Electrochemical Evaluation of the Equilibrium Constant of Keto-enol Tautomerism in Piroxicam

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Piroxicam(I) was found to exhibit keto-enol tautomeric equilibrium between the keto(1A) and enol(1B) forms in aqueous media with the enol form as the predominant species (about 80%). Making use of the electroanalytical methods, differential pulse polarography and cyclic voltammetry, the keto-enol tautomeric equilibrium constant, K_t, was evaluated. Below pH 5, it was found that pH had hardly any effect on the equilibrium constant suggesting that the proton exchange across the keto and enol forms to be taking place *via* an intramolecular hydrogen bond. In basic pH's, due to possible deprotonation and other accompanying acid-base equilibria the keto-enol tautomerism was observed to be disturbed. The K_t value (C_{keto}/C_{enol}) is found to be 0.224 while the average diffusion coefficient of piroxicam as $1.2020 \times 10^{-6} cm^2 s^{-1}$.

INTRODUCTION

Piroxicam shown in structure-I is used as a muscular pain relieving drug. Even though considerable extent of electrochemical work is available on heterocyclic compounds containing nitrogen and sulphur atoms[1–4], no electrochemical characterisation of piroxicam which possesses a facile double bond is reported yet. As a part of our continuous interest in the spectral, electrochemical, medicinal and structural studies of several drugs, we report here the electrochemical method of determining the equilibrium constant of the keto-enol tautomerism in piroxicam while using cyclic voltammetry as an electrochemical diagnostic tool to understand the electrochemical reduction behaviour of the compound.

It is possible to visualise on the merits of steric considerations and on the basis of hydrogen bonding between C—OH and amide's —CO— of the enol form that the enol form is thermodynamically more stable than the keto form. If both k_1 and k_2 are significantly low, one can evaluate the equilibrium constant of the tautomerism by polarographic method of estimating the relative concentrations

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of the keto and enol forms. Cyclic voltammetry and differential pulse polarography were adopted for this purpose in four different aqueous buffered solutions.

EXPERIMENTAL

Piroxicam was extracted from commercial sample and recrystallised from ethyl alcohol. A 0.0012 M stock solution of the sample was prepared in absolute ethanol in a 25 mL standard flask. All the buffers which were used for maintaining pH and for serving as the supporting electrolytes were prepared by employing analytical grade chemicals by standard procedures[5-7] while using stock 0.3 M KCl to maintain uniform ionic strength at 0.05 M in all the buffers. The cyclic voltammograms and differential pulse polarograms were recorded on a PARC Model 264 A3 Polarographic Analyzer/Stripping Voltammeter. INSREF Cryostatic water bath equipped with proportional control was used for thermostatting ($25 \pm 0.20°C$) the electrochemical cell. A typical cyclic voltammogram or differential pulse polarogram was recorded by mixing 1 mL of the stock sample solution with 9 mL of the buffer in the electrochemical cell. Pure nitrogen gas saturated with water vapour was purged to remove the dissolved oxygen before recording the cyclic voltammograms.
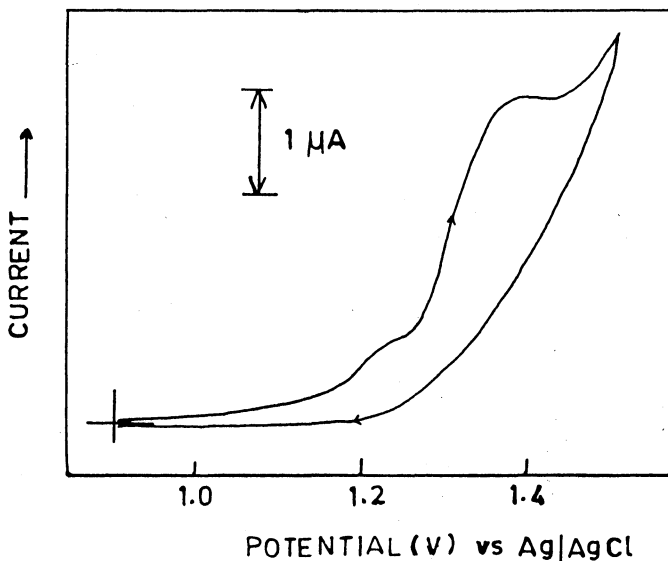

Fig. 1   Cyclic Voltammogram of Piroxicam in aqueous buffer of pH 4.50 at stationary mercury drop electrode (SMDE) of drop area 0.0096 cm^2 and scan rate 50 mV s^{-1}

