

Electrochemical Interpretation of Parabolic Relation between the Hydrophobicity and the Permeability of Tetraalkylammonium Chlorides

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Abstract

Transport of hydrophobic tetraalkylammonium chlorides (tetrabutylammonium, tetrapentylammonium, tetrahexylammonium and tetraheptylammonium) across a porous polytetrafluoroethylene resin film impregnated by 1-octanol between two aqueous phases is interpreted by considering the steady-state flows of both the tetraalkylammonium ion and the chloride ion within both the aqueous and the membrane phases. The parabolic relation between the hydrophobicity and the permeability in the quantitative structure-activity relationship is attributable to whether the transport of both ions within the aqueous phases or that within the membrane phase is the rate-determining step in the cell system.

1. Introduction

The relation between the physiological activity of a drug against a diseased area and the hydrophobicity of the drug has been investigated for more than 100 years [1-4]. First, Crum-Brown and Fraser indicated the concept that the physiological action of the drug is dependent on its chemical composition and molecular structure [5]. Richet subsequently showed that the cytotoxicity of the simple organic molecule is inversely proportional to its water solubility [6]. Meyer and Overton reported the linear dependence of the distribution coefficient of inhalation anesthetics between water and olive oil on the anesthetic activity [7,8]. In 1939, Ferguson proposed that the physiological activity of volatile compounds depends on the hydrophobicity and the relative saturation in the aqueous phase [9]. By considering the interaction of the drugs with specific receptors, the quantitative structure-activity relationships (QSAR) represented by the Hansch-Fujita approach (the parabolic model) have been developed during the last 40 years and is recognized as a powerful method to predict pharmaceutical potencies [2,10,11]. Taking into account a kinetic model, the parabolic model has been empirically derived. McFarland then physicochemically developed the parabolic relationship (McFarland model) based on the permeation model composed of some aqueous and membrane phases [12]. In addition, Kubinyi improved the understanding of QSAR (the bilinear model) by keeping the volume ratio between the aqueous and the membrane phases in mind [13]. However, since the distribution coefficient has been simply treated as a kinetic parameter in these cases, it is necessary to clarify the relation between the steady-state flows of drugs in both the aqueous and membrane phases and the distribution coefficients of drugs between the aqueous and the membrane phases. Recently, Kano proposed a new model (Kano model) that the rate-determining step depends on the steady-state flow due to the distribution coefficient of the drug between the aqueous and membrane phases [14, 15].

In the present study, the transport of tetraalkylammonium chlorides (tetrabutylammonium ion (TBA^+), tetrapentylammonium ion (TPA^+), tetrahexylammonium ion (THxA^+) and tetraheptylammonium ion (THpA^+)) as hydrophobic drugs across porous films impregnated with 1-octanol between two aqueous phases was investigated by voltammetry. Based on the Kano model, the rate-determining step is the electrophoresis of both the tetraalkylammonium ion (TAA^+) and chloride ion (Cl^-) in the aqueous or membrane phase, and the steady-state fluxes of both TAA^+ and Cl^- are determined by the magnitude of the electrophoretic current within the membrane or aqueous phases.

2. Experimental

2.1. Chemicals

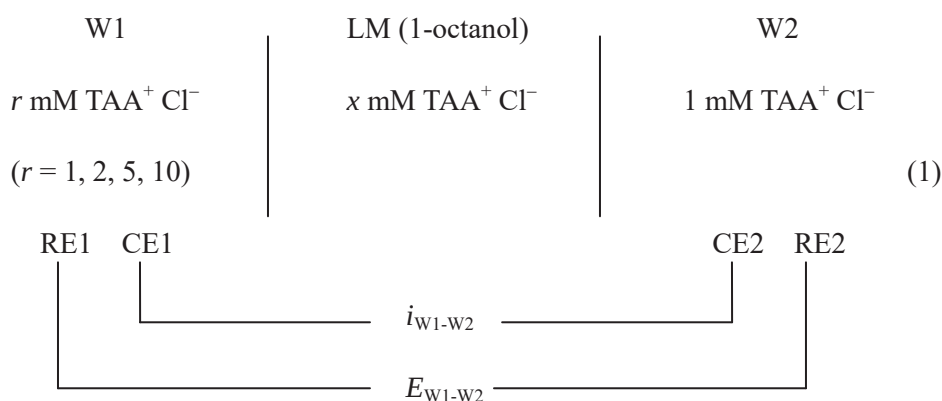
A membrane filter, which was made from polytetrafluoroethylene, with a diameter of 25 mm, a thickness of 50 μm and a pore size of 1 μm , was purchased from ADVANTEC Co., Ltd. Acetone and 1-octanol were obtained from Wako Pure Chemical Ind., Ltd. The chloride salts of TBA^+ , TPnA^+ and THxA^+ were from Tokyo Chemical Industry Co., Ltd. A chloride salt of THpA^+ was bought from Kanto Chemical Co., Inc. These chlorides, which are typical quaternary ammonium compounds, were used as permeable objective drugs. The other chemicals were purchased from Wako Pure Chemical Ind., Ltd. All reagents were of reagent grade and were used without further purification.

2.2. Electrochemical measurements

After the membrane filters were soaked in acetone, the filters were soaked in 1-octanol. The filters were then immersed in pure 1-octanol, and we duplicated the soakage to remove residual acetone in the filters. Two filters were set up together to become a symmetrical

Fig. 1

membrane impregnated by 1-octanol, as shown in Fig. 1. The cell was composed of two aqueous compartments (W1, W2) and one liquid membrane (LM; about 100 μm in thickness). The interfacial area of the liquid membrane was $0.707 \pm 0.008 \text{ cm}^2$, since the diameter of the hole drilled in the cell was 0.95 cm. W1 and W2 contained a chloride salt of TAA⁺ (TBA⁺Cl⁻, TPA⁺Cl⁻, THxA⁺Cl⁻ and THpA⁺Cl⁻), as represented by eqn. (1).



