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A comparative study of electrochemical reduction of isatin and its synthesized Schiff bases at HMDE

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Abstract. The electrochemical behaviour of a series of Schiff base i.e. 3-[5-phenylpyrazol-3-ylimino]indol-2-ones (IIa–e) synthesized by the reaction of various 5-substituted isatins with 3-amino-5-phenyl-pyrazole has been investigated and compared with corresponding isatin in dimethylformamide in 0·1 M LiCl using cyclic voltammetry at Hanging Mercury Drop Electrode. All synthesized Schiff bases exhibit a single irreversible two-electron reduction wave in contrast with the two discrete one-electron transfer reduction waves observed for isatin in this medium. Observation of a well-developed single reduction wave can be attributed to the higher basicity of the nitrogen species of the imine bond of Schiff bases, making proton abstraction as well as second electron transfer both rapid. The compounds are subjected to constant potential preparative electrolysis. The products are identified as secondary amines by spectroscopic methods. A mechanism for the electro-reduction process has been proposed. Kinetic parameters have also been calculated.

Keywords. Isatin; 3-amino-5-phenyl-pyrazole; Schiff bases; electro reduction and HMDE.

1. Introduction

Synthetically versatile heterocycle, isatin (indole 2,3-dione) is well known to act as a potent endogenous neurochemical regulator in brain in mammals.[1,2] Isatin's concentration in urine is to become a diagnostic marker for the clinical severity of Parkinson's disease in humans however electrophysiology, synthetic and metabolic pathways of isatin in human system are yet to be fully established.[3,4]

The electrochemical determination of isatin[5] and other nitrogen heterocycles using various electrode systems[6,7] attain prominence in recent years. 3-Arylimino derivatives (Schiff bases) obtained by the condensation of aromatic amines with isatin are powerful anticonvulsant, antiviral, antibacterial and antifungal agents.[8–10] Copper (II) complexes with isatin Schiff base ligands are potential antitumoral agent.[11] Recent findings indicate that isatin interact with a wide range of monoamines in biological systems.[12]

Encouraged by these facts and non availability of reports on the electrochemical behaviour of imine compounds obtained by condensation of isatin and pyrazole moiety till date, in the present work, first a new series of Schiff bases of 5-halo substituted isatins with 3-amino-5-phenyl-pyrazole are synthesized and secondly their electrochemical behaviour on HMDE is examined and compared with corresponding isatin, mainly: (a) to decide about the rate of electro reduction process (b) to elucidate the mechanism of electro reduction and (c) to find out the effect of various experimental conditions.

Number of electrons transferred is determined by conducting controlled potential electrolysis. Reduction products have been isolated and identified by spectroscopic methods. Kinetic parameters i.e. charge transfer coefficient (α_{na}), forward rate constant ($K_{f,h}$), Diffusion constant ($D_0^{1/2}$) have also been calculated.

2. Experimental

2.1 *Instrumentation*

A Potentiostat/Galvanostat Model 263A Electrochemical Analyzer (make Princeton Applied Research, Princeton, USA) with Power suite software was used for all electrochemical experiments. The working electrode was a Static Mercury Drop Elec-

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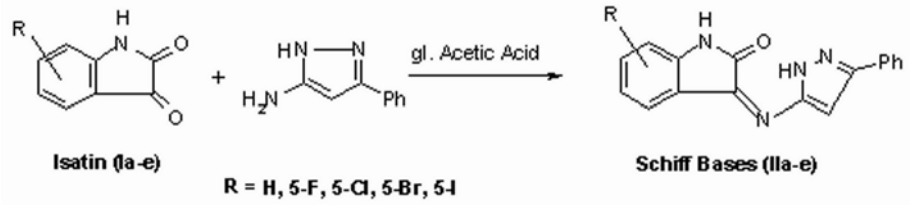


Scheme 1.

trode, model PAR 303A, auxiliary electrode was a platinum wire and reference electrode Ag/AgCl in saturated KCl.

