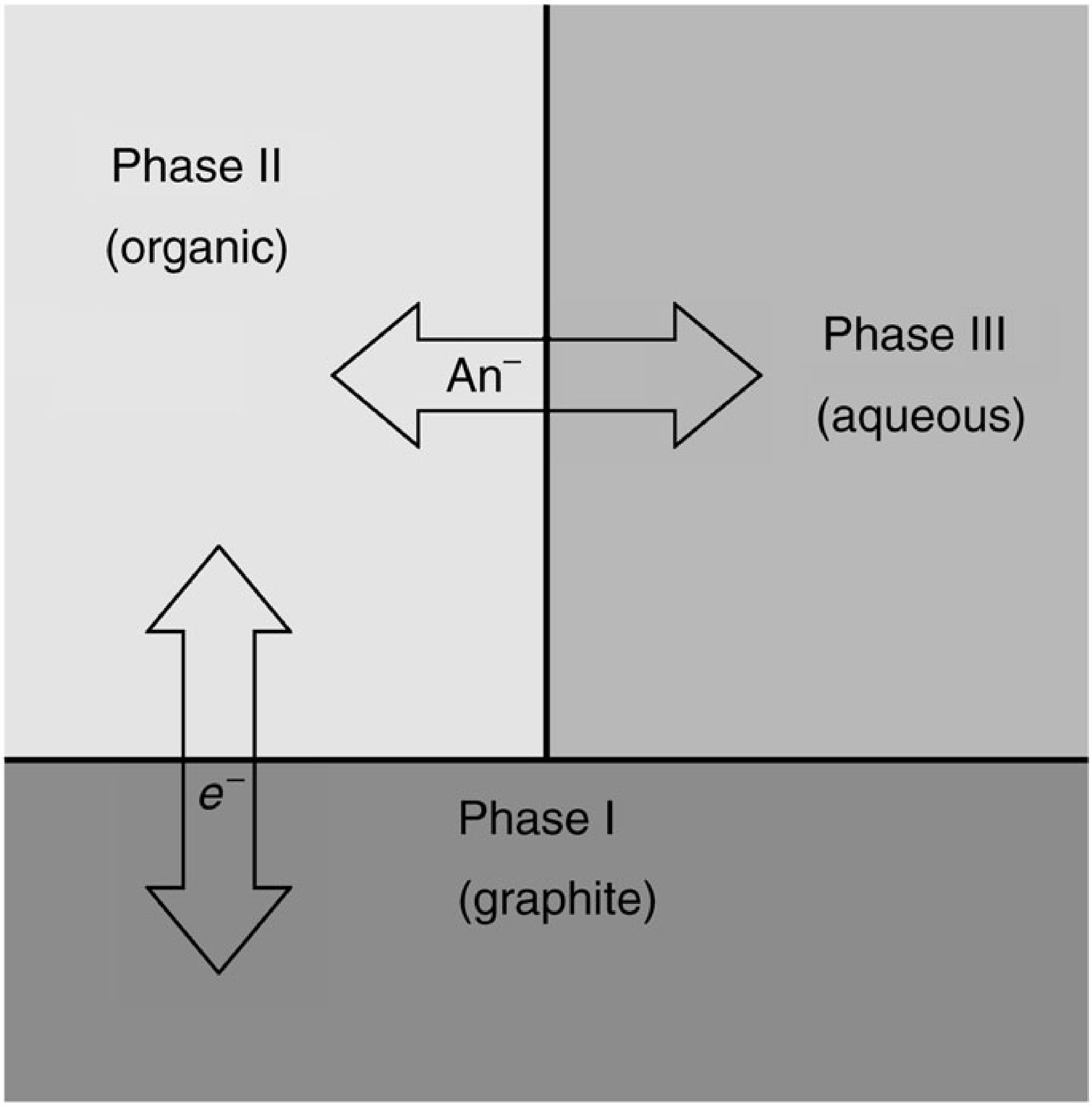
A redox probe in phase II drives the ion transfer between phase II and phase III:



Three-phase electrode

$$\mathrm{Red}_{(\text{phase II})} + \mathrm{An}^-_{(\text{phase III})} \leftrightarrows \mathrm{Ox}^+_{(\text{phase II})} + \mathrm{An}^-_{(\text{phase II})} + e^-$$

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Determining the Gibbs Energy of Ion Transfer Across Water–Organic Liquid Interfaces with Three-Phase Electrodes

Fritz Scholz* and Rubin Gulaboski[a]

Ions can be transferred between immiscible liquid phases across a common interface, with the help of a three-electrode potentiostat, when one phase is an organic droplet attached to a solid electrode and containing a redox probe. This novel approach has been used in studies to determine the Gibbs energy of anion and cation transfer, ranging from simple inorganic and organic ions to the ionic forms of drugs and small peptides. This method of studying ion transfer has the following advantages: 1) no base electrolytes are necessary in the organic phase; 2) the aqueous phase contains only the salt to be studied; 3) a three-electrode potentiostat is used; 4) organic solvents such as n-octanol *and chiral liquids such as* D- *and* L-*2-octanol can be used; 5) the range of accessible Gibbs energies of transfer is wider than in the classic 4-electrode experiments; 6) the volume of the organic phase can be very small, for example, 1 μL or less; 7) the experiments can be performed routinely and fast. Herein, the basic principle is outlined, as well as a summary of the results obtained to date, and a discussion on the theoretical treatments concerning the kinetic regime of the three-phase electrodes with immobilized droplets.*

1. Introduction

The lipophilicity of a compound is its affinity toward apolar solvents, whereas its hydrophilicity describes its affinity toward the polar solvent water. The higher the lipophilicity of a compound is, the better its solubility in organic solvents, such as benzene and paraffin oils. Lipo- and hydrophilicity are two sides of one coin; that is, they are complementary properties. Because in all living cells and higher biological structures there are hydrophilic and lipophilic compartments in close proximity, and because the chemical compounds in these systems have to cross these different parts, for example, lipophilic membranes, the lipophilicity of a compound decides—to a great extent—its distribution, transport, metabolism, toxicity, and thus its biological activity. Although many other and much more specific factors are also involved, a compound's lipophilicity is recognized as one of the most important properties for understanding their role in living systems. The common method of assessing the lipophilicity of a compound is to determine its *partition coefficient* in a two-solvent system using water as one solvent and an organic, rather apolar solvent as the other. *n*-Octanol was once proposed as the standard organic solvent because, although being reasonably apolar due to its C_8-tail, it still has a polar head group.[1] Thus, the *n*-octanol molecule has similarities with lecithins, the major constituents of biological membranes. The *n*-octanol/water partition coefficient, the so-called K_{OW}, is routinely determined for all potential pharmaceuticals[1,2a] and is also used to assess the environmental impact of a compound.[2b] These data are accessible from simple shake-flask partition experiments. To avoid these labor-intensive determinations, high performance liquid chromatography (HPLC) is routinely used, and empirical correlations between retention data for compounds on specific columns with the *n*-octanol/water data allow the calculation of K_{OW} for new compounds.[2a] For ionic species, the assessment of their lipophilicities is more complex because the partition of the counterions must always be taken into account, and the distribution data of single ionic species have to rely on an extra-thermodynamic assumption. Very early, Grunwald et al. proposed the assumption that the Gibbs energy of transfer of tetraphenylarsonium cations and tetraphenylborate anions are equal.[3] Later, other systems have been proposed, but the Grunwald assumption is still the most frequently accepted. In principle, the partition coefficient of an ion, that is, its Gibbs energy of transfer, is accessible in the same way as that of a neutral compound. However, since ions posses a charge, electrochemical techniques lend themselves to this purpose. A conscious description of the evolution of ideas leading to the present understanding of the potential difference at the liquid–liquid interface of two immiscible electrolyte solutions has been given by Girault and Schiffrin.[4] Based on the experiments of Beutner,[5a] Leonor Michaelis, a pioneer of enzyme kinetics, gave, in 1922, a lucid description of the interfacial potential (*Phasengrenzpotentiale*) at a liquid–liquid interface, and an ordering of ions according to their lipophilicities.[5b] Following the first experiments of Nernst and Riesenfeld with liquid–liquid interfaces published in 1902,[6] it took almost 70 years before Guastella and others undertook four-electrode measurements at such interfaces.[7,8] In the last three decades of the 20th century, voltammetric as well as other electrochemical techniques have been applied to study the interface between

