INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

Volume: 3: Issue-1: Jan - Mar-2012 *ISSN 0976-4550*

Accepted: Dec-2011 *Research Article*

SPECTRAL AND ELECTROCHEMICAL STUDIES OF FLUVOXAMINE

Vijaybhaskar P and Ramachandraiah A*

Department of Chemistry, National Institute of Technology Warangal, Warangal,
Andhra Pradesh, India, 506004
Email: podarillu@gmail.com

ABSTRACT: The spectral and voltammetric behavior of fluvoxamine (**1**) in aqueous buffers of varied pH is presented. Spectrophotometry, cyclic voltammetry, differential pulse polarography and coulometry were utilized to study its proton and electron transfer characteristics. Relevant thermodynamic and electrochemical data such as charge transfer co-efficient (α_{na}), heterogeneous forward rate constant ($k^0_{f,h}$), etc, have been evaluated. An excellent electroanalytical assaying of **1** has been developed in differential pulse polarography at pH = 3. Molecular modeling on various acid-base conjugates of **1** and their several conformers has been carried out to arrive at the thermodynamic and conformational issues to correlate to the spectral and electrochemical observations.

Key words: Fluvoxamine, acid-base equilibria, cyclic voltammetry, molecular modeling

INTRODUCTION

Fluvoxamine (**1**), a selective serotonin reuptake inhibitor (SSRI), is primarily used as an antidepressant drug but is also used to treat other psychological problems, such as obsessive–compulsive, panic and post-traumatic stress disorders. After administration, **1** is extensively metabolized and excreted unchanged in the urine without formation of any active metabolites. Its concentration in blood is difficult to predict, because of high variability between individuals, and no therapeutic window has been established[1–3]. Hence, the lookout for methods of therapeutic monitoring of **1** is still an active area of pharmaceutical research.[4–9] Electrochemical studies on the determination of **1** have also have been reported, but without looking into the details of the acid-base equilibria, speciation in aqueous buffers and electron transfer and proton-transfer characteristics as a function of pH. In this paper, we present the details of the electrochemical behavior of **1** in aqueous media of varied pH so as to obtain not only its electron- and proton-transfer kinetics but also to provide faster and more reliable electroanalytical assaying methods of **1**. Preliminary molecular modeling studies are also done to correlate the spectral and electrochemical characteristics of it.

EXPERIMENTAL

All the chemicals used were of AnalaR grade. Stock solutions of **(1)** (1×10^{-3} M) were prepared in aqueous alcohol media. Buffers of different pH (ionic strength = 0.05 M) were prepared according to literature procedure.[10] An ATI Orion Model 902 Ion Meter was used for pH-metry. The UV-visible spectra of the solutions were recorded on an AnalyticJena Specord Ratio Recording Spectrophotometer. The electrochemical measurements such as cyclic voltammetry, differential pulse polorography etc., were recorded on a Metrohm 663 VA Stand whereas coulometry was on a BAS Model CV-27 Voltammograph. Molecular modeling was carried out on ChemOffice Pro 10.0 platform.

The electrochemical recordings were run on a 25 mL sample solution, containing 5 mL of stock solution of the sample and 20 mL of the desired buffer, transferred into the electrochemical cell. Before each run, nitrogen or argon gas was purged for about 4 minutes to dispel the dissolved oxygen. 20 mL of buffer and 5 mL of water were mixed for the blank run.

RESULTS AND DISCUSSIONS

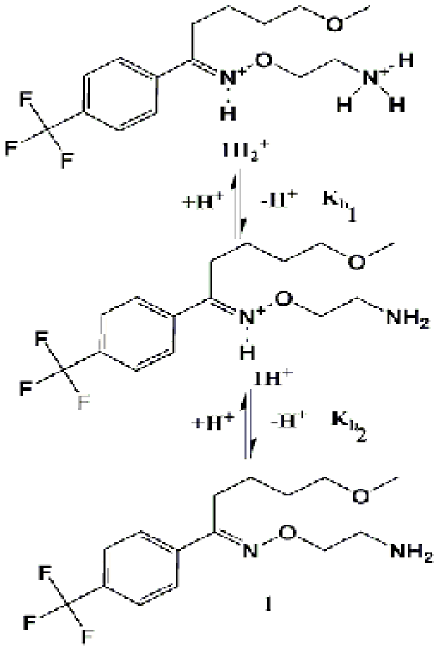
Spectral Studies and Acid-Base Equilibria

The electronic spectra of 1 in various aqueous buffers are shown in Figure 1.

