Differential Pulse Voltammetry for Ion Transfer at Liquid Membranes with Two Polarized Interfaces

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A simple analytical expression for the response of the double-pulse technique differential pulse voltammetry (DPV) corresponding to ion transfer processes in systems with two liquid/liquid polarizable interfaces has been deduced. This expression predicts lower and wider curves than those obtained with a membrane system with a single polarizable interface. Moreover, the peak potential of these systems is shifted 13 mV from the half-wave membrane potential. We have applied this expression to study the ion transfer of drugs with different pharmacological activities (verapamil, clomi-pramine, tacrine, and imipramine), at a solvent polymeric membrane ion sensor.

Ion transfer across the interface between two immiscible electrolyte solutions (ITIES) is a fundamental charge-transfer process that has applications in several fields, such as electroanalysis, liquid–liquid extraction, electroassisted extraction, phase transfer catalysis, and electrocatalysis.1–3 In addition, it serves as a simplified model for ion transfer in biomembranes.4,5 Interestingly, it provides a direct way to quantify the ion lipophilicity through the electrochemical determination of the standard ion transfer potential.6

Many of the systems used in electrochemical studies on ion transfer at ITIES consist of a membrane separating two aqueous solutions, i.e., the sample solution and an inner solution. In these systems the polarization is usually only effective at the sample solution/membrane interface (outer interface), since the potential drop through the inner solution/membrane interface can be kept constant by using a sufficiently high concentration of a common ion in both adjacent phases. To achieve this, two salts of this common ion with hydrophilic and lipophilic counterions are dissolved in the inner aqueous and organic phases, respectively.

A particular case arises when it is not possible to find two salts containing a common ion with the above characteristics and enough solubility in the respective phases to achieve sufficiently high concentrations in the membrane and in the inner aqueous phase. In this situation, both liquid/liquid interfaces in the membrane system are polarized.5,7–10

In a previous paper we obtained easy, analytical, explicit expressions for the $I–E$ response and concentration profiles corresponding to the ion transfer through a membrane system with two polarizable interfaces, which are valid for any multipulse potential technique.11 The aim of this paper is to give the steps for the application of the double-pulse technique differential pulse voltammetry (DPV) to these systems, because this technique is one of the most suitable for quantitative analysis and determination of the characteristic parameters of the system, such as the standard ion transfer potential, owing to its high sensitivity, resolving power, and also to the fact that the undesirable effects on the currents can be minimized.12,13 It therefore enables small differences in the standard ion transfer potentials of species with very similar chemical structure to be distinguished. For this purpose, we have deduced a simple, explicit, and analytical expression of the $I–E$ curve in DPV which has allowed us to fully characterize this response for reversible systems. From this expression, we have obtained those corresponding to the peak parameters and we have observed that the peak potential of these systems is shifted 13 mV from the half-wave membrane potential. Moreover, the DPV curves obtained in this system are lower and wider than those obtained at a membrane system with a single polarizable interface (i.e., the half-peak width is around 130 mV vs the 90 mV which is obtained when only one interface is considered).

We have applied the expressions deduced for DPV response to study the ion transfer of several drugs with different pharmacological activities at a solvent polymeric membrane ion sensor in order to determine the standard potentials corre-
sponding to the ion transfer from water to the solvent polymeric membrane. The ion transfer standard potential of an ionizable drug allows the quantifying of its lipophilicity, which is one of the most significant physicochemical properties related with its pharmacological activity. The drugs studied here are verapamil, an antiarrhythmic drug also used in treating hypertension and angina pectoris, tacrine, the first centrally acting cholinesterase inhibitor approved for the treatment of Alzheimer’s disease, imipramine, a tricyclic antidepressant, and clomipramine, a tricyclic drug with both antidepressant and antiobsessional properties.

EXPERIMENTAL SECTION

Apparatus. The design of the voltammetric ion sensor has been previously reported. Briefly, a Pt wire counter electrode was accommodated inside the inner solution compartment of a Fluka ion-selective electrode (ISE) body. This permits the use of a four-electrode potentiostat like that described in ref 15. A glass ring of 28 mm i.d. and 30 mm height, glass plate, vial, and punch were purchased from Fluka for the construction of the membranes.

Reagents and Solutions. Poly(vinyl chloride) (PVC) high molecular mass, 2-nitrophenyl octyl ether (NPOE), and tetrahydrofuran (THF) were Selectophore products from Fluka. Tetradecylammonium tetrakis-(4-chlorophenyl) borate (TDDA-TClPB), tetrabutylammonium chloride (TBAC), and (10,11-dihydro-1,4,2-dibenz[b,f]azepine-5-propanamine) (imipramine, Im), (3-chloro-10,11-dihydro-N,N-dimethyl-5H-dibenzo[b,f]azepine-5-propanamine) (clomipramine, Cm), 9-amino-1,2,3,4-tetrahydroacridina hydrochloride (tacrine, Tc), and 5-[N-(3,4-dimethoxyphenylethyl)methylaminol]-2-(3,4-dimethoxy-phenyl)-2-isopropylvaleronitrile (verapamil, Vr) were purchased from Sigma and its pharmacological activity.

