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Electrocatalytic Oxidation of Chlorpromazine in Phosphate Solution

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The kinetics of electrocatalytic oxidation process of chlorpromazine (CPZ) at a pyrolytic graphite electrode in a phosphate solution was investigated by rotating disk voltammetry. The reactions involving regeneration process of CPZ through the disproportionation of reaction intermediates are proposed and the rate constants of the chemical reaction (k_{obsd}), following the electrochemical oxidation of CPZ to the CPZ cation radical, were evaluated from the electrode rotation-rate dependence of the limiting currents obtained in the CPZ solution with and without phosphate. The proportional relations between the logarithm of k_{obsd} and pH, and between k_{obsd} and the concentration of $H_2PO_4^-$ were obtained.

In a previous paper,[1] we proposed an electrochemical oxidation mechanism of chlorpromazine (CPZ) involving the regeneration processes of CPZ through the disproportionation of reaction intermediates at the electrode surface, as given by Eqs. 1—4,

$$\mathrm{CPZ} \underset{+e}{\overset{-e}{\rightleftharpoons}} \mathrm{CPZ}^{\cdot +} \qquad (1)$$

$$\mathrm{CPZ}^{\cdot +} + \mathrm{H_2PO_4}^- \overset{K_1}{\rightleftharpoons} [\mathrm{CPZ(HPO_4)}]^{\cdot -} + \mathrm{H}^+ \qquad (2)$$

$$[\mathrm{CPZ(HPO_4)}]^{\cdot -} + \mathrm{CPZ}^{\cdot +} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [\mathrm{CPZ(HPO_4)}]^0 + \mathrm{CPZ} \qquad (3)$$

$$[\mathrm{CPZ(HPO_4)}]^0 + \mathrm{H_2O} \xrightarrow{k_3} \mathrm{CPZO} + \mathrm{H_2PO_4}^- + \mathrm{H}^+ \qquad (4)$$

where $\mathrm{CPZ}^{\cdot +}$ and CPZO are the CPZ cation radical and CPZ S-oxide, respectively. Chlorpromazine is a well-known drug in phenothiazines and frequently used as a major tranquilizer. Thus, further confirmation of the oxidation mechanism of CPZ may give more significant informations for determination of the best conditions for highly sensitive electrochemical analysis of CPZ and understanding of the drug metabolic pathway.

In this paper, we examine in detail the mechanism of the electrocatalytic oxidation of CPZ in phosphate media. Although our proposed reaction mechanism of CPZ is somewhat complicated, it is reported that the following simplified expression, so-called "half-generation reaction";

$$\mathrm{A} \xrightarrow{e} \mathrm{B}$$

$$2\mathrm{B} \xrightarrow{k} \mathrm{A} + \mathrm{C}$$

suffices Eqs. 1—4 and the k value can be obtained from the voltammetric limiting current, using a rotating disk electrode (RDE) according to the procedure of Holub.[2]

Experimental

Chemicals. Chlorpromazine hydrochloride was obtained from Sigma Chemical Co. All other chemicals were of analytical grade and were used without further purification. A perchlorate salt of the chlorpromazine cation radical was prepared electrochemically according to the procedure of McCreery *et al.*[3] Phosphate buffers, prepared by mixing of H_3PO_4 and NaOH solutions, were used as supporting electrolyte solution and the pH's of the buffers were measured at 25 °C with a Toa pH meter HM-5ES.

Apparatus. Measurements of current-potential curves and controlled potential electrolysis were carried out using an HA-301 potentiostat (Hokuto Denko Ltd.) and a function generator HB-104 (Hokuto Denko Ltd.). In these experiments, a pyrolytic graphite disk was chosen as a working electrode so as to render the adsorption of CPZ on the electrode surface negligibly small.[4] To prepare the rotating disk electrode, the pyrolytic graphite disk (Union Carbide Co.) was sealed with the heat shrinkable teflon tubing. The graphite disk was connected to a stainless steel shaft attached to rotating disk rotor RRDE-1 (Nikko Keisoku Ltd.) and motor speed controller SC-5 (Nikko Keisoku Ltd.). A fresh electrode surface with an area of 0.19 cm^2 was produced by cleaving the disk with a stainless steel cutter. The potentials are quoted with respect to a saturated calomel electrode (SCE). The electrolysis solution was deaerated by bubbling nitrogen gas. During the experiment, the solutions were shielded from light and air, and the temperature was maintained at 25 °C.

