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Cyclic Voltammetric Study of Chlorambucil in the presence of 4-Chloro Butyronitrile in Aqueous Solution

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Abstract: Interactions of chlorambucil with water in the presence of 4-chloro butyronitrile has never been reported to be conducted electrochemically. We presented the investigation of electrochemical oxidation and reduction of chlorambucil in the presence of 4-chloro butyronitrile in aqueous solution using cyclic voltammetric technique. The results showed that the values of the anodic's and cathodic's peak currents of chlorambucil in the presence of 4-chloro butyronitrile in aqueous solution were higher than that without 4-chloro butyronitrile. The anodic's and cathodic's peak potentials of chlorambucil shifted to more negative value in the addition of this substance. The anodic's peak shifted from 0.896 V to 0.855 V while the cathodic's peak shifted from 0.788 V to 0.742 V. We found that the values of chemical reactivity of chlorambucil in aqueous solution, in the presence and the absence of 4-chloro butyronitrile were 0.4897 s^{-1} and 0.4485 s^{-1}, respectively. These results strongly suggested that chlorambucil is easier to be oxidized in the presence of 4-chloro butyronitrile.

Keywords: chlorambucil; chemical reactivity; cyclic voltammetry; nucleophile; aqueous solution.

Introduction

Cyclic voltammetry (CV) has become an important electroanalytical technique in many areas of chemistry. It is widely used for studying of redox reactions based process, for identifying reaction intermediates, and for obtaining stability of reaction products. This technique is based on varying an applied potential at a working electrode in both forward and reverse directions (at some scan rates) while monitoring the current.[1]

Interest on the application of cyclic voltammetric technique in electrochemical studies are increasing.[2-6] It is an alternative method to run an analysis in a relatively short time. Our previous work on chlorambucil in the presence of 4-chloro butyronitrile in organic solution have successfully shown strong correlation between the chemical reactivity of chlorambucil and type of the used solvent and we also have concluded that the mathematic model developed by Nicholson Shain for E_rC_i mechanism and Nucleophile Subtitution 1 (SN-1) reactions can be applied to explain the reactivity of chlorambucil.[5, 7]

Although the study of chlorambucil using voltammetric technique have been previously undertaken, but the oxidation and reduction response of this substance in aqueous solution remain unknown. It is very important to know how the oxidation and reduction response of chlorambucil is actually occurred in aqueous solution to mimic a similar reaction of this substance in human body.

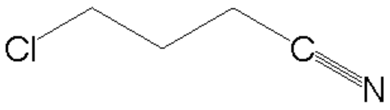


Fig. 1. Chemical structure of 4-chloro butyronitrile

4-chloro butyronitrile (C_4H_6ClN) (Fig. 1.) is a small molecule with molecular weight of 103.55 $gmol^{-1}$. This molecule is slightly miscible in water and commonly used for an intermediate in organic synthesis.[8] We used this molecule to figure out how the competition effects occurred during nucleophilic attack takes place, after carbocation formed electrochemically.

Experimental

Reagents and chemicals

All chemicals used in this work are in p.a grade. Chlorambucil and 4-chloro butyronitrile were obtained from Sigma while sodium perchlorate, potassium dihydrogen phosphate and sodium hydroxide were obtained from Merck. All the solutions were prepared by using double distilled water.

Apparatus and procedures

Cyclic voltammetric (CV) measurements were performed on BASi Epsilon Electrochemical analyzer. A standard three-electrode electrochemical cell was used for all electrochemical measurements with a platinum electrode (1 mm diameter) as working electrode, a platinum (Pt) wire as an auxiliary electrode and a Ag/AgCl (KCl 3 M) as a reference electrode. Cyclic voltammetric measurements were conducted in a homemade 10 mL glass cell. Working electrode was polished with alumina suspension. All data in the calculation was subtracted to the blank.

An amount of chlorambucil were weighed and dissolved in a solvent containing sodium perchlorate 0.1 M and was added by 1 mL of potassium dihydrogen phosphate buffer solution (0.1 M) so that its concentration become 1 mM.