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two immiscible electrolyte solutions (ITIES) and determine the partition coefficient of ions. These achievements are associated with the names of Koryta,[9] Girault and Shiffrin,[4] Samec,[10] Vanysek,[11] Marecek,[12] Kakiuchi,[13] and Hundhammer,[14] and they are reviewed in various places.[15,16] All these studies are based on polarizing the ITIES with the help of a four-electrode potentiostat using cells as depicted in Figure 1. This technique allowed, for the first time, polarization measurements at an ITIES to be performed, and led to most significant advances in the understanding of liquid–liquid interfaces.[16,17] However, four-electrode potentiostatic measurements at ITIES are not as simple to perform as three-electrode potentiostatic measurements at metal–electrolyte solution interfaces. The handling of the cell needs skill and experience. To give an example, keeping the interface in a stable position with respect to the two Luggin capillaries approaching the interface from both sides, needs special attention. Despite these experimental difficulties, which kept the technique confined to use by specialists, there are other more serious obstacles involved: 1) The necessity to have foreign electrolytes in *both* solvents severely limits the range of accessible potentials; 2) The number of organic solvents for which suitable electrolytes could be found to polarize the interface with an aqueous solution is rather small. Thus it is a real misfortune that *n*-octanol could not be used in ITIES experiments because, to date, no suitable base electrolyte has been found that would allow to polarize the interface with an aqueous solution; 3) For most cells, the necessary volume of the organic solvent is rather large, preventing the use of expensive solvents.

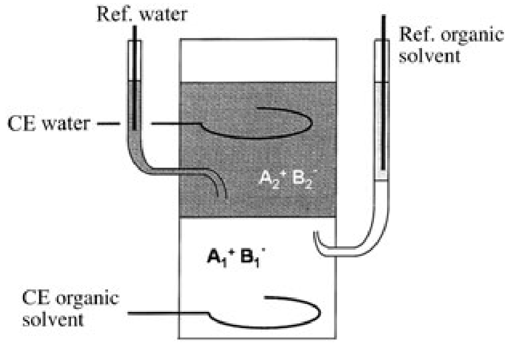

Figure 1. *Representation of the arrangement used in four-electrode voltammetric measurements at ITIES; Ref. = reference electrode, CE = counter electrode. $A_1^+B_1^-$ is a highly hydrophilic salt and $A_2^+B_2^-$ is a highly lipophilic salt.*

Fritz Scholz was born in 1955 and studied chemistry at the Humboldt University, Berlin, where he received a Diploma in 1978, his Ph.D. in 1982, and finished his habilitation in 1987. At the Humboldt University he held the position of a Dozent from 1989 to 1993 and of a Professor from 1993 to 1998. Since 1998 he is Professor at the University of Greifswald. In 1987 and 1989 he worked with Alan M. Bond in Australia. Beside various contributions to electroanalysis, he developed a new kind of mercury flow-through electrodes (bubble electrodes), established the voltammetry of immobilized particles as a technique to study the electrochemistry of solid compounds, and invented a method to measure Gibbs energies of ion transfer with the help of three-phase electrodes. His scientific achievements have been published in more than 200 papers and two books. He founded the *Journal of Solid State Electrochemistry* and serves as its Editor-in-Chief since 1987. His current scientific interests are focused on three-phase electrodes, electrochemical transformations of solid particles, new pH-sensors, bioelectrochemical fuel cells, and the interaction of suspended liposomes and clay particles with electrodes.

Rubin Gulaboski, born in 1972 in Prilep, Macedonia, studied chemistry at the St. Kiril i Metodoij University, Skopje, where he received the title of Graduate Engineer in Chemistry, and later a M.Sci. in Chemistry. He was the first Macedonian student to be awarded a DAAD fellowship to perform Ph.D. studies in Germany. He joined the group of Fritz Scholz in 2001. In 2004 he received his Ph.D. from the University of Greifswald. Currently, he holds a postdoc position at the University of Porto, Portugal. He is co-author of 30 papers and one book.

In the last four years, a new, rather revolutionary approach for performing an electrochemically driven phase-transfer of ions has been developed that uses a three-electrode potentiostat. This is possible when a three-phase electrode is used where an electron transfer proceeds coupled to an ion transfer. This Review is aimed at outlining the basic principle of such measurements and summarizing the results obtained so far. Eventually, we will discuss the future prospects of the method.

2. Three-Phase Electrodes

Electrodes with three phases participating actively in an electrode reaction are very common. Each of the three phases must share an interface with *both* other phases. This situation exists in most of the so-called surface-modified or film electrodes, many battery and fuel cell electrodes, and electrodes of the second kind. In fact, the majority of surface-modified electrodes have arrays of particles that partially cover the electrode surface. Instead of attaching particles to the surface of an electrode, droplets of a water-immiscible liquid can also be attached. Figure 2 depicts the situation at a three-phase electrode; phase II is a droplet or a particle. Since the particle or droplet contains neutral molecules and ions with equal amounts of positive and negative charges, any electron transfer between phase I and II must be accompanied by an ion transfer between phases II and III. The ion transfer is an indispensable reaction for maintaining the electroneutrality of phase II, provid-

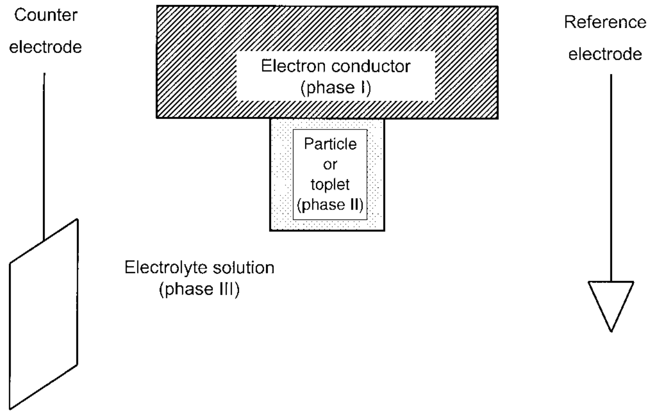

Figure 2. *Schematic drawing of a three-electrode cell with a working electrode on a surface to which a particle or a droplet is attached (reproduced from ref. [54]).*

ed that phase II does not only pass the electrons on from phase I to a redox species in solution. The latter may happen in systems where the droplets (or particles) exhibit electrocatalytic activity. It is a most important feature of the three-phase electrode with immobilized electroactive droplets or particles that the *electron* and *ion* transfer must take place simultaneously at one electrode (compare with Figure 3). The electron transfer between phase I and II can be disregarded only when phase II is a metal to be oxidized because then both phases are metals.[1] Three-phase electrodes are very well-known as rechargeable electrodes in batteries, where phase II is a redox-active phase, capable of housing charge compensating ions exchanged with an adjacent solution. The observed electrochemistry is called “insertion electrochemistry” since ions are inserted and expelled parallel to the electron exchange. A very similar electrochemistry can be arranged when phase II is a droplet of an organic solvent containing a redox active compound, or when the liquid organic phase II is itself electroactive. Thermodynamically speaking, the three-*phase* electrode comprising phase II possessing redox centers and ion conductivity, is a *double electrode* (the German expression is *zweifache Elektrode*[18]). The formal thermodynamic analysis of a three-phase electrode is rather simple: One can split an overall equilibrium equation, Equation (1):

