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# Facilitated proton transfer or protonated species transfer reactions across oil|water interfaces

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## ABSTRACT

The main purpose of this paper is to develop the equations for the half-wave potential of facilitated proton transfer or protonated species transfer across liquid|liquid interfaces, including ion pairing. The main equation developed in this research allows simulating different chemical systems (hydrophilic and hydrophobic neutral base, multiple protonated species, ion-pair formation in the organic phase). Five representative chemical systems are studied in detail in order to demonstrate the usefulness of the equations developed. In addition, the effect of the hydrophilicity of neutral weak bases on the domains of predominance of each species is analysed. Finally, the half-wave potential as a function of the pH obtained using the developed equations, are compared to simulated results and to pH-potential diagram.

## 1. Introduction

The transfer of protonated species across liquid|liquid interfaces is reported in several experimental works in the literature [1–7]. In many of these studies, the transfer of weak acids and bases has been found to depend on the pH of the aqueous phase and on their partition coefficient [8–39]. A theoretical approach for modelling the facilitated proton transfer or protonatable species transfer across liquid|liquid interfaces was developed by several authors [21,25,33,34,38,40,41].

Girault and coworkers [19] constructed complete potential-pH diagrams at liquid–liquid interfaces for a number of ionisable drugs. These diagrams, which are a transposition to biphasic systems of the well-known Pourbaix's pH-potential diagrams, give the complete picture of the effect of both the pH and an interfacial potential difference on drug partition. The methodology of the ionic partition diagrams consists in determining equiconcentration boundaries as a function of the interfacial Galvani potential difference and aqueous pH by taking account of the thermodynamic equilibria governing the distribution of the various acid-base forms of the molecule involved in the transfer. Ionic partition diagram defines the domains of predominance of each species either in the aqueous or in the organic phase, and it offers a global and direct visualisation of all the transfer mechanisms [1–5,7]. In recent years, a large number of ionisable drugs, such as acids, bases, ampholytes or zwitterionic species, have been characterised using ionic partition diagrams by different authors, showing the usefulness of the methodology [18–20,22,26,28,42–59]. As expected for the proposed methodology for the construction [19], these ionic partition diagrams do not reproduce satisfactorily the boundary lines where two processes coexist. Additionally, these diagrams do not include the ion pairing between the protonated species and the counterion of the supporting electrolyte.

The main purpose of this paper is to develop the equations for the half-wave potential of facilitated proton transfer or protonated species transfer across liquid|liquid interfaces, including ion-pair formation in the organic phase. The main equation developed in this research allows simulating different chemical systems (hydrophilic and hydrophobic neutral base, multiple protonated species, ion-pair formation in the organic phase). Five representative chemical systems are studied in detail in order to demonstrate the usefulness of the equations developed. In addition, the effect of the hydrophilicity of neutral weak bases on the domains of predominance of each species is analysed. Finally, the half-wave potential as a function of the pH obtained using the developed equations, are compared to simulated results [40] and to pH-potential diagrams [19].

### 1.1. Theory

Summary of the general model described in the previous paper [40] for the transfer of protonated species in buffered solutions. To derivate the current–potential equation for the facilitated proton

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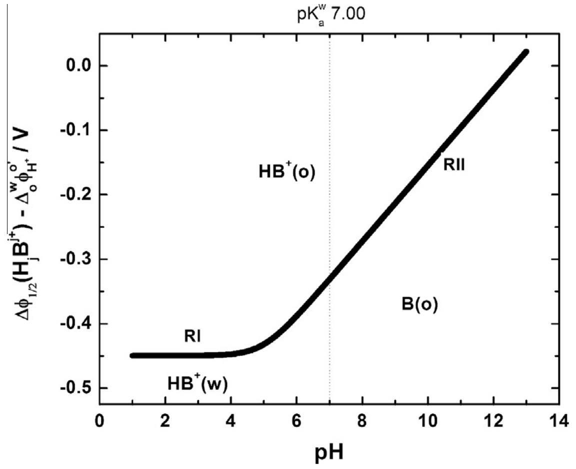

**Fig. 1.** Dependence of the half-wave potential on the pH of the aqueous phase for a hydrophobic weak base ($n = 1$). Simulation parameters: $pK^w_{a,HB^+} = 7.00$; $\log(K_{D,B}) = 2.00$; $\Delta^w_o\phi^{o'}_{HB^+} = 0.100$ V and $\xi = 1.00$.

transfer by a weak base present in multiple protonated forms, the following suppositions are made:

(a) The interface between the aqueous and the organic phase is stationary and planar.

(b) Both phases contain enough inert electrolytes so that migration of the transferring ion can be neglected.

(c) The rates of the acid-base association and dissociation processes are sufficiently large in comparison with the corresponding diffusion rates, so that it may be assumed that acid-base association and dissociation are at equilibrium even when current is flowing.

(d) The transfer of all species through the interface is reversible and diffusion controlled. The diffusion occurs in the $x$ coordinate, normal to the interface. The interface is defined at $x = 0$.

(e) Double layer effects and adsorption are not considered in the model, as well as acid dissociation constant change between the bulk and the interface.