Results and Discussion

The effects of pH, voltammogram profiles and the applied scan rate

The supporting electrolyte was choosen based on our previous work.[5] In our recent experiment, the optimum pH of chlorambucil in aqueous solution was determined from pH range when chlorambucil was activated (Fig.2).[9] The result showed that in KH_2PO_4.NaOH buffer solution (0.1 M), the optimum pH value was about 7.0. The currents decreased along with the increasing of pH of the buffer solution. The decrease of currents reflect to the lower of hydrogen ion concentration in solution.

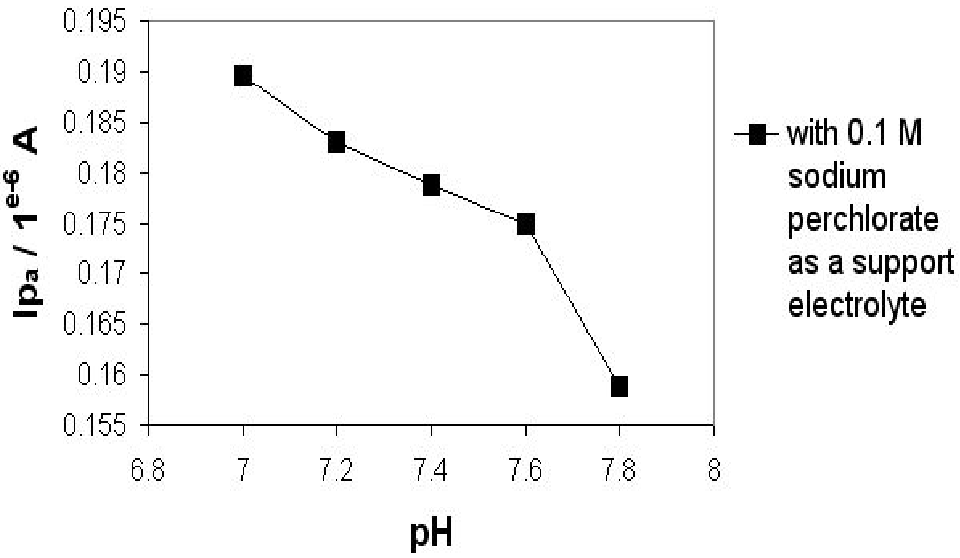


Fig. 2. Effects of pH for 0.1M KH_2PO_4.NaOH buffer solution.

Cyclic voltammogram profiles of chlorambucil in the presence and absence of 4-chloro butyronitrile in aqueous solution are presented in Fig. 3. A pair of reversible redox peaks denoted as P1 and P2 at scan rate of 1 Vs^{-1} appeared at potentials of $Ep_a = 0.855$ V and $Ep_c = 0.742$ V with E^0 ($E_{1/2} = 0.804$ V); while for P3 and P4 peak pairs, $Ep_a = 0.896$ V and $Ep_c = 0.788$ V with $E^0 = 0.842$ V. From the values above, we found that our CV gave 41 mV and 46 mV potential shifting of anodic's and cathodic's peak potentials, respectively, when 100 mM of 4-chloro butyronitrile was added into 1 mM of chlorambucil in aqueous solution. In CV profiles, currents of P1 is higher than that of P3. This CV profile indicated that the number of electric charge occurred in the presence of 4-chloro butyronitrile is relatively greater than that without 4-chloro butyronitrile. These results thus strongly suggested that there is competition between weak and strong nucleophiles i.e. 4-chloro butyronitrile and water.