Here, M means mol L^{-1} (mol dm^{-3}). Two reference electrodes (RE1, RE2) that were inserted into W1 and W2, respectively, were Ag|AgCl|0.1 M KCl electrodes. RE1 and RE2 were used for the voltammetric and potentiometric measurements. For the voltammetric measurements, RE1 was treated as the criterion for evaluating the membrane potential, $E_{\text{W1-W2}}$, and $E_{\text{W1-W2}}$ was applied and controlled by the use of RE1 and RE2. Two platinum electrodes (CE1, CE2), which were used for the current-recording, were placed in W1 and W2, respectively. The distance between the couples of electrodes (RE1 and CE1/RE2 and CE2) and the membrane surface was fixed at $1.5 \pm 0.1 \text{ cm}$. The relation between the applied potential and the steady-state current was measured by staircase voltammetry (SCV). The current, $i_{\text{W1-W2}}$, was recorded at 10 s after every step of the applied $E_{\text{W1-W2}}$. The current density, $j_{\text{W1-W2}}$, was obtained by dividing $i_{\text{W1-W2}}$ by the area of the liquid membrane. The $E_{\text{W1-W2}}$ value was changed from 0 mV to +100 mV with an increase of a +10 mV step, and then the $E_{\text{W1-W2}}$ value was varied from 0 mV to -100 mV with a decrease of a -10 mV step. The concentration of the

TAA⁺Cl⁻ salts was checked by use of Cl⁻-ISE (Ag|AgCl electrode). The influence of the supporting electrolyte (MgSO₄) in W1 and W2 on the transport of TAA⁺ Cl⁻ was voltammetrically evaluated by adding MgSO₄ to W1 and W2 to become 1 M.

The SCVs were measured by a four-electrode potentiostat, HA1010mM1A (Hokuto Denko Co.), a function generator, HB-105 (Hokuto Denko Co.), and an A/D converter, GL900 (Graphtec Co.). The membrane potential at $i_{W1-W2} = 0$, $E_{I=0}$, was recorded by a hand-made potentiometer. The relative conductivity of the aqueous or the 1-octanol solution containing TAA⁺Cl⁻ was determined by a conductivity meter, SC51 (Yokogawa Hokushin Electric Co.). The cell system was placed in a Faraday cage to reduce the electric noises.

All measurements were performed at room temperature (298 ± 2 K).

2.3. Evaluation of distribution coefficients of tetraalkylammonium chlorides between 1-octanol and aqueous phases

The aqueous solutions containing 5 mM of TAA⁺Cl⁻ (TAA⁺ = TBA⁺, TPA⁺, THxA⁺ and THpA⁺) were initially prepared. After 10 mL of each aqueous solution was gently mixed with 10 mL of 1-octanol so as not to foam, the aqueous and the 1-octanol phases were isolated after a 24 h-rest. The concentration of TAA⁺Cl⁻ in the aqueous solution was potentiometrically evaluated by the Cl⁻-ISE (Ag|AgCl electrode). As for the concentration of TAA⁺ Cl⁻ in the 1-octanol solution, 3 mL of the 1-octanol solution was removed, and was mixed with 3 mL of the aqueous solution containing 5 mM sodium picrate (Na⁺Pic⁻). The aqueous and the 1-octanol solutions were then isolated after a 24 h-rest. The absorbance of Pic⁻ in the aqueous solution was measured at 350 nm [16], and the concentration of TAA⁺ in the 1-octanol solution was evaluated by the back extraction method.

3. Theory

3.1. Transport of tetraalkylammonium chloride across a porous film impregnated by 1-octanol between two aqueous phases by applying the membrane potential

In order to simplify, $\text{TAA}^+ \text{Cl}^-$ was used as a 1:1 electrolyte and the ratio of the volume of the aqueous phase(s) to that of the 1-octanol phase was constant. When the distribution of $\text{TAA}^+ \text{Cl}^-$ between the aqueous phase (W1 and/or W2) and the membrane phase (M) was equilibrated, eqn. (2) is given.

$$\frac{c_{\text{TAA}^+, \text{M1}} c_{\text{Cl}^-, \text{M1}}}{c_{\text{TAA}^+, \text{W1}} c_{\text{Cl}^-, \text{W1}}} = \frac{c_{\text{TAA}^+, \text{M2}} c_{\text{Cl}^-, \text{M2}}}{c_{\text{TAA}^+, \text{W2}} c_{\text{Cl}^-, \text{W2}}} \quad (2)$$

Here, $c_{\text{TAA}^+, \text{M1}}$ and $c_{\text{Cl}^-, \text{M1}}$ represent the concentrations of TAA^+ and Cl^- in the vicinity of the W1|M interface of LM, respectively. Similarly, $c_{\text{TAA}^+, \text{M2}}$ and $c_{\text{Cl}^-, \text{M2}}$ indicate the concentrations of TAA^+ and Cl^- in the vicinity of the W2|M interface of LM, respectively. Then, $c_{\text{TAA}^+, \text{W1}}$, $c_{\text{TAA}^+, \text{W2}}$, $c_{\text{Cl}^-, \text{W1}}$ and $c_{\text{Cl}^-, \text{W2}}$ are the concentrations of TAA^+ in W1, TAA^+ in W2, Cl^- in W1 and Cl^- in W2, respectively. Taking into account the electroneutrality in each phase, eqns. (3)-(6) hold by use of c_{M1} , c_{M2} , c_{W1} and c_{W2} that denote the concentrations of $\text{TAA}^+ \text{Cl}^-$ in the vicinity of the W1|M interface of LM, in the vicinity of the W2|M interface of LM, in W1 and in W2, respectively.

$$c_{\text{TAA}^+, \text{M1}} = c_{\text{Cl}^-, \text{M1}} = c_{\text{M1}} \quad (3)$$

$$c_{\text{TAA}^+, \text{M2}} = c_{\text{Cl}^-, \text{M2}} = c_{\text{M2}} \quad (4)$$

$$c_{\text{TAA}^+, \text{W1}} = c_{\text{Cl}^-, \text{W1}} = c_{\text{W1}} \quad (5)$$

$$c_{\text{TAA}^+, \text{W2}} = c_{\text{Cl}^-, \text{W2}} = c_{\text{W2}} \quad (6)$$

When the concentration of the electrolyte ($\text{TAA}^+ \text{Cl}^-$) in W1 is equivalent to that in W2, eqn. (7) is defined by the concentration of $\text{TAA}^+ \text{Cl}^-$ (c_{W}) in both aqueous phases (W1 and W2).

$$c_{\text{W1}} = c_{\text{W2}} = c_{\text{W}} \quad (7)$$

Analogous with the above relation, eqn. (8) is given.

$$c_{M1} = c_{M2} = c_M \quad (8)$$

The potential difference between W1 and W2 (E_{W1-W2}) is defined as the sum of the potential difference at the W1|M interface ($E_{W1|M}$), the diffusion potential within LM (E_M) and the potential difference at the M|W2 interface ($E_{M|W2} = -E_{W2|M}$) in the presence of sufficient electrolyte ions in W1 and W2, as shown by eqn. (9).

$$E_{W1-W2} = E_{W1|M} + E_M + E_{M|W2} \quad (9)$$

Here, $E_{W1|M}$ and $E_{M|W2}$ are, respectively, represented by eqns. (10) and (11) with the standard potentials for the transfer of TAA^+ and Cl^- at the interface between W and LM ($E_{TAA^+, W|M}^\circ$ and $E_{Cl^-, W|M}^\circ$) [17,18].