RESULTS AND DISCUSSION

Organic compounds having electron withdrawing —C=X— and >C—Y— groups at 1,3 positions where X and Y are electronegative atoms and a double

bond between 1,2 carbons generally exhibit tautomerism[8–10]. As piroxicam has —C=O— and >C—OH— moieties on the two carbon atoms connected by a double bond (Structure IB) it is possible for it to exhibit similar tautomerism as shown in Scheme 1, *i.e.*,

$$IA \text{ (keto form)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} IB \text{ (enol form)} \tag{1}$$
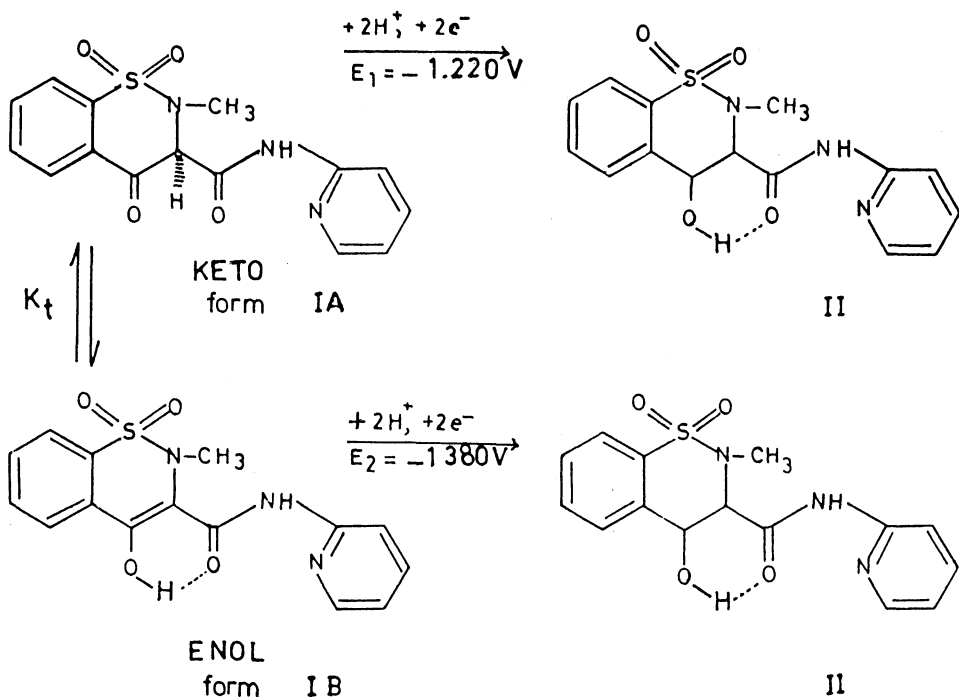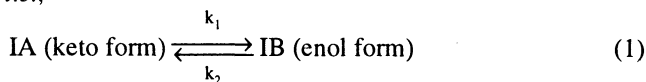
Scheme 1.   Electrochemical reduction mechanism

The system as expected shows two distinct irreversible reductive peaks in nearly all the buffers. A typical cyclic voltammogram is shown in Figure 1. Results of detailed electrochemical characterisation of piroxicam are reported elsewhere[11] and these studies have suggested that the two irreversible electron transfer processes were due to the electrochemical steps shown in Scheme 1. Only the E_{pc}'s vary with pH whereas the ΔE_{pc}, the difference between the two irreversible cathodic peaks is nearly independent of the pH implying negligible effect of pH on the chemical reaction rates k_1 and k_2 and thereby on K_t. The drift in E_{pc} to more cathodic potentials with increasing pH is attributed to the fact that at low pH's the two ring nitrogens are protonated enabling the overall molecule be as a positively charged species. This facilitates the addition of electrons due

to electrostatic considerations. Further, as pH increases the E_{pc} shifts cathodically owing to poorer concentration of H^+ ions.

It is well known that a carbonyl group is electrochemically reducible to give a secondary alcohol by a two electron reduction through inclusion of two hydrogen atoms[12, 13]. It is also vastly reported that olefinic double bonds which bridge any two electron withdrawing functional groups undergo similar electrochemical reduction to yield saturated compounds. On these lines it is expected that both the keto and the enol forms of I are likely to be electroreducible at different potentials as shown in Scheme 1. It is interesting to note that both the electrochemical processes give identical final products[11].

