

Electrochemical study on quantitative structure-activity relationship (QSAR) analysis under steady-state conditions

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Keywords:

Drug delivery

Tetraalkylammonium chloride

Steady-state flow

QSAR

Bilinear model

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Abstract

The influence of the volume ratio of the aqueous to 1-octanol phase on drug delivery under steady-state conditions in a tubular electrolytic cell composed of an organic phase and two aqueous phases was elucidated. Electrochemical measurements on the transport of six quaternary ammonium chlorides were performed using three types of membrane filters of different thickness. The electric resistance of each system was evaluated, and the distribution coefficient of each chloride was estimated from the extraction experiments. The permeation process within the organic phase was the rate-determining step for tetrapropylammonium, tetrabutylammonium, tetrapentylammonium and tetrahexylammonium chlorides. On the other hand, for tetraoctylammonium chloride, which was the most hydrophobic ion among the six tested, the salt was easily distributed into the organic phase. Therefore, the rate-determining step changed to the permeation process within the aqueous phase. In addition, the influence of ion-pair formation on drug delivery was evaluated.

1 Introduction

The pharmacological effects of compounds, such as medicines and endocrine disruptors, are influenced not only by their physiological functions but also by their physical properties, molecular structures and dosage at exposure [1-3].

The distribution coefficient (β) between 1-octanol and water is used as a general indicator of hydrophobicity for drug compounds [4]. The permeability (P) of the drug from the absorption site to the action site has been proven to be proportional to the drug's activity [4]. Hansch *et al.* empirically demonstrated the linear free energy relationship between drug activity and drug hydrophobicity.^[4] However, the activity of a drug often decreases as the drug becomes more hydrophobic has also been reported on numerous occasions [5]. Hansch and Fujita then presented a parabolic model indicating that the activity was a quadratic function of $\log\beta$ [6]. The concept of quantitative structure activity relationship (QSAR) has been developed to estimate the activities of chemical compounds based on their physicochemical properties [5,7]. QSAR empirically deduced that the drug activity depends on the distribution coefficient, surface charge density and steric hindrance.

McFarland *et al.* attempted to physicochemically explain permeability and introduced a system composed of several organic phases (O) and aqueous phases (W) formed in series [8]. They defined a system where permeability to the O from the W and permeability to the W from the O ($P_{W/O}$ and $P_{O/W}$, respectively) were proportional to the distribution coefficient between the W and the O and that between the O and the W ($\beta_{W/O}$ and $\beta_{O/W}$, respectively) and suggested a bilinear model whereby the rate-determining step of drug transport within the O or W was dependent on β . Therefore, the activity was expressed as a symmetric bilinear function of $\log \beta$. However, in this model, the optimum value of $\log \beta$ is always zero. Kubinyi, *et al.* then proposed a new expression by considering the volume ratio of the O to the W [9]. According to his proposal, the optimum value is different for each situation. However, the model still uses the misconception that kinetic mass transfer can be expressed by the equilibrium process and that kinetic mass transfer is not treated using the steady-state.

Shirai, *et al.* have reported another model based on kinetic processes [10,11]. Permeability is determined by the rate-determining step of drug permeation within the W or O. The reason why P correlates to both β and the diffusion coefficients (D) of the ions in each phase could be kinetically explained.

Usami *et al.* proved that the permeability of the liquid membrane system using quaternary ammonium (tetraalkylammonium, TAA) chlorides was determined based on the analysis of the rate-determining process [12].

As for the ion transport between two aqueous phases across a liquid membrane, the author's group and Horváth and Horvai reported the analytical method by considering the ion transfers at two W|O interfaces [13-15]. Several research groups have studied the permeation properties based on the analysis of the interfacial transfer and the membrane transport [16-22]. Nakamura and Osakai

explained the plateau region observed for hydrophobic drugs based on the theoretical analysis of PAMPA [23].

In the present study, the permeability of six types of TAA chlorides across O between two W's was measured. The test cell had a cylindrical hole, and the ratio of the volume of W to that of O and the length of O were moderately regulated. The permeability of TAA chlorides in each phase was analyzed as a function of volume ratio and length of O. In addition, the influence of ion-pair formation was estimated.

2 Experimental

2.1 Chemicals

Polytetrafluoroethylene membrane filters were purchased from Advantec Co. Ltd. (diameter: 25 mm ϕ , pore size: 1 μ m, thickness: 25 and 75 μ m) and Wintec Co. Ltd. (diameter: 25 mm, pore size: 1 μ m, thickness: 250 μ m). Acetone, methanol and 1-octanol were obtained from Wako Pure Chemical Ind., Ltd. The chloride salts of tetrapropylammonium (TPrA⁺), tetrabutylammonium (TBA⁺), tetrapentylammonium (TPnA⁺), tetrahexylammonium (THxA⁺) and tetraoctylammonium (TOcA⁺) were obtained from Tokyo Chemical Industry Co., Ltd. The chloride salt of tetraheptylammonium (THpA⁺) was available from Kanto Chemical Co., Inc. These typical quaternary ammonium chloride salt compounds (TAACl) were used as permeable drug model systems. All other chemicals were purchased from Wako Pure Chemical Ind., Ltd.

All reagents were of reagent grade and were used without further purification.

2.2 Measurement of electric resistance

After the membrane filters were cleaned by soaking in acetone or methanol, the filters were washed by soaking in 1-octanol twice. The 1-octanol double-soaking treatment was designed to remove residual acetone or methanol. Fig. 1a shows the structure of the electrochemical cell. The electrochemical cell was composed of two aqueous compartments (W1, W2) and one liquid membrane (LM), as shown in Fig. 1b.