$$E_{W1|M} = E_{TAA^+, W|M}^\circ + \frac{RT}{F} \ln \frac{c_{TAA^+, W1}}{c_{TAA^+, M1}} = E_{Cl^-, W|M}^\circ - \frac{RT}{F} \ln \frac{c_{Cl^-, W1}}{c_{Cl^-, M1}} \quad (10)$$

$$E_{M|W2} = -E_{TAA^+, W|M}^\circ + \frac{RT}{F} \ln \frac{c_{TAA^+, M2}}{c_{TAA^+, W2}} = -E_{Cl^-, W|M}^\circ - \frac{RT}{F} \ln \frac{c_{Cl^-, M2}}{c_{Cl^-, W2}} \quad (11)$$

Here, R , T and F indicate the gas constant, the absolute temperature and the Faraday constant, respectively. In the present case ($E_{W1|M} = -E_{M|W2}$, $j_{W1-W2} = 0$ A), E_{W1-W2} is equivalent to E_M .

If the potential difference (E_{W1-W2}) is applied between W1 and W2, $E_{W1|M}$ and $E_{M|W2}$ slightly change and the current (i_{W1-W2}) flows between W1 and W2. Based on Henderson's assumption, the current density flowing between W1 and W2 (j_{W1-W2}) is expressed as follows [19]:

$$j_{W1-W2} = \frac{F^2 c_M}{RTd} E_M (D_{M, TAA^+} + D_{M, Cl^-}), \quad (12)$$

where D_{M, TAA^+} and D_{M, Cl^-} indicate the diffusion coefficients of TAA^+ and Cl^- , respectively, within the LM. By considering the above-mentioned relation ($E_{W1-W2} = E_M$), eqn. (12) can be rewritten as eqn. (13).

$$j_{W1-W2} = \frac{F^2 c_W}{RTd} E_{W1-W2} \beta (D_{M, TAA^+} + D_{M, Cl^+}) \quad (13)$$

Thus, the current is attributable to the anti-transport of TAA^+ and Cl^- across the LM. On the other hand, $E_{\text{W1-W2}}$ can be represented by eqn. (14) by using the solution resistances in both W1 and W2 (R_{W}) and in the LM (R_{M}).

$$E_{\text{W1-W2}} = i_{\text{W1-W2}} (R_{\text{W}} + R_{\text{M}}) \approx i_{\text{W1-W2}} R_{\text{M}} \quad (14)$$

On the contrary, the current flowing between W1 and W2 is controlled by the transports of TAA^+ and Cl^- within the aqueous phases (W1 and W2) when the conductance in the LM is much higher than that in W1 or W2. In such a case, the concentration of TAA^+ Cl^- in the LM seemed to be much higher than that in the aqueous phases. Therefore, the potential drop in the aqueous phases cannot be neglected and $E_{\text{W1-W2}}$ is expressed by the potential drops in W1 and W2 (E_{W1} and E_{W2}) as eqn. (15).

$$E_{\text{W1-W2}} \approx E_{\text{W1}} + E_{\text{W2}} = i_{\text{W1-W2}} (R_{\text{W1}} + R_{\text{W2}}) = i_{\text{W1-W2}} R_{\text{W}} \quad (15)$$

Here, R_{W1} and R_{W2} indicate the solution resistance within W1 and that within W2, respectively. R_{W} is the sum of R_{W1} and R_{W2} . This equation indicates that the electrophoretic migration of both TAA^+ and Cl^- in the aqueous phases is the rate-determining step. By use of Henderson's equation, the flux of TAA^+ from W1 (W2) to LM ($J_{\text{W1,TAA}^+}$ ($J_{\text{W2,TAA}^+}$)) and that of Cl^- from W1 (W2) to LM ($J_{\text{W1,Cl}^-}$ ($J_{\text{W2,Cl}^-}$)) are given by eqns. (16) and (17) [19], respectively.

$$J_{\text{W1,TAA}^+} = \frac{F}{RTd_{\text{W1}}} c_{\text{W1}} D_{\text{W,TAA}^+} E_{\text{W1}} \quad (J_{\text{W2,TAA}^+} = \frac{F}{RTd_{\text{W2}}} c_{\text{W2}} D_{\text{W,TAA}^+} E_{\text{W2}}) \quad (16)$$

$$J_{\text{W1,Cl}^-} = -\frac{F}{RTd_{\text{W1}}} c_{\text{W1}} D_{\text{W,Cl}^-} E_{\text{W1}} \quad (J_{\text{W2,Cl}^-} = \frac{F}{RTd_{\text{W2}}} c_{\text{W2}} D_{\text{W,Cl}^-} E_{\text{W2}}) \quad (17)$$

Here, $D_{\text{W,TAA}^+}$ and $D_{\text{W,Cl}^-}$ indicate the diffusion coefficients of TAA^+ and Cl^- , respectively, within W, and d_{W1} (d_{W2}) denotes the distance between the electrode surface and the W1|M interface (the W2|M interface). The current densities at the W1|M and the W2|M interfaces (j_{W1} and j_{W2}) are given by eqns. (18) and (19), respectively.

$$j_{W1} = F(j_{W1,TAA^+} - j_{W1,Cl^-}) \quad (18)$$

$$= \frac{F^2}{RTd_{W1}} c_{W1} E_{W1} (D_{W,TAA^+} + D_{W,Cl^-})$$

$$j_{W2} = F(j_{W2,TAA^+} - j_{W2,Cl^-}) \quad (19)$$

$$= \frac{F^2}{RTd_{W2}} c_{W2} E_{W2} (D_{W,TAA^+} + D_{W,Cl^-})$$

Assuming that the steady-state current flows through the cell system, the magnitude of j_{W1} is identical to that of j_{W2} in order to maintain the electroneutrality in each phase, as written by eqn. (20).

$$j_{W1} = j_{W2} = j_{W1-W2} \quad (20)$$

Here, j_{W1-W2} is defined as the current density at the W1|M (W2|M) interface between W1 and W2. When the thickness of W1 is identical to that of W2 ($d_{W1} = d_{W2} = d_w$), eqn. (21) is derived by considering eqns. (16) and (17).

$$E_{W1} = E_{W2} = E_{W1-W2} / 2 \quad (21)$$

Eqn. (22) is obtained by considering eqns. (13) and (21).

$$j_{W1-W2} = \frac{F^2 c_w}{2RTd_w} E_{W1-W2} (D_{W,TAA^+} + D_{W,Cl^-}) \quad (22)$$

Accordingly, the current density depends on the diffusion coefficients of TAA^+ and Cl^- within W1 and W2.