Measurements of ^{31}P-NMR spectra were carried out using a FX-200 spectrometer (JEOL). The crystallized $\mathrm{CPZ}^{\cdot +}$ perchlorate was directly dissolved in methanol containing 7.8% D_2O with 1.0×10^{-2} mol dm^{-3} NaH_2PO_4 and the spectra of NaH_2PO_4–$\mathrm{CPZ}^{\cdot +}$ solution were measured immediately.

Results and Discussion

The current-potential (i-E) curves of 1.0×10^{-3} mol dm^{-3} CPZ obtained by using the stationary graphite electrode are shown in Figs. 1 and 2. The oxidation peaks appear clearly on the anodic scan, and the peak current (i_p) at 0.65 V *vs.* SCE becomes large at higher pH and higher phosphate concentrations. This trend is essentially the same as that observed previously by using a stationary glassy carbon electrode.[1] Thus, the electrochemical oxidation of CPZ is also catalyzed by phosphate anion at the graphite electrode.

The anodic current-potential curves of 1.0×10^{-3} mol dm^{-3} CPZ obtained by RDE are shown in Figs. 3 and 4. A well-defined oxidation wave is observed with a half-wave potential of 0.60 V *vs.* SCE. The limiting current, i_{lim}, of the oxidation increases with increasing the phosphate concentration, whereas the half wave potential is independent of the phosphate concentration (Fig. 3). The value of i_{lim} also depends on pH. A larger i_{lim} is observed at higher pH (Fig. 4).

Figure 5 shows the Levich plot, *i.e.*, the reciprocal of the limiting current (i_{lim}^{-1}) *vs.* that of the square root of the rotation rate ($\omega^{-1/2}$) obtained for the CPZ oxidation wave. At a pH lower than 3, i_{lim}^{-1} is in proportion to $\omega^{-1/2}$, but not so at higher pH. This indicates that the limiting current is diffusion-controlled at lower pH, but kinetic in nature at higher pH. The contribution of chemical reactions to the overall electrode process of CPZ thus becomes apparent.

From the plot of log $(i/(i_{\mathrm{lim}}-i))$ *vs.* *E* (Fig. 6), the number of electrons, *n*, involved in the oxidation process of CPZ (Eq. 1) is estimated to be unity.

The electrolysis products were produced by controlled potential electrolysis and detected by UV-visible absorption spectroscopy, and thin-layer chromatography. Electrolysis was carried out in a 0.1 mol dm^{-3} phosphate solution (pH 2—7) at a fixed potential of 0.72 V *vs.* SCE, until the limiting current dropped below 0.5% of the initial value. When the solution showed below pH 3, it was tinged red during the electrolysis. The solution showed an absorption peak due

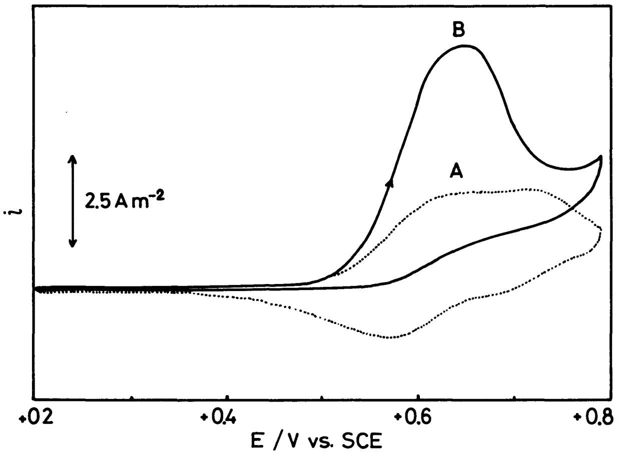

Fig. 1. Current-potential curves of 1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} CF_3COONa solution using the stationary graphite electrode.
Phosphate concentration: (curve A): 0 mol dm^{-3}, (curve B): 0.1 mol dm^{-3}.
Scan rate: 100 mV s^{-1}.

