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Promazine π-mers formation at a 1,2-dichloroethane/water interface

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Abstract

The behavior of promazine in 1,2-dichloroethane was studied using cyclic voltammetry at the ITIES and UV–vis spectrophotometry. The analysis of voltammograms and spectra obtained varying promazine concentration, pH, nature and concentration of organic electrolyte and applying positive polarisation at the interface allowed us to postulate a reaction scheme consisting in a first step of promazine partition to organic phase, followed by a charge transfer complex (CTC) formation with 1,2-dichloroethane. This CTC induces the oxidation of promazine to the corresponding radical cation which is stabilised in organic phase by π-mers formation. π-mer complexes form ion pairs with the anions of the organic base electrolyte. Similar results were found using methotrimeprazine, another phenothiazine derivative, with a methoxyl group attached to the ring. Chlorpromazine, trifluprazine, perphenazine and fluphenazine were stable in 1,2-dichloroethane.

Keywords: Liquid/liquid interfaces; Phenothiazines; Promazine; π-mers; Charge transfer complexes

1. Introduction

The interface between two immiscible electrolyte solutions (ITIES) has been employed to study direct transfer mechanisms of different ions from the aqueous to the organic phase, to analyze and understand interfacial phenomena such as electrodeposition of metallic particles [1,2], adsorption of amphiphilic molecules or ions with interfacial activity [3–8] and electron transfer reactions [9–14]. Facilitated cation [15–18], or proton [19–22] transfer followed by complexes or ionic pairs formation also takes place at these interfaces [23–25].

Phenothiazines, PZ, are known for their antischizophrenic and tranquilizer activities [26], and as potent modulators of multidrug resistance because they block the anticancer drug transport by binding either the drug's interaction site (competitive inhibition) or to other binding site, leading to allosteric inhibition on the outward transport of anticancer agent [27,28]. They are easily oxidized photochemically [29–33] or electrochemically [34], resulting in the formation of a stable cation radical as an intermediary of the final product, the corresponding sulfone.

When PZ is present in water, it tends to self-assemble because of its amphiphilic nature, giving micellar structures [35–41]. Under the critical micelle concentration, they have a non-ideal behavior, which has been interpreted in terms of the formation of small premicellar aggregates (dimers, trimers and possibly tetramers).

Nath and Sapre studied the electron transfer reaction from several PZ derivatives to chloroalkanes, namely carbontetrachloride and chloroform, by steady-state fluorescence, ground state and transient absorption techniques [32]. They found that absorption spectra of promethazine and chlorpromazine in chloroalkane solvents show changes: the spectrum in CCl_4 is slightly red shifted with an enhanced absorption compared to that obtained in dioxane or acetonitrile. The authors attributed this shift to the formation of a charge transfer complex (CTC) between phenothiazine and chloroalkane molecules, since PZs are very good electron donors ($E^{OX}_{1/2} = 0.865$ V vs. SCE and 0.835 V vs. SCE for promethazine and chlorpromazine, respectively) and chloroalkanes (RX) are fairly good electron acceptors ($E_{RX/R^{\bullet}+X^-} = -0.66$ V vs. SCE for CCl_4 and -1.15 V vs. SCE for $CHCl_3$)[1] [32]:

$$PZ + RX \rightleftarrows [PZ^{\delta+} \cdots RX^{\delta-}] K_{CT} \quad (1)$$

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[1] $E_{RX/R^{\bullet}+X^-}$ is the redox potential of haloalkanes in acetonitrile.

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The formation of this CTC occurs without laser excitation. They measured the ground state complex formation constant (K_{CT}) and the values obtained were 1.01 ± 0.18 and $0.41 \pm 0.17\,M^{-1}$ for promethazine and chlorpromazine, respectively. These results show that K_{CT} value increases with the electron donating power of PZ molecules, therefore the association in the ground state is due to charge-transfer type of interaction. The authors found that the formation of the CTC is greater in less polar solvents (contrary to the usual observation). Such an unusual trend observed in this study may result from the structural changes in the PZ moiety; PZ derivatives have nonplanar structure [33], while in CTC the ring system is forced to attain a near planar structure. In nonpolar solvents, the interaction between the solute and the solvent is weak and the change from the typical V shape to almost plane is relatively easy to occur; whereas in polar solvents, where the solute–solvent interactions are relatively strong, such structural changes do not take place. In consequence, the complex is more stabilised in nonpolar solvents.

