Interfaces

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Ion-Transfer Reactions at the Nanoscopic Water/*n*-Octanol Interface[**]

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Lipophilicity is recognized as one of the most important properties for understanding the role of drugs in living systems. The common method of assessing the lipophilicity of

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a compound is to determine its partition coefficient in a two-solvent system. *n*-Octanol has similarities with lecithins, which are the main constituent of biological membranes, and that attribute makes the water/*n*-octanol (W/OC) interface a suitable system to mimic the charge-transfer processes through biomembranes. The partition coefficients ($\log P$) measured in the W/OC system are standard data in chemistry and pharmacy.[1] Experimentally, there are several methods that can be employed to determine the $\log P$ values of neutral compounds, such as HPLC, but the $\log P$ of ionic species in this system is seldom reported. Several works have shown that ion partition diagrams can be satisfactorily used for evaluation of the lipophilicity of ionizable compounds at a water/1,2-dichloroethane (W/DCE) interface.[2,3] The standard potentials, the Gibbs energies of transfer, and the $\log P$ can be evaluated from these ion partition diagrams, and these parameters have well-defined relationships that are summarized in Equation (1), where z and F are the number of ions transferred and the Faraday constant, respectively.[3,4]

$$z F \Delta_{\mathrm{O}}^{\mathrm{W}}\phi_{\iota}^{0} = \Delta G_{\mathrm{tr,i}}^{0,\mathrm{w}\rightarrow\mathrm{o}} = -2.303\, R\, T \log P_{\mathrm{i}}^{0} \tag{1}$$

Scholz et al.[4,5] studied ion transfer (IT) at the W/OC interface by the three-phase junction method for a series of anions. Using an electrochemical technique, they were able to measure the standard potential of tetraphenylborate (TPB^-) IT at the W/OC interface ($\Delta_{\mathrm{OC}}^{\mathrm{W}}\phi_{\mathrm{TPB}^-}^{0} = 160$ mV). According to Born theory the Gibbs energy of an IT has a linear relationship with $1/r$. The radius r of the TPB^- anion is almost same as that of a tetraphenylarsonium (TPAs^+) cation, so their values of the Gibbs energy of transfer are assumed to be equal. This constitutes the principle known as the TATB assumption (TATB = tetraphenylphosphonium tetraphenylborate),[6] which has been widely used in electrochemistry at liquid/liquid interfaces.

The use of a W/OC interface for performing electrochemical measurements is usually difficult, mainly because there are very few base electrolytes that can dissolve reasonably in the *n*-octanol phase. Kihara et al.[7] reported that tetrapentylammonium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate ($\mathrm{TPenA^+TFPB^-}$) can dissolve in *n*-octanol, but they did not provide any direct transfer wave at a micro-W/OC interface. In addition, the presence of hydrogen bonds between water and *n*-octanol at the interface introduces dramatic changes in the interfacial structure of such a system. Molecular dynamic studies present a value for the width of the W/OC interface of 5.5 Å,[8,9] which is similar to that of the W/DCE interface of 6 Å.[10] However, at the W/DCE interface an interfacial mixed-solvent region, which is not thicker than two to three molecule diameters,[11] is observed at both sides of the interface, whereas in the case of the W/OC interface there are drastic effects from the structure of the solvents. Particularly, a depletion layer (alkane-like region) is observed on the organic side of the interface with a minimum at about 6 Å from the Gibbs surface but which exerts its effect up to 20 Å from the Gibbs surface.[12] Compared to a W/DCE interface, a W/OC interface is broader and rougher.

A liquid/liquid interface supported at the tip of a nanopipette was first introduced in 1997,[13] and the main advantages of such a technique are the possibility of reducing the *iR* drop completely, increasing significantly the mass transport, and performing measurements with or without supporting electrolyte.[14] These valuable features make it a viable method to polarize the W/OC interface supported on a nanopipette.

Herein, we report that the W/OC interface supported at the tip of a nanopipette can be polarized. The transfer waves of anionic form of lauric acid (LA^-), TPAs^+, and tetrabutylammonium (TBA^+) were obtained and their thermodynamic data were evaluated. The kinetic behavior of LA^- was analyzed and compared with that at the W/DCE system. Among familiar supporting electrolytes in the organic phase, bis(triphenylphosphoranylidene)ammonium tetrakis(4-chlorophenyl)borate (BTPPATPBCl) can dissolve in small amounts in *n*-octanol and be used as the supporting electrolyte.