Controlled Potential Electrolysis (CPE) was carried out in a micro cell with a mercury pool as the working electrode, a platinum sheet as auxiliary electrode and an Ag/AgCl as reference electrode keeping a blanket of nitrogen over the surface of the solution. The progress of the electrolysis was monitored by recording cyclic voltammograms and UV-Vis spectra of the electrolyzed solution at different time intervals. Purging and blanketing of nitrogen were done for analyte solution placed in the electrochemical cell of 15 ml capacity for 15 min prior to each experiment for deaeration.

IR spectra of synthesized compounds were recorded in KBr on a Perkin-Elmer 557 spectrophotometer (ν_{max} in cm^{-1}). ^{1}HNMR spectra were in DMSO-d_6 on a Jeol FX 90 Q spectrometer at 89·9 MHz using TMS as internal reference. Purity of the synthesized compounds was checked for by TLC on silica gel plates using benzene: ethyl acetate (3 : 1, v/v) as eluent. A Systronics model 106 Spectrophotometer was used to record UV-Visible spectra.

2.2 *Chemicals*

5-halogen substituted isatins (Ia-e) and 3-amino-5-phenyl-pyrazole were purchased from Sigma-Aldrich and were used as received. Schiff bases (IIa–e) were prepared according to literature method.[13] The general synthetic approach involved condensation of an equimolar mixture of corresponding indole 2,3-dione (0·01 mol) and 3-amino-5-phenyl-pyrazole (0·01 mol) in absolute ethanol in the presence of 2,3-drops of glacial acetic acid for 3–4 h. On cooling, flakes separated out which were filtered and recrystallised from hot ethanol to give shining brightly coloured needles of 1,3-dihydro-3-[1H-(5-phenyl-pyrazol-3-yl)imino]-2H-indol-2-ones (IIa–e) in 70–80% yield (scheme 1). Synthesized compounds were characterized by their IR and ^{1}H NMR studies. Formation of Schiff bases was indicated by the disappearance of one CO frequency of the isatin moiety and free primary amino frequency of aminopyrazole in the IR spectra. Also in ^{1}HNMR spectra, signals due to NH_2 were lacking and characteristic signals were observed at δ 10·98 (indole NH), 8·40 (pyrazole NH) and 7·87 (pyrazole methine) in addition to that for aromatic protons.

2.3 *Sample preparation*

0·01 M Stock solution of depolarizer was prepared by dissolving accurately weighed amount in purified DMF owing to low solubility of Schiff bases in water. More dilute solutions were prepared from the stock with supporting electrolyte i.e. 0·1M LiCl solution in double distilled water just prior to analysis.

3. Results and discussion

3.1 *Cyclic voltammetric studies*

0·1 M solution of LiCl is found to be a suitable supporting electrolyte for electro reduction studies of isatin and its Schiff bases at HMDE. All Schiff bases (IIa-e) are characterized with a single two-electron reduction peak for scan rates 20 to 250 mV s^{-1} in this medium at all concentration range chosen (table 1). The anodic half cycle does not show any peak indicating that the concerned electro reduction is irreversible. The behaviour of all the imines under study is same but completely in contrast to that of isatin which shows two separate well defined one-electron reduction peaks c1, c2 and one small irreversible anodic peak a in this medium.[14,15] Figure 1 depicts the comparative cyclic voltammograms of isatin (I) and Schiff base (IIa) in DMF in 0·1 M LiCl at scan rate 100 mV s^{-1}. In case of Schiff bases, due to the higher basicity of the nitrogen species of their imine bond, both proton abstraction as well as second electron transfer step are rapid and hence a single well developed reduction wave is observed instead

Table 1. Electrochemical characteristics of Schiff bases, 3-[5-phenylpyrazol-3-ylimino]indol-2-ones (IIa–e).