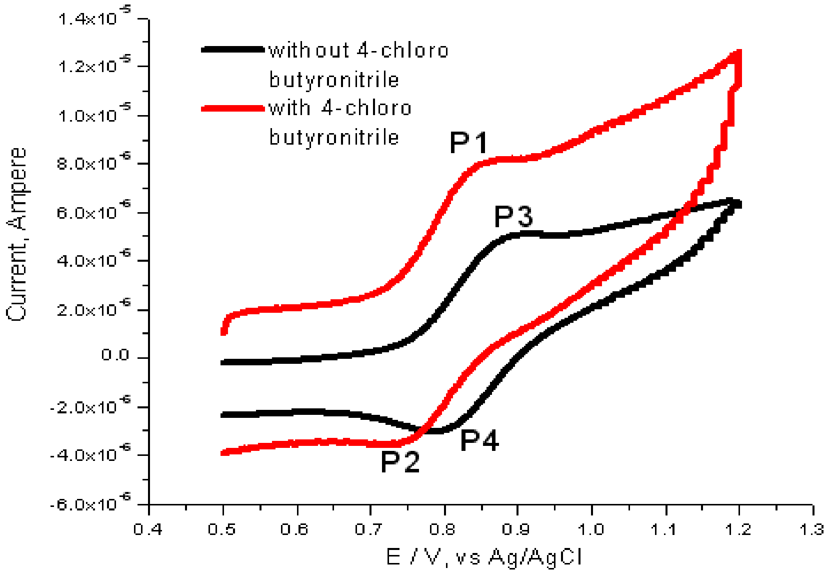


Fig. 3. Cyclic voltammograms of chlorambucil in aqueous solution in the presence and absence of 4-chloro butyronitrile.

Table I presented a small increase of peak separation (ΔEp). In our experiment, we found that ΔEp values increased in accordance with the increased of the scan rate values. At initial scan rate of 0,18 Vs^{-1}, ΔEp value was 0,089 V but after the scan rate adjusted to 1,0 Vs^{-1}, ΔEp value was only 0,113 V. This slight increased in the peak separation indicated that chlorambucil reaction in aqueous solution is most likely reversible following E_rC_i mechanism. The peak current ratio (Ip_c/Ip_a) in Fig.4, whose value was less than 1, supported the proposed reaction mechanism. The peak current ratio increased gradually along with the increased of the scan rate. These results also proved the characteristic of an E_rC_i mechanism. [5, 10, 13]

TABLE I. Voltammetric data of the peak potential as a function of scan rates of chlorambucil in the presence of 4-chloro butyronitrile.

Scan Rate (V/s)	Potential (V)		Peak Separation (V)
	Ep_a	Ep_c	ΔEp
0.18	0.842	0.753	0.089
0.20	0.842	0.753	0.089
0.30	0.845	0.750	0.095
0.40	0.847	0.750	0.097
0.50	0.847	0.748	0.099
0.60	0.850	0.748	0.102
0.70	0.850	0.744	0.106
0.80	0.853	0.742	0.111
0.90	0.855	0.742	0.113
1.00	0.855	0.742	0.113

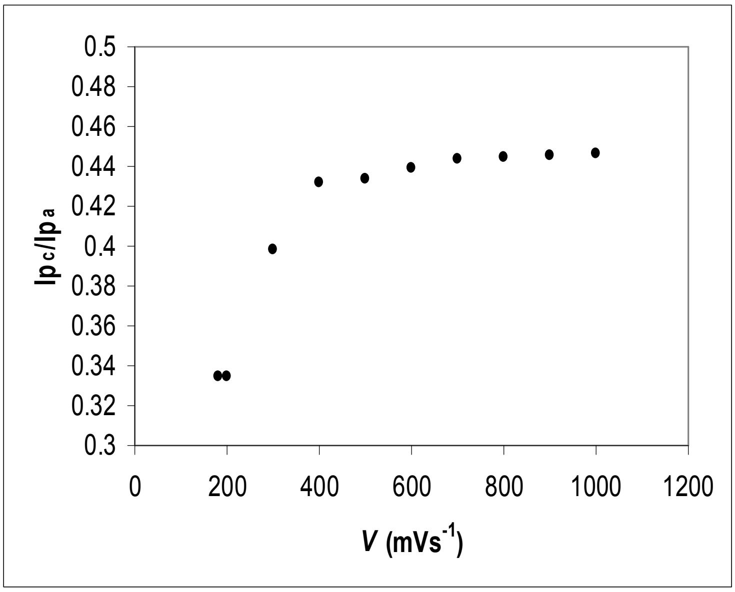


Fig. 4. The plot of Ip_c/Ip_a versus scan rate obtained for chlorambucil in the presence of 4-chloro butyronitrile.