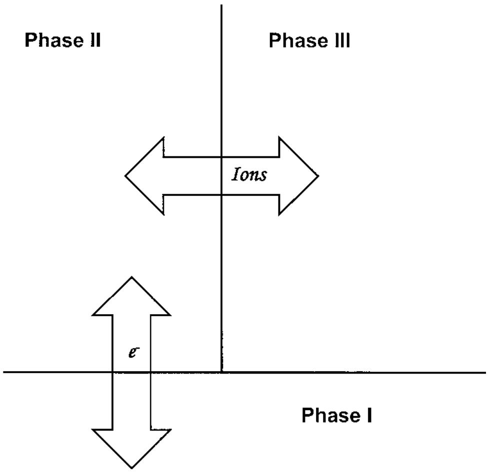

Figure 3. *Scheme of the simultaneous electron and ion transfer at a three-phase electrode (reproduced from ref. [54]).*

$$\mathrm{Ox}^{x+}_{\text{phase II}} + ne^{-}_{\text{phase I}} + n\mathrm{Cat}^{+}_{\text{phase III}} \rightleftharpoons \mathrm{Red}^{(x-n)+}_{\text{phase II}} + n\mathrm{Cat}^{+}_{\text{phase II}} \tag{1}$$

with the Nernst equation, Equation (2):

$$E = E^{\ominus}_{\mathrm{Ox/Red/Cat}} + \frac{RT}{nF}\ln\frac{a_{\mathrm{Ox}^{x+}_{\text{phase II}}}\, a^{n}_{\mathrm{Cat}^{+}_{\text{phase III}}}}{a_{\mathrm{Red}^{(x-n)+}_{\text{phase II}}}\, a^{n}_{\mathrm{Cat}^{+}_{\text{phase II}}}} \tag{2}$$

into two equilibria, one involving the transfer of electrons, Equation (2a):

$$\mathrm{Ox}^{x+}_{\text{phase II}} + ne^{-}_{\text{phase I}} \rightleftharpoons \mathrm{Red}^{(x-n)+}_{\text{phase II}} \tag{2a}$$

and one involving the transfer of ions, Equation (2b):

$$\mathrm{Cat}^{+}_{\text{phase III}} \rightleftharpoons \mathrm{Cat}^{+}_{\text{phase II}} \tag{2b}$$

with the following Nernst equations, Equations (3) and (4):

$$E_{\mathrm{I/II}} = E^{\ominus}_{\mathrm{Ox/Red}} + \frac{RT}{nF}\ln\frac{a_{\mathrm{Ox}^{x+}_{\text{phase II}}}}{a_{\mathrm{Red}^{(x-n)+}_{\text{phase II}}}} \tag{3}$$

$$E_{\mathrm{II/III}} = E^{\ominus}_{\mathrm{Cat}} + \frac{RT}{F}\ln\frac{a_{\mathrm{Cat}^{+}_{\text{phase III}}}}{a_{\mathrm{Cat}^{+}_{\text{phase II}}}} \tag{4}$$

The standard potentials are interrelated by Equation (5):

$$E^{\ominus}_{\mathrm{Ox/Red/Cat}} = E^{\ominus}_{\mathrm{Ox/Red}} + E^{\ominus}_{\mathrm{Cat}} \tag{5}$$

Equations (2a) and (2b) both represent *electrochemical* equilibria, since a transfer of charged species between two phases takes place. When phase II is a solid, it is not yet clear how the activities of the species Ox, Red, and Cat^{+} in the solid have to be defined and how they could be determined. Furthermore, experimentally, a separation of the free energies of the reactions given by Equations (2a) and (2b) is not possible in the case of solids (because of the inaccessibility of single Galvani potential differences). When phase II is a solution phase, the activities of Ox, Red, and C^{+} are in principle accessible, however, it remains that an extra-thermodynamic assumption is necessary in order to quantify the free energy of ion transfer between the liquid phases II and III.

Figure 4 illustrates the situation in which an electroactive compound dissolved in a droplet of an organic solvent is oxi-

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[1] *When a metal particle, for example, silver, attached to a gold electrode is anodically oxidized, the ion transfer is the transfer of* Ag^{+} *ions from the metal to the solution and the electron transfer occurs between gold and silver. Such electron transfer between electronically conducting phases will, of course, always occur in electrochemistry, because any electrode needs another conductor at its terminal. It should be remembered that the interfacial potentials that build up between the electrodes and its terminal conducting connectors are responsible for the inaccessibility of single electrode potentials.*

dized, accompanied by a simultaneous ion transfer between the aqueous environment of the droplet and the organic phase. In Figure 4, it is assumed that a neutral electroactive compound is dissolved in the organic phase of the attached droplet. This compound Red can be oxidized to Ox^+. The oxidation is accompanied by a charge compensating transfer of anions An^- from the aqueous solution to the organic droplet. Reduction of Ox^+ will reverse the ion transfer. When the droplet does not contain any deliberately added electrolyte, its initial conductivity is very low and the entire electrode reaction can start only at the three-phase junction, that is, the line surrounding the droplet, since only near to that line will the interface graphite|organic phase attain the applied potential to drive the reaction given by Equation (1), at least as long as the ionic conductivity of the droplet is very low. Figure 5 depicts the potential drop at such a three-phase electrode. The potential drop $\Delta\phi_{graph|aq}$ at the aqueous solution|graphite interface is as adjusted by the potentiostat, however, the potential drop $\Delta\phi_{graph|org}$ at the interface graphite|organic solution is $\Delta\phi_{graph|aq}$ diminished by the potential drop $\Delta\phi_{aq|org}$ at the organic solution|aqueous solution interface and by the ohmic drop ΔU_{ohmic} inside the organic phase, Equation (6):

$$\Delta\phi_{graph|org} = \Delta\phi_{graph|aq} - \Delta U_{ohmic} - \Delta\phi_{aq|org} \tag{6}$$

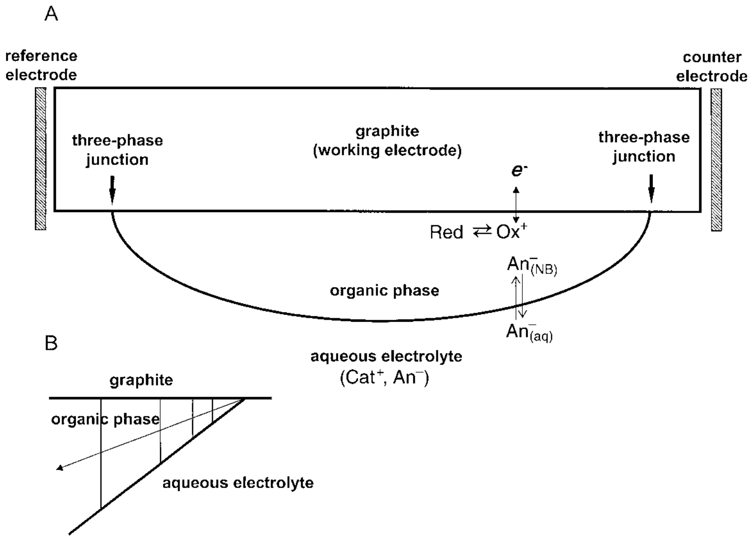

Figure 4. A) Schematic representation of the situation in which an organic droplet contains an electroactive species Red, which is oxidized to Ox^+ accompanied by the transfer of anions An^- from an aqueous electrolyte solution to the organic phase. B) Shows how the reaction products Ox^+ and An^- spread from the three-phase junction into the droplet, creating an ionic conductivity in the organic phase (reproduced from ref. [54]).

The three-phase junction line is a unique feature of the three-phase electrode. It is a one-dimensional entity at which the organic liquid, the aqueous electrolyte, and the working electrode are in intimate contact. At the electrode–aqueous solution interface, as well as along the three-phase junction line, an electric double layer is created, providing an abrupt potential drop that is able to drive the electron-transfer reaction. However, it is only along the three-phase junction line that: 1) The organic phase provides the material to be transformed electrochemically; and 2) The aqueous phase provides the necessary counter ions. Thus, it is understandable that the electrochemical reaction commences along the three-phase junction and proceeds later on in the course of the voltammetric experiment, without any significant constrains, into the interior of the droplet.