Schiff base no.	R	Scan rate (mV s^{-1})	$-E_{pc}$ (mV)	I_{pc} (μA)	Slope (mV)	α_{na}	$D_0^{1/2} \times 10^{-3}$ (cm^2 s^{-1})	$K_{f,h} \times 10^{-8}$ (cm s^{-1})
IIa	H	20	727·7	1·20	102	0·56	5·22	5·54
		50	758·3	3·10	100	0·57	5·72	5·08
		100	818·8	5·63	103	0·56	5·31	6·58
IIb	F	20	677	2·98	98	0·58	4·82	3·57
		50	698·7	4·54	99	0·58	4·86	4·81
		100	752	7·69	98	0·58	4·72	8·43
IIc	Cl	20	650·6	2·87	121	0·48	6·29	2·79
		50	675·4	4·88	118	0·50	5·66	6·82
		100	717·4	8·83	120	0·49	5·24	7·81
IId	Br	20	601·9	3·15	123	0·47	5·19	1·31
		50	624	5·59	120	0·48	5·24	2·28
		100	688·4	9·64	126	0·46	5·47	3·48
IIe	I	20	582·6	4·14	103	0·56	6·25	2·76
		50	607·5	8·4	98·5	0·58	6·47	4·33
		100	673·3	14·5	99·3	0·58	5·90	5·88

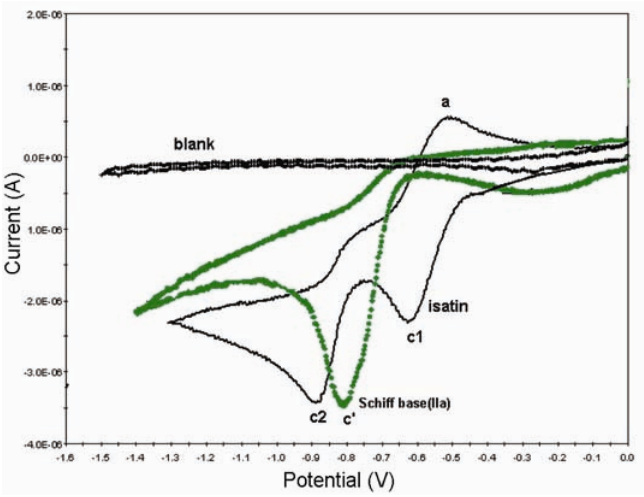


Figure 1. Comparative CVs of isatin and Schiff base (IIa) in DMF with aqueous 0·1 M LiCl as supporting electrolyte at HMDE at scan rate 100 mV s^{-1}, concentration 0·2 mmol.

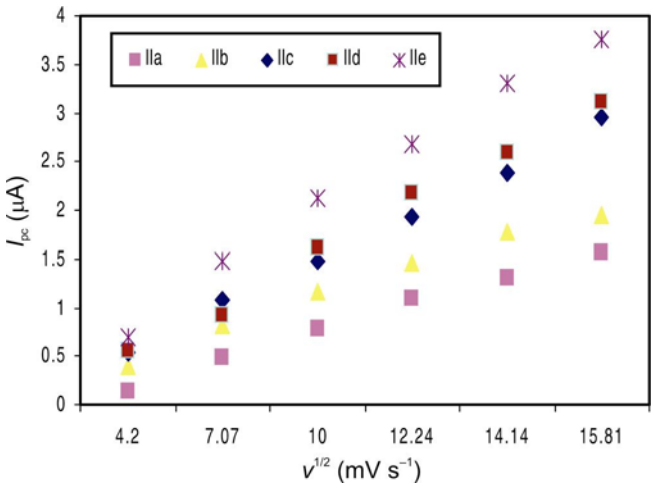


Figure 2. Plot of peak current (I_{pc}) Vs square root of the sweep rate ($v^{1/2}$) for Schiff bases(IIa–e) at concentration 0·1 mmol.

of two separate one electron reduction waves as observed in case of isatin.

