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Research Article

POLAROGRAPHIC REDUCTION BEHAVIOUR OF SOME POTENTIAL ANTIBIOTIC CEPHALOSPORINS

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ABSTRACT

The electrochemical reduction behaviour of cephalosporin such as ceftazidime, ceftizoxime and ceftriaxone has been studied by employing d.c.polarography, cyclic voltametry and differential pulse polarography in universal buffers of pH 2.0-12.0. The kinetic parameter such as transfer coefficient, diffusion coefficient and heterogeneous forward rate constant values are evaluated. The reduction of >C=N- group was confirmed by I.R. Spectral studies with absence of band at 1600 – 1700 cm^{-1}. The data obtained have been utilized to describe the electrode kinetics and mechanism.

Keywords: Ceftizidime, Ceftrizoxime, Cefriaxone, Electrode mechanism, Polarography

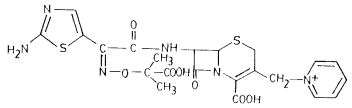
INTRODUCTION

Cephalosporins are semi-synthetic antibiotics of beta lactum family and because of their convenient antibacterial activity, beta lactamases resistance and pharmacokinetic properties, now-a-days they are widely used in clinical practice for treatment of severe infections in India[1]. Simple heterocyclic systems are not electrochemically active, while the corresponding cephalosporins are electro reducible. The main electrode reaction responsible for the polarographic activity of cephalosporin is claimed to be the reduction of >C=N- of the cephem nucleus which is dependent on the presence and nature of substituent. Information on the action of drugs in vivo. Certain electrochemical parameters have been reported[2] through cyclic voltametric studies for cephalosporins such as cefazoline, cefmatazole and cefatoxime.

El-Hefnawey et.al.[3] were discussed the voltametric behaviour and quantification of the sedative-hypnotic drug chlordiazepoxide in bulk form, pharmaceutical formulation and human serum at a mercury electrode. L.Wang et.al.[4] studied on the electrochemical behavior of the anticancer herbal drug emodin. M.L.P.M.Arguelho et.al.[5] explained the electrochemical study of the hydroxyl chloroquine and its determination in plaquenil by differential pulse voltametry. S.Lu et.al.[6] studied the electrochemical reduction and voltametric determination of metronidazol at a nanomaterial thin film coated glassy carbon electrode. Madhusudhana Reddy et.al.[7] explained the voltametric behavior of cefixime and cefodoxime proxetil and determination in pharmaceutical formulations and urine. E.Hammam et.al.[8] discussed the voltametric studies on the antibiotic drug cefoperazone. This research group a fully validated simple, sensitive and selective square -wave stripping voltametry procedure was described for the trace quantification of cefoperazone in bulk form, formulations and human serum/plasma. The pharmacokinetic parameters of cefoperazone in plasma of hospitalized volunteers were successfully estimated. V.S.Ferreira et.al [9] showed that the differential pulse polarographic determination of ceftazidime in urine samples with and without prior extraction.

In this communication, reduction of extranuclear azomethine containing cephalosporins such as ceftazidime (I), ceftizoxime (II) and ceftriaxone(III) are chosen to get a clear information on the reduction mechanism of the O-methyl oxime group present in their nuclei and to explore the electrode kinetics concerned in detail using advanced electrochemical techniques. The kinetic parameters such as transfer coefficient, diffusion coefficient and heterogeneous forward rate constant values are calculated. Chemical structures of the present investigated compounds are:

Structural representation of ceftazidime (I), ceftizoxime (II) and ceftriaxone(III)



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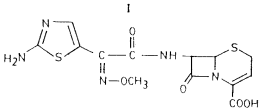

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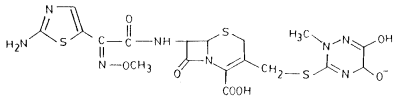


III

MATERIALS AND METHODS

D.C.Polarographic analyzer coupled with BD8 Kipp & Zonen x-t recorder. A dropping mercury electrode (flow rate 2.48055 mg/s) was used as working electrode, a saturated calomel electrode (SCE) was used as reference electrode and platinum wire as auxiliary electrode. Differential pulse polarographic measurements were performed with a Metrohm E 506 polar record connected to an E 612 VA scanner. The three electrode assembly consisted of DME (with an area 0.023 cm^2) working electrode, a platinum wire as auxiliary electrode and a saturated Ag/AgCl (s) Cl^- reference electrode. The cyclic voltammograms were obtained with the digital electronic 2000 x-y/t recorder in conjunction with the above unit (the working electrode was HMDE having an area of 0.0433 cm^2). The I.R. spectra of the compounds I - III were taken with the model PYE UNICAM SP. 3300 spectrophotometer. The pH measurements were carried out with an Elico digital pH meter. All the experiments were conducted at 25 ± 1^0 C. The stock solutions (1mM) of the samples were prepared in doubled distilled methanol. The supporting electrolyte ranging from pH 2.0-12.0 were prepared using 0.2 M boric acid , 0.05M citric acid and 0.1 M trisodium orthophosphate[10]. The test solutions were prepared by dissolving required quantity of stock solution with the supporting electrolyte to get 10 ml. The solutions were de-aerated by purging with oxygen free nitrogen gas for 15 minutes and then polarograms were recorded. The pure compounds were supplied by Glaxo India Ltd , Bombay and were used without further purification. All the chemicals were used of analar-grade.