The spectra exhibit a small amount of bathochromic shift with increased pH. The spectra of the other compounds are similar to this one. There are two potentially basic nitrogen atoms in 1, viz, the amino and the azomethine nitrogens. The hydrazenic hydrogen has been reported to be usually acidic. It may be tentatively suggested that the compounds exhibit acid-base equilibria as in Scheme 1.

Electrochemical Studies

It has been shown above that the compounds do not exhibit appreciable pH dependence in their electronic spectral profiles due to poor effect of proton transfer. However, the electron transfer characteristics are expected to very much species-dependent.



Scheme 1

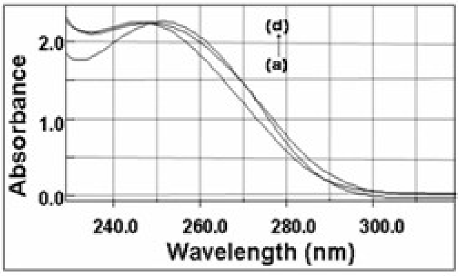


Figure 1: *Uv-vis spectra of 1 at pH (a) 2.17, (b) 5.35, (c) 8.64, and (d) 10.28*

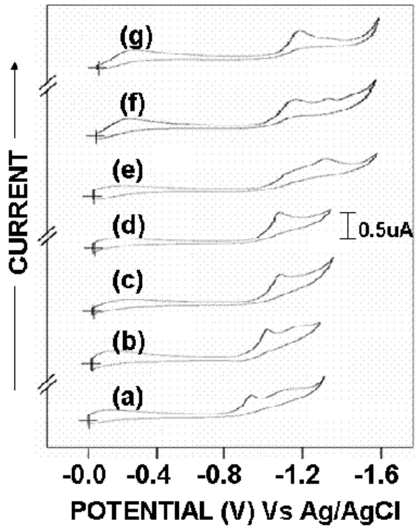


Figure 2: *Cyclic voltammograms of **1** (2.06 x 10^{-4} M) in buffers (ionic strength* = 0.05M) of pH (a) 2.56, (b) 4.03, (c) 5.80, (d) 7.62 and (e) 9.28 f) 10.50 g) 11.25

The cyclic voltammograms of 1, in several buffers, are presented in Figure 2. All the compounds offer irreversible reduction peaks in aqueous solution in the pH range 2-11. It is also obvious that the peak potentials drift cathodically with increased pH indicating the involvement of H^+ ions in the electrochemical reduction mechanism as shown in Figure 3& 5 and effect of peak current on pH is shown in Figure 4.

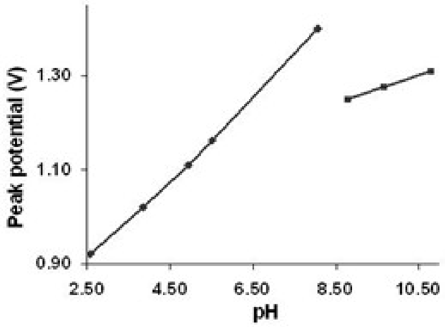


Figure 3: *Effect of the pH on the peak potential of **1***

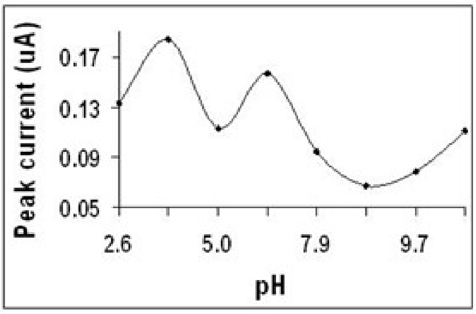


Figure 4: *Effect of pH on the peak current of **1***

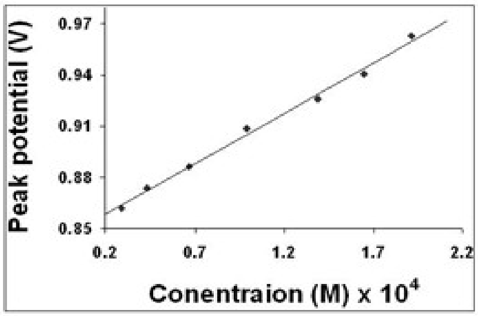


Figure 5: *Effect of concentration on peak potential of* ***1***

Even though, **1** appear to have several electrochemically active sites, many of them are hard to be reduced due to aromatic stability.