3.2 Ion transport under the asymmetric system of the electrolyte concentration in two aqueous phases

Figure 2(a) indicates the concentration profile of the electrolyte at $j_{W1-W2} = 0$ when the ion transport across LM is the rate-determining process. By applying the potential difference (E_{W1-W2}) to make the W1 side the positive potential, both the cation (TAA^+) and the counter anion (Cl^-) begin to transport in the opposite direction. Since the ion transport at the W1|M and M|W2 interfaces is much faster than the ion transport within M, the concentration ratio of

Fig. 2

the electrolyte ions in W1 (W2) to that in LM around the W1|M (M|W2) interface is affected by both the distribution coefficient of the cation and that of the anion. The electric current then started to flow by the transport of both ions themselves within LM. In W1 and W2, the potential drop is negligibly small since ions sufficiently exist in comparison with the concentration of the electrolyte in LM.

When the concentration of the objective electrolyte in W1 is not equivalent to that in W2, the potential difference across the membrane between W1 and W2 is usually generated as the membrane potential. In the case when the concentration ratio of W1 to W2 is determined as r , the relation between j_{W1-W2} and E_{W1-W2} can be represented by eqn. (23) on the basis of Henderson's equation.

$$j_{W1-W2} = \frac{F^2}{dRT} P_{CW} \left[\frac{E_M}{\ln r} (D_{M, TAA^+} + D_{M, Cl^-}) + \frac{RT}{F} (D_{M, TAA^+} - D_{M, Cl^-}) \right] \quad (23)$$

In this case, the potential difference between W1 and W2 at $j_{W1-W2} = 0 \text{ A cm}^{-2}$ is determined as the membrane potential at zero current ($E_{i=0}$), as presented by eqn. (24).

$$E_{i=0} = - \frac{D_{M, TAA^+} - D_{M, Cl^-}}{D_{M, TAA^+} + D_{M, Cl^-}} \frac{RT}{F} \ln r \quad (24)$$

On the other hand, the concentration profile of the electrolyte ions at $j_{W1-W2} = 0 \text{ A}$ when the electrophoretic movement of both TAA^+ and Cl^- within W1 and W2 is the rate-determining step is shown in Fig. 2(b). When the W1 side becomes the positive potential by applying a given potential difference, TAA^+ is transported from W1 to W2 and Cl^- moved from W2 to W1 at the same time. Assuming that the interfacial transfers of both TAA^+ and Cl^- are sufficiently faster than the electrophoretic migration of both TAA^+ and Cl^- within W1, W2 and M, either the migration within W1 and/or W2 or that within M becomes the rate-determining step. In this case, the applied E_{W1-W2} is mainly used as the potential drop due to the diffusion of the electrolyte ions in W1 and/or W2, since LM contains a sufficient amount of electrolyte ions.

Since the equilibrium distribution of the electrolyte between W1 (W2) and M might be achieved, eqn. (25) seems to be formed.

$$\frac{c_{M1}}{c_{W1|M}} = \frac{c_{M2}}{c_{W2|M}} = \beta \quad (25)$$

Here, $c_{W1|M}$ and $c_{W2|M}$ are the concentrations of the electrolyte in the vicinity of the interface within W1 and W2, respectively, and c_M indicates the concentration of the electrolyte in LM. Based on Henderson' assumption, the steady-state fluxes of the electrolyte cation and anion from the electrode surface to the membrane surface are represented by eqns. (26) – (29) [19].

$$J_{W1,TAA^+} = \frac{FE_{W1}}{RTd_{W1}} \frac{c_{W1} - c_{W1|M}}{\ln \frac{c_{W1}}{c_{W1|M}}} D_{W,TAA^+} + \frac{c_{W1} - c_{W1|M}}{d_{W1}} D_{W,TAA^+} \quad (26)$$

$$J_{W1,Cl^-} = \frac{FE_{W1}}{RTd_{W1}} \frac{c_{W1} - c_{W1|M}}{\ln \frac{c_{W1}}{c_{W1|M}}} D_{W,Cl^-} + \frac{c_{W1} - c_{W1|M}}{d_{W1}} D_{W,Cl^-} \quad (27)$$

$$J_{W2,TAA^+} = \frac{FE_{W2}}{RTd_{W2}} \frac{c_{W2} - c_{W2|M}}{\ln \frac{c_{W2}}{c_{W2|M}}} D_{W,TAA^+} + \frac{c_{W2} - c_{W2|M}}{d_{W2}} D_{W,TAA^+} \quad (28)$$

$$J_{W2,Cl^-} = \frac{FE_{W2}}{RTd_{W2}} \frac{c_{W2} - c_{W2|M}}{\ln \frac{c_{W2}}{c_{W2|M}}} D_{W,Cl^-} + \frac{c_{W2} - c_{W2|M}}{d_{W2}} D_{W,Cl^-} \quad (29)$$

The density of the current that flowed within W1 or W2, j_{W1} or j_{W2} , is expressed by eqn. (30)

or (31).

$$j_{W1} = \frac{F^2(c_{W1} - c_{W1|M})}{RTd_{W1}} \left[\frac{E_{W1}}{\ln \frac{c_{W1}}{c_{W1|M}}} (D_{W,TAA^+} + D_{W,Cl^-}) + \frac{RT}{F} (D_{W,TAA^+} - D_{W,Cl^-}) \right] \quad (30)$$

$$j_{W2} = \frac{F^2(c_{W2|M} - c_{W2})}{RTd_{W2}} \left[\frac{E_{W2}}{\ln \frac{c_{W2|M}}{c_{W2}}} (D_{W,TAA^+} + D_{W,Cl^-}) + \frac{RT}{F} (D_{W,TAA^+} - D_{W,Cl^-}) \right] \quad (31)$$

Usually, the current density through the whole cell is determined by the lower one (j_{W1} or j_{W2}).

In the steady-state condition, j_{W1} and j_{W2} seem to get closer to the same value.

$$\frac{c_{W1} - c_{W1|M}}{d_{W1}} = \frac{c_{W2} - c_{W2|M}}{d_{W2}} \quad (32)$$

The concentration of TAA^+Cl^- is then assumed to be almost constant ($c_{W1|M} = c_{W2|M} = c_{W|M}$).