RESULTS AND DISCUSSION

All compounds (I - III) studied gave a single well defined wave / peak in the universal buffer medium of pH 2.0-12.0 with all the techniques (Figs.1-3). The wave/peak is assigned to the reduction of

extra nuclear azomethine group present in the investigated compounds with four electron addition forming saturated amine. The wave /peak in all the compounds is found to be diffusion controlled and absorption free[11,12] as shown by linear plots of i_d vs. $h^{1/2}$, i_p vs. $v^{1/2}$, i_m vs. $t^{2/3}$ passing through origin. The height of the wave shows linear dependence on the concentration of depolarizer. This fact also indicates the diffusion controlled nature of the waves. The half-wave potentials ($E_{1/2}$), peak potentials (E_p,E_m) shift towards more negative potentials with increase in concentration of depolarizer showing that the electrode process in irreversible[13]. This is further confirmed by log plot analysis. The half-wave potential shifts towards more negative value with pH indicating that protons are involved in reduction process[14]. The dependence of i_p/pH curves shows behavior in accordance with a process in which a proton transfers to form an electroactive protonated species, non-protonated cephalosporin being electro inactive. The n_a value (the product of transfer coefficient and number of electrons involved) and value of P(number of protons involved in the rate determining step) are found using the expressions:

$$n_a = 0.0517/E_{3/4} - E_{1/4}$$

$$E_{1/2}/pH = 0.05915/n_a \times P$$

The plots of $E_{1/2}$ vs. pH and E_P vs. pH give straight lines with a slope of 0.0605, which confirm proton involvement during the rare determining step. The Variation of peak potentials with scan rate from 40mVs^{-1} to 300 mVs^{-1} indicates irreversible nature of electrode process. It is also confirmed from the absence of anodic peak in the reverse scan of cyclic voltammogram.

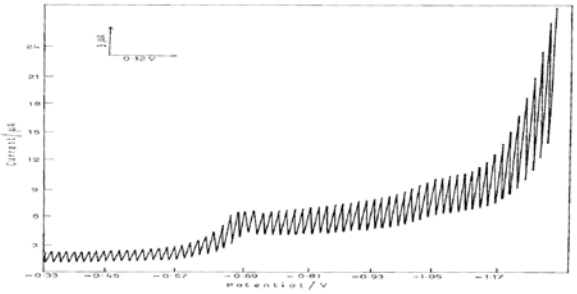


Fig. 1: Typical D.C.polarogram of ceftizoxime in pH 4.0

Concentrtion: 0.5 mM Drop Time: 3 seconds

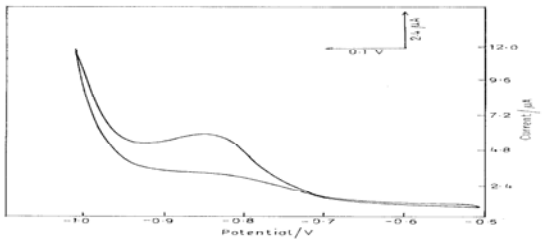


Fig. 2: Typical cyclic voltammogram of ceftizoxime in pH 8.0

Concentration : 0.5mM Scan rate : 40mV/s

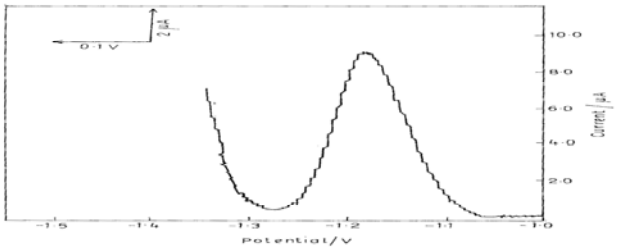


Fig. 3: Typical differential pulse polargoram of ceftriaxone

Concentration: 0.5 mM; Drop Time: 2 seconds; Pulse Amplitude: 65 mV

Effect of solvent

Generally in pharmaceutical firms for their analysis, non-aqueous solvents are used. When the percentage of non-aqueous solvent increases to the test solution, the reduction potential shifts towards more negative value with decrease in diffusion coefficients [15]. Good results were observed in 40% methanol.