When the formation of the PZ cation radical occurs and the PZ concentration is high enough, the cation radical spontaneously associates with a neutral PZ molecule leading to the formation of a stable dimeric aromatic cation radical. These species are known as π-mers (pimers) complexes[2] [42]:

$$PZ + PZ^{\bullet +} \rightleftarrows [PZ, PZ]^{\bullet +} \quad (2)$$

It is important to point out that these π-mers complexes can also be formed with other π donors, such as phenyl groups present in other molecules. While the neutral phenothiazine has no color, the cation radical absorbs in the visible region (around 525 nm). The cation radical also has weak absorption bands in the near IR region. According to Sun and coworkers when π-mers are present the spectra are modified [43].

In a previous work [44] we studied the transfer of several protonated phenothiazine derivatives using cyclic voltammetry at 1,2-dichloroethane interface. In addition to the direct transfer of protonated promazine, PMZ, a second positive peak was observed and, according to our experimental results, we are able to postulate that this process is related to π-mers formation. So that, the aim of the present paper is elucidate the π-mers formation process at a liquid–liquid interface. The analysis of the effect of PMZ concentration, pH as well as the nature and concentration of electrolyte solutions is the main tool employed to postulate a mechanism for the global process.

2. Experimental

The voltammetric experiments were performed in a four-electrode system using a conventional glass cell of $0.18\,cm^2$ interfacial area. Two platinum wires were used as counter-electrodes and the reference electrodes were Ag|AgCl. The reference electrode in contact with the organic solution was immersed in an aqueous solution of 1×10^{-2} M tetraphenylarsonium chloride (TPhAsCl, Merck) or tetrapentylammonium chloride (TPACl, Merck).

Aqueous electrolyte solutions were prepared using ultrapure water. Lithium chloride (Mallinckrodt A.R.), sodium chloride (Merck) and potassium chloride (Aldrich) were employed as background electrolyte and reference solutions in the aqueous phase (typically 1×10^{-2} M concentration).

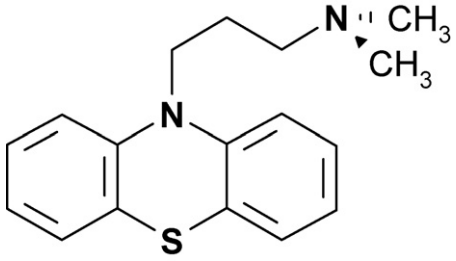
The following salts were prepared to be used as supporting electrolytes in the organic phase in a final concentration of 1×10^{-2} M: tetraphenylarsonium dicarbollylcobaltate, TPhAsDCC, tetraphenylarsonium tetraphenylborate, TPhAsTPhB, and tetrapentylammonium tetrakis(4-chlorophenyl)borate, TPATPhBCl. 1,2-Dichloroethane was used as solvent for the organic solutions (1,2-DCE, Dorwil). TPhAsDCC was obtained by metathesis of tetraphenylarsonium chloride (Sigma) and cesium dicarbollylcobaltate (Lachema). Similarly, TPhAsTPhB and TPATPhBCl were prepared by mixing an aqueous solution of tetraphenylarsonium chloride (TPAsCl, Sigma) [or tetrapentylammonium chloride (TPACl, Merk)] with an ethanol:water (2:1) solution of sodium tetraphenylborate (NaTPhB, Sigma) [or potassium tetrakis(4-chlorophenyl)borate (KTPhBCl, Aldrich)]. Each precipitate was recrystallized from an ethanol:acetone or water:acetone mixture and then dried in an oven at 30 °C for 2 days.

Promazine hydrochloride was used as received from Sigma. This compound was added to the aqueous phase in a concentration ranged from 1×10^{-4} to 1×10^{-3} M. The pH of the aqueous phase was varied in the range 2–12 by addition of HCl (Merck) and LiOH, NaOH or KOH, depending on the base electrolyte. Promazine, PMZ, can be present as a neutral molecule, X, or as a monocation, XH^+, species, according to the pH of the aqueous phase ($pK_a = 9.43$ [44]). The molecular structure of PMZ is shown in Scheme 1.

The electrochemical cell was filled using 2 mL of the organic phase in contact with 8 mL of aqueous phase. The potential E applied between the two Ag|AgCl reference electrodes is related to the Galvani potential difference ($\Delta_o^w\phi$) across the interface by

$$E = (\Delta_o^w\phi) + \Delta E_{ref} \quad (3)$$

where ΔE_{ref} depends on the reference electrodes and the reference solutions employed. For all the figures shown in Section 3, the E scale was referred to the standard potential transfer of $TPhAs^+$ ($\Delta_o^w\phi^0_{tr,TPhAs^+} = -0.364$ V) [45].



Scheme 1. Molecular structure of promazine, PMZ.

[2] The notation π-mers is used to distinguish the dimeric cation radical from the premicellar aggregates formed with two monomers.