The shape of the W compartment was cylindrical (diameter: 1 cm, length: 1 cm). The filter impregnated by 1-octanol was installed between the two aqueous compartments so that the interfacial area of the LM was 0.785 cm².

Two planar Ag|AgCl disc electrodes (RE1 and RE2) were installed on each of the two aqueous phases (W1 and W2) so that the reaction area of the electrodes was 0.785 cm². The electrolyte concentration was 0.1 mmol dm⁻³ (mM), and the electrolyte was injected from small pinholes drilled on the upper side of the aqueous compartments using a syringe. For recording cyclic voltammograms (CVs), the potential difference between RE1 and RE2 was scanned, and the current was recorded. An

HA1010mM1A (Hokuto Denko Co.) was used with an electrometer, HB-105 (Hokuto Denko Co.) as a function generator, and GL500 (Graphtec Co.) as an A/D converter. The potential scanning rate was 5 mV s^{-1} , and the potential range was from -100 to $+100 \text{ mV}$. The shape of the CV was almost linear in the potential range, and no charging current was observed. The slope of the voltammogram was evaluated as the electric resistance.

The electric conductivities of the W and O were measured using a SC51 (Yokogawa electric Co.) conductivity meter. The concentration of each TAACl was prepared at 1 mM .

For TBACl, TPnACl, THxACl, and THpCl, the distribution coefficients obtained from a previous paper were used [12]. The distribution coefficients of TPrACl and TOcACl were evaluated using the same method in reference 12.

All experiments were performed at room temperature ($298 \pm 2 \text{ K}$).

3 Theory

According to the Nernst–Planck equation, the driving force (f) that 1 mol of cations (i^{z+}) experiences from an electric field can be expressed as eqn. (1).

$$f = -\frac{RT}{c} \left(\frac{dc}{dx} \right) - zF \left(\frac{d\phi}{dx} \right), \quad (1)$$

where, R , T , c , x , z , ϕ , and F represent the gas constant, the absolute temperature, concentration of i^{z+} , position, electric charge of i^{z+} , potential and Faraday constant, respectively. In eqn. (1), the first term on the right side represents the force due to diffusion, and the second term represents the force due to electrophoresis. Since c_i of i^{z+} in the W1 phase is identical to that in the W2, the electrophoretic effect is dominant, and the first term in this cell system under a steady-state current can be ignored. Thus, in this system, eqn. (1) can be rewritten as eqn. (2).

$$f \approx -zF \left(\frac{d\phi}{dx} \right). \quad (2)$$

On the other hand, the f value can be expressed by eqn. (3), when 1 mol of particles moves at a constant velocity (v) within the medium.

$$f = N_A \xi v, \quad (3)$$

where, N_A and ξ are the Avogadro's number and the coefficient of friction, respectively. Using eqns. (2) and (3), eqn. (4) can be obtained.

$$v = -\frac{zF}{N_A \xi} \left(\frac{d\phi}{dx} \right). \quad (4)$$

The flux (J) is defined as the product of the concentration and the velocity; thus, J can be expressed as eqn. (5).

$$J = -\frac{czF}{N_A \xi} \left(\frac{d\phi}{dx} \right). \quad (5)$$

Since the current density (I) is given as $I = zFJ$, eqn. (6) is obtained.

$$I = -\frac{cz^2F^2}{N_A\xi}\left(\frac{d\phi}{dx}\right). \quad (6)$$

$N_A\xi$ can be expressed using the diffusion coefficient (D) as eqn. (7).

$$N_A\xi = \frac{1}{\omega} = \frac{RT}{D}, \quad (7)$$

where ω is the molar mobility of ions. By substituting eqn. (7) to eqn. (6), eqn. (8) is obtained.

$$I = -\frac{cDz^2F^2}{RT}\left(\frac{d\phi}{dx}\right). \quad (8)$$

On the basis of the Goldman assumption (constant field assumption) [24], the relation expressed by eqn. (9) is formed.

$$\frac{d\phi}{dx} = \frac{\Delta\phi}{d}, \quad (9)$$

where d and $\Delta\phi$ are the thickness of a certain phase and the potential difference between the phase ends, respectively. Thus, eqn. (8) can be rewritten as eqn. (10).

$$I = -\frac{cDz^2F^2}{RTd}\Delta\phi. \quad (10)$$

Since this relation holds in each phase, eqns. (11) and (12) can be obtained in the present cell system.

$$I_w = -\frac{c_w D_w z^2 F^2}{RTd_w} \Delta\phi_w, \quad (11)$$

$$I_o = -\frac{c_o D_o z^2 F^2}{RTd_o} \Delta\phi_o. \quad (12)$$

Here, D/d corresponds to the permeability in the Goldman—Hodgkin—Katz (GHK) equation. The subscripts (W and O) of I and $\Delta\phi$ indicate the aqueous and organic phases, respectively.