Membrane Preparation. The membranes were prepared by dissolving 200 mg of NPOE, 100 mg of PVC, and 8.4 mg of TDDA-TClPB in 3 mL of THF. This solution was poured into the glass ring resting on the glass plate and was left overnight to allow the solvent to evaporate slowly. A 7 mm diameter piece was cut out with the punch and incorporated into the modified ISE body described above.

Electrochemical Measurements. The electrochemical cell used can be expressed as

\[ \text{Ag|AgCl}|5 \times 10^{-2} \text{ M LiCl}|4 \times 10^{-2} \text{ M TDDA-TClPB}|5 \times 10^{-2} \text{ M LiCl}, x \text{ M X}^-|\text{AgCl}|\text{Ag} \]

with X\(^+\) = Im\(^+\), Cm\(^+\), Tc\(^+\), Vr\(^+\), TBA\(^+\).

The applied potential, \( E_M \), is defined as the potential difference between the right- and left-hand terminals. \( E_M \) is maintained at the preset value by means of the four-electrode potentiostat that applies the necessary potential between the right and left counter electrodes. A positive current corresponds to the transfer of positive charge from the outer aqueous solution to the organic phase, i.e., through the working interface, which implies the same current sign for the coupled transfer of positive charge from the organic phase to the inner aqueous solution.

The potential–time waveform used in the DPV and the general procedure to obtain the DPV recordings were described in ref 12. In our study, consecutive potential steps (\( E_{M1} \) and \( E_{M2} \)) with a pulse amplitude (\( \Delta E = E_{M1} - E_{M2} \)) of 50 mV were applied on a base potential (\( E_0 \)) of 75 mV, during times \( t_1 = 12.5 \text{ s} \) and \( t_2 = 0.25 \text{ s} \), respectively, being the current measured at the end of each potential step (see Figure 1). The magnitude of \( E_{M1} \) was linearly changed between consecutive double pulses. The delay time between each pair of pulses, \( t_d \), was 50 s.

THEORY

Let us consider the ion transfer through a liquid membrane system like that described in ref 11, consisting of a planar organic phase (the membrane, M), separating two aqueous solutions, \( w_1 \) and \( w_2 \) phases, with the former containing the X\(^+\) ion whose transfer across a liquid/liquid interface (\( w_1/M \)) is going to be studied. The cell used for this study can be described by the following scheme:

\[ \text{B}^+\text{A}^- (w_2) || \text{R}^+\text{Y}^- (M) || \text{B}^+\text{A}^-, \text{X}^+\text{A}^- (w_1) \]  

(1)

where B\(^+\)A\(^-\) is the supporting electrolyte for the aqueous phases \( w_1 \) and \( w_2 \), and R\(^+\)Y\(^-\) is the supporting electrolyte for the organic phase.
This type of membrane system in which there is no common ion in the liquid membrane and aqueous phases implies two polarizable liquid/liquid interfaces. So, when an external polarization is applied, it is distributed between the two interfaces and the potential drop through each interface cannot be controlled individually, although the electrochemical processes occurring at each interface are linked to each other by virtue of the same intensity of electrical current.

We assume that all the phases, \( w_1, w_2, \) and \( M \), contain sufficient concentrations of electrolytes such that the different ionomic drops can be neglected.

In these conditions the applied potential, \( E_M \) (membrane potential), can be written as the difference of the two interfacial potential differences, \( E_M = E_{\text{out}} - E_{\text{inn}} \), due to the transfer of \( X^+ \) through the outer interface \( w_1/M \) \( (E_{\text{out}} = \Delta \phi_{W_1^X}) \) coupled with the transfer of the membrane electrolyte cation, \( R^+ \), through the inner interface \( w_2/M \) \( (E_{\text{inn}} = \Delta \phi_{W_2^M}) \).

In a previous paper \(^{11} \) we developed the theory for the response corresponding to the reversible ion transfer through a membrane system with any multipotential technique. This theory provides an explicit general expression for the current response corresponding to the reversible ion transfer through \( w_1/M \) and \( w_2/M \) interfaces, respectively, although the electrochemical processes occurring at the potential drop through each interface cannot be controlled individually.

The half-wave potential, \( E_{M}^{1/2} \), is given by \(^{11} \)

\[
E_{M}^{1/2} = E_M - \frac{RT}{F} \ln \lambda^+ \tag{8}
\]

where \( \lambda^+ \) is the limiting current density corresponding to the transfer of \( X^+ \) through the outer interface \( w_1/M \) and \( R^+ \) through the inner interface \( w_2/M \).