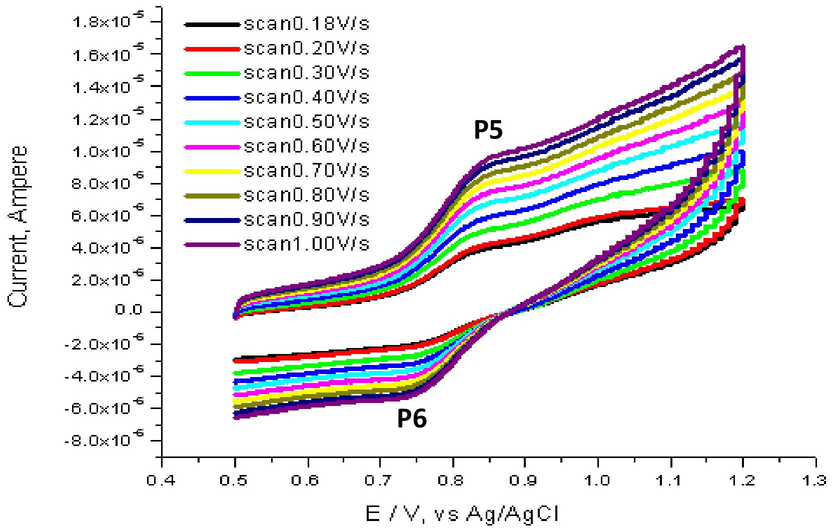


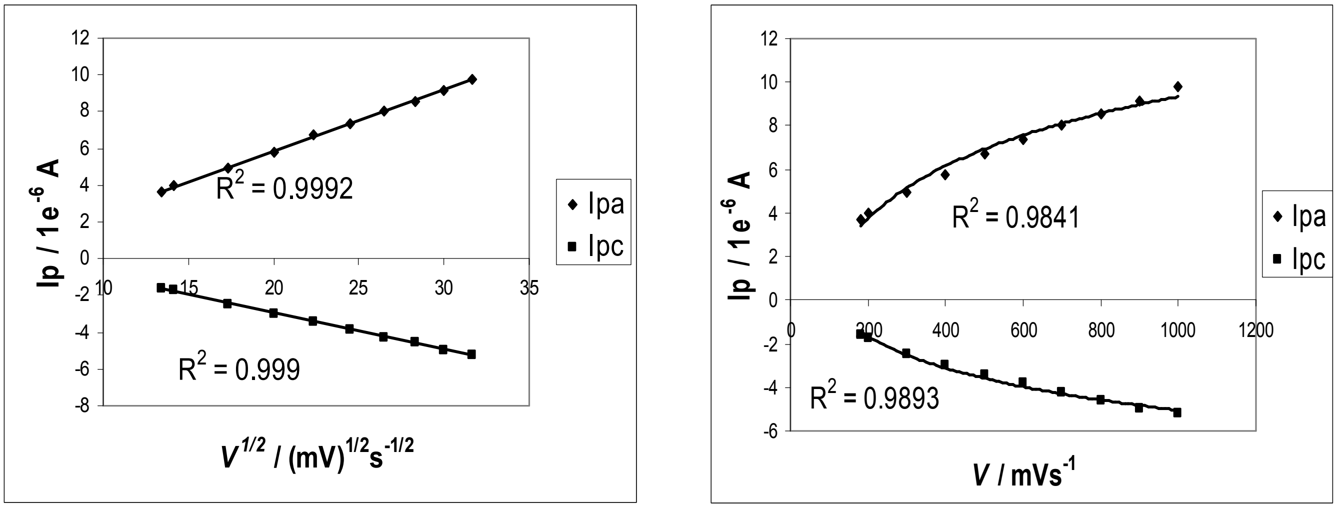
Fig. 5. Cyclic voltammograms of chlorambucil in aqueous solution in the presence of 4-chloro butyronitrile. Scan rates from inner to outer: 0.18; 0.20; 0.30; 0.40; 0.50; 0.60; 0.70; 0.80; 0.90 and 1.00 Vs^{-1}.

Figure 5 showed the effect of scan rate, which were investigated in the range of 0.1 to 1.0 Vs^{-1}. The potential peaks of P5 and P6 are a pair of the reversible redox peaks. The cyclic voltammograms did not change when the initial potential varied between the value of 0.5 V and 1.2 V. The result indicated that there is equilibrium between the oxidation and reduction forms of chlorambucil.