3. Three-Phase Electrodes with an Immobilized Droplet of a Dissolved Electroactive Compound

According to the scenario depicted in Figure 4, the overall reaction proceeding at a droplet-modified electrode can be written by Equation (7):

$$Red_{(o)} + An^-_{(aq)} \rightleftharpoons Ox^+_{(o)} + An^-_{(o)} + e^- \tag{7}$$

If no kinetic constrains exist with respect to the electron and ion transfer, the thermodynamic treatment applied to the reaction described by Equation (7) leads to Equation (8), a form of the Nernst equation:

$$E = E^{\ominus}_{Ox^+_{(o)}/Red_{(o)}} + \Delta\phi^{o\ominus}_{aq,An^-} + \frac{RT}{F}\ln\frac{a_{Ox^+_{(o)}}\,a_{An^-_{(o)}}}{a_{Red_{(o)}}\,a_{An^-_{(aq)}}} \tag{8}$$

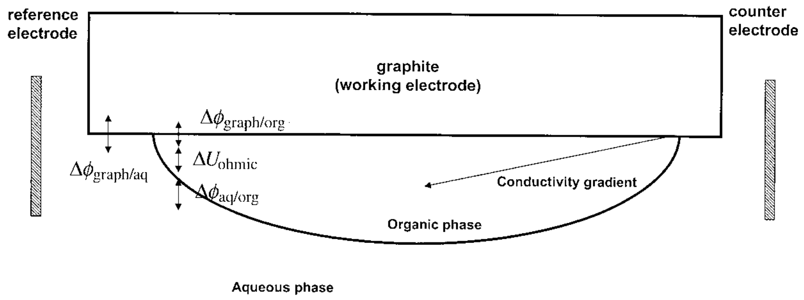

Figure 5. Potential drops at the different interfaces of a three-phase electrode with an immobilized droplet of an organic solvent immersed in an aqueous solution (reproduced from ref. [55]).

In Equation (8) E is the applied potential between the working and the reference electrodes, $E^{\ominus}_{\mathrm{Ox}^+_{(o)}/\mathrm{Red}_{(o)}}$ is the standard redox potential of the redox couple $\mathrm{Ox}^+/\mathrm{Red}$ in the organic solvent, $\Delta\phi^{o\ominus}_{\mathrm{aq,An^-}}$ is the standard potential of transfer of anions from the aqueous phase to the organic phase, $a_{\mathrm{Ox}^+_{(o)}}$ and $a_{\mathrm{Red}_{(o)}}$ are the activities of the oxidized and reduced forms, respectively, of the electroactive compound in the organic phase; $a_{\mathrm{An}^-_{(o)}}$ and $a_{\mathrm{An}^-_{(aq)}}$ are the activities of anions in the organic phase and in the aqueous solution, respectively. To a first approximation, the activities in the Nernst equation can be replaced by concentrations. Since the concentration of the anions in the aqueous phase is kept in great excess of $c_{\mathrm{Red}_{(o)}}$, it does not change significantly during the experiment, and Equation (8) can be rewritten as Equation (9):

$$E = E^{\ominus}_{\mathrm{Ox}^+_{(o)}/\mathrm{Red}_{(o)}} + \Delta\phi^{o\ominus}_{\mathrm{aq,An^-}} - \frac{RT}{F}\ln c_{\mathrm{An}^-_{(aq)}} + \frac{RT}{F}\ln\frac{c_{\mathrm{Ox}^+_{(o)}}\,c_{\mathrm{An}^-_{(o)}}}{c_{\mathrm{Red}_{(o)}}} \tag{9}$$

Due to the requirements of electroneutrality of the organic phase, Equation (10) holds:

$$c_{\mathrm{Ox}^+_{(o)}} = c_{\mathrm{An}^-_{(o)}} \tag{10}$$

The mass conservation law with respect to the organic phase leads to Equation (11)

$$c_{\mathrm{Red}_{(o)}} + c_{\mathrm{Ox}^+_{(o)}} = c^*{}_{\mathrm{Red}_{(o)}} \tag{11}$$

where $c^*{}_{\mathrm{Red}_{(o)}}$ is the initial concentration of the oxidizable compound in the organic phase. When the applied potential is equal to the formal potential of the redox pair in the organic solvent, we have Equation (12):

$$c_{\mathrm{Red}_{(o)}} = c_{\mathrm{Ox}^+_{(o)}} \tag{12}$$

By substituting Equations (10)–(12) into Equation (9), the equation for the formal potential $E_c^{\ominus\prime}$ of the system, Equation (13) is obtained:

$$E_c^{\ominus\prime} = E^{\ominus}_{\mathrm{Ox}^+_{(o)}/\mathrm{Red}_{(o)}} + \Delta\phi^{o\ominus}_{\mathrm{aq,An^-}} - \frac{RT}{F}\ln c_{\mathrm{An}^-_{(aq)}} + \frac{RT}{F}\ln\frac{c^*{}_{\mathrm{Red}_{(o)}}}{2} \tag{13}$$

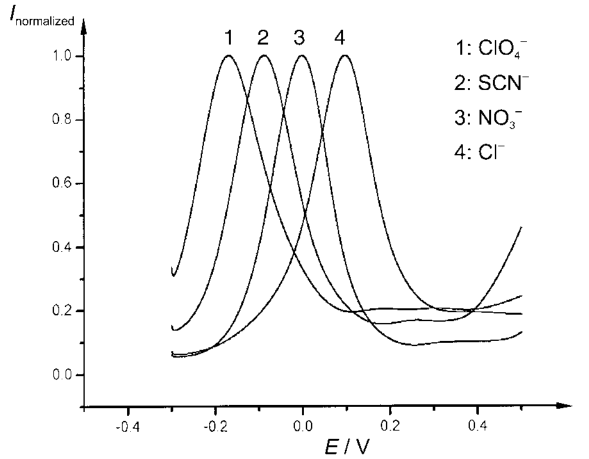

Figure 6. *Normalized square-wave voltammograms recorded at droplet-modified electrodes with dmfc dissolved in nitrobenzene (0.1 mol L^{-1}) and immersed in 1 mol L^{-1} aqueous solutions of different sodium salts. The instrumental parameters were: frequency (f), 100 Hz; amplitude (E_{sw}), 50 mV; scan increment (dE), 0.15 mV (reproduced from ref. [54]).*

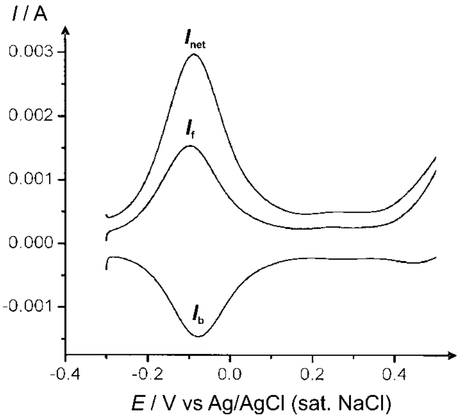

Figure 7. *Forward (I_f), backward (I_b), and net (I_{net}) current components of the square-wave voltammetric response of a nitrobenzene droplet containing 0.1 mol L^{-1} dmfc attached to the surface of the working electrode and immersed in a 1 mol L^{-1} aqueous solution containing SCN^- anions. The experimental conditions were: frequency f = 100 Hz; amplitude E_{sw} = 50 mV; and scan increment dE = 0.15 mV (reproduced from ref. [27]).*

Since the voltammetric systems measured in such experiments possess all features of electrochemical reversibility and the transfer coefficients can be assumed to be near to 0.5 (see later Figure 7), it is reasonable to take the mid-peak potentials of cyclic voltammograms as the formal potential of the system. The deviations expected due to the diffusion coefficients of the involved species can also be neglected, at least to a first approximation (compare with refs. [21,61]). Equation (13) shows that the formal potential of the voltammograms that portray the coupled electron and ion transfer processes occurring at the three-phase electrode depends on the *nature of the anions in the aqueous phase* via the values of $\Delta\phi^{o\ominus}_{\mathrm{aq,An^-}}$. Generally, the more lipophilic the anions are, the more negative is $\Delta\phi^{o\ominus}_{\mathrm{aq,An^-}}$. Consequently, the oxidation of the compound Red in the organic phase will be shifted to more negative potentials when the lipophilicity of the transferable anions increases. Furthermore, for a ten-fold increase in the activity of anions in the aqueous phase, the formal potential must shift by about 59 mV in the negative direction. This criterion, taken together with the stability of the voltammograms recorded during consecutive cycling, is a good proof that the electrode reaction proceeds according to Equation (7).

