



# Electrochemical interpretation of parabolic relation between the hydrophobicity and the permeability of tetraalkylammonium chlorides

Riku Usami, Osamu Shirai \*, Yuki Kitazumi, Kenji Kano

Division of Applied Life Sciences, Graduate School of Agriculture, Kyoto University, Sakyo, Kyoto 606-8502, Japan

## ARTICLE INFO

### Article history:

Received 9 September 2016

Received in revised form 3 October 2016

Accepted 10 October 2016

Available online 13 October 2016

### Keywords:

Linear relationship

Membrane

Ion transport

Tetraalkylammonium chlorides

Hydrophobicity

Voltammetry

QSAR

## 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.

© 2016 Elsevier B.V. All rights reserved.

## 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<sup>+</sup>), tetrapentylammonium ion (TPA<sup>+</sup>), tetrahexylammonium ion (THxA<sup>+</sup>) and tetraheptylammonium ion (THpA<sup>+</sup>)) 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<sup>+</sup>) and chloride ion (Cl<sup>−</sup>) in the aqueous or membrane phase, and the steady-state fluxes of both TAA<sup>+</sup> and Cl<sup>−</sup> 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

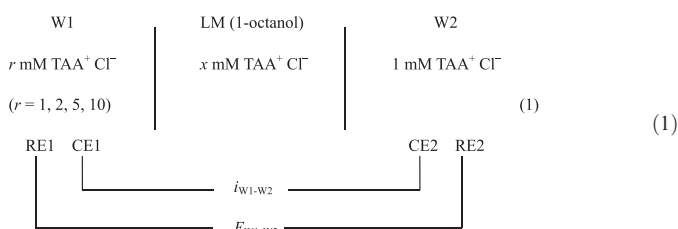
\* Corresponding author.

E-mail address: [shirai@kais.kyoto-u.ac.jp](mailto:shirai@kais.kyoto-u.ac.jp) (O. Shirai).

of TBA<sup>+</sup>, TPnA<sup>+</sup> and THxA<sup>+</sup> were from Tokyo Chemical Industry Co., Ltd. A chloride salt of THpA<sup>+</sup> 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 soaking to remove residual acetone in the filters. Two filters were set up together to become a symmetrical 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<sup>+</sup> (TBA<sup>+</sup>Cl<sup>-</sup>, TPA<sup>+</sup>Cl<sup>-</sup>, THxA<sup>+</sup>Cl<sup>-</sup> and THpA<sup>+</sup>Cl<sup>-</sup>), as represented by Eq. (1).



Here, M means mol L<sup>-1</sup> (mol dm<sup>-3</sup>). 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<sup>+</sup>Cl<sup>-</sup> salts was checked by use of Cl<sup>-</sup>-ISE (Ag|AgCl

electrode). The influence of the supporting electrolyte (MgSO<sub>4</sub>) in W1 and W2 on the transport of TAA<sup>+</sup>Cl<sup>-</sup> was voltammetrically evaluated by adding MgSO<sub>4</sub> 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  $i_{\text{W1-W2}} = 0$ ,  $E_l = 0$ , was recorded by a hand-made potentiometer. The relative conductivity of the aqueous or the 1-octanol solution containing TAA<sup>+</sup>Cl<sup>-</sup> 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 ( $298 \pm 2 \text{ K}$ ).

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

The aqueous solutions containing 5 mM of TAA<sup>+</sup>Cl<sup>-</sup> (TAA<sup>+</sup> = TBA<sup>+</sup>, TPA<sup>+</sup>, THxA<sup>+</sup> and THpA<sup>+</sup>) 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<sup>+</sup>Cl<sup>-</sup> in the aqueous solution was potentiometrically evaluated by the Cl<sup>-</sup>-ISE (Ag|AgCl electrode). As for the concentration of TAA<sup>+</sup>Cl<sup>-</sup> 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<sup>+</sup>Pic<sup>-</sup>). The aqueous and the 1-octanol solutions were then isolated after a 24 h-rest. The absorbance of Pic<sup>-</sup> in the aqueous solution was measured at 350 nm [16], and the concentration of TAA<sup>+</sup> 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, TAA<sup>+</sup>Cl<sup>-</sup> 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 TAA<sup>+</sup>Cl<sup>-</sup> between the aqueous phase (W1 and/or W2) and the membrane phase (M) was equilibrated, Eq. (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<sup>+</sup> and Cl<sup>-</sup> 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<sup>+</sup> and Cl<sup>-</sup> 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<sup>+</sup> in W1, TAA<sup>+</sup> in W2, Cl<sup>-</sup> in W1 and Cl<sup>-</sup> in W2, respectively. Taking into account the electroneutrality in each phase, Eqs. (3)–(6) hold by use of  $c_{\text{M1}}$ ,  $c_{\text{M2}}$ ,  $c_{\text{W1}}$  and  $c_{\text{W2}}$  that denote the concentrations of TAA<sup>+</sup>Cl<sup>-</sup> 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 (TAA<sup>+</sup>Cl<sup>-</sup>) in W1 is equivalent to that in W2, Eq. (7) is defined by the concentration of

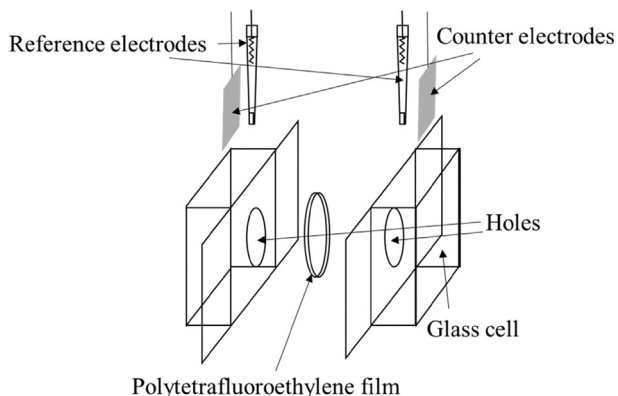


Fig. 1. Electrochemical cell system.

Download English Version:

<https://daneshyari.com/en/article/4908248>

Download Persian Version:

<https://daneshyari.com/article/4908248>

[Daneshyari.com](https://daneshyari.com)