However, the azomethine site sandwiched between fluoro benzene and aliphatic amino group must be readily reducible. The electrochemical reduction behaviour of Schiff bases is well documented.[11, 12] Curve fitting of Randles-Sevscik equation besides coulometric analyses establishes the number of electrons involved as 2.

Since the compounds undergo neither hydrolysis like many Schiff bases are famous for [13] nor any other chemical reaction in these buffers, the 2-electron transfer is attributed to the reduction of the -C=N- moiety of 1 or protonated 1 i.e., $1H^{2+}$ or $1H^{+}$ as

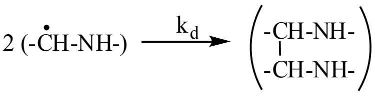
(1)

In many cases, the 2-electron reduction of the azomethine group of the Schiff bases intrinsically happens in a consecutive pair of single electron transfer processes as

$$\text{-C=N-} + e^- + H^+ \xrightarrow{k_1} \text{-}\dot{\text{C}}\text{H-NH-} \qquad (2a)$$

$$\text{-}\dot{\text{C}}\text{H-NH-} + e^- + H^+ \xrightarrow{k_2} \text{-CH}_2\text{-NH-} \qquad (2b)$$

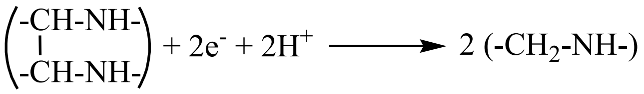
giving two successive reduction current peaks.[14] If $k_2 >>> k_1$, one obtains a single but two electron reduction peak with k. The second consecutive reaction has a parallel dimerization process [15] as



$$2\,(\text{-}\dot{\text{C}}\text{H-NH-}) \xrightarrow{k_d} \begin{pmatrix} \text{-CH-NH-} \\ | \\ \text{-CH-NH-} \end{pmatrix}$$

(3)

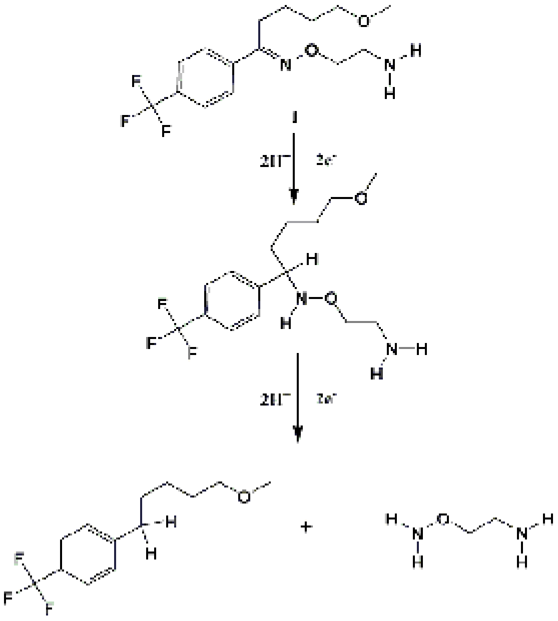
Usually, the k_d value is far slower (due to steric restrictions) than k_2 and the chemical dimerization step, (3), would influence the cyclic voltammetric profile when only the k_2 is slow. If the on-setting of the potential responsible for the second consecutive reduction, (2b), is delayed, there is a finite probability of the formation of the dimer which would undergo an easier electrochemical reduction as



$$\begin{pmatrix} \text{-CH-NH-} \\ | \\ \text{-CH-NH-} \end{pmatrix} + 2e^- + 2H^+ \longrightarrow 2\,(\text{-CH}_2\text{-NH-})$$

(4)

The presence of only a single but two electron-two proton reduction indicates that the k_2 is very fast and k_d is very slow. The effect of scan rate on the cyclic voltammetric response of **1** in low pH buffers was studied. A shoulder was observed at lower cathodic potential due to (4) at slow scan rates because of the finite life for the product of (2a) to engage in (3). At faster scan rates the potential needed for (2b) is too quickly reached to allow any scope for (3).