The relationship between anodic's peak current (Ip_a) and cathodic's peak current (Ip_c) corresponding to square root of scan rate ($V^{1/2}$) is presented on the figure 6a. The two plots of Ip versus $V^{1/2}$ gave a straight line with $R^2 > 0.99$. These results reflect conditions of diffusion control of the charge transport process. The rate of charge transfer is controlled by the rate of supply of material to the electrode by the diffusion process.[11] As shown in Randles-Sevcik equation below,[12] the peak current depends on the square root of scan rate in a oxidation-reduction process.

$$Ip = (2.69 \times 10^5)\, n^{3/2} A D^{1/2} C V^{1/2} \qquad \ldots(1)$$

In the different way, figure 6b showed the relationship between Ip's peak current and the scan rate (V). The two plots of Ip versus V gave a logarithmic relationship with $R^2 > 0.98$. The logarithmic of the plot between Ip and V reflect to the diffusion controlled of the reversible redox reaction of chlorambucil.



(a) (b)

Fig. 6. The changes in current value to the square root of scan rate ($V^{1/2}$) (a) and the value of scan rate (V) (b) of chlorambucil.

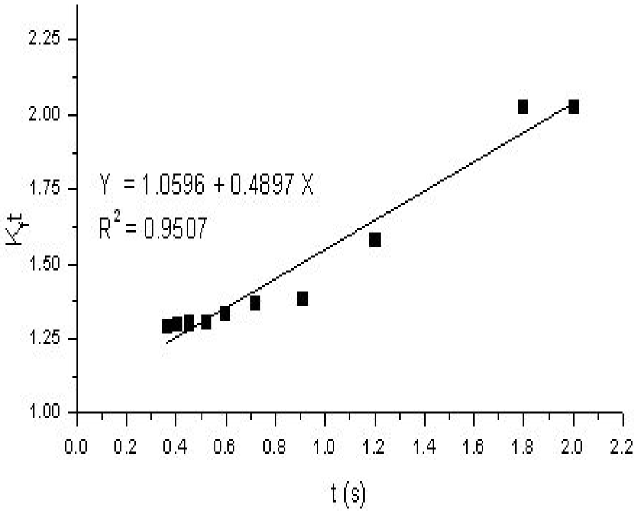


Fig. 7. The plot of K_ft versus t to find the value of K_f of chlorambucil in the presence of 4-chloro butyronitrile in aqueous solution.

The rate constant for the forward reaction of chlorambucil

Cyclic voltammogram profiles in Fig. 5, was obtained at the scan rate range from 0.1 to 1.0 Vs^{-1}. The CV profile showed the oxidation-reduction behavior of chlorambucil in aqueous solution with the presence of 4-chloro butyronitrile. We calculated all of electrochemical parameters to each analyte to obtain the values of Ip_c/Ip_a, E^0 and t. Based on Nicholson's curve,[7] we determined the values of K_ft. By plotting the value of K_ft versus t (Figure 7.), a linear curve was obtained with the slope of 0.4897 s^{-1}. The slope indicated the value of rate constant of chlorambucil in forward reaction. The value of rate constant of chlorambucil in forward reaction, in the presence of 4-chloro butyronitrile is greater than in the absence of 4-chloro butyronitrile i.e. 0.4485 s^{-1}. Addition of 4-chloro butyronitrile caused the shifted of anodic's and cathodic's peak potential to be more negative, so that chlorambucil is easily oxidized. The increased of anodic's and cathodic's peak current due to the existence of 4-chloro butyronitrile in chlorambucil solution. The facts of our experiment proved that there is a competition between the nucleophilic compounds i.e. water and 4-chloro butyronitrile in the alkylation reaction of chlorambucil. This competition affects to the amount of chlorambucil's carbocation formed. Refer to our previous work, the values of chemical reactivity of chlorambucil in the presence of 4-chloro butyronitrile in acetone and acetonitrile were 0.2715 s^{-1} and 0.2676 s^{-1}, respectively,[5] which were smaller than that in aqueous solution. We concluded that the chemical reactivity of chlorambucil in aqueous solution is better than in organic solvent.

Conclusions

The oxidation-reduction behavior of chlorambucil in aqueous solution containing 4-chloro butyronitrile was studied using cyclic voltammetric technique. In general, the chemical reactivity of chlorambucil in aqueous solution is greater than that in non-aqueous solution. This finding is consistent with our previous work which reported the interaction of chlorambucil in organic solution.[5] To the best of our knowledge, it is the first time that the chemical reactivity of chlorambucil in aqueous solution were reported experimentally with an electrochemical approach.

Acknowledgments

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