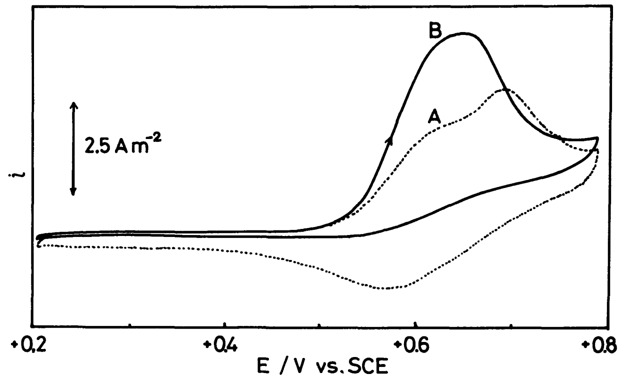

Fig. 2. Current-potential curves of 1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} phosphate solution using the stationary graphite electrode.
(curve A): pH 3.10, (curve B): pH 6.90.
Scan rate: 100 mV s^{-1}.

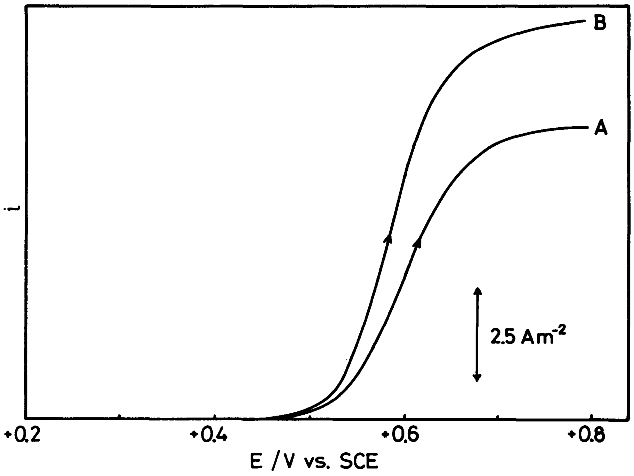

Fig. 3. Current-potential curves of 1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} CF_3COONa solution using the rotating disk electrode.
Phosphate concentration: (curve A): 0 mol dm^{-3}, (curve B): 0.1 mol dm^{-3}.
Scan rate: 2 mV s^{-1}.
Rotation rate: 2500 min^{-1}.

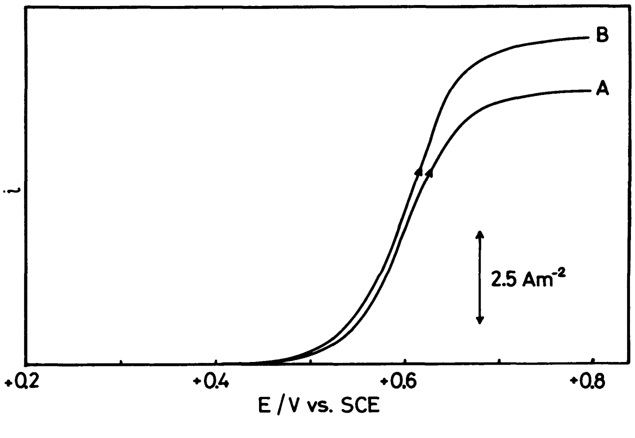

Fig. 4. Current-potential curves of 1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} phosphate buffer using the rotating disk electrode.
(curve A): pH 3.10, (curve B): pH 6.90.
Scan rate: 2 mV s^{-1}.
Rotation rate: 2500 min^{-1}.

to $CPZ^{\cdot +}$ at 524 nm. The final electrolysis product was found to be CPZO on the basis of a comparison with an authentic sample.