When the length of W1 is identical to that of W2 ($d_{W1} = d_{W2} = d_W$), eqn. (33) is derived.

$$c_{W|M} = \frac{r+1}{2} c_{W2} \quad (33)$$

Therefore, eqn. (34) is obtained by substituting eqn. (33) in eqns. (30) and (31).

$$E_{W1} = \frac{\ln \frac{2r}{r+1}}{\ln \frac{r+1}{2}} E_{W2} \quad (34)$$

The relation between E_{W1-W2} and E_{W2} can be described as eqn. (35).

$$E_{W2} = \frac{\ln \frac{1+r}{2}}{\ln r} E_{W1-W2} \quad (35)$$

By considering the above relations, j_{W1-W2} is expressed by eqn. (36).

$$j_{W1-W2} = \frac{F^2}{d_W RT} (r-1) c_{W2} \left[\frac{E_{W1-W2}}{\ln r} (D_{W,C^+} + D_{W,A^-}) + \frac{RT}{F} (D_{W,C^+} - D_{W,A^-}) \right] \quad (36)$$

At j_{W1-W2} is zero in eqn. (36), $E_{i=0}$, is solved as eqn. (37).

$$E_{i=0} = - \frac{D_{W,C^+} - D_{W,A^-}}{D_{W,C^+} + D_{W,A^-}} \frac{RT}{F} \ln r \quad (37)$$

4. Results and Discussion

4.1. Evaluation of the distribution coefficients of quaternary ammonium chlorides between aqueous and 1-octanol phases

Based on the solvent-extraction technique, the distribution coefficients ($\beta_{1\text{-octanol/water}}$) of

Table 1

TAA⁺Cl⁻ between 1-octanol and the aqueous phases were evaluated, as indicated in Table 1. The distribution coefficient linearly increases with an increase in the number, n , of methylene groups in each of their alkyl chains. The transfer energies of the TAA⁺ cations from the aqueous to non-aqueous solutions such as alcohol, formamide, etc., have been evaluated by several groups [17,20], and it is well known that the transfer enthalpy from an aqueous to an organic solution decreases as the size of the alkyl chain increases. In addition, the transfer energy of TAA⁺ from the aqueous to 1,2-dichloroethane solution decreased by 13.0 kJ mol⁻¹ for each increase in n [17]. Since Cl⁻ is selected as the counter ion in all cases, the distribution coefficients of TAA⁺ Cl⁻ are dependent on the transfer energy of TAA⁺. Therefore, it seems that the present data are reasonable.

4.2. Evaluation of permeation coefficients of tetraalkylammonium chlorides in aqueous phase

Figure 3 shows the SCVs obtained in the cell system containing 1 mM TBA⁺Cl⁻, TPeA⁺Cl⁻, THxA⁺Cl⁻ and THpA⁺Cl⁻ in W1 and W2. These are the steady-state voltammograms, and the j_{W1-W2} value linearly increased with an increase in E_{W1-W2} . As the rate-determining step of the ion transport across the filter impregnated with 1-octanol between W1 and W2, the ion transport within the aqueous phase(s) (W1 and/or W2), the ion transport within the membrane phase and the interfacial transport of the electrolyte ions at the W1|M and/or M|W2 interfaces are selected. Since it is well known that the interfacial transport of ions is faster than other steps [17], the solution resistances in W1 (W2) and LM that are attributed to the electrophoretic migration determine the rate-determining step. When TBA⁺, TPnA⁺ or THxA⁺ exists in W1 and W2, j at a given E_{W1-W2} increased with an increase in the hydrophobicity of the additive electrolyte. In these cases, the migration of the electrolyte ions (antiport of TAA⁺ and Cl⁻) within LM can be regarded as the rate-determining step. Since THpA⁺ is more

Fig. 3

hydrophobic than THxA^+Cl^- , it is predictable that the concentration of THpA^+Cl^- in LM is much higher than that of THxA^+Cl^- . On the contrary, $j_{\text{W1-W2}}$ at a given $E_{\text{W1-W2}}$ is slightly lower than that of THxA^+Cl^- . This is because the concentration of THpA^+Cl^- in W1 and W2 became lower than that of THxA^+Cl^- in W1 and W2 to maintain the total amounts of electrolyte ions (TAA^+Cl^-) constant in the cell system. Therefore, the rate-determining step of the ion transport across the LM between W1 and W2 changed from the ion transport within LM to the ion transport within the aqueous phase(s) (W1 and/or W2).

The effect of the supporting electrolyte (MgSO_4) on the ion transport across the LM was evaluated in the following manner. Under the initial conditions, the concentration of the respective TAA^+Cl^- in W1 and W2 was fixed at 0.1 mM. After the respective staircase voltammogram was measured, the aqueous solution was replaced by the aqueous solution containing not only 0.1 mM of TAA^+Cl^- , but also 0.1 M MgSO_4 . Curves 2 of Figs. 4 (a)-(d) are SCVs observed in the presence of 0.1 M MgSO_4 . In the case of TBA^+Cl^- and TPnA^+Cl^- , curves 1 and 2 almost overlapped. Since the electrophoretic migration of TAA^+Cl^- within the LM is the rate-determining step, it can be concluded that the relation between $j_{\text{W1-W2}}$ and $E_{\text{W1-W2}}$ is not affected by the presence of the supporting electrolyte. On the other hand, the $j_{\text{W1-W2}}$ values at a given $E_{\text{W1-W2}}$ in the case of THxA^+Cl^- and THpA^+Cl^- in the presence of 0.1 M MgSO_4 were about 1.6 and 7.1 times, respectively, greater than those in the absence of 0.1 M MgSO_4 . Since the solution resistances in W1 and W2 decreased by the addition of 0.1 M MgSO_4 into W1 and W2, it is thought that $j_{\text{W1-W2}}$ increased with an increase in the concentration of TAA^+Cl^- in the LM. Taking into account the ratio of $\beta_{1\text{-octanol/water}}$ of THxA^+Cl^- to that of THpA^+Cl^- , it is reasonable that the $j_{\text{W1-W2}}$ value at a given $E_{\text{W1-W2}}$ in the presence of THpA^+Cl^- and MgSO_4 is about 4 times greater than that in the presence of THxA^+Cl^- and MgSO_4 .