Using the electric resistance (R_w and R_o), eqns. (13) and (14) are accessible.

$$1/R_w = \left| -\frac{c_w D_w z^2 F^2}{RTd_w} \right|, \quad (13)$$

$$1/R_o = \left| -\frac{c_o D_o z^2 F^2}{RTd_o} \right|. \quad (14)$$

Since the cell system was setup as a series circuit, eqn. (15) can be derived.

$$R_{\text{total}} = R_w + R_o, \quad (15)$$

where R_{total} is the electric resistance of the whole cell system. Additionally, eqn. (16) is also true. The current flowing through W (I_w) matches that through O (I_o) and that through the whole cell (I_{total}).

$$I_{\text{total}} = I_w = I_o. \quad (16)$$

Using the potential drops in W, O, and the whole cell ($\Delta\phi_w$, $\Delta\phi_o$, and $\Delta\phi_{\text{total}}$, respectively), eqn. (17) is obtained.

$$\begin{aligned}\Delta\phi_{\text{total}} &= I_{\text{W}}R_{\text{W}} + I_{\text{O}}R_{\text{O}} \\ &= \Delta\phi_{\text{W}} + \Delta\phi_{\text{O}} = I_{\text{total}}(R_{\text{W}} + R_{\text{O}}).\end{aligned}\quad (17)$$

Here, we represent the ratios of d , D , and c in W to those in O as the following:

$$d_{\text{O}} = rd_{\text{W}} \quad (18)$$

$$D_{\text{O}} = sD_{\text{W}} \quad (19)$$

$$c_{\text{O}} = \beta c_{\text{W}}, \quad (20)$$

where r , s and β are the coefficients, respectively. Since a cylindrical cell was used in this study, the use of volumes of W and O (V_{W} and V_{O}) gives eqn. (21).

$$V_{\text{O}} = rV_{\text{W}}. \quad (21)$$

According to the law of mass conservation, the relation between the initial concentrations in W and O and the concentrations in W and O after the distribution equilibrium can be expressed as eqn. (22).

$$\begin{aligned}n_{\text{total}} &= V_{\text{W}}c_{\text{W}}^0 = V_{\text{W}}c_{\text{W}} + V_{\text{O}}c_{\text{O}} \\ &= V_{\text{W}}c_{\text{W}}(1 + r\beta),\end{aligned}\quad (22)$$

where c_{W}^0 is the initial concentration in W and is equal to 1 mM. From eqn. (22), the concentrations after the permeation in each phase become eqns. (23) and (24).

$$c_{\text{W}} = \frac{c_{\text{W}}^0}{1 + r\beta} \quad (23)$$

$$c_{\text{O}} = \frac{\beta c_{\text{W}}^0}{1 + r\beta}. \quad (24)$$

Considering eqns. (13) – (15), (18), (21), (23), and eqn. (24), eqn. (25) can be formed.

$$\begin{aligned}\log 1/R_{\text{total}} &= \log \frac{1}{R_{\text{W}} + R_{\text{O}}} \\ &= -\log \left\{ -\frac{RT}{z^2 F^2} \frac{d_{\text{W}}}{D_{\text{W}}} \left(\frac{1}{c_{\text{W}}} + \frac{r}{sc_{\text{O}}} \right) \right\} \\ &= \log \left(-\frac{z^2 F^2}{RT} \frac{c_{\text{W}}^0 D_{\text{W}}}{d_{\text{W}}} \right) - \log(1 + r\beta) \left(1 + \frac{r}{s\beta} \right) \\ &= \log(1/R_{\text{W}}^0) - \log(1 + r\beta) \left(1 + \frac{r}{s\beta} \right).\end{aligned}\quad (25)$$

$1/R_{\text{W}}^0$ is defined by eqn. (26), and R_{W}^0 represents the electric resistance of a single W of which the concentration is c_{W}^0 . The second term on the right-hand side of eqn. (25) expresses the function on the permeation properties. Thus, the flux of the electrolyte ions at a certain $\Delta\phi$ is represented using $1/R_{\text{total}}$ ($= 1/(R_{\text{W}} + R_{\text{O}})$). Therefore, the permeability is proportion to the value of $1/R_{\text{total}}$.

$$1/R_{\text{W}}^0 = \left| -\frac{z^2 F^2}{RT} \frac{c_{\text{W}}^0 D_{\text{W}}}{d_{\text{W}}} \right|. \quad (26)$$

On the basis of eqn. (25), ion permeation can be described by the electric resistance of the cell system. We analysed the voltammograms according to eqn. (25) and considered the effects of the parameters

(r , s) on ion permeation.

4 Results and Discussion

4.1 Effect of the volume ratio r of W to O

Fig. 2 shows the relation between $\log \beta$ and $\log 1/R_{\text{total}}$ for each value of r . The error bars express 95% confidence levels.

Bilinear relationships were observed at $r = 0.00375$ and $r = 0.0125$ as shown in Fig. 2. The positive-slope region in which the rate-determining step is caused by drug permeation within the O shifted towards the negative direction, comparing case $r = 0.00375$ to $r = 0.0125$. On the other hand, the positive slope was not clear in case $r = 0.00125$. In each plot, the W rate-determining step, which is illustrated by a negative slope, was observed in the region of $\log \beta > 1.7$.

Fig. 3 shows the relation between the second term of the right side of eqn. (25) and $\log \beta$. It suggests that a plateau region appears when r is smaller than 0.2. In case of $r = 0.00125$, 0.00375 and 0.0125, such a plateau region is clearly visible.

As shown in Fig. SI1, the average value of r in the living body is expected to be approximately 0.2 [25]. Accordingly, bilinear relation conditions would be applicable to live systems.

Incidentally, the r value of the PAMPA assay lies within the range from 0.00125 to 0.0125.[26], and that of the Caco-2 cell assay is somewhat smaller [27]. Thus, the plateau region commonly observed in the PAMPA or the Caco-2 assays might be caused by the same reasons as the cases where $r = 0.00125$, 0.00375 and 0.0125.