Scheme 2

The linearity of the plots of peak current, i_p, vs ν, the scan rate, suggests **(Figure 6)** that the electrochemical reduction in the entire pH range, 2-12, is adsorption controlled. The cathodic shift of peak potential, E_p, with increased scan rate also supports the irreversible nature of the electrode reaction. From plots of E_p vs ν, at different pH values, the transfer coefficients, α_{na}, were evaluated. The plots of E_p vs pH of **1** are linear with the slopes compatible to a 2-proton participation. With the knowledge of n and α_{na}, we could evaluate the diffusion coefficient, D, for the electroactive species, of **1**, from the Randles-Sevcik equation,

$$i_p = 2.69 \times 10^{-5} n(\alpha n_a)^{1/2} A D^{1/2} v^{1/2} c \qquad (5)$$

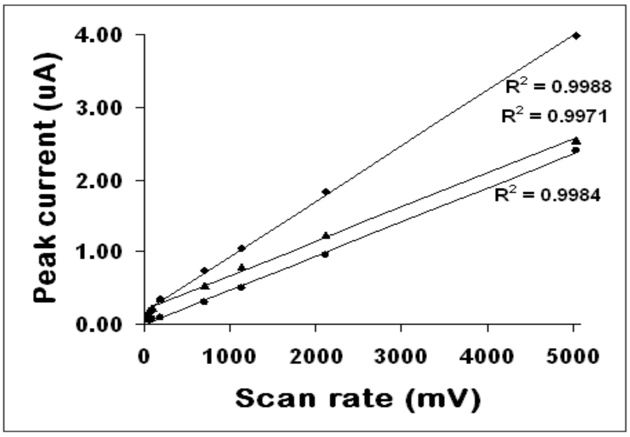


Figure 6: *Effect of peak current on the scan rate of* ***1***

applicable for an irreversible but adsorption controlled electron transfer cyclic voltammetirc peaks, where i_p is the peak current, A is the area of the electrode, ν is the scan rate and c is the concentration of the electro active species.

Compounds, **1** have additional reducible steps in their C–F bonds. The electrochemistry of organo halogen compounds is well documented.[16] The –C–X– bond (where X is a halogen substituent) is known to offer an irreversible electron transfer due to the process,

$$-C-X \xrightarrow{e^-,\ H^+} -CH + X^- \qquad (6)$$

in aqueous media. However, in the present case of **1**, wherein the C-X is on a stable aromatic ring, such reduction has been found to be very near to the hydrogen evolution and hence could not be investigated further. The electrochemical data of **1** are presented in **Table 1** and plausible electrochemical mechanism presented in **Scheme 2**.

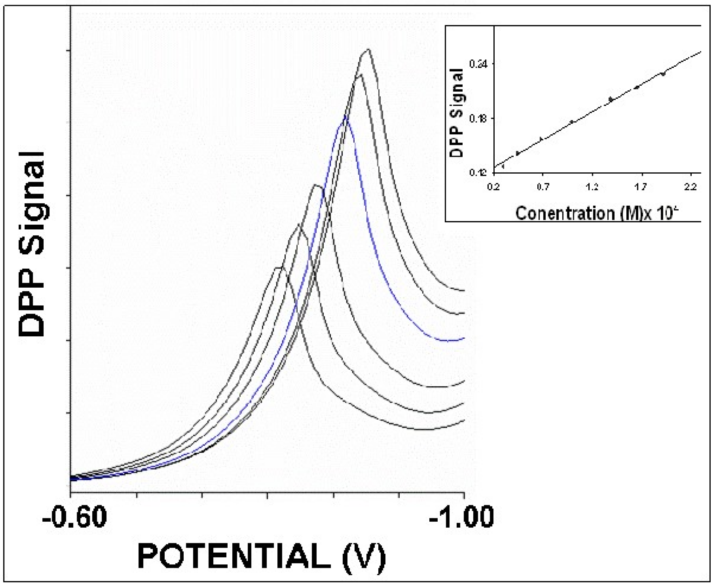


Figure 7*: Differential pulse polarograms and the voltammetirc calibration plot of* ***1*** *(scan rate = 5 mV s-1and pulse height = 25 mV) in buffer of pH = 3.7*

Assaying of **1**:

Based on the electrochemical response of **1**, an excellent electrochemical assaying of **1**, in differential pulse polarography (DPP), has been developed. The DPP curves of **1** at pH=3.00 along with the calibration curve (inset) are shown in **Figure 7**.

Table 2- Cyclic voltammetric data of **1**

Compound	**pH**	**-E$_p$** (V)$^{\#}$ vs Ag|AgCl	**α_{na}**	**k^o_h** x10^9 (cm^2 /s)	**D$_o$** x 10^6 (cm^2 /s)
1				41.36	
	2.56	0.92	0.98	35.97	0.89
	4.05	1.02	0.73	35.95	2.27
	5.76	1.12	0.67	12.18	1.82
	7.62	1.26	0.10	57.17	4.11
	9.28	1.30	0.98	28.72	3.15
	10.58	1.50	0.36		1.62

on SMDE with scan rate at 100 mV/s

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