Based on the data of Fig. 4, the solution resistances (R and R_s) in the absence and presence, respectively, of MgSO_4 were evaluated using eqns. (14) and (15), as summarized in Table 2. The relative conductances of the aqueous and 1-octanol solutions containing each TAA^+Cl^- was measured, as shown in Table 3. The solution resistances (R_w and R_M) of W1 (W2) in the presence of 0.1 mM TAA^+Cl^- were estimated using these data. Here, the water and the membrane phases are treated as cylinder shapes (cross-sectional area: 1.8 cm^2 , cell length: 1.5 cm) and disc shape (cross-sectional area: 1.8 cm^2 , thickness: 100 μm), respectively. Incidentally, the concentration of TAA^+Cl^- in M under the distribution equilibria is predictable by considering the $\beta_{1\text{-octanol/water}}$ value of TAA^+Cl^- (Table 1). Accordingly, the R_M values of TAA^+Cl^- were estimated from the electric conductivities of the 1-octanol solutions containing 0.02 mM TBA^+Cl^- , 0.07 mM TPnA^+Cl^- , 2 mM THxA^+Cl^- and 7 mM THpA^+Cl^- . On the other hand, the relative conductivity of each TAA^+Cl^- in W1 (W2) was almost equivalent regardless of their hydrophobicity. This indicates that the solution resistance in W1(W2) does not depend on the cation species and is almost constant (70-80 k Ω).

In any case, the R_s value almost agreed with the sum of the 2-fold R_w (W1 and W2) and R_M . This means that the electrophoretic process within W1 (W2) or that within the LM is the rate-determining step in the present experiments. In addition, $E_{i=0}$ in the cell system having an asymmetrical ionic composition was measured to evaluate the ratio of the diffusion coefficient of TAA^+ to that of Cl^- in W1 (W2) or the LM. Since the liquid junction potential in W1 (W2) or the LM depends on the concentration and the ratio of the diffusion coefficient of TAA^+ to that of Cl^- in W1 (W2) or the LM, the influence of $E_{i=0}$ on r was evaluated, as shown in Fig. 5. When THxA^+Cl^- and THpA^+Cl^- were used as the electrolyte, the rate-determining step was the electrophoretic migration of both TAA^+ and Cl^- within W1 (W2). On the other hand, the rate-determining step was the electrophoretic migration of both TAA^+ and Cl^- within the LM

in the case of TBA^+Cl^- and TPnA^+Cl^- . Therefore, the $E_{i=0}$ values in the presence of TBA^+Cl^- and TPnA^+Cl^- are attributed to the ratio of the transference number of TAA^+ to that of Cl^- in W1 (W2). On the other hand, those in the presence of THxA^+Cl^- and THpA^+Cl^- resulted from the ratio of the transference number of TAA^+ to that of Cl^- in the LM. Table 4 represents the ratio of the diffusion coefficient of TAA^+ to that of Cl^- in W1 (W2) or LM. The ratio of the diffusion coefficient of TAA^+ to that of Cl^- was evaluated by fitting eqns. (24) and (37) to the experimental data. When TBA^+Cl^- or TPnA^+Cl^- was used as the electrolyte, the permeability of TBA^+ or TPnA^+ within the LM was derived by considering the relation expressed by eqn. (24). Similarly, the permeability of THxA^+ or THpA^+ within W was obtained using eqn. (37). It is recognized that the permeability is in direct proportion to $j_{\text{W1-W2}}$ [19]. Figure 6 indicates the relation between the $j_{\text{W1-W2}}$ value of TAA^+Cl^- and the $\beta_{1\text{-octanol/water}}$ value of TAA^+Cl^- . The maximum point appeared as observed in the bilinear model, and it became clear that the change in the rate-determining steps is responsible for this bilinear shape [14,15].

Conclusion

The bilinear model of the quantitative structure-activity relationships (QSAR) was interpreted by considering the steady-state flow of electrolyte ions. The transport of hydrophobic TAA^+Cl^- (TBA^+ , TPnA^+ , THxA^+ and THpA^+) across the porous polytetrafluoroethylene resin film impregnated by 1-octanol between two aqueous phases is interpreted by considering the steady-state flows of both TAA^+ and Cl^- within both the aqueous and membrane phases. The parabolic model of the relation between the hydrophobicity and the permeability in the quantitative structure-activity relationship can be electrochemically explained by considering the rate-determining step on the transport of both ions in the cell system.

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Table 1 Distribution coefficient of quaternary ammonium chloride between 1-octanol and aqueous phases.

tetraalkylammonium chloride	$\beta_{1\text{-octanol} / \text{water}}$
TBA ⁺ Cl ⁻	$(2 \pm 2) \times 10^{-2}$
TPeA ⁺ Cl ⁻	$(7 \pm 3) \times 10^{-1}$
THxA ⁺ Cl ⁻	$(2 \pm 0) \times 10^1$
THpA ⁺ Cl ⁻	$(7 \pm 5) \times 10^1$

Error bars show 95 % confidence intervals.

Table 2 Solution resistances of the aqueous phase (R_w), the membrane phase (R_M) and the whole cell (R and R_s)

electrolyte	$R_w / \text{k}\Omega$ *	$R_M / \text{k}\Omega$ **	$R / \text{k}\Omega$ ***	$R_s / \text{k}\Omega$ ***
TBA ⁺ Cl ⁻	$(8 \pm 3) \times 10^1$	$(3 \pm 3) \times 10^2$	$(3.9 \pm 0.6) \times 10^2$	$(6 \pm 2) \times 10^2$
TPnA ⁺ Cl ⁻	$(7 \pm 3) \times 10^1$	$(1.7 \pm 0.7) \times 10^2$	$(2.2 \pm 0.6) \times 10^2$	$(4 \pm 2) \times 10^2$
THxA ⁺ Cl ⁻	$(8 \pm 4) \times 10^1$	3.9 ± 0.9	$(8 \pm 2) \times 10^2$	9 ± 1
THpA ⁺ Cl ⁻	$(8 \pm 3) \times 10^1$	1.9 ± 0.4	$(6.1 \pm 0.6) \times 10^2$	2.1 ± 0.3

* The distance between two counter electrodes: 1.5 ± 0.5 cm, the cross-sectional area: 1.8 cm^2

** The thickness of the membrane: 100 μm , the cross-sectional area: 1.8 cm^2

*** Estimated from the currents at 40 mV of the voltammograms, as shown in Fig.1

Error bars show 95 % confidence intervals.

Table 3 Relative conductance of aqueous and 1-octanol solutions containing quaternary

ammonium chlorides

	$\kappa_{\text{water}} / \mu\text{S cm}^{-1}$	$\kappa_{\text{1-octanol}} / \mu\text{S cm}^{-1}$
TBA ⁺ Cl ⁻	10 ± 0	$(2 \pm 1) \times 10^{-2}$
TPnA ⁺ Cl ⁻	12 ± 1	$(3 \pm 1) \times 10^{-1}$
THxA ⁺ Cl ⁻	10 ± 2	1.5 ± 0.3
THpA ⁺ Cl ⁻	10 ± 0	3.0 ± 0.7

Error bars show 95 % confidence intervals.

Table 4 The ratio of the diffusion coefficient of TAA^+ to that of Cl^- .