The above findings are important in regard to the validity of our assumption previously proposed for the electrode processes of CPZ.[1] The presence of an intermediary adduct between $CPZ^{\cdot +}$ and phosphate given in Eq. 2 is suggested from the data of ^{31}P-NMR of the $CPZ^{\cdot +}$-$H_2PO_4^-$ system. The ^{31}P-NMR spectra were measured in methanol containing 7.8% D_2O at pH 3.75 to avoid rapid decomposition of $CPZ^{\cdot +}$. A distinct peak can be seen in the ^{31}P-NMR spectrum of a 1.0×10^{-2} mol dm^{-3} NaH_2PO_4 solution (pH 3.75) without $CPZ^{\cdot +}$ (Fig. 7A). When 1.0×10^{-2} mol dm^{-3} $CPZ^{\cdot +}$ coexists with NaH_2PO_4, the peak of NaH_2PO_4 shifts upfield (Fig. 7B) and is little affected by the presence of 1.0×10^{-2} mol dm^{-3} CPZ (Fig. 7C). This implies an interaction between $CPZ^{\cdot +}$ and $H_2PO_4^-$.

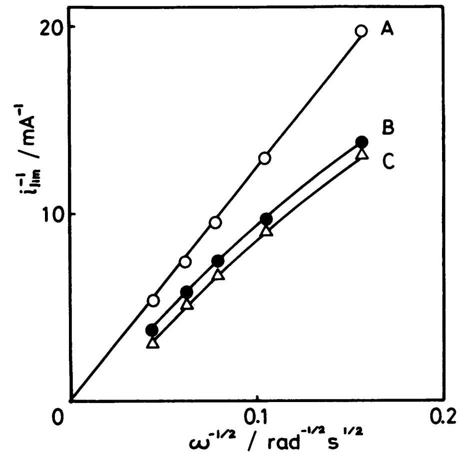

Fig. 5. Plots of reciprocal of the limiting current (i_{lim}^{-1}) *vs.* reciprocal of square root of rotation rate of RDE ($\omega^{-1/2}$) for the oxidation of 1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} phosphate solution.
(curve A): pH 3.0, (curve B): pH 5.9, (curve C): pH 6.9.

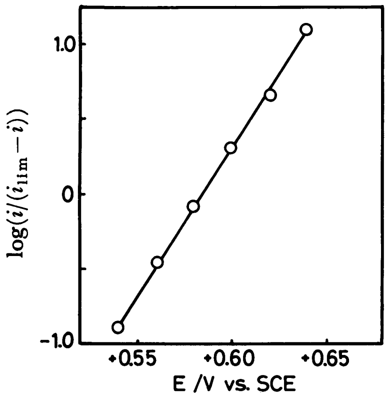

Fig. 6. Plot of $\log(i/(i_{lim}-i))$ *vs.* *E*.
1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} phosphate solution (pH 6.9).
Rotation rate: 900 min^{-1}.

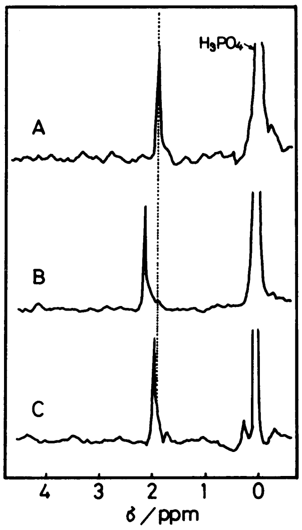

Fig. 7. ^{31}P-NMR spectra of $H_2PO_4^-$ with and without $CPZ^{\cdot +}$ and CPZ in methanol containing 7.8% D_2O at pH 3.75.
(A): 1.0×10^{-2} mol dm^{-3} NaH_2PO_4, (B): 1.0×10^{-2} mol dm^{-3} NaH_2PO_4 with 1.0×10^{-2} mol dm^{-3} $CPZ^{\cdot +}$, (C): 1.0×10^{-2} mol dm^{-3} NaH_2PO_4 with 1.0×10^{-2} mol dm^{-3} CPZ.

