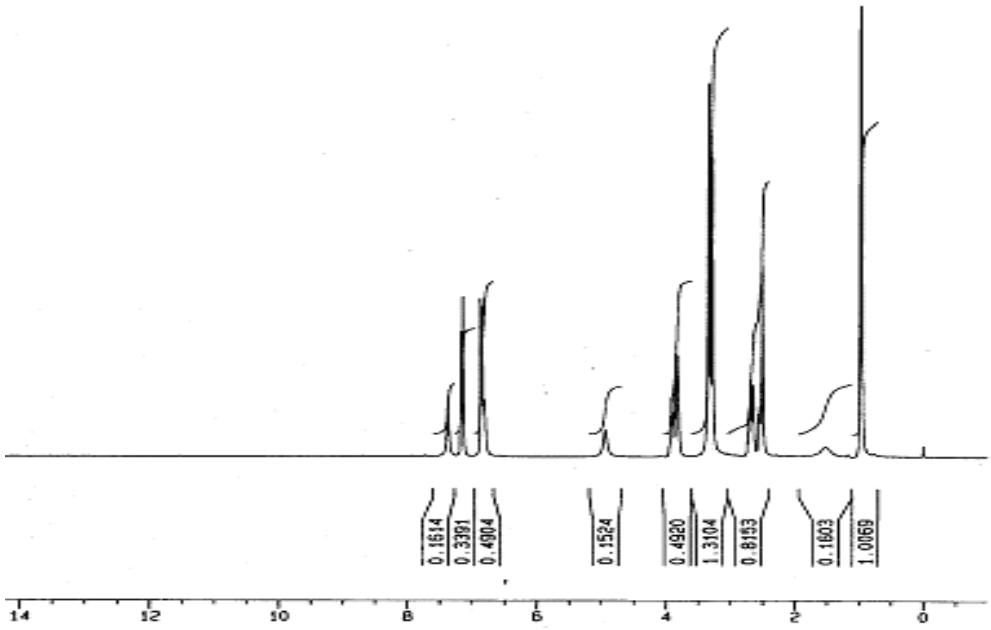


Figure 13. ^{1}HNMR spectra of atenolol.

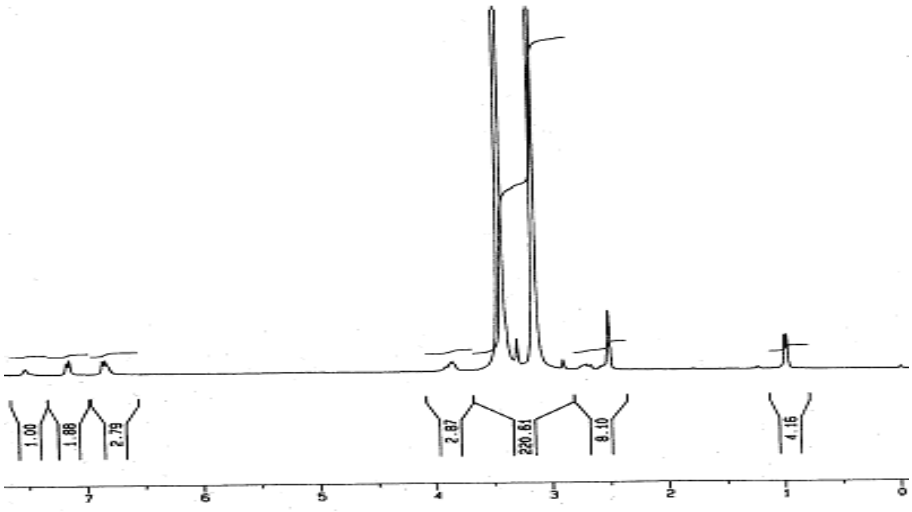


Figure 14. ^{1}HNMR spectra of 2-[4-(3-isopropylamino-2-oxo-propoxy)-phenyl]-acetamide.

The oxidation of secondary alcoholic group in atenolol to the corresponding ketone can be explained from its ^{1}HNMR data (Fig.13 & 14). In ^{1}HNMR spectrum of oxidized product we got two singlets at δ 3.42 and δ 3.13 due to $OCH_2$and $COCH_2$ protons respectively instead of two doublets. We also observed the disappearance of a multiple due to CH_3-CH-CH_2 protons at δ 3.8 and a broad singlet at δ 4.9 due to –OH protons, which indicates the conversion of –CH-OH functionality to –CO- group.

4. CONCLUSIONS

This study shows that atenolol, a β-blocker drug with a broad range of applications in biological and clinical activity, undergoes oxidation at a glassy carbon electrode. In the literature (12,13) they used the modified glassy carbon electrodes for the determination of atenolol. But in our study we have shown the electro-oxidation of atenolol at bare GCE in 0.1 M TMAC in methanol media. The oxidation of atenolol was an irreversible process and occurs in a single step, with two electrons and two protons transferred, leading to the formation of an electroactive oxidation product that adsorbs on the GCE surface.

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