A study of effect of scan rate is made in order to evaluate the mechanism and the feasibility of electrochemical reactions involved at HMDE in this medium. Good linear plots of I_{pc} vs $v^{1/2}$ are obtained for all concentration of depolariser showing the reduction of Schiff base in this medium is diffusion controlled within the scan rate employed (figure 2). The shift of peak potential towards more negative values with the increase in scan rate indicates a diffusion controlled irreversible nature of the system[16] (table 1), the peak potential is given by

$$E_p = E^0 - (RT/\alpha n_a F)\,[0{\cdot}78 - \ln(k^0/D^{1/2}) + \ln(\alpha n_a F v/RT)^{1/2}],$$

where α is the cathodic charge transfer coefficient, n_a is the number of electrons involved in the rate determining step, D_0 the diffusion coefficient and k^0 is the standard rate constant of the electrochemical reaction.[17] In case of Schiff bases, the variation of the peak potential with log of scan rate is linear and has a slope close to the theoretical value characterizing first order kinetics[18] (figure 3).

The peak current for a diffusion controlled irreversible system is given by Randle Sevick equation,

$I_{pc} = (2{\cdot}99 \times 10^5)n(\alpha n_a)^{1/2} ACD_0^{1/2}v^{1/2}$, where A is the area of electrode in cm^2, D_0 the diffusion coefficient in $cm^2\ s^{-1}$, C the concentration in mol cm^{-3} and v is in Vs^{-1}. The D_0 values for Schiff bases can be determined from the slope of I_{pc} vs $v^{1/2}$ plot after careful substitution and unit analysis. A plot of $\ln(I_p)$ vs $Ep - E^0$ determined at different scan rates has a slope of equal to $-0{\cdot}542/\alpha_{na}$ and an intercept proportional to K_s. Values of kinetic parameters have been calculated in table 1.[18]

The reduction mechanism is of the ECE type which occurs through a rate determining protonation of the anion radical followed by further electron transfer leading to the formation of saturated amine (scheme 2). This is consistent with the far stronger basicity of the imine anion radical as compared to the ketyl ion of isatin which shows two separate one electron transfer waves.[19–21] Ease of reduction follows the order IIe > IId > IIc > IIb > IIa. This can be attributed to the shifts in the reduction potential caused by changes in the halogen-substituted aromatic ring[22] of indole moiety.

3.2 *Controlled potential preparative electrolysis*

Controlled potential preparative electrolyses of compounds IIa–e were carried out at a potential about 100 mV more negative than the peak potential of irreversible reduction wave. The number of electrons was calculated from the plot of amount of charge passes vs $t^{1/2}$ and the value was found to be two. For compound IIa, with the progress of the electrolysis, absorbance at 396 nm in UV-Vis spectra systematically decreases and finally disappeared (figure 4). These observations showed that no intermediate with sufficient half-life was generated during electro-reduction of the Schiff bases. For product identification, 8–10 mg of compound IIa was exhaustively electrolyzed till the reduction peak c′ almost disappeared. Solution was filtered and evaporated to dryness in a rotary evaporator after electrolyses. The solid residue was triturated with diethyl ether several times and the ether soluble portion was separated and evaporated to dryness. Pale yellow colored compounds (IIIa, m.p. 213°C, IIIb 267°C, IIIc 226°C, IIId 252°C and IIIe 277°C) obtained were analysed by FT–IR and ^{1}H NMR studies and were found to be secondary amines. As a typical example for IR spectrum of compound IIIa, the following assignments were made: ν_{max} (KBr)/cm^{-1}: 3200–3350 (>NH), 2815, 2364 (=C–H), 1704 (>C=O), 1618,1500 (C=C/C=N), 1410 (C–N), 1327 (C–C), 1132 (N–N) and 745, 696, 625 (C–H, aromatic), 574 (C–C). FT–IR spectra of compounds IIIb-e were also similar except for the expected differences in the fingerprint region. ^{1}HNMR spectrum of the product IIIa showed characteristic signals at δ 10·83–12·48 (hump, 2H, –NH), 7·96 (*s*, 1H, pyrazole methine), 6·76–7·87 (*m*, 10H, aromatic protons and –NH) and 4·3 (*s*, 1H, aliphatic). The product of two-electron reduction in case of isatin was found to