Using these electrochemical reductions as the electroanalytical steps, the concentrations of the keto and enol form were determined by differential pulse polarography and cyclic voltammetry. If C_0 is the analytical concentration of the drug and C_{keto} and C_{enol} are the individual concentrations of the keto and enol forms respectively in the solution and if the drug does not exist in any other form, it is true that

$$C_0 = C_{keto} + C_{enol} \qquad (2)$$

and,

$$\frac{C_{keto}}{C_{enol}} = \frac{k_1}{k_2} = K_t \qquad (3)$$

where K_t is the equilibrium constant for the tautomerism. For diffusion controlled electrochemical reactions the peak current in cyclic voltammetry and the concentration of the electroactive species are related through the Randles Sevčik equation,

$$i_p = 3.05 \times 10^5 n^{3/2} A D_0^{1/2} v^{1/2} c \qquad (4)$$

where i_p is peak current in μA; n, the number of electrons involved in the reduction process; A, the area of the electrode in cm^2; v, the scan rate in $mV\ s^{-1}$; D_0, the diffusion coefficient in $cm^2\ s^{-1}$ and c is the concentration of the electroactive species in mM. As the keto and the enol forms are simple tautomers they may be expected to have near equal diffusion coefficients and transfer coefficients. Then we have

$$\frac{i_{P_{keto}}}{i_{P_{enol}}} = \frac{c_{keto}}{c_{enol}} = K_t \qquad (5)$$

for a given set of experimental conditions. Solving simultaneous equations (2) and (5) with the help of known C_0 (0.00012 M) and $i_{P_{keto}}$ and $i_{P_{enol}}$ one can evaluate c_{keto} and c_{enol} for a given buffer and the equilibrium constant K_t. Back substitution of i_p and c_{keto} or c_{enol} values in equation (4) along with the other experimental parameters gave the diffusion coefficients of both keto and enol forms. These diffusion coefficients which would obviously be close to one another are collected in Table-1 along with the K_t values. Differential pulse polarography of the compound also gave two peaks and the ratio of their current heights gave very close K_t values which in turn were not different from those listed in Table-1.

TABLE-1

CYCLIC VOLTAMMETRIC DATA OF PIROXICAM AT ROOM TEMPERATURE[a]

Buffer	Keto form/enol form				K_t
	c $(M) \times 10^5$	$-E_p$ (V)	i_p (μA)	D $(cm^2 s^{-1}) \times 10^6$	
1.90	2.26	1.02	1.40	1.1190	0.232
	9.73	1.26	6.03	1.1199	
3.50	2.16	1.06	1.41	1.2426	0.220
	9.83	1.33	6.41	1.2399	
4.50	2.17	1.22	1.39	1.1965	0.221
	9.81	1.38	6.29	1.1989	
4.90	2.71	1.24	1.42	1.2487	0.221
	9.82	1.40	6.43	1.2503	

[a] At the analytical concentration $c_0 = 12 \times 10^{-5}$ M; scan rate $v = 50$ mV s^{-1}; electrode area $A = 0.0096$ cm^2

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REFERENCES

1. Y.T. Pratt, in R.C. Elderfield (ed.), A Text Book of Heterocyclic Compounds, Wiley, New York, Vol. 6, p. 377 (1957).
2. A.C. Bedford, A.E. Beezer and C.T. Mortimer, *J .Chem. Soc.*, 2039 (1963).
3. I.M. Kolthoff and J.J. Lingane, in Polarography, Vol. II, Interscience, New York, p. 814 (1952)
4. J.M. Rodriguiz Mellado and R. Martin Galvin, *Bulletin of Electrochemistry,* 7, 142 (1991).
5. Louis Meites, in Polarographic Techniques, Interscience, New York (1955).
6. E.G. and G. Princeton, Applied Research Corporation, Application Briefs and Application Notes.
7. A.I. Vogel, Text Book of Quantitative Chemical Analysis, ELBS, 5th edn., p. 830 (1991).
8. John W. Buntin and J.P. Kanter, *J. Am. Chem. Soc.*,115, 11705 (1993).
9. H. Lian and Christian P. Whiteman, *J. Am. Chem. Soc.*, 115, 7978 (1993).
10. K. Lammertsma and B.V. Prasad, *J. Am. Chem. Soc.*, 116, 642 (1994)
11. G.S. Moses, K.M. Rao, S. Suryanarayana Raju and A. Ramachandraiah, *Indian J. Chem. (B)* (communicated).
12. K. Vijayakumar Reddy and S. Jayarama Reddy, *Indian J. Chem., 25A,* 223 (1986)
13. A. Sivakumar, S. Jayarama Reddy and V.R. Krishnan, *J. Electrochem. Soc. (India),* 32, 129 (1983).