4.2 Effect of the diffusion coefficient on the electrophoretic migration

The value of s depends on both solution viscosity and ion solvation, since s is the ratio of the diffusion coefficient within 1-octanol phase to that within aqueous phase. The dynamic viscosities of water and 1-octanol are 0.89 and 7.36 mPa s, respectively. The Stokes radius ratio of Cl^- to TAA^+ is roughly constant in each phase [28-30]. Since the practical ion radius (Stokes radius) is inversely proportional to the dynamic viscosity by Stokes law, the value of s is estimated to be approximately 0.1 [28-30].

The relations between the effect of the corrective term in eqn. (25) on $\log (1/R)$ and $\log \beta$ in the case of $r = 0.0125$ and 0.2 are shown in Figs. 4a and 4b, respectively.

In the case of $r = 0.2$, which is close to the value of r in the living body, the QSAR relationship is bilinear, as shown in Fig. 4a. This suggests that an increase of s causes the shift of the QSAR relationship inflection point to the negative direction of $\log \beta$ (hydrophilic side). On the other hand, in the case of $s \ll 0.2$, like in the Caco-2 or PAMPA assays, the figure around the turning point is flat, as shown in Fig. 4b. It is expected that an increase of s shifts the positive-slope region in the negative direction of $\log \beta$.

4.3 The effect of ion solvation in the O

In PAMPA, Caco-2 cell assays and measurements of *in vivo* bioactivities, the logarithm of the permeability of the drug lies on the vertical axis of a QSAR relationship. The distribution coefficient between water and 1-octanol seems to be proportional to that between water and the BLM, indicated as eqn. (27) [31].

$$\log \beta_{\text{BLM}} = a \log \beta_{1\text{-octanol}} + b, \quad (27)$$

where a and b are coefficients. Thus, eqn. (25) can be replaced by eqn. (28).

$$\log 1/R_{\text{total}} = \log(1/R_{\text{W}}^0) - \log\left(1 + rb\beta^a\right)\left(1 + \frac{r}{sb\beta^a}\right). \quad (28)$$

The influence of a on the second term of the right-hand side of eqn. (28) for cases $r = 0.00125$ ($\approx$ *in vitro*) and $r = 0.2$ ($\approx$ *in vivo*) is represented in Figs. 5a and 5b, respectively. Figs. 5c and 5d show the influence of b on the QSAR relationships for cases $r = 0.00125$ and $r = 0.2$, respectively. In PAMPA and Caco-2 assays, it is well known that $\log P$ usually reaches a plateau [26,27]. This seems to be attributed to small r values. Since the maximum value of $\log P$ cannot be evaluated, it will be difficult to design the optimum conditions.

Thus, the slope of the linear region increases with a . The maximum point shifts in the negative direction (the hydrophilic side) as the b value increases.

4.4 The effect of the ion-pair formation constant

TAA⁺ and Cl[−] form an ion-pair in solution, as expressed by eqn. (29).



The dissociation constants, K_{W} and K_{O} in W and O, are defined by eqns. (30) and (31), respectively.

$$K_{\text{W}} = \frac{c_{\text{W,TAA}^+} c_{\text{W,Cl}^-}}{c_{\text{W,TAACl}}} \quad (30)$$

$$K_{\text{O}} = \frac{c_{\text{O,TAA}^+} c_{\text{O,Cl}^-}}{c_{\text{O,TAACl}}} \quad (31)$$

Since it is difficult to form a contact ion-pair in an aqueous solution, K_{W} is estimated to be smaller than K_{O} as expressed in eqn. (30).

$$K_{\text{W}} > K_{\text{O}}. \quad (32)$$

The degree of association can be described by a dissociation constant (K) as shown in eqn. (33).

$$\alpha = \frac{\sqrt{1 + 4cK} - 1}{2cK}. \quad (33)$$

From eqns. (23), (24) and (33), the concentration of chloride ion in the W and O can be expressed as eqns. (34) and (35), respectively.

$$c_{w,Cl^-} = c_w \alpha_w = \frac{K_w}{2} \left(\sqrt{1 + \frac{4c_w^0 / K_w}{1 + r\beta}} - 1 \right) \quad (34)$$

$$c_{o,Cl^-} = c_o \alpha_o = \frac{K_o}{2} \left(\sqrt{1 + \frac{4\beta c_w^0 / K_o}{1 + r\beta}} - 1 \right). \quad (35)$$

According to eqns. (34) and (35), $\log \beta$ can be expressed as eqn. (36).

$$\log 1/R = \log 1/R_w^0 - \log 2 \left\{ \frac{c_w^0}{K_w W} + \frac{r}{s} \frac{c_w^0}{K_o O} \right\}, \quad (36)$$

where,

$$W = \sqrt{1 + \frac{4c_w^0 / K_w}{1 + rb\beta^a}} - 1 \quad (37)$$

$$O = \sqrt{1 + \frac{4b\beta^a c_w^0 / K_o}{1 + rb\beta^a}} - 1. \quad (38)$$

Here, W and O means the apparent dissociation coefficients of the drug within the W and O phases, respectively. The influence of K values (K_w : $10^{-3} - 1$ and K_o : $10^{-5} - 10^{-3}$) on the second term of the right-hand side of eqn. (36) in cases $r = 0.0125$ and 0.2 is depicted in Figs. 6a and 6b, respectively.