	$D_{\text{m}, \text{X}^+} / D_{\text{m}, \text{Cl}^-}$	$D_{\text{w}, \text{X}^+} / D_{\text{w}, \text{Cl}^-}$
TBA^+Cl^-	0.2	-
TPnA^+Cl^-	0.4	-
THxA^+Cl^-	-	0.3
THpA^+Cl^-	-	0.3

Figure captions

Fig. 1 Electrochemical cell system

Fig. 2 The concentration profile of TAA^+Cl^- at $j_{\text{W1-W2}} = 0$ A in the cell system. (a): the rate-determining step is the ion transport within the membrane phase, (b): the rate-determining step is the ion transport within the aqueous phase(s).

Fig. 3 Staircase voltammograms in the presence of quaternary ammonium chlorides (1 mM) in W1 and W2. Electrolytes: TBA^+Cl^- (curve 1), TPnA^+Cl^- (curve 2), THxA^+Cl^- (curve 3), THpA^+Cl^- (curve 4). Error bars show 95 % confidence intervals.

Fig. 4 Staircase voltammograms across the membrane between W1 and W2 containing (a) 0.1 mM TBA^+Cl^- , (b) 0.1 mM TPnA^+Cl^- , (c) 0.1 mM THxA^+Cl^- and (d) 0.1 mM THpA^+Cl^- in the presence (■, curve 1) and the absence (◆, curve 2) of 0.1 M MgSO_4 .

Fig. 5 Relation between the zero-current potential ($E_{\text{I}=0}$) and the ratio of the concentration of TAA^+ to that of Cl^- (r).

■: TBA^+Cl^- , ◆: PnA^+Cl^- , ●: HxA^+Cl^- , ▲: THpA^+Cl^- , Fitting lines: Calculation by use of eqns. (24) and (37). Error bars show 95 % confidence intervals.

Fig. 6 The relation between the logarithm of the $j_{\text{W1-W2}}$ value of TAA^+Cl^- and that of the $\beta_{\text{1-octanol/water}}$ value of TAA^+Cl^- .

Error bars show 95 % confidence intervals.

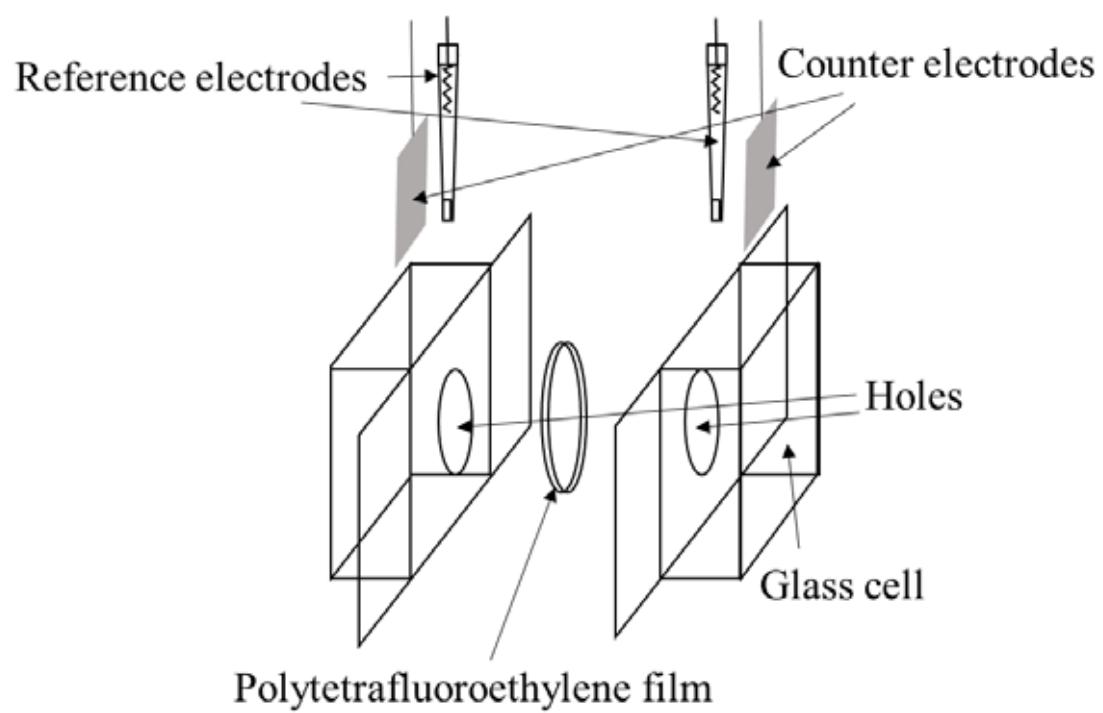


Fig. 1 R. Usami, et al.

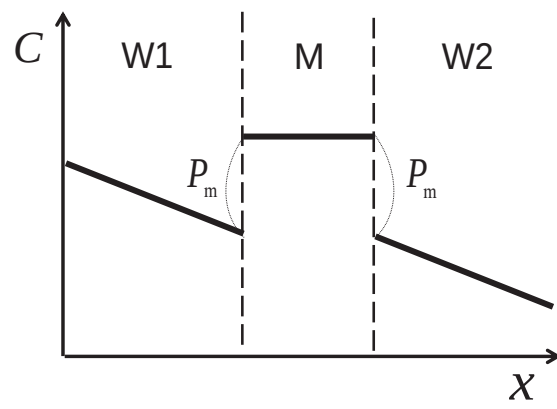
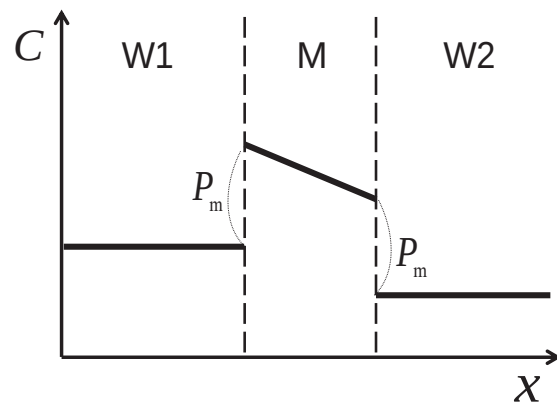


Fig.2 R. Usami, et al.

