

Contents lists available at [ScienceDirect](http://www.sciencedirect.com/science/journal/15726657)

Journal of Electroanalytical Chemistry

journal homepage: www.elsevier.com/locate/jelechem

Effect of charge of quaternary ammonium cations on lipophilicity and electroanalytical parameters: Task for ion transfer voltammetry

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ARTICLE INFO

Keywords: ITIES Muscle relaxants Partition coefficient Gallamine Succinylcholine Acetylcarrnitine

ABSTRACT

The electrochemical behavior of three differently charged drug molecules (zwitter-ionic acetylcarnitine, bicationic succinylcholine and tri-cationic gallamine) was studied at the interface between two immiscible electrolyte solutions. Tetramethylammonium was used as a model mono cationic molecule and internal reference. The charge and molecular structure were found to play an important role in the drug lipophilicity. The studied drugs gave a linear correlation between the water – octanol (log $P_{octanol}$) partition coefficients and the electrochemically measured water - 1,2-dichloroethane ($logP_{DCE}$) partition coefficients. Comparison with tetraalkylammonium cations indicating that the correlation between $logP_{octmol}$ and $logP_{DCE}$ is molecular structure dependent. The highest measured sensitivity and lowest limit of detection were found to be 0.543 mA·dm³·mol⁻¹ and 6.25 μM, respectively, for the tri-cationic gallamine. The sensitivity for all studied ions was found to be a linear function of molecular charge. The dissociation constant of the carboxylic group of zwiter-ionic acetylcarnitine was calculated based on voltammetric parameters and was found to be 4.3. This study demonstrates that electrochemistry at the liquid – liquid interface is powerful technique when it comes to electroanalytical or pharmacokinetic drug assessment.

1. Introduction

Electrochemistry at the liquid – liquid interface or the interface between two immiscible electrolyte solutions (ITIES) is considered as a biomimetic approach [\[1,2\].](#page--1-0) This is due to discontinued properties of the liquid – liquid interface that find analogy to lipid membranes in contact with aqueous solutions. Another similarity lies in the ionic transport. ITIES allows studying interfacial ion transfer reactions, as this gives rise to an electric current that can be quantified via a number of electrochemical techniques, including ion transfer voltammetry. Detection – that is not restricted to oxidation and reduction reactions – allows straightforward and direct molecular sensing, which is not always feasible with conventional, solid-state electrodes. Examples include a broad class of molecules containing a quaternary ammonium group (e.g., ionic drugs [\[3\]](#page--1-1)) or illicit amphetamine drugs, which are inactive at a glassy carbon electrode $[4]$, but do give a signal at the ITIES $[5,6]$. Furthermore, a list of analytes detectable at electrified liquid – liquid interfaces span of a different class of molecular species. For example, macromolecules, such as dendrimers [\[7,8\],](#page--1-4) polyelectrolytes [\[9,10,11\]](#page--1-5) and proteins [\[12,13\]](#page--1-6) were found to give a characteristic voltammetric behavior indicating interfacial adsorption processes [\[7,14,15\].](#page--1-4) Direct electrochemical detection of alkali and alkaline earth metals from aqueous solutions is also possible [\[16\].](#page--1-7) A commonly used methodology involves hydrophobic ionophores dissolved in the organic phase [\[17,18,19\].](#page--1-8) The presence of ionophores lowers the standard Gibbs energy of ion transfer from one phase to the other, which is of ultimate interest since alkali and alkaline earth cation transfers are usually hindered by a potential window limiting current or is beyond the available potential window. Ionophores were also used for the detection of inorganic anions, as in the work by Kivlehan et al. where a ureacalix [\[4\]](#page--1-2)arene was used for phosphate sensing [\[20\].](#page--1-9) A lot of attention was given to the interfacial behavior of bio- and bio-relevant molecules as described in a comprehensive review by Arrigan et al. [\[21\]](#page--1-10).

Besides sensing, electrochemistry at the ITIES plays an increasingly prominent role in pharmacokinetics, especially when it comes to the evaluation of partitioning coefficients (P, expressed as logP). Such an approach was for the first time proposed by Kontturi and Murtomäki [\[22\]](#page--1-11) and further developed by others [\[23,24,25\]](#page--1-12). As octanol, typically used as a hydrophobic phase, is inappropriate for electrochemical measurements, other solvents like 1,2–dichloroethane (DCE), orthonitrophenyl n-octyl ether (oNPOE) and nitrobenzene (NB) were used [\[26\]](#page--1-13). Besides being fast, accurate and relatively easy, current state-of-

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<http://dx.doi.org/10.1016/j.jelechem.2017.04.051>

Received 2 February 2017; Received in revised form 3 April 2017; Accepted 26 April 2017 Available online 03 May 2017 1572-6657/ © 2017 Elsevier B.V. All rights reserved.

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the-art highlights the advantages of the ITIES over other conventionally used methods for logP determination (e.g., shake flask or HPLC measurements): (i) Pharmacological activity of drugs is directly related to its lipophilicity as is the half-wave potential of the ion transfer reaction [\[24\]](#page--1-14). (ii) Partition of ionic drugs (containing ionizable functional group) as function of pH can be readily established in a form of so-called Pourbaix-like pH – Galvani potential difference diagrams [\[27,28\].](#page--1-15) (iii) According to the Nernst-like equation for ion transfer reaction [\[29\],](#page--1-16) ion (e.g., a charged drug) distribution across two immiscible phases (or lipid bilayer contacted with aqueous fluids by analogy) is Galvani-potential dependent and easily measurable with electrochemistry.