Accordingly, the slope of the region where the drug permeation within W decreases the rate-determining step as a decrease of K_w under the condition of $K_w < 1$. The slope of the region where the drug permeation within O decreases the rate-determining step as a decrease of K_o under the condition of $K_o < 1$. Also, the difference value of K causes a symmetric bilinear curve in the condition of $K < 1$.

4.5 Fitting parameters for electric conductivity

The fitting parameters for $r = 0.0125$ were estimated as $r = 0.00625$, $s = 0.08$, $K_w = 9 \times 10^{-8}$, $K_o = 3 \times 10^{-8}$ and $\log 1/R_w^0 = 0.61$ using eqn. (36).

Here, the volume ratio $r = 0.00125$ was calculated by the volume of O derived from eqn. (39) in the case of the void ratio of membrane filters $k_{void} = 0.50$.

$$V_o = k_{void} d_o A \quad (39)$$

Here, A is the interfacial area of O . The theoretical curve in the case of $r = 0.0125$ derived from eqn. (36) is presented in Fig. 7. The theoretical curve predicts the existence of the bilinear relation.

The electric conductivities of the W and O containing 1 mM TAACl are presented in Fig. 8. The error bars express a 95% confidence level.

In Fig. 8, the conductivity of each TAACl was almost equal in the W . In the O , the conductivity of each TAACl was almost equal except for THpACl and TOcACl. The higher the hydrophobicity of TAA, the lower its conductivity. Clearly, this trend can be attributed to ion-pair formation.

5 Conclusions

In this study, the effect of the volume ratio between the aqueous and organic phases on the permeability of the W1|LM|W2 system was investigated using a cylindrical electrochemical cell. Although the equations expressing the characteristics on the drug delivery (bell-type model, bilinear model, etc.) were led based on the kinetics, they depend on the distribution coefficient which is one of equilibrium constants. Since the interfacial transfer is faster than the diffusion within the bulk phase, the flow of drugs under the steady-state condition is determined by the volume ratio. The conductivity of an electrolyte solution can be primarily determined by the distribution coefficient in each phase.

In addition, the mechanism for forming a 'plateau region', typically seen in QSAR graphs for the PAMPA or Caco-2 cell assays was revealed. The plateau region is caused by the effects of each physicochemical parameter on the QSAR graphs based on an analytical formula. Therefore, it needs to modify these assays in order to evaluate optimum conditions for drug permeation.

Acknowledgement

The authors would like to thank Enago ([www. Enago.jp](http://www.Enago.jp)) for English language review.

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Figure captions

Fig. 1 a) The structure of the cell b) The components in each phase after the distribution equilibrium

Fig. 2 The relation between $\log \beta$ and $\log 1/R$

Fig. 3 The relation between $\log \beta$ and $\log 1/R$ in each value of r

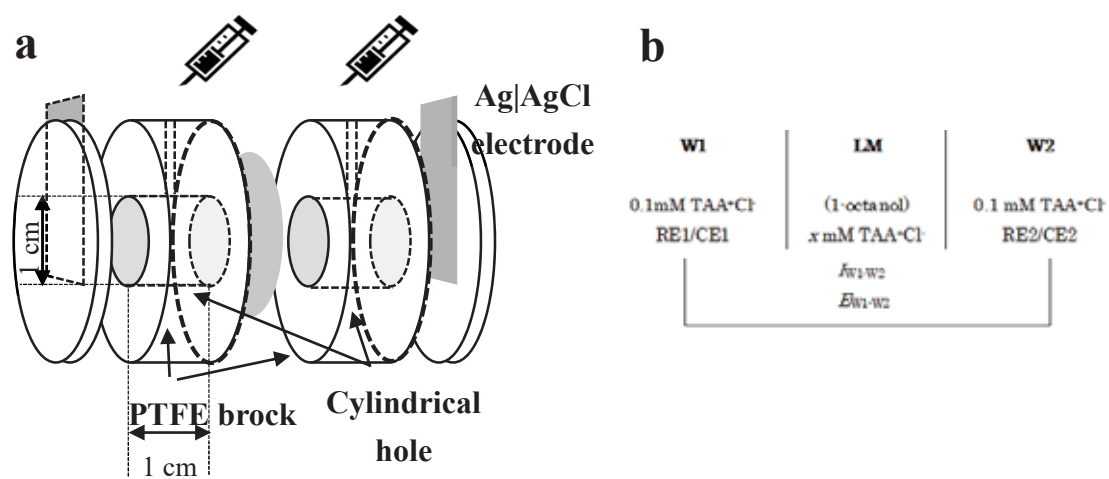
Fig. 4 The relation between $\log \beta$ and the permeability of the W and O for each s , (a) $r = 0.0125$, (b) $r = 0.2$

Fig. 5 The relation between $\log \beta$ and the permeability of the W and O at each value of a , (a) $r = 0.0125$ and (b) $r = 0.2$. The relation between $\log \beta$ and the permeability of the W and O at each value of b , (c) $r = 0.0125$ and (d) $r = 0.2$

Fig. 6 The relation between $\log \beta$ and the permeability of the W and O at each value of K_W and K_O , (a) $r = 0.0125$, (b) $r = 0.2$