Assuming the reaction given by Eq. 2 always to be in equilibrium and the reactions expressed by Eqs. 3 and 4 to be of comparable rate,[5] the observed rate constant, k_{obsd}, for a series of reactions expressed by Eqs. 2—4 may be written as

$$k_{obsd} = \frac{2K_1k_3(k_2/k_{-2})[H_2O][H_2PO_4^-]}{([CPZ]+k_3[H_2O]/k_{-2})[H^+]} \tag{5}$$

Provided the concentration of CPZ is virtually constant at the electrode surface, the following two relations can be expected to hold.

$$k_{obsd} \propto [H^+]^{-1} \tag{6}$$

$$k_{obsd} \propto [H_2PO_4^-] \tag{7}$$

The values of k_{obsd} can be calculated from the ratio of the kinetic current to diffusion current, according to Holub's analysis of the half-generation mechanism.[2] First, the quantity *J*, defined as $(i_c-i_0)/i_0$, is calculated, where i_c and i_0 are the limiting currents obtained in the CPZ solution with and without phosphate, respectively. It is then possible to obtain κ by using Holub's table which tabulates the relation between *J* and κ. The κ is expressed as

$$\kappa = (2k_{obsd}\,a^*/(0.51^{2/3}\omega))(\nu/D)^{1/3} \tag{8}$$

where a^* is the bulk concentration of CPZ, ν the kinematic viscosity and *D* the diffusion coefficient of CPZ. From the slope of the Levich plot, the value of *D* is obtained as 6.53×10^{-10} m^2 s^{-1}. The value of ν is then assumed to be 1.0×10^{-6} m^2 s^{-1}, the viscosity of water.

The plot of log k_{obsd} *vs.* pH and k_{obsd} *vs.* $H_2PO_4^-$ concentration are shown in Figs. 8 and 9, from which the relations 6 and 7 are found to hold except at pH

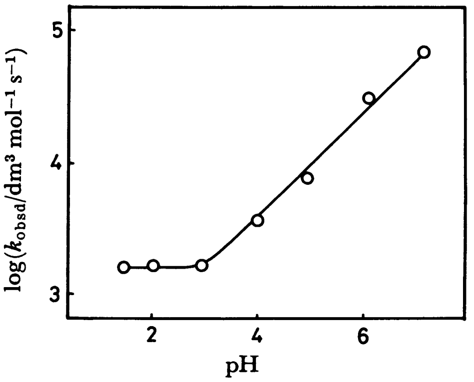

Fig. 8. Plot of the $\log k_{obsd}$ *vs.* pH.
1.0×10^{-3} mol dm^{-3} CPZ in a 0.1 mol dm^{-3} phosphate solution.

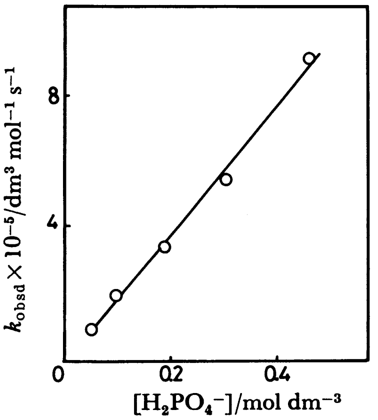

Fig. 9. Plot of k_{obsd} *vs.* $H_2PO_4^-$ concentration.
1.0×10^{-3} mol dm^{-3} CPZ; pH 6.8.

lower than 3. The deviation from the relation 6 at pH lower than 3.0 may attributed to the fact that the reaction expressed by Eqs. 2—4 is not established in the strong acidic solution and that other unknown regeneration processes of CPZ occur. Since the solubility of CPZ greatly decreases at pH higher than 7, the measurement of k_{obsd} cannot be made in such a pH region. Thus the kinetics of the electrocatalytic oxidation processes of CPZ described above is valid in the pH range 3—7.

McCreery *et al.*[3] studied the degradation of $CPZ^{\cdot+}$ in bulk solution by spectrophotometric technique and obtained the value of 177 dm^3 mol^{-1} s^{-1} for the rate constant (k_{obsd}) in a 0.1 mol dm^{-3} phosphate solution at pH 3.99 in the presence of 2.0×10^{-3} mol dm^{-3} CPZ, assuming the same reaction sequence as Eqs. 2—4. Under the same conditions, determination of k_{obsd} was made by the present method for comparison and the value of 142 dm^3 mol^{-1} s^{-1} was obtained. This value is essentially the same as above, indicating the validity of the electrode processes of CPZ presented by Eqs. 1—4.

The results presented in this paper confirm the mechanism previously proposed for the anodic oxidation processes of CPZ.[1]

References

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