The $logP_{DCE}$ available from electrochemical experiments can be correlated with the $logP_{octanol}$ [\[22\]](#page--1-11). Interestingly, two good linear correlations were found: (1) for drugs being able to form hydrogen bonds and (2) for drugs without hydrogen-bond formation ability. In recent work, Nakamura and Osakai studied the interfacial behavior of nine drugs containing amine groups [\[30\].](#page--1-17) $logP_{\text{octanol}}$ and $logP_{\text{PAMPA}}$ (parallel artificial membrane permeation test) were correlated with the standard Galvani potential of ion transfer ($\Delta_{org}^{aq} \phi_i^0 \propto \log \! P_{\textrm{DCE}}^{i}$) as well as the distribution constant (K_D) of its neutral equivalent. Once again, some deviations from $logP_{octanol} \propto logP_{DCE}$ ⁱ were attributed to the presence of hydroxyl groups being able to form hydrogen bonds. On the other hand, good correlation between $\Delta_{org}^{aq} \phi_i^0$ and $\log \! P_{\text{PAMPA}}$ suggested that DCE gives better representation of the nonpolar part of lipid bilayers as compared with the octanol.

Drugs and other molecules containing a quaternary ammonium functionality play an important role in neuromuscular blocking and transmission [\[31\]](#page--1-18). Some of these drugs interact with acetylcholine receptors, which results in a deficiency of their functioning – the action of utmost interest for anesthesia. Potential candidates for neuromuscular blocking need to be characterized in terms of (i) duration of action; (ii) time of onset; (iii) built-in, self-destruction mechanism, and (iv) possible side effects. In other words, the link between physiology and pharmacology has to be addressed and the electrochemistry at the liquid – liquid interface is a potential method in this regard. In this study, we have investigated the electrochemical behavior of quaternary ammonium drugs (zwitter-ionic acetylcarnitine, bi-cationic succinylcholine and tri-cationic gallamine) at the water – 1,2-dichloroethae (DCE) interface. In [Section 3.1](#page--1-19) we present and discuss $logP_{DCE}$ values calculated based on the standard ion transfer potential. Next, these $logP_{DCE}$ values were correlated with calculated $logP_{octanol}$ data. In [Section 3.2](#page--1-20) the effect of molecular charge on the electroanalytical properties (sensitivity and limit of detection (LOD)) is evaluated and discussed. In [Section 3.3](#page--1-21) we report on the calculation of the acid dissociation constant for carboxylic group of acetylcarnitine based on diffusion coefficient values measured at pH below and above its pK_a .

2. Experimental section

2.1. Chemicals

Potassium tetrakis(4-chlorophenyl)borate (KTPBCl, Sigma-Aldrich, 98%) and bis(triphenylphosphoranylidene)ammonium chloride (BT-PPACl, Sigma-Aldrich, 97%) were used to prepare the organic phase electrolyte bis(triphenylphosphoranylidene)ammonium tetrakis(4 chlorophenyl)borate (BTPPATPBCl) via a simple metathesis reaction according to the protocol published elsewhere [\[27\].](#page--1-15) The aqueous phase electrolyte was sodium chloride (NaCl, Sigma Aldrich, ≥99%). Studied ions: tetramethylammonium chloride (TMACl, purity, 97%), O-Acetyl-L-carnitine hydrochloride (ACHCl, ≥99%), succinylcholine chloride dihydrate (SCCl₂, 98–102%) and gallamine triethiodide (GAl₃, \geq 99%) were all purchased from Sigma Aldrich. The pH of the aqueous phase was adjusted with 1 M HCl. Ag/AgCl reference electrodes were made via potentiostatic silver oxidation in a 1 M HCl solution.

2.2. Electrochemistry at ITIES

All measurements were performed in a four-electrode glass cell with an interface having a surface area equal to 1.13 cm^2 . The cell configuration was as follows:

The reference electrodes were Ag/AgCl immersed into the Luggin capillaries of each phase. The organic phase reference electrode was immersed into the aqueous supporting electrolyte containing NaCl and BTPPA⁺ (Cl[−] was the counter-ion) as the common ion with the organic phase, which resulted in the formation of the unpolarised interface [\[29\]](#page--1-16). Counter electrodes were coiled Pt wires ($\varnothing = 2$ mm, \sim 6 cm in length). The organic phase counter electrode was additionally embedded in the glass capillary in order to avoid the short circuit with the aqueous phase. The potential difference across the water∥1,2-dichloroethane interface was controlled with an Autolab potentiostat PGSTA-T302N. Voltammograms used to measure the half-wave potential of ion transfer $(E_i^{1/2})$ were calibrated according to:

$$
\Delta E = \Delta_{org}^{aq} \phi + \Delta_{org}^{aq} \phi_{TMA^+}^{0}
$$
\n(2.1)

The ΔE is the potential difference measured between the reference electrodes in the aqueous and the organic phase. The $\Delta_{org}^{aq}\phi$, is the Galvani potential difference across water/DCE interface. The $\Delta_{org}^{aq} \phi_{TMA}$ ⁰ is the reference potential equal to the standard potential of the ion transfer for TMA⁺ $(\Delta_{org}^{aq} \phi_{TMA+}^{0}) = 160$ mV) [\[2,32\].](#page--1-22) [Fig. 1](#page-1-0) shows a blank voltammogram calibrated according to Eq. [\(2.1\)](#page-1-1). Three characteristic regions can be distinguish here: (b) potential window that is determined by (a and c) potential window limiting currents.

Fig. 1. Blank cyclic voltammogram recorded at the ITIES composed from a 10 mM NaCl (aq, blue, top) and a 10 mM organic electrolyte (org, orange, bottom). The forward scan was from a less positive to a more positive potential. The scan rate was 10 mV/s. See [Cell I](#page-1-2) $(X = 0$ mM) for detail on the configuration of the cell. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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