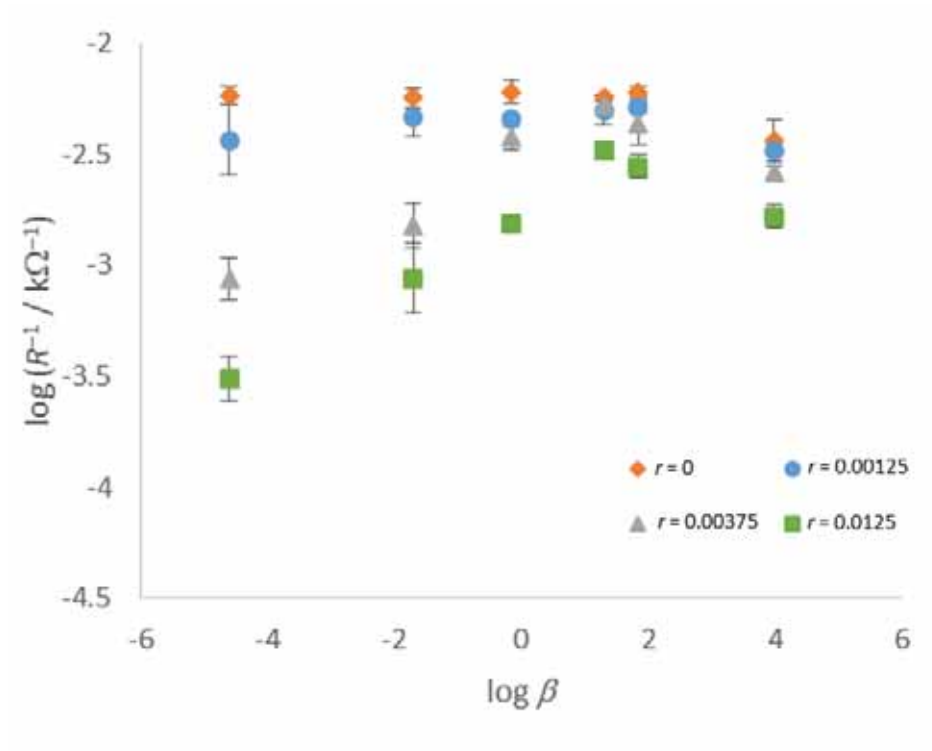
Fig. 7 The relation between $\log (1/R)$ and $\log \beta$

Fig. 8 The conductance of the O ($\sigma_O / \mu\text{S M}^{-1} \text{ cm}^{-1}$; red) and W ($\sigma_W / \text{mS M}^{-1} \text{ cm}^{-1}$; blue)