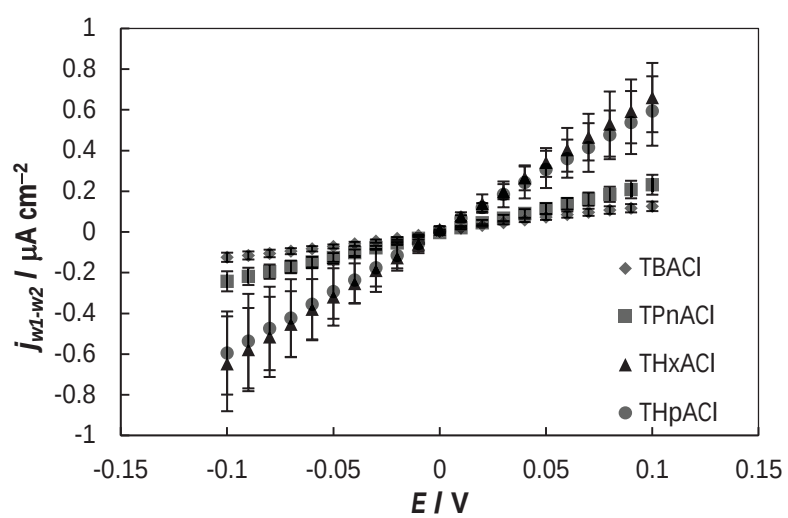
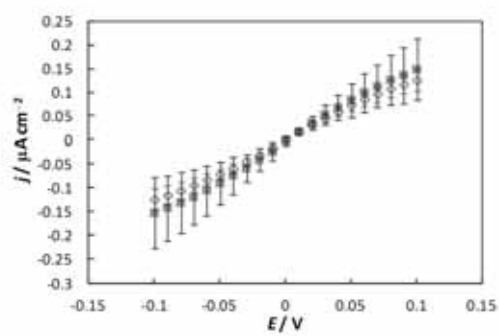
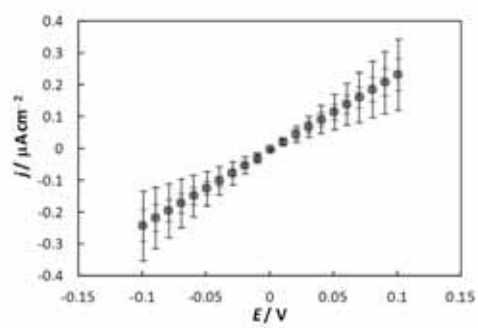


Fig. 3 R. Usami, et al.

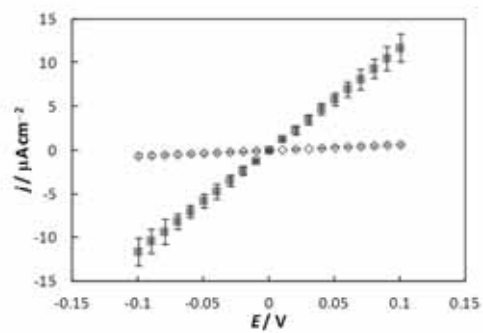
(a)



(b)



(c)



(d)

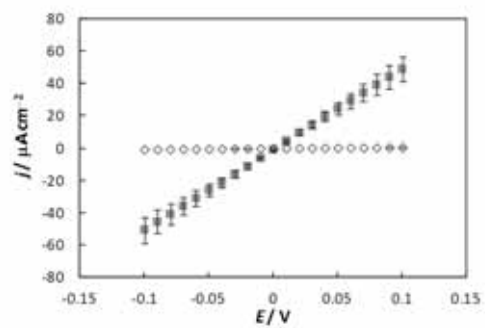


Fig. 4 R. Usami, et al.

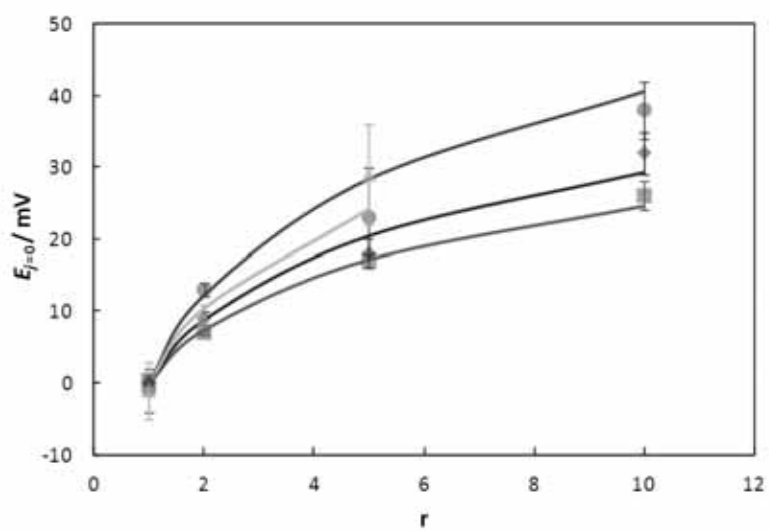


Fig. 5 R. Usami, et al.

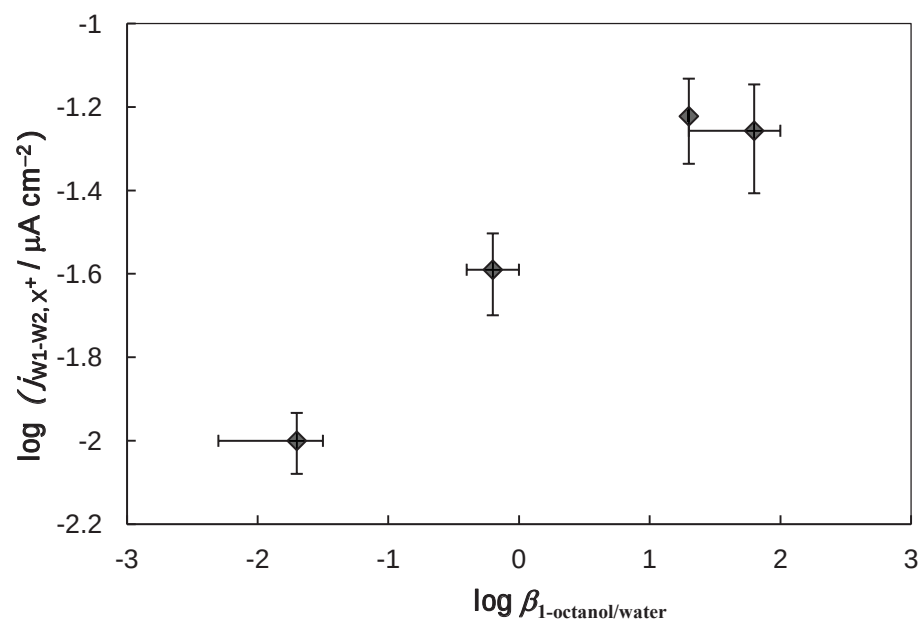


Fig.6 R. Usami, et al.