Substituent effect

The structures of the compounds show that all the compounds have the same electro active azomethine functional group with different environment. As a result these are reduced at DME at various potentials. In ceftizoxime and ceftriaxone, >C=N- linked with –OCH_3 group, which is electron releasing in nature functional gets reduced at more negative value than normal azomethine functional group. In the case of ceftazidime, the >C=N- group is planked with two methyl and one carboxylic group. The electron releasing nature of two –CH_3 groups were compensated by the carboxylic group which is electron withdrawing in nature. Hence it is reduced at normal potential.

The number of electrons involved during the electrode reaction, was determined by millicoulometry with a platinum wire as anode and mercury pool as cathode to be four. Controlled Potential

Electrolysis experiments were conducted at -0.80 V, -0.90 V and -1.0 V vs SCE in pH 4.0, 4.0 and 6.0 for I, II and III compounds respectively. After electrolysis, the reduction products were extracted with ether.

The ether layer was evaporated on water bath. The obtained compounds exhibited strong doublet absorption bands at 3415 cm^{-1} (I), 3450 cm^{-1} (II) and 3500 cm^{-1} (III) in I.R.Spectra, where as weak bands appeared in the original compounds I.R.spectra for >C=N- group at 1600-1700 cm^{-1} are disappeared and strong bands in the range 3300-3500 cm^{-1} confirmed the reduction of >C=N- functional group.

The kinetic parameter such as transfer coefficient, diffusion coefficient and heterogeneous forward rate constant values are evaluated and reported in Tables 1-3. The diffusion coefficient values are noticed to be in good agreement in all the techniques for each compound. But these values are found to vary from compound to compound on their molecular weight difference. Rate constant values are found to decrease with pH as expected. The rate constant values are observed to be high in acidic media in all the techniques indicating the rate of the reaction to be fast. Proton involvement seems to make the reduction easier. But in basic media, the reduction process in not easily facilitated owing to the non-availability of protons[16].

Table 1: Typical palarographic data of ceftizidime, concentration: 0.5 mM.

Buffer	D.C Polarography Droptime: 3 Sec				Cyclic Voltammetry Scan rate:40 mv/s				D.P.Polarography Drop time 2 Sec			
pH	$-E_{1/2}$ volts	i_d µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s	$-E_{1/2}$ V	i_p µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s	$-E_{1/2}$ volts	i_m µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s
2.0	0.56	8.20	6.59	$2.2x10^{-8}$	0.55	7.99	6.84	$2.14x10^{-8}$	0.56	11.54	6.78	$7.88x\ 10^{-8}$
4.0	0.66	7.43	5.04	$1.23x10^{-10}$	0.65	7.46	5.14	$1.32x10^{-10}$	0.63	9.40	5.22	$4.89x10^{-9}$
6.0	0.84	6.26	3.72	$1.36x10^{-11}$	0.76	6.30	3.52	$1.41x10^{-11}$	0.77	8.92	3.64	$8.11x10^{-10}$
8.0	0.96	4.42	1.99	$1.67x10^{-12}$	0.89	4.60	2.12	$1.2x10^{-12}$	0.92	7.51	2.30	$6.24x10^{-11}$
10.0	1.04	3.91	1.59	$7.16x10^{-14}$	0.98	3.82	1.62	$7.21x10^{-14}$	0.99	6.58	1.89	$2.89x10^{-13}$
12.0	1.18	3.60	1.50	$2.41x10^{-16}$	1.20	3.64	1.58	$2.39x10^{-16}$	1.13	4.26	1.24	$6.42x10^{-16}$

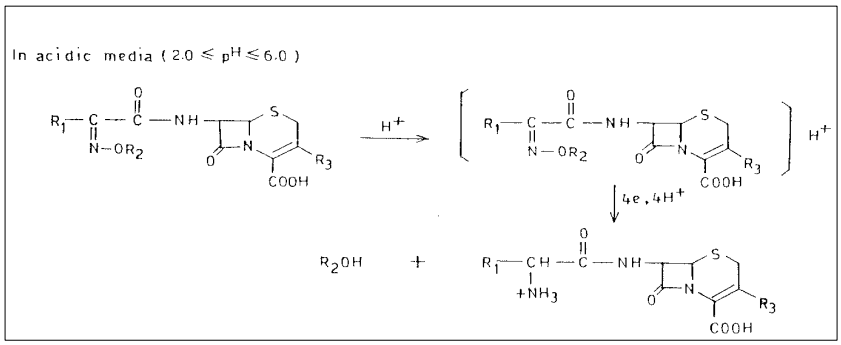
Table 2: Typical palarographic data of ceftizoxime concentation: 0.5 mM