(f) The distribution constant of the neutral weak base B does not depend on the potential applied and is defined by: $K_{D,B} = \frac{c^o_B}{c^w_B}$.

(g) All the charged species are perturbed by the potential applied to the interface and depend on the Nernst equation.

(h) The diffusion coefficients in one phase are the same for all species. Of course, this assumption is not real for the H$^+$ in the aqueous phase, but it is necessary to apply the Matsudás approach [60]. This assumption allows an important simplification of the mass balance equations which may in this way be reduced to standard mass transport equations, similar to Fick's laws for the total concentrations. Furthermore, the electrochemical signal in the limiting current region is always controlled by the diffusion of the weak base species in aqueous buffered solutions.

(i) The total buffer concentration is higher than the total weak base concentration so that the pH value is constant.

(j) Ion-pair formation is considered only in the organic phase. Ion-pair association and dissociation are at equilibrium even when current is flowing, since the rates of the ion-pair association and dissociation processes are sufficiently high in relation to the corresponding diffusion rates.

(k) Although the activity coefficients are functions of the composition of the solution phase, we neglect the concentration dependence of the activity coefficients for simplicity.

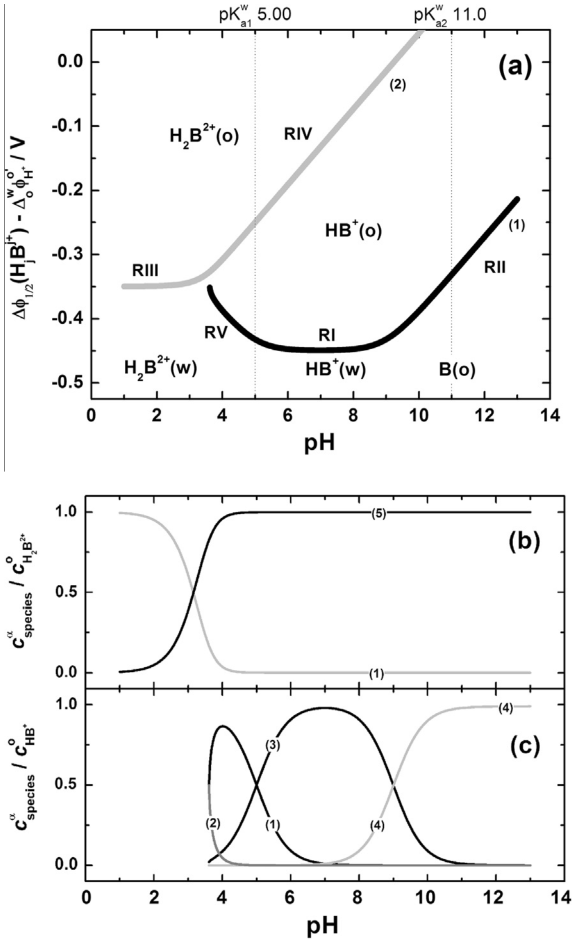

**Fig. 2.** Dependence of the half-wave potential on the pH of the aqueous phase for a hydrophobic weak base ($n = 2$) (a). HB$^+$ (1) and H$_2$B$^{2+}$ (2). Species distributions on the pH of the aqueous phase for a hydrophobic weak base ($n = 2$) ((b) and (c)). H$_2$B$^{2+}$ in the aqueous (1) and organic phase (2); HB$^+$ in the aqueous (3) and organic phase (5); and B in the organic phase (4). Simulation parameters: $pK^w_{a1,H_2B^{2+}} = 5.00$; $pK^w_{a2,HB^+} = 11.0$; $\log(K_{D,B}) = 2.00$; $\Delta^w_o\phi^{o'}_{HB^+} = 0.100$V; $\Delta^w_o\phi^{o'}_{H_2B^{2+}} = 0.200$V and $\xi = 1.00$.

(l) The proton transfer is negligible in the potential range where the transfer of protonated species is observed and the free proton concentration in the organic phase is also negligibly small.

The acid-base equilibria of the weak base are the following:

$$H_iB^{i+} \rightleftarrows H^+ + H_{(i-1)}B^{(i-1)+}$$

the $i$-acid dissociation constant in the $\alpha$ phase is defined by:

$$K^\alpha_{ai} = \frac{c^\alpha_{H_{(i-1)}B^{(i-1)+}}\, c^\alpha_{H^+}}{c^\alpha_{H_iB^{i+}}} \tag{1}$$

for $i = 1, \ldots n.$ and $\alpha$ = organic phase (o) or aqueous phase (w).

The ion-pair equilibria of the $i$-protonated species with the anion (X$^-$) of the supporting electrolyte in organic phase are the following:

$$H_iB^{i+}(o) + pX^-(o) \rightleftarrows H_iBX_p^{(i-p)+}(o)$$

where the net charge of the ion-pair $(i - p)$ may not be necessarily zero [61]. The overall ion-pair association constant is defined by:

$$K^o_{H_iBX_p^{(i-p)+}} = \frac{c^o_{H_iBX_p^{(i-p)+}}}{c^o_{H_iB^{i+}}\, c^o_{X^-}} \tag{2}$$