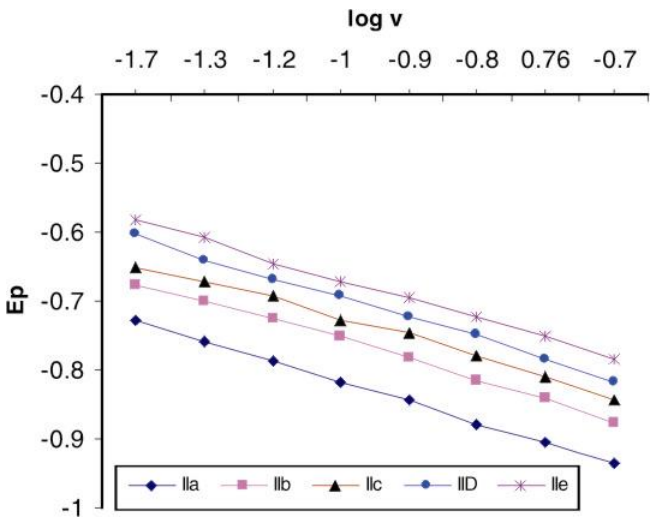


Figure 3. Plot of peak potential vs log of scan rate for Schiff bases (IIa–e) at concentration 0·1 m mol.

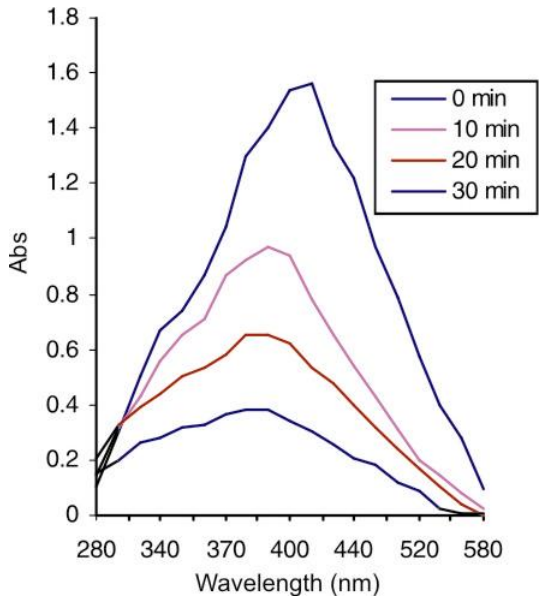
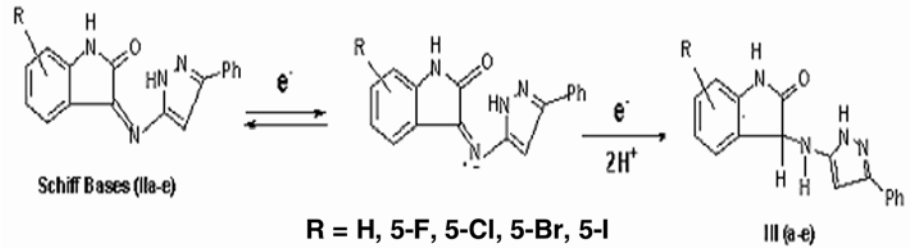


Figure 4. UV-Vis absorption spectra of compound IIa at different time intervals during constant potential electrolysis.



Scheme 2.

be dioxindole by conducting controlled potential coulometry as reported in our earlier work.[14]

4. Conclusions

The present studies indicate that investigated Schiff bases i.e. 3-[5-phenylpyrazol-3-ylimino]indol-2-ones (IIa–e) are reduced to secondary amines in a single step involving two electrons in aqueous LiCl/ DMF medium via ECE mechanism. This behaviour contrasts with the two discrete one-electron transfer reduction processes observed for isatin in this medium. This can be explained as in case of Schiff bases, owing to higher basicity of the nitrogen species of imine bond, proton abstraction as well as second electron transfer are both rapid and hence a single well developed irreversible reduction wave corresponding to two electron process is observed. The predominant product of the two-electron reduction in case of Schiff bases was a secondary amine whereas in case of isatin it was found to be a dioxindole by conducting controlled potential coulometry.

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