When an *electroreducible* compound is dissolved in the organic phase, its reduction at a three-phase electrode will provoke the transfer of cations from the aqueous to the organic phase, Equation (14):

$$\mathrm{Ox}_{(o)} + \mathrm{Cat}^+_{(aq)} + e^- \rightleftharpoons \mathrm{Red}^-_{(o)} + \mathrm{Cat}^+_{(o)} \tag{14}$$

Analogous to the previous case, a thermodynamic treatment of the reaction given in Equation (14) leads to the following form of the Nernst equation, Equation (15), which is valid when cations are transferred from the aqueous to the organic phase:

$$E_c^{\ominus\prime} = E^{\ominus}_{\mathrm{Ox}_{(o)}/\mathrm{Red}^-_{(o)}} + \Delta\phi^{o\ominus}_{\mathrm{aq,Cat}^+} + \frac{RT}{F}\ln c_{\mathrm{Cat}^+_{(aq)}} + \frac{RT}{F}\ln\frac{2}{c^*_{\mathrm{Ox}_{(o)}}} \tag{15}$$

The more lipophilic the cations in the aqueous phase are, the more *positive* will be the value of $\Delta\phi^{o\ominus}_{\mathrm{aq,Cat}^+}$. Consequently, the reduction of the organic compound Ox in the oil phase will occur at more positive potentials as the lipophilicity of the cations in the aqueous phase increases. The formal potential of the coupled electron/ion reaction at a three-phase electrode will shift 59 mV in the positive direction for a ten-fold increase in the concentration of the transferable cations in aqueous solution.

To apply Equations (13) and (15) to the determination of the standard potentials of anion and cation transfer, respectively, in both cases the values of the standard redox potentials $E^{\ominus}_{\mathrm{Ox}_{(o)}/\mathrm{Red}_{(o)}}$ of the redox couples in the organic phase must be known. They can be obtained either by measurements in a conventional, nonaqueous, three-electrode cell in the presence of an internal reference standard, or, alternatively, $E^{\ominus}_{\mathrm{Ox}_{(o)}/\mathrm{Red}_{(o)}}$ can be determined from the intercept of the dependence of peak potentials of the voltammetric responses recorded with three-phase electrodes versus known standard ion transfer potentials.

3.1. The Transfer of Anions at Three-Phase Electrodes

To achieve a transfer of anions across the liquid|liquid interface at a three-phase electrode, one needs a neutral lipophilic organic compound dissolved in an organic solvent[2]. This compound must be reversibly oxidizable. A very suitable compound possessing all these properties is decamethylferrocene (dmfc), that is, bis(pentamethylcyclopentadienyl)iron(II). It is a very lipophilic compound, highly soluble in various organic solvents, but almost insoluble in water.[19] It undergoes a one-electron electrochemically reversible redox reaction in many organic solvents and it is commonly used as a reference standard for measurements performed in nonaqueous media. The oxidation of dmfc in a nitrobenzene (NB) solution attached as a droplet to the working electrode and immersed in aqueous solutions of different sodium salts gives rise to well-defined square-wave voltammograms, the peak potentials of which are sensitive to the nature and the concentration of the anions present in the aqueous solutions (see Figure 6). The overall electrode reaction of dmfc at the three-phase electrode is given by Equation (16)

$$\mathrm{dmfc}_{(NB)} + \mathrm{An}^-_{(aq)} \rightleftharpoons \mathrm{dmfc}^+_{(NB)} + \mathrm{An}^-_{(NB)} + e^- \tag{16}$$

The dependence of the formal potentials of the square-wave voltammograms on the standard potentials of transfer of the anions from water to nitrobenzene is linear and characterized by a slope of 0.95 and an intercept of −0.259 mV (see Figure 2 in ref. [27]). The slope of this dependence is almost one, as predicted by Equation (13). From the intercept of this dependence, one can evaluate the standard redox potential of the couple dmfc$^+$/dmfc in NB as −0.184 V (versus Ag/AgCl, saturated KCl). According to Equation (13), by knowing the value of the standard redox potential of dmfc$^+$/dmfc, and by studying the oxidation of dmfc dissolved in an organic solvent at a droplet-modified electrode which is immersed in different aqueous solutions, one is able to estimate the standard potential of transfer and the standard Gibbs energy of transfer of these anions from water to the organic solvent, simply by measuring the formal potential of the recorded voltammograms. As diagnostic criteria for recognizing whether the entire reaction occurs as indicated by Equation (16), one can use the dependence of the formal potential versus the logarithm of the anion concentration in the aqueous phase and the stability of the voltammetric response during consecutive cycling. The electrochemical reversibility of the entire process should be checked by inspecting the dependence of the formal potential of the voltammogram on the frequency in square-wave voltammetry, or on the scan rate in cyclic voltammetry. A representative square-wave voltammogram that depicts all components of the redox process of dmfc obtained at a three-phase electrode coupled with the transfer of thiocyanate anions is given in Figure 7. This approach has been successfully utilized for determining the standard Gibbs energy of transfer of inorganic anions,[20–26] as well as of various organic anions, for example, aliphatic and aromatic carboxylic acids,[22,27] substituted phenols,[22,24,26] drugs,[24] amino acids and peptides.[23,28,29] In addition to the traditionally used organic solvents nitrobenzene and dichloroethane,[20–23,26–29] *n*-octanol,[22,25] nitrophenyl octyl ether,[30] D- and L-menthol[31] and D- and L-2-octanol can be utilized.[32] Similar experiments have been reported by Marken and Compton et al.[33,34], who pioneered the study of immobilized electroactive organic liquids. Since in these cases the standard potential of the redox system was not known, and because the entire liquid compound was converted into another compound, no quantification of the Gibbs energy of ion transfer could be obtained. However, the study of the electrochemistry of electroactive oils with three-phase electrodes is a very elegant way to access the voltammetric features of oils, including vitamin K,[35] vitamin B12,[36] *n*-butylferrocene,[37] or nitrophenyl nonyl ether.[38] Several studies by Compton et al. focused on the oxidation of microdroplets of *N*,*N*,*N*′,*N*′-tetrahexyl-para-phenylendiamine (THPD).[33,34,39–41] This material, when deposited in the form of microdroplets on an electrode surface, can undergo two one-electron oxidations. The formation of radical cations is usually followed by an up-take of anions from the aqueous phase. These authors showed that ionic liq-

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[2] *In principle, an ionic oxidizable species may also be used; however, in that case, it is essential that the oxidation is not accompanied by the transfer of ions from the organic to the aqueous phase. It seems that suitable compounds for this approach are not readily available.*

uids can be generated via the oxidation of these oils as immobilized droplets. Whereas Compton et al. have reported that in some cases phase separation occurs as a result of the electrochemical transformations and ion transfer processes, this has never been observed in the case of solutions of organic redox probes in organic solvent drops. Neither microscopy[55] nor electrochemical measurements (e.g., refs. [20–32]) have indicated such phase separation, and this is understandable because the rather dilute solutions of organic salts in organic solvents are not known to be prone to such phenomena.