Electrochemical studies of the transfer processes of these species at the W/OC interface were carried out using a two-electrode setup, and cells I and II:

Cell I: Ag | AgTPBCl | BTPPATBCl (0.12 mM) (*n*-octanol or DCE) | | $\mathrm{Li_2SO_4}$ (10 mM) + TBACl or TPAsCl (*x* mM) | | $\mathrm{Ag_2SO_4}$ | Ag

Cell II: Ag | AgTPBCl | BTPPATPBCl (0.12 mM) (*n*-octanol or DCE) | | $\mathrm{Li_2SO_4}$ (10 mM) + Lauric acid (*y* mM) (+ LiOH or $\mathrm{HNO_3}$ to desired pH) | | $\mathrm{Ag_2SO_4}$ | Ag

Figure 1 shows that the cyclic voltammograms of these IT reactions can be observed within the potential window, and they have reasonably good steady-state waves after background subtraction. For micro- and nanopipettes, an asymmetric cyclic voltammogram should normally be obtained because of the hemispherical diffusion of ions from the outside to the inside of the pipette; the peak-shaped wave is a result of the linear diffusion of ions from the inside to the outside of the pipette.[15] However, for the cases of very short and sharp nanopipettes, nearly steady-state voltammograms have already been reported.[16] This is probably a consequence of the special shape of the nanopipettes, which have a

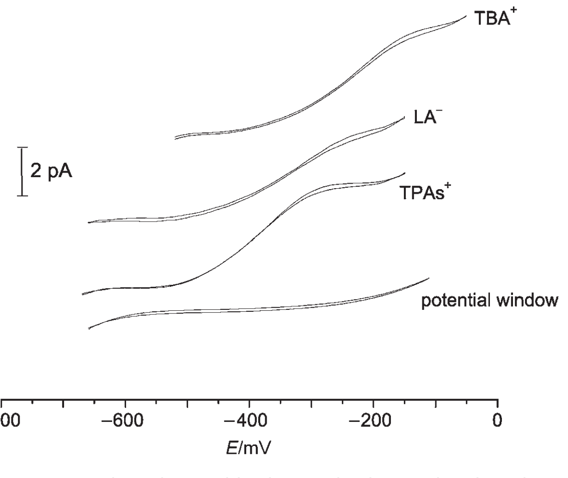

Figure 1. Potential window and background-subtracted cyclic voltammograms of IT at the W/OC interface. The systems are shown in Cells I and II: $x = 1$ mM, $y = 1$ mM. The sweep rate is 50 mV s^{-1}. The radii of the nanopipettes are 45, 60, 56, and 42 nm for TPAs^+, LA^-, TBA^+, and the potential window, respectively.

hemispherical diffusion field at both sides (see Figure 2). As a result of the shape of the cyclic voltammograms and the evident difficulties in analyzing the experimental data, differential pulse voltammetry (DPV) was applied in further studies. Using the TATB assumption and published data for the standard potential of TPB$^-$ transfer at the W/OC interface, the value for the standard potential of TPAs$^+$ transfer at the W/OC interface can be evaluated as $\Delta_{OC}^{W}\phi_{TPAs^+}^{0}=-160$ mV. To evaluate the formal transfer potential of TBA$^+$ across the W/OC interface, TPAsCl and TBACl were mixed together to experimentally assess the potential separation between the peaks of their transfers. From Equation (2) and Figure 3, the formal potential of TBA$^+$ transfer

$$\Delta_{OC}^{W}\phi_m^{0\prime}-\Delta_{OC}^{W}\phi_n^{0\prime}=\Delta_{OC}^{W}\phi_m^{p}-\Delta_{OC}^{W}\phi_n^{p} \quad (2)$$

across the W/OC interface can be calculated as -20 mV, where $\Delta_{OC}^{W}\phi_i^{0\prime}$ is the formal Galvani potential of transfer for an ion and $\Delta_{OC}^{W}\phi_i^{p}$ is the experimental peak potential of this ion.

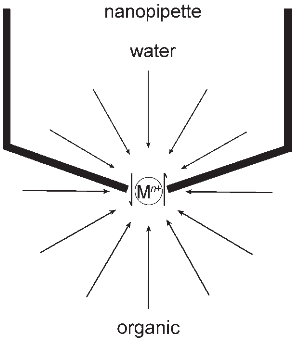

Figure 2. The possible diffusion field at a very short and sharp nanopipette.

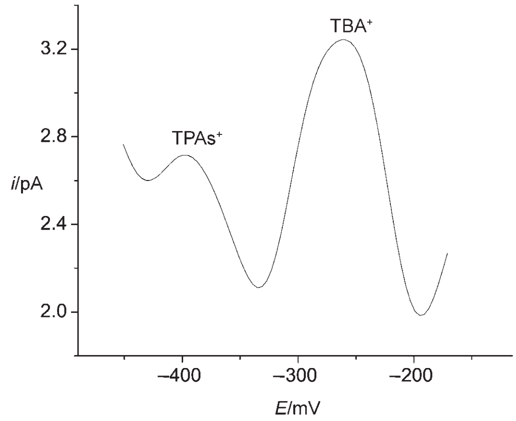

Figure 3. Differential pulse voltammograms of TBA$^+$ and TPAs$^+$ at the W/OC interface with Cell I. The concentrations of TBA$^+$ and TPAs$^+$ are both 0.5 mM.

Based on Figure 1 and the Supporting Information, it is possible to obtain the formal potential of LA$^-$ transfer at the W/OC interface, which is equal to -134 mV. The peak potential of LA$^-$ transfer at the W/OC interface remains almost unchanged between pH 8 and 12. It is not possible to access experimentally the transfer of LA$^-$ when the pH values are lower than 7.5, which is similar to the case of a W/DCE system.[3] As expected, the peak potential of LA$^-$ transfer at a liquid/liquid interface is not affected by pH when it is higher than the pK_a of lauric acid (p$K_a=4.98$).[3]

Clearly, it is easier to analyze experimental data by DPV. The diffusion coefficients of TBA$^+$, TPAs$^+$, and LA$^-$ can be calculated (see the Supporting Information) and the values are listed in Table 1.

Table 1: Thermodynamic data for LA$^-$, TPAs$^+$, and TBA$^+$ obtained at W/DCE and W/OC interfaces.

	W/OC		
	Diffusion coefficient D [$\times10^{-6}$ cm^2 s^{-1}]	Formal potential $\Delta_O^W\phi_m^{0\prime}$ [mV]	log P
LA$^-$	2.89 ± 0.04	−134	−2.29
TBA$^+$	2.53 ± 0.03	−20	0.34
TPAs$^+$	0.85 ± 0.01	−160	2.73
	W/DCE		
	Diffusion coefficient D [$\times10^{-6}$ cm^2 s^{-1}]	Formal potential $\Delta_O^W\phi_m^{0\prime}$ [mV]	log P
LA$^-$	3.49 ± 0.02	−179[3]	−3.03
TBA$^+$	2.95 ± 0.02	−230[19]	3.93
TPAs$^+$	1.03 ± 0.01	−364[19]	6.22

Cell II was employed to compare the results with IT at the W/DCE interface. In this system a nearly steady-state cyclic voltammogram for IT at the W/DCE interface was also obtained (see Figure 4). The tetraethylammonium ion (TEA$^+$) was used as the internal reference in the DCE phase ($\Delta_{DCE}^{W}\phi_{TEA^+}^{0\prime}=48$ mV).[11] The diffusion coefficient can also be calculated from Equation (3),[15,17] where i_{ss} is the

$$i_{ss}=3.35\,n\,\pi F\,D\,c\,r \quad (3)$$

steady-state current, r is the inner pipette radius, and the other parameters have the usual meanings. The thermody-

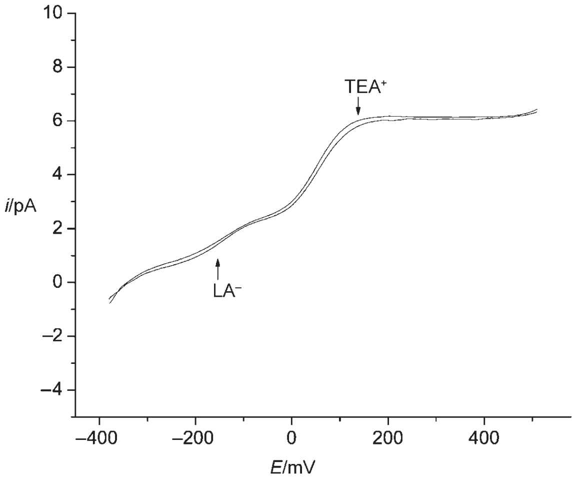

Figure 4. Cyclic voltammograms of LA$^-$ and TEA$^+$ transfer at the W/DCE interface with Cell II. The radius of the nanopipette is 39 nm; $y=1$ mM, pH 10.47.

namic parameters of the two systems including log*P* are summarized in Table 1.