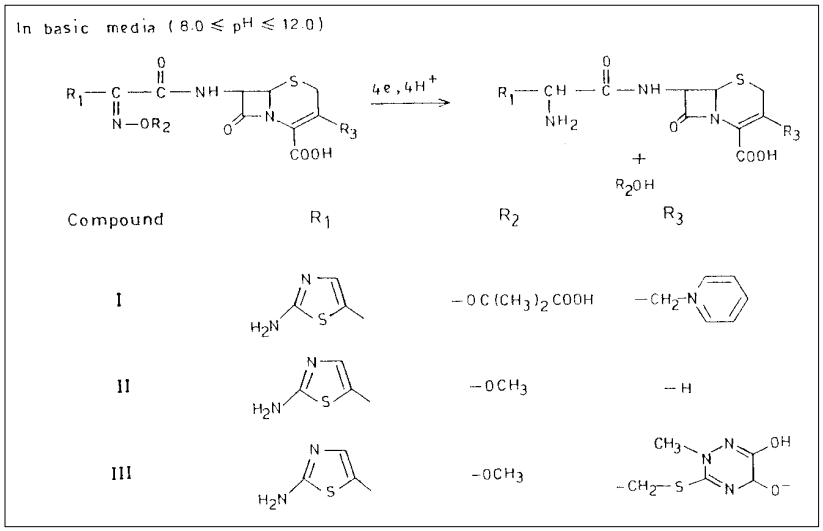
Buffer	D.C Polarography Droptime: 3 Sec				Cyclic Voltammetry Scan rate:40 mv/s				D.P.Polarography Drop time 2 Sec			
pH	$-E_{1/2}$ volts	i_d µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s	$-E_{1/2}$ V	i_p µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s	$-E_{1/2}$ volts	i_m µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s
2.0	0.62	8.62	6.42	$3.20x10^{-9}$	0.60	8.42	6.32	$2.0x10^{-9}$	0.64	10.20	6.32	$8.62x\ 10^{-8}$
4.0	0.69	7.74	6.26	$4.26x10^{-11}$	0.68	7.61	6.28	$4.36x10^{-11}$	0.70	9.10	5.82	$6.42x10^{-10}$
6.0	0.78	6.42	5.91	$3.96x10^{-12}$	0.79	6.54	5.87	$3.98x10^{-12}$	0.89	8.42	5.21	$4.26x10^{-11}$
8.0	0.99	4.68	3.60	$6.42x10^{-13}$	0.96	4.64	3.59	$6.38x10^{-13}$	1.15	7.32	5.01	$2.44x10^{-12}$
10.0	1.18	4.38	3.24	$4.61x10^{-14}$	1.14	4.32	3.26	$4.64x10^{-14}$	1.24	5.81	4.89	$5.53x10^{-14}$
12.0	1.28	3.82	2.91	$2.84x10^{-16}$	1.30	4.10	2.89	$3.01x10^{-16}$	1.34	4.95	4.21	$4.24x10^{-16}$

Table 3: Typical palarographic data of ceftriaxone, Concentration: 0.5 mM

Buffer	D.C Polarography Droptime: 3 Sec				Cyclic Voltammetry Scan rate:40 mv/s				D.P.Polarography Drop time: 2 Sec			
pH	$-E_{1/2}$ volts	i_d µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s	$-E_{1/2}$ volts	i_p µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s	$-E_{1/2}$ volts	i_m µA	$Dx10^6$ cm^2/s	k^0_{fh} cm/s
2.0	0.69	8.50	5.20	$2.42x10^{-9}$	0.67	8.49	5.36	$2.39x10^{-9}$	0.60	12.00	5.46	$7.31x\ 10^{-8}$
4.0	0.74	7.10	4.94	$5.26x10^{-11}$	0.75	7.20	4.92	$5.26x10^{-11}$	0.73	11.20	4.86	$4.22x10^{-10}$
6.0	1.00	6.90	4.21	$4.20x10^{-12}$	0.99	6.80	3.87	$8.32x10^{-12}$	0.98	10.00	4.32	$2.64x10^{-11}$
8.0	1.19	6.24	3.98	$5.83x10^{-13}$	1.18	5.28	3.59	$5.80x10^{-13}$	1.15	8.90	3.89	$6.36x10^{-12}$
10.0	1.24	5.42	3.24	$5.82x10^{-14}$	1.24	4.80	3.36	$6.14x10^{-14}$	1.23	8.50	3.58	$5.58x10^{-14}$
12.0	1.32	4.60	2.49	$2.84x10^{-16}$	1.31	4.23	2.89	$2.86x10^{-16}$	1.32	5.70	2.89	$6.42x10^{-16}$

Based on the results obtained from all the techniques the electrochemical reduction mechanism of I - III can be given as follow:





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