3.2. The Transfer of Cations at Three-Phase Electrodes

Following the principles outlined for the anion transfer with three-phase electrodes, the *reduction* of an electroreducible lipophilic compound dissolved in an organic liquid requires the transfer of cations from water to an organic liquid. The reduction of Fe(III) tetraphenyl porphyrine chloride [Fe(III)TPP-Cl] in a nitrobenzene microdroplet gives rise to well-developed square-wave voltammetric signals with a peak potential that depends on the nature of the cations present in the aqueous phase.[26] This compound is only slightly dissociated in nitrobenzene. The more lipophilic the cation in the aqueous phase is, that is, the more *positive* the standard potential of the cation transfer from water to the organic liquid is, the more feasible is the reduction of [Fe(III)TPP-Cl]. Representative voltammograms showing the transfer of cations across the water|NB interface are shown in Figure 8. This approach has been used to determine the standard Gibbs energy of transfer of various inorganic cations, as well as of some tetraalkylammonium cations[26] across the water|NB interface. Girault and coworkers[60] achieved a cation transfer using an electrolyte-supported aqueous droplet containing equimolar concentrations of Fe(II) and Fe(III) salts attached to the surface of a platinum electrode and immersed in an organic phase that also contained a supporting electrolyte. The redox transformation of the Fe(III)/Fe(II) couple in the aqueous phase is accompanied by the transfer of cations between the organic and aqueous phases. Although this method possesses similarities with the three-phase electrode approach, it differs because: 1) There is no three-phase junction, and 2) Supporting electrolytes are present in both phases.

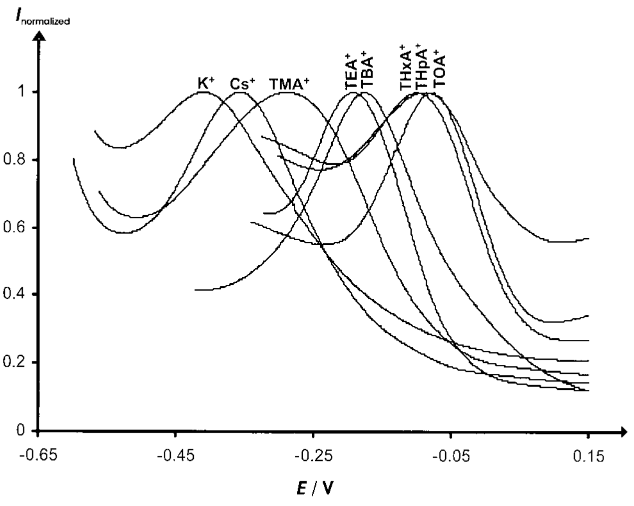

Figure 8. *Normalized square-wave voltammograms of the redox reaction of Fe(III)TPP-Cl in NB droplets accompanied by the transfer of cations from aqueous solution to NB (reproduced from ref. [26]); TMA$^+$ = trimethylammonium, TEA$^+$ = tetraethylammonium, TBA$^+$ = tetrabutylammonium, THxA$^+$ = tetrahexylammonium, THpA$^+$ = tetraheptylammonium, TOA$^+$ = tetraoctylammonium.*

Another method to study the transfer of cations is based on the electrochemical reduction of iodine dissolved in an immobilized droplet of nitrobenzene. In these experiments, a very special behavior of iodine was observed when the chloride salts of different cations were present in the aqueous phase.[24,42] In addition to the peak of iodide expulsion (peak I in Figure 9), a new reversible process occurs at more positive potentials than the first one (peak II in Figure 9). This signal shifts by about 60 mV in the negative direction per decade of increasing chloride concentration, and it is attributed to the reduction of iodine in the NB droplet followed by the *expulsion of chloride ions from the NB* to the aqueous phase. The electrochemical behavior of the system can be explained by assuming a preceding partition of the chloride salt between the aqueous and the NB phases, mainly driven by the formation of I_2Cl^- ions in NB.[24] The ratio I_p(II)/I_p(I) of the peak currents of peaks II and I increases linearly with increasing concentration of chloride anions in the water phase, mainly due to the absolute increase in the peak current I_p(II). In chloride solutions with *different* cations, this ratio depends linearly on the standard Gibbs energy of transfer of the cations across the water|NB interface (Figure 10). The overall reaction associated with peak II is of CE-type (electrochemical reaction coupled to a preceding

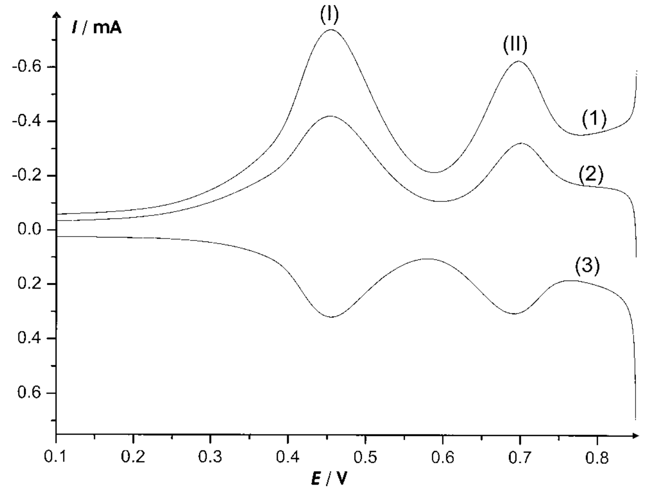

Figure 9. *The net (1), forward (2), and backward (3) components of the square-wave voltammetric response of a NB droplet containing 0.1 mol L^{-1} iodine attached to a paraffin-impregnated graphite electrode and immersed in a 0.25 mol L^{-1} aqueous solution of NaCl. The experimental conditions were: SW frequency f = 50 Hz; SW amplitude E_{sw} = 50 mV; scan increment dE = 0.15 mV; and starting potential E_s = +0.90 V (reproduced from ref. [24]).*

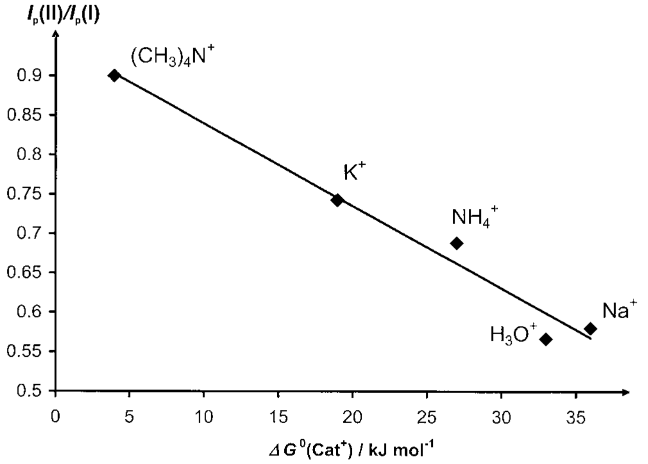

Figure 10. Correlation of the peak-current ratio with the standard Gibbs energy of transfer of cations across the water|NB interface. The other conditions are the same as those in Figure 9 (reproduced from ref. [24]).

chemical reaction)[24] and can be formulated by Equations (17)–(19).

$$I_{2(NB)} + Cl^-_{(w)} + Cat^+_{(w)} \rightleftharpoons I_2Cl^-_{(NB)} + Cat^+_{(NB)} \quad (17)$$

$$I_{2(NB)} + 2e^- \rightleftharpoons 2I^-_{(NB)} \quad (18)$$

$$Cl^-_{(NB)} \rightleftharpoons Cl^-_{(w)} \quad (19)$$

The equation corresponding to the calibration line given in Figure 10 can be used to determine the standard Gibbs energy of transfer of cations present in aqueous chloride solutions. This approach has been exploited to determine these data for several amino acid cations across the water|NB interface.[24,28] The major limitations of this approach are caused by the high reactivity of iodine towards organic compounds, as well as by the complexity of the entire mechanism. This approach is not purely thermodynamic: It relies on the kinetics of the overall electrode reaction. Hence it is certainly less robust than the methods described before.

4. Determining the Standard Gibbs Energy of Transfer of Ions

Herein, we will review the recent achievements regarding the determination of the standard Gibbs energy of transfer across the interface between water and several important organic solvents. All standard Gibbs energy of transfer data are given in Tables 1S and 2S (see Supporting Information).

4.1. The Nitrobenzene–Water System

Nitrobenzene is the most widely used solvent in electrochemical studies of ion transfer processes across liquid|liquid interfaces.[15] This is due to its low miscibility with water and its relatively high dielectric constant ($\varepsilon = 35.6$), allowing a rather good dissociation of electrolytes.[43] The aromatic part of the molecule ensures good solvation of the nonpolar sites of the ions, while the polar nitro group is an appropriate centre for interactions with charged or polar parts of the transferable ions. These properties make nitrobenzene a good solvent for both lipophilic and hydrophilic ionic species.