RESULTS AND DISCUSSION

In the DPV technique two consecutive potential steps, \( E_{\text{out}} \) and \( E_{\text{inn}} \), are applied over times \( t_1 \) and \( t_2 \), with \( t_1 \gg t_2 \). The signal is built by subtracting the currents obtained at the end of both pulses, \( I_{\text{dpv}} = I_2 - I_1 \). The magnitude of \( E_M \) is linearly changed between consecutive double pulses, while the pulse amplitude, \( \Delta E = E_M^{\text{inn}} - E_M^{\text{out}} \), is kept constant.

Figure 1 shows the potential–time waveform used in this technique for three different values of the potentials applied \( E_M^{\text{inn}} \) and \( E_M^{\text{out}} \) (solid lines) and its distribution between the outer (dotted lines) and the inner (dashed lines) interfaces calculated from eq \( 10 \). As can be seen, the inner interface is quite sensitive to the external polarization at those potential values corresponding to the beginning of the dc wave \( (E_M \approx E_M^{1/2}) \). However, as the applied potential is scanned toward the limiting current region \( (E_M \gg E_M^{1/2}) \), the potential drop through this inner interface becomes constant (compare Figure 1, part A with parts B and C).

This behavior also can be observed in Figure 2, where we have plotted the current corresponding to the first potential pulse (curves a), to the second pulse (curves b) and to the DPV response (curves c) versus the membrane potential (solid curve).
lines) and versus the potential drops in the outer interface (dotted lines) and in the inner one (dashed lines).

From eqs 2 and 3, and taking into account that in DPV the condition \( t_1 \gg t_2 \) is fulfilled (i.e., \( t_1 + t_2 = t_1 \)), the following simple expression for the response in this technique is obtained:

\[
I_{DPV} = FA \sqrt{\frac{D^*_X}{\pi \tau_x} c_X [g(\eta^2_\text{M}) - g(\eta^-_\text{M})]}
\]  

(11)

with \( g(\eta) \) given by eq 4.

From these equations we have obtained by mean numerical fitting that the peak parameters, \( I_{DPV}^\text{peak} \) and \( I_{DPV}^\text{peak} \), for \( \Delta E \) values less than 50 mV, are given by

\[
I_{DPV}^\text{peak} (\text{mV}) = E_M^{1/2} + 13.0
\]  

(12)

\[
I_{DPV}^\text{peak} = FA \sqrt{\frac{D^*_X}{\pi \tau_x} c_X (8.91 \times 10^{-3}) \Delta E}
\]  

(13)

and the half-peak width is

\[
W_{DPV}^{1/2} (\text{mV}) = 131 + (2.43 \times 10^{-5}) \Delta E
\]  

(14)

with \( \Delta E \) in the above equations expressed in millivolts.

Figure 3 shows the DPV curves corresponding to a membrane system with two polarizable interfaces (solid lines) and also to a system with a single polarizable interface (dashed lines), obtained for two values of the pulse amplitude \( \Delta E \). The current \( I_{DPV} \) has been plotted in all the cases versus the difference \( E_{\text{index}} - E_M^* \), with \( E_{\text{index}} = (E_M + E_M^*)/2 \). The use of \( E_{\text{index}} \) instead of the usual \( E_M \) is of great interest because the \( I_{DPV} - E_{\text{index}} \) plots are centered about the half-wave potential in the case of a single polarizable interface system (see dashed curves).

As can be seen, the DPV peaks obtained for the liquid membrane system are shifted 13 mV with respect to those obtained when only one polarizable interface is used, in agreement with eq 12. Moreover, in the first case the \( I_{DPV} - E_{\text{index}} \) curves are lower (around 40–45%) and wider than those obtained in the second case (\( W_{DPV}^{1/2} = 131 \text{ mV} \) vs the 90 mV observed when only one interface is considered).

In Figure 4, we have evaluated the effect of the concentration of the target ion \( X^+ \) (Figure 4a) and of the membrane electrolyte cation \( R^+ \) (Figure 4b) on the DPV curves of a liquid membrane system for a pulse amplitude of 50 mV. From these figures it is clear that the increase of \( c_R^* \) has a double effect—an increase of the peak current (see eq 13) and a shift of the peak potential toward more positive values through an increase of \( E_M^* \) (or \( \lambda^* \), see eqs 7 and 8). The increase of \( c_R^* \) only causes a shift of the peak potential toward more negative values (see eq 7).