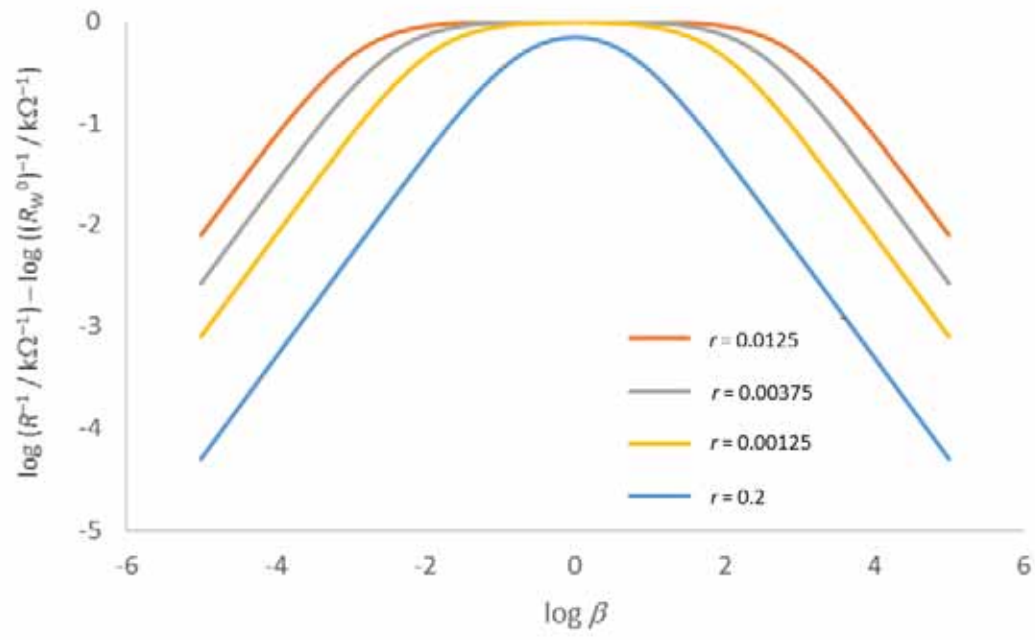
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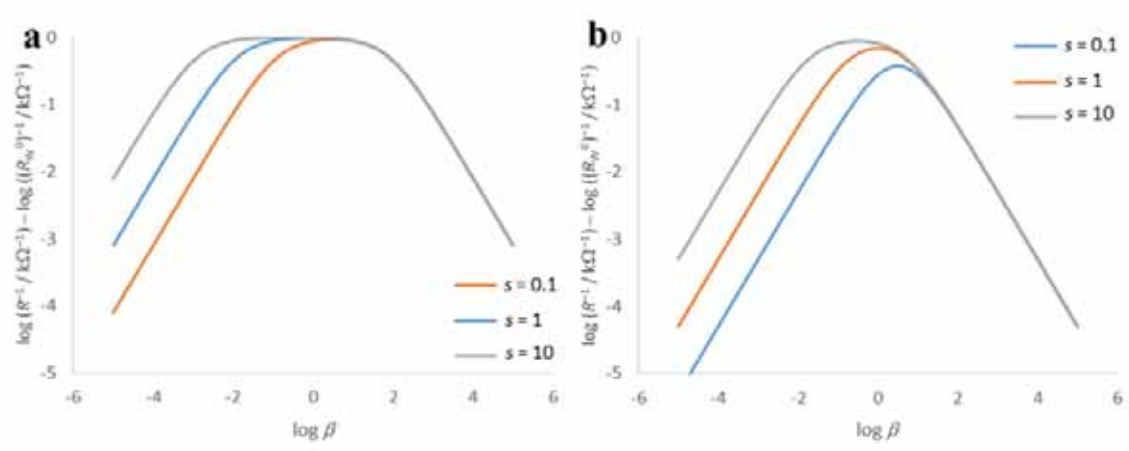
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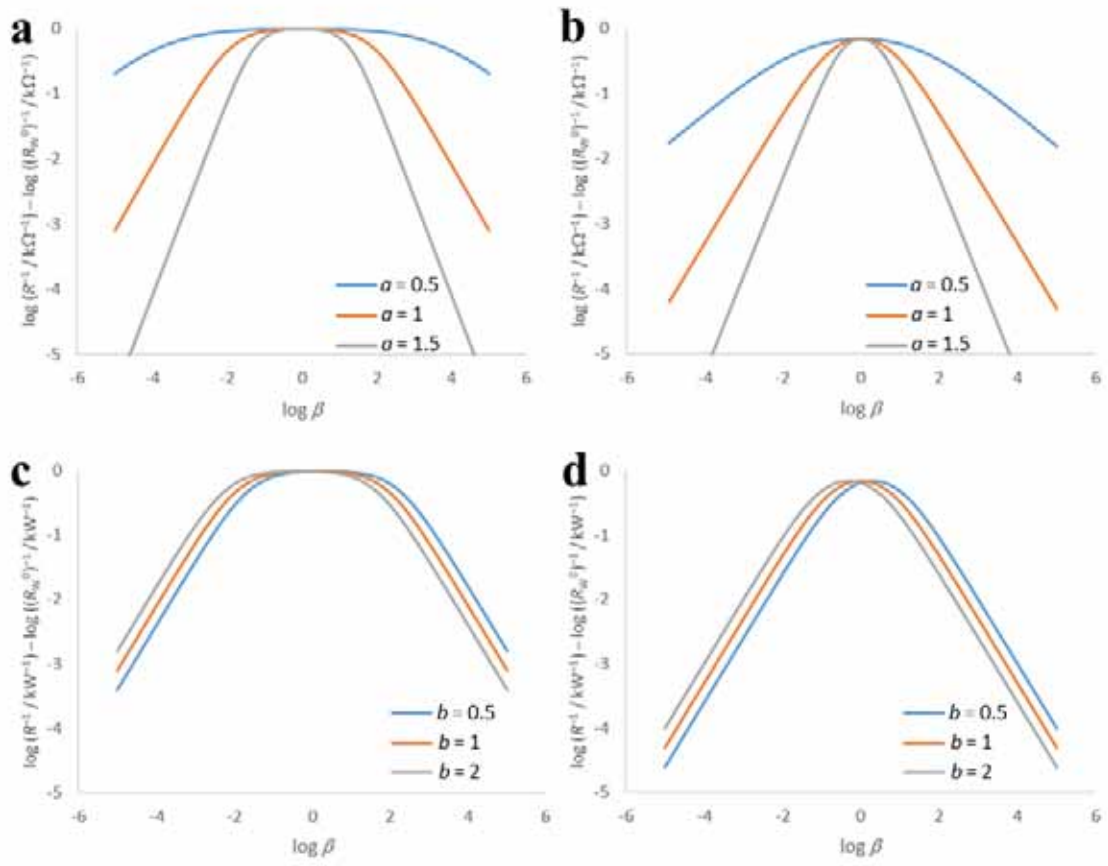
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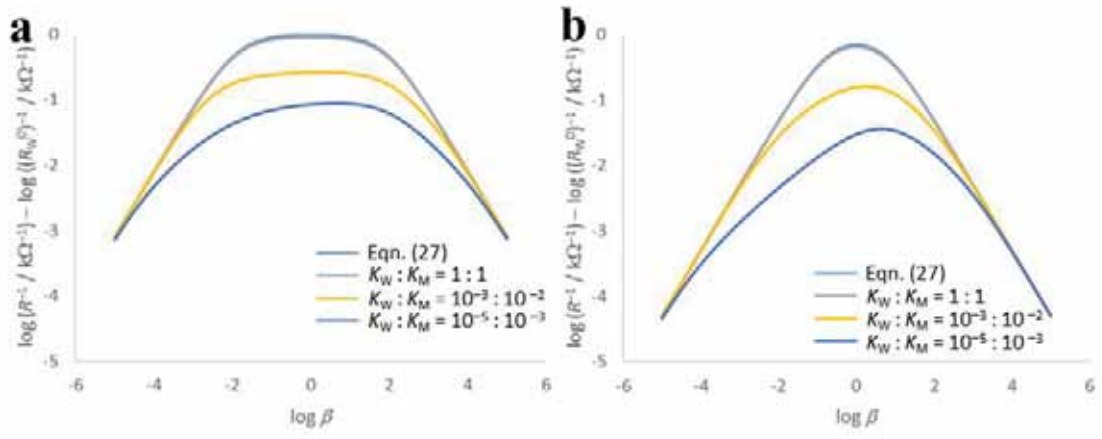