The three-phase electrode arrangement has been used to study the lipophilic properties of various inorganic[20,21,23] and organic anions[23,27–30] and cations,[26] as well as the anions of some drugs.[30] Studying a series of similar inorganic anions was important in order to understand how the standard Gibbs energy of anion transfer agrees with data calculated on the basis of the electrostatic Born theory.[46] Although the simple Born theory is still widely used, a more recent approach based on quantum mechanical calculations, proposed by Osakai et al., also takes into account nonelectrostatic interactions.[59] Furthermore, the study of the lipophilicity of various substituted phenolates[27,30] was a good opportunity to investigate how the standard Gibbs energy of transfer of an anion is affected by charge delocalization effects caused by the presence of different substituents in the structure of phenolates.

The use of three-phase electrodes offered the chance to determine the standard Gibbs energy of transfer of the monoanionic forms of amino acids and different di- and polypeptides.[24,28,29] Hitherto, this has not been achieved. The lipophilicities of amino acids and peptides are of great importance because of their biological activity and the applicability of these compounds in different areas.[2a] A knowledge of the lipophilicities of amino acids is needed for calculating the so-called distribution diagrams of amino acids. Provided that the values of the partition coefficients of the neutral and monocationic forms of the amino acid are also known, distribution diagrams can be used to predict how the distribution of all the amino acid species, that is, the zwitterionic, anionic, and cationic forms, in the organic phase will change with pH.

A knowledge of the lipophilicities of amino acids and peptides is also necessary to understand their biological activity, peptide interactions, and peptide folding. The transfer of mono-anionic forms of various oligopeptides was studied in order to determine the individual contributions of the amino acid units to the overall lipophilicity of the oligopeptide.[29] The effect of the *position* of an amino acid unit in the chain of a peptide is in some cases very pronounced, especially when an aromatic amino acid is placed next to the terminal amino acid at which the negative charge is located in the anionic form. Therefore, it is unreasonable to approximate the entire lipophilicity of peptide anions as additive functions of the contributions of their amino acid residues, as has been proposed in all theoretical models for neutral peptides.

4.2. The *n*-Octanol–Water and NPOE–Water Systems

During the last decades, considerable effort has been invested to develop relationships between the physicochemical properties of compounds and their ability to induce a given biological effect.[2,16] In particular, the partition coefficients measured in the system water|*n*-octanol have been widely used in quantitative structure–activity relationships (QSAR), and they are used in pharmacology to predict the bioactivity of drugs.[2a]

Leo, Hansch, and Elkins selected *n*-octanol as a reference solvent for log*P* measurements[1] due to its similarity to the phospholipids which are the major constituent of biological membranes. The long lipophilic chain of *n*-octanol, which is connected to the hydrophilic hydroxyl group make it an ideal organic solvent to mimic the transfer processes through biological membranes. However, though the partition coefficients of a large number of *neutral* organic compounds for the system water|*n*-octanol have been determined by various techniques and a huge data base of log*P* values of neutral compounds exist,[1,43] until quite recently no data were accessible for the partition coefficients of *ionic species* in this system.[15] Owing to the nonpolarizability of the interface between water and *n*-octanol,[15,16] the four-electrode voltammetric technique was not applicable to the determination of standard Gibbs energy of ion transfer in this solvent system.

The problem in applying the dmfc droplet-modified electrode to the determination of the standard Gibbs energy of transfer of an anion across the water|*n*-octanol interface was that the standard redox potential of dmfc$^+$/dmfc in *n*-octanol was not known. Attempts to determine this standard potential by recording voltammograms in *n*-octanol failed to yield precise data, presumably because of the rather high resistance of the solution. Since no ion transfer energies of any ions are known, it was also not possible to use the three-phase electrode to determine the standard potential of dmfc$^+$/dmfc in *n*-octanol, as could be done with nitrobenzene or nitrophenyl octyl ether. Fortunately, the values of the standard potentials of transfer of several inorganic anions across the interface of water|*n*-alcohols (for $n = 1, 2, 3, 4$) can be found in the literature.[15] By applying a nonlinear regression analysis to these sets of data, it was possible to extrapolate the values of standard potentials of transfer of chloride, iodide, and bromide for the system water|*n*-octanol.[22] By applying Equation (13), and by utilizing the peak potentials of the voltammograms of dmfc dissolved in *n*-octanol and the simultaneous transfer of the anions across the water|*n*-octanol interface, the standard redox potential of dmfc$^+$/dmfc in *n*-octanol has been determined.[22] In order to ensure the reliability of the approach used, the values of the standard Gibbs energy of transfer across the water|*n*-octanol interface of halide anions—estimated by employing Equation (13) and using the determined value of $E^{\ominus}_{\mathrm{dmfc}^+|\mathrm{dmfc}(n\text{-octanol})}$—were compared with the values calculated using the electrostatic Born theory.[46] The correlation between both sets of data was very good ($R^2 = 0.99$) and had a slope of 1.[22] This supports the correctness of the standard potential. Now, for the first time, it became possible to determine the standard Gibbs energy of transfer of several inorganic anions,[22] as well as of anions of organic model compounds and drugs[25,30] across the water|*n*-octanol interface. Some square-wave voltammograms showing the transfer of anions across the water|*n*-octanol interface are shown in Figure 11.

Recently, 2-nitrophenyl octyl ether (NPOE) has been widely used as an alternative solvent for *n*-octanol in lipophilicity measurements of ionic compounds.[44] It possesses interesting physicochemical properties: It has a very low miscibility with water, a moderate dielectric constant, and a rather light viscosity.[43] Therefore, NPOE has been used as a model solvent for studying the kinetics of ion transfer across the water|NPOE interface.[45]

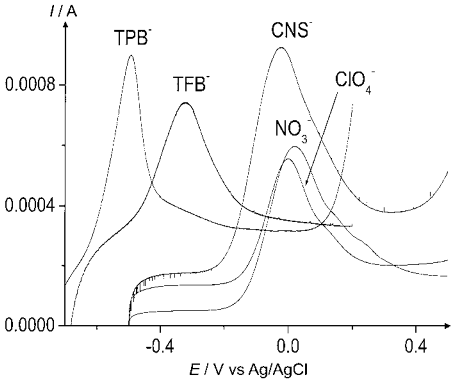

Figure 11. *SW voltammetric responses of an* n*-octanol droplet-modified electrode containing 0.05 mol L^{-1} dmfc attached to a paraffin-impregnated graphite electrode which is immersed in a 1 mol L^{-1} aqueous solutions of* $(C_6H_5)_4B^-$ *(TPB)$^-$ = tetraphenylborate,* BF_4^- *(TFB)$^-$ = tetrafluoroborate,* SCN^-*,* ClO_4^-*, and* NO_3^- *(reproduced from ref. [22]).*

Since NPOE formally shares the structures of both *n*-octanol and nitrobenzene, a study of the lipophilicities of the anionic forms of twenty-seven model compounds and drugs (see, e.g., Figure 1 in [30]) has been undertaken[30] in order to compare the solvation properties of NPOE with those of NB and *n*-octanol. This study revealed several interesting features about the solvation abilities of the organic solvents. It has been observed that the lipophilicities of the anionic forms of these compounds, as well as of some common inorganic anions, determined in the systems water|NPOE and water|NB are very well correlated.[30] However, the lipophilicity data measured in the system water|NPOE do not correlate well with the data obtained in the system water|*n*-octanol (see Figure 12). This means that the solvation properties of NPOE and NB are rather similar, whereas the poor correlation between the data deter-

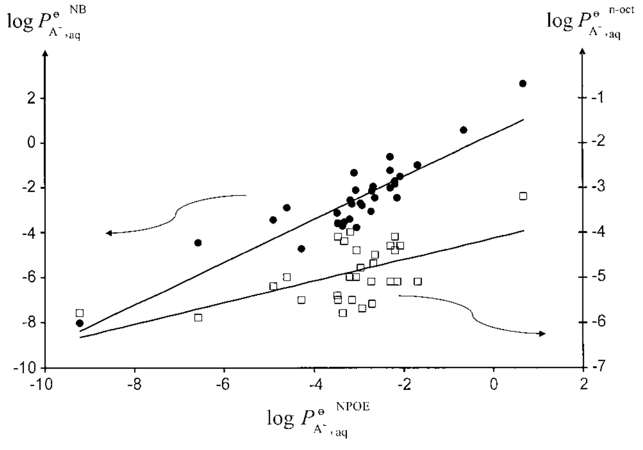

Figure 12. *Correlation between the standard partition coefficients of organic anions measured in the system water|NPOE, water|NB, and that measured in the system water|n-octanol for the compounds given in Figure 1 of ref. [30] (reproduced from ref. [30]).*

mined for water|NPOE and water|*n*-octanol systems suggests that NPOE should not be regarded as an alternative solvent for *n*-octanol, since both solvents possess rather different solvation features. Furthermore, whereas the charge delocalization effects of the various substituted phenolates are significantly pronounced in the systems water|NPOE and water|NB, that is not the case in the system water|*n*-octanol. The reason for such behavior can be ascribed to the different amounts of water in these organic solvents. In contrast to NB and NPOE, which have a low miscibility with water,[30] *n*-octanol contains a significant amount of water which obviously plays a role in solvating ions in *n*-octanol.

4.3. The D- and L-2-Octanol–Water Systems

Chiral recognition is of high importance in living systems and it is an important subject for chemical separations and chemical analysis. Chiral recognition with the help of electrochemical means is potentially attractive due to the simplicity of the measurements. Therefore, experiments were undertaken to probe the possibility of transferring chiral ions from water to chiral solvents with the help of three-phase electrodes. By depositing a single droplet of a *chiral organic liquid* containing decamethylferrocene onto a paraffin-impregnated graphite electrode, and immersing this electrode in an aqueous solution containing *chiral* anions, it was indeed possible to obtain an enantiomeric discrimination. This enantiomeric discrimination appears to be due to the different solvation interactions between enantiomeric anions and enantiomeric liquid oils. Square-wave voltammetric experiments conducted in aqueous solutions containing D- or L-anionic forms of some amino acids (phenylalanine, tyrosine, and lysine) performed with a droplet of dmfc solution in D- and L-2-octanol provided measurable differences between the solvation interactions of the chiral anions and the molecules of the chiral solvents. In these experiments a symmetrical solvation behavior was observed,[32] that is, the energy of interaction between the D-anions and D-2-octanol was identical to that between the L-anions and L-2-octanol. The same holds true for the interactions between D-anions and L-2-octanol and L-anions and D-2-octanol (see the example in Figure 13 and Table 1S in the Supporting Information).

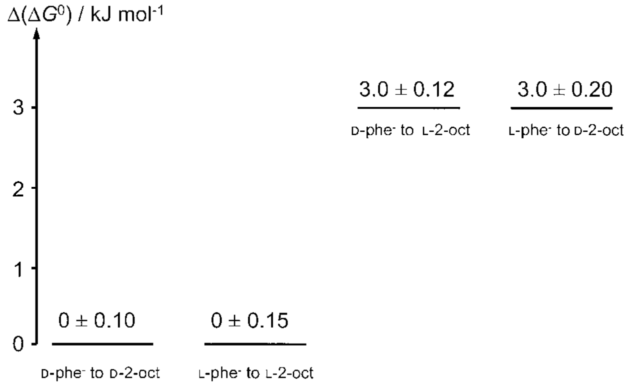

Figure 13. *Differences in the standard Gibbs energies determined for the transfer of the anions of D- and L-phenylalanine from water to D- and L-2-octanol (reproduced from ref. [32]).*

5. Summary and Outlook

For the first time, it became possible to determine the Gibbs energy of ion transfer with *three-electrode* potentiostatic measurements when *three-phase electrodes* with immobilized droplets of an organic solution of a redox probe were introduced. Both anions and cations can be transferred, depending on the redox probe used in the organic droplet. Using decamethylferrocene as a redox probe in a nitrobenzene droplet allows the determination of the standard Gibbs energy of anion transfer in the range from -41 to $+37$ kJ mol^{-1}. The upper limit is set by the transfer of dmfc$^+$ ions from NB to water, and the lower limit results from the reduction of NB[47]. Also for the first time, the three-phase electrodes allow the study of the transfer of ions between water and solvents like *n*-octanol, and D- and L-2-octanol. Using nitrobenzene as the organic phase and performing measurements in salt solutions in H_2O and D_2O, it was possible to determine the Gibbs energy of ion transfer between light and heavy water.[57] A serious advantage of the three-phase electrodes is that no additional electrolytes are necessary in the organic and aqueous phases: In the aqueous phase, only the salt to be studied is present and it provides the necessary conductivity, and, in the organic droplet, the conductivity is attained as a result of the redox reaction and the coupled ion transfer. It is also very advantageous that only very tiny amounts of the organic solution are necessary to immobilize: 1 µL or even less is sufficient. This pays off very well when highly expensive solvents must be studied. It is also of great value that the measurements can be routinely performed by anybody who has access to a commercial 3-electrode potentiostat. Measurements can be performed with any voltammetric technique: cyclic voltammetry and square-wave voltammetry are always a good choice. For most of the inorganic ions, as well as organic ions, the standard Gibbs energy of ion transfer determined using the three-phase electrode technique is in very good agreement with the data obtained by the classical four-electrode technique (compare the data in refs. [23,27] with that in ref. [15]; and the data in ref. [30] with that in refs. [5,44]). Disagreements can be explained by obvious experimental errors in the work with the four-electrode technique.[23,26] The three-phase electrode approach can be routinely used in future.

From a thermodynamic point of view, the three-phase electrodes and the evaluation of data with respect to the Gibbs energy of ion transfer is rather simple. However, the kinetics of the electrode reaction is certainly much more complex, partly because of the geometry of the immobilized droplets. With the help of microelectrodes inserted into the droplet,[56] and with the help of a spectroelectrochemical cell allowing the electrode reactions at different locations within the droplet to be followed,[55] it was possible to show experimentally that the advancement of the reaction into the droplet proceeds surprisingly fast. It has been assumed that the anion concentration gradient in the droplet is kept almost constant, but advances into the droplet as a result of activating the electrode|droplet interface due to the increasing conductivity. The first theoretical simulations of cyclic voltammograms at three-phase electrodes with immobilized droplets have been published by Myland and Oldham.[49,53] These authors assumed that the initial conductivity of the organic phase in the vicinity of the three-phase junction is attained as a result of the electrochemical reaction. Later, cyclic voltammograms at three-phase electrodes were simulated assuming a conic shape of the droplet, and the effect of the ohmic resistance within the droplet was evaluated.[48] In that paper, the authors assumed that the initial conductivity of the droplet is attained by free partition of the salt from the aqueous solution. Additional semi-empirical models developed for the droplet-modified electrodes can be found in the works of Aoki and co-workers.[50,51] The effect of uncompensated resistance in thin-film experiments has been studied to obtain hints on that effect in droplet experiments.[52] For the same reason, the effect of migration and distribution of all species in thin-film experiments was theoretically treated.[58] It can be expected that more realistic, however, also more sophisticated models will be developed in future to improve the simulation of the kinetics of the electrode reactions at three-phase electrodes.

Experimentally, one can expect that in future work much more ionic data will be harvested in routine applications. However, more importantly, the three-phase approach may be used in biomimetic studies simulating ion recognition processes at membranes, catalytic systems at membranes, and redox-driven ion pumping at membranes. The latter is obvious, by appreciating that the ion transfer achieved at three-phase electrodes is rather similar to the ion pumping through living membranes, which is coupled to redox chains of ubiquinones, to give an example. Doubtless the study of the redox reactions of redox probes at three-phase electrodes will also receive more attention, and this will expand our knowledge of electrochemical reactions in complex arrangements.

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Keywords: electrochemistry · Gibbs energies · ion transfer · solvation · thermodynamics

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