In Figure 5, we have evaluated the effect of the concentration of the target ion \( X^+ \) (Figure 4a) and of the membrane electrolyte cation \( R^+ \) (Figure 4b) on the DPV curves of a liquid membrane system for a pulse amplitude of 50 mV. From these figures it is clear that the increase of \( c_R^* \) has a double effect—an increase of the peak current (see eq 13) and a shift of the peak potential toward more positive values through an increase of \( E_M^* \) (or \( \lambda^* \), see eqs 7 and 8). The increase of \( c_R^* \) only causes a shift of the peak potential toward more negative values (see eq 7).

Figure 5 shows the background-corrected experimental DPV curves corresponding to four different drugs obtained for a pulse amplitude of \( \Delta E = 50 \text{ mV} \). The measured values of \pH for the 1 \times 10^{-4} \text{ M} \) solutions used of the different drugs in 0.05 M LiCl were around 5.7. The reported \( pK_a \) values of imipramine, verapamil, tacrine, and clomipramine are 9.5, 10, 9, and 9, respectively.


Figure 4. Theoretical $i_{DPV} - E_{wave}$ curves calculated from eq 11 with $E^*_0 = 80.0$ mV, $A = 0.15$ cm$^2$, $\Delta E = 50$ mV. (a) $c_{DPV} = 40$ mM and $c_{TP}^*$ values are on the curves; (b) $c_{DPV} = 0.1$ mM and $c_{TP}^*$ values are on the curves. Other conditions were the same as in Figure 2.

Figure 5. Background-subtracted DPV recordings obtained for 1 $\times 10^{-4}$ M solutions of (black circles) imipramine, (white triangles) clomipramine, (white squares) verapamil, and (black diamonds) tacrine. Solid lines correspond to the theoretical DPV curves obtained from 1 $\times 10^{-4}$ M solutions of (black circles) imipramine, (white triangles) clomipramine, (white squares) verapamil, and (black diamonds) tacrine. Other conditions were the same as in Figure 2.

Table 1. Standard Ion Potentials Obtained from DPV Curves of Figure 5

<table>
<thead>
<tr>
<th>Drug</th>
<th>$\Delta E_{M}^{0}$ / mV</th>
</tr>
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<tbody>
<tr>
<td>imipramine</td>
<td>-163</td>
</tr>
<tr>
<td>verapamil</td>
<td>-157</td>
</tr>
<tr>
<td>tacrine</td>
<td>-115</td>
</tr>
<tr>
<td>clomipramine</td>
<td>-175</td>
</tr>
</tbody>
</table>

Drug is in its protonated form, such that the measured currents correspond to the simple ion transfer of the corresponding protonated drugs. In order to obtain values of the ion transfer potentials of these drugs, we have chosen the reference ion TBA$^+$ due to the proximity between its own ion transfer potential and those corresponding to the different species analyzed.

$E_{M}^{0}$ and $A(DX)_{M}^{1/2}$ have been obtained from values of the peak potentials and currents by means of eqs 12 and 13. Once we have obtained both set of values, we have calculated theoretical DPV curves by using eq 11. As can be seen, an excellent agreement was obtained in all the cases.

The standard ion transfer potential of each ionic drug $X^+$ was calculated from the difference between its half-wave potential and that corresponding to the reference ion TBA$^+$, obtained by using the same pulse amplitude and concentrations for both ions. Thus, by applying eq 8 and taking into account the relation between formal and standard ion transfer potentials

$$E_{M}^{1/2} - E_{M,TBA}^{1/2} = \Delta E_{M}^{0} - \Delta E_{M,TBA}^{0} + \frac{RT}{F} \ln \left( \frac{f_{M}}{f_{X}} \right)$$

where $\gamma_f$ and $Df$ are the activity and the diffusion coefficient of ion $j$ in the phase $p$, respectively. This difference is independent of the ion transfer at the inner interface, be it that of the cation of the membrane electrolyte ($R^+$) or that of the anion of the inner aqueous solution ($A^-$).

In the above equation, the two last terms on the right-hand side are practically zero, in such a way that

$$E_{M}^{1/2} - E_{M,TBA}^{1/2} = \Delta E_{M}^{0} - \Delta E_{M,TBA}^{0}$$

In order to calculate $\Delta E_{M}^{0}$, we have used a value for $\Delta E_{M,TBA}^{0} = -242$ mV.

The values obtained are shown in Table 1. From these, several conclusions can be drawn. First, this system with two polarizable interfaces allows us to determine standard ion transfer potentials of drugs which are much more lipophilic than those studied with an analogous system consisting of a single polarizable interface. Second, the use of DPV with this system is able to distinguish small differences between standard potentials corresponding to drugs with very similar chemical structures, such as imipramine and clomipramine. Third, the value found for tacrine is equal to that previously reported.

for a membrane containing a much lower PVC content than
our membrane (5% instead of 32%). This extends to higher PVC
contents the observation that the presence of PVC in the
membrane composition does not alter the standard ion transfer
potential values with respect to the plasticizer NPOE alone.

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