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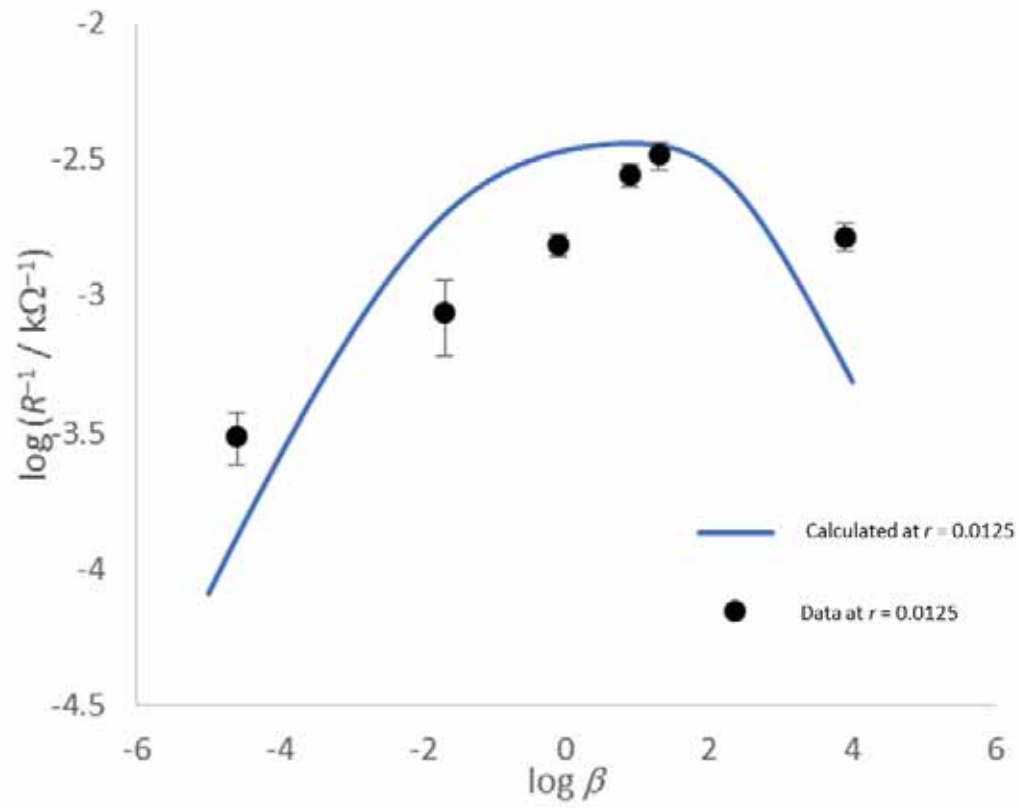
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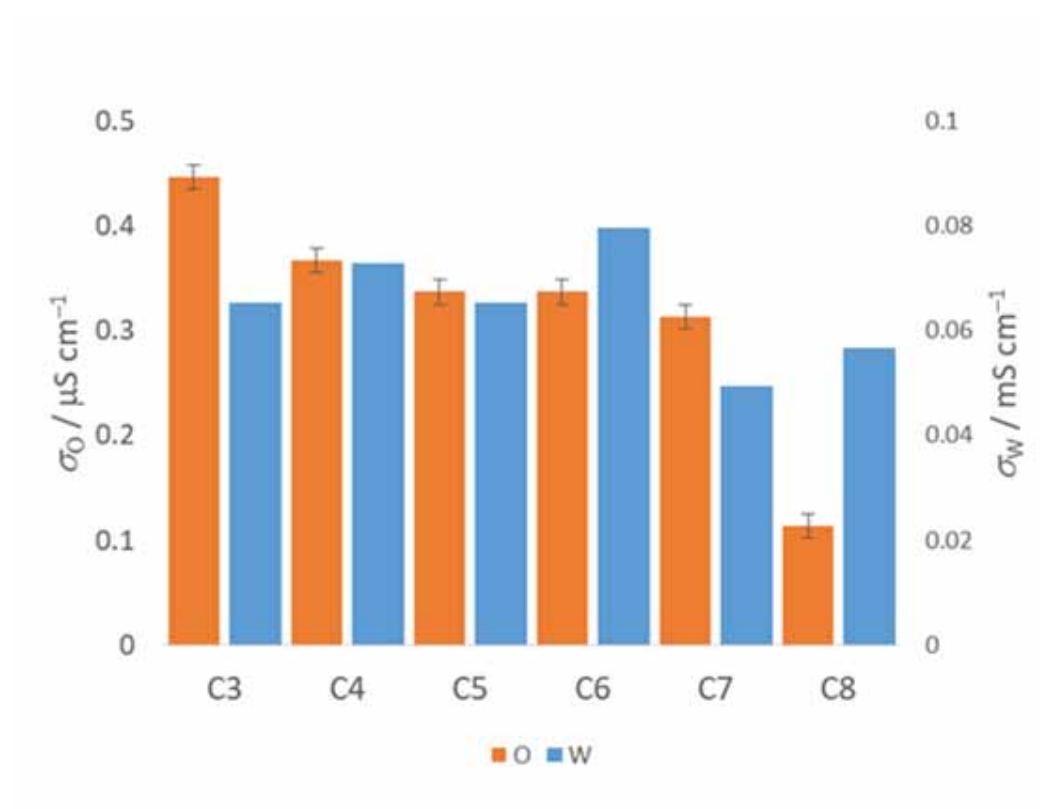
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