At these soft nano-liquid/liquid interfaces, both W/OC and W/DCE systems show a nearly (or pseudo) steady-state quasi-reversible voltammogram. Bard and Mirkin[18] developed a three-point method for extracting the heterogeneous electron-transfer kinetic parameters from the steady-state voltammogram of a quasi-reversible reaction, and Shao and Mirkin[13] introduced this method into charge transfer at liquid/liquid interfaces. Table 2 shows the kinetic parameters calculated according to this method for transfer of LA^- at both interfaces. The mean values of the standard rate constants (k^0) obtained are (0.24 ± 0.05) and (1.35 ± 0.65) $cm\,s^{-1}$ at the W/OC and W/DCE systems, respectively. These results are further evidence that the W/OC interface is broader and rougher than the W/DCE interface. The mean values of the transfer coefficient (α) are 0.71 ± 0.24 for the W/OC system and 0.74 ± 0.10 for the W/DCE system.

Table 2: Kinetic parameters for LA^- transfer at the W/OC and W/DCE interfaces.

	Radius [nm]	$\Delta E_{1/4}$ [mV]	$\Delta E_{3/4}$ [mV]	α	k^0 [$cm\,s^{-1}$]
W/OC	71	36.0	39.0	0.73	0.265
	60	35.0	37.0	0.78	0.211
	48	33.0	34.5	0.86	0.198
	42	49.0	55.0	0.47	0.295
W/DCE	55	37.0	34.0	0.65	1.07
	45	33.0	34.0	0.68	2.02
	39	32.0	35.0	0.74	1.30
	28	31.5	32.5	0.88	1.01

In conclusion, we have shown that the W/OC interface can be polarized, and that a potential window of about 400 mV can be obtained and some IT processes observed by using the nano-W/OC interface supported on the tip of a nanopipette. This actually opens up a new and more straightforward way of obtaining the log*P* values of ionizable drugs. The diffusion coefficients of IT at the W/OC interface are slightly smaller than those at the W/DCE interface. The formal potentials of these ions at the W/OC interface are shifted to less negative values compared with those of the transfer processes at the W/DCE interface. As the effective width of a W/OC interface is wider than that of the W/DCE interface, the kinetic rate constant of LA^- is about six times less than that at the W/DCE interface. However, the potential window remains rather small for carrying out studies of drug lipophilicity and establishing partition diagrams of ionizable drugs. Work with the goal of extending the potential window is being undertaken.

Experimental Section

Chemicals: 1,2-Dichloroethane (DCE), lithium sulfate, lithium hydroxide, nitric acid, and lauric acid (LAH) were obtained from Beijing Chemical Co. and were all A.R. grade. Tetrabutylammonium chloride (TBACl, $\geq 97\%$), tetraphenylarsonium chloride (TPAsCl, $\geq 97\%$), bis(triphenylphosphoranylidene)ammonium chloride (BTPPACl, $\geq 98\%$), potassium tetrakis(4-chlorophenyl)borate (KTPBCl, $\geq 98\%$), and *n*-octanol ($\geq 99.5\%$) were purchased from Fluka. Bis(triphenylphosphoranylidene)ammonium tetrakis(4-chlorophenyl)borate (BTPPATPBCl) was synthesized according to published procedures[14a] and used as the supporting electrolyte in the organic phase. Millipore water was employed for the preparation of aqueous solutions.

Fabrication of nanopipettes: A Model P-2000 laser puller (Sutter Instruments) was used to fabricate the nanopipette with an orifice radius in the range of 20–100 nm from quartz capillaries (1 mm outer diameter, 0.7 mm inner diameter). The aqueous solution was filled from the back of the nanopipette using a 10-μL syringe. The nanopipette was checked with an optical microscope (BX-51, Olympus) prior to each measurement to ensure there was no bubble trapped inside.

Electrochemical measurements: Cyclic and differential pulse voltammetry were performed by a BAS 100B electrochemical workstation (Bioanalytical Systems). Silver wire (0.125 mm in diameter) coated with Ag_2SO_4 was inserted into the nanopipette as the reference electrode. A Ag|AgTPBCl electrode was the reference electrode in the organic phase. All the experiments were carried out at room temperature (22 ± 2 °C).

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