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Scope of Electrochemistry at Liquid/liquid Micro-Interfaces

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Abstract

Electrochemistry at the interface between two immiscible electrolyte solutions (ITIES) has become an important and powerful platform for the detection and characterization of a wide variety of organic and inorganic species. Liquid/liquid electrochemistry overcomes some limitations faced in conventional solid/liquid electrochemistry. These include employment ofion transfer voltammetry across the ITIES as the basis for detection of non-redoxactive ions. The analytical sensitivity increasedon miniaturisation of the interface with an improvement insensitivity due to the enhanced mass transport via convergent diffusionas the size of the ITIES is minimised. In this review article, the ITIES is briefly described along with the scope of electrochemical research at micro-ITIES.

Keywords: ITIES, liquid/liquid electrochemistry, ion transfer voltammetry, miniaturisation of interface.

I. Introduction

Liquid/liquid electrochemistry background

The interface between two immiscible electrolyte solutions or the ITIES is formed when two nearly immiscible liquid solvents (one aqueous and the other organic) are brought into contact (Figure 1). Gavach and co-workers developed the liquid/liquid system by showing that the interface can be polarized by applying a voltage and that charge transfer reactions can control the Galvani potential difference of the two phases [1]. Koryta and co-workers further advanced this polarizability of the ITIES by showing that the mechanism of transport across the ITIES [2] is similar to that of redox processes on solid/liquid electrode surfaces [3, 4]. Samec and his group studied the kinetics of the charge transfer process at the ITIES by developing the concept of the 4-electrode potentiostat with ohmic drop compensation [5, 6].

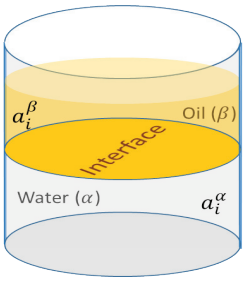

Fig. 1. interface between two immiscible electrolyte solutions.

In the ITIES, a hydrophilic electrolyte salt, usually LiCl or Li_2SO_4, is use in the aqueous phase solvent, while the organic solvent [e.g. 1,6-dichlorohexane (DCH), 1,2-dichloroethane (DCE)] is polar and has enough dielectric permittivity to dissociate the polar hydrophobic electrolyte salt, commonly bis(triphenylphosphoranylidene) ammonium tetrakis (4-chlorophenyl) borate (BTPPATPBCl) [7-9]. This polarisable interface commonly involves an ion transfer from one phase to the other phase [5, 10-12] or it could be also a redox reaction at this interface [13, 14].

Ion transfer voltammetry at the ITIES overcomes the drawbacks of the solid/liquid (conventional electroanalytical methods) interface, mainly that non-redox-active species may not be detected at solid electrodes immersed in a liquid electrolyte [8], whereas the ITIES can detect non-redox species as well. The liquid/liquid interface system is more flexible as both phases can be changed according to the needs of interesting molecules. But in a conventional solid/liquid electrochemical system, generally the liquid electrolyte can change, while the solid electrode is fixed [15].

Types of charge transfer processes

Electrochemistry at the ITIES can follow different forms of charge transfer (CT). The first and the simplest CT process is ion transfer (IT), which is the movement of ions from either phase across the interface because of applying an external potential difference and continuing until reaching an equilibrium according to the Nernst equation (Figure 2a)[7, 16]. This transfer potential can be measured if it falls within the potential window set by the transfer of the background electrolytes.

The second charge transfer process is facilitated ion transfer (FIT) [7, 16]. That can be further classified in four categories based on thecomplexation mechanism between the ion and the ionophore charge transfer [16, 17]. Those are, namely, Transfer by Interfacial Complexation (TIC), Transfer by Interfacial Dissociation (TID), Aqueous Complexation followed by Transfer (ACT) and Transfer to the Organic phase followed by Complexation (TOC). These four assisted ion transfer processes are described in Figure 2b.

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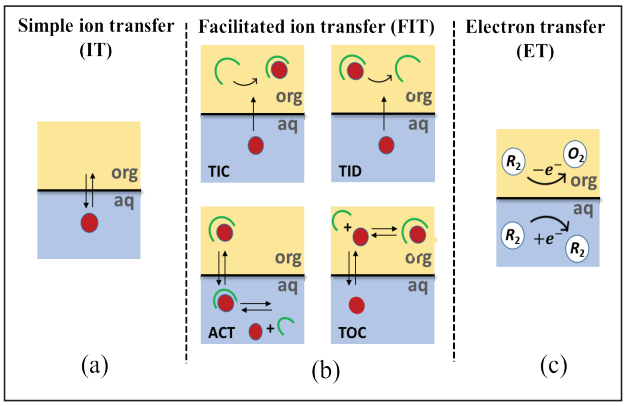

Fig. 2. Schematic presentation of the types of charge transfer process. (a) Simple ion transfer (IT), (b) Facilitated/assisted ion transfer (FIT) and (C) Electron transfer (ET) process.

The third CT process is electron transfer (ET) [16], which occurs between redox species in each phase and is more complex than other two CT processes (Figure 2c). Choosing the redox couples is the difficult part and ideally the redox products should not transfer across the ITIES, otherwise this could produce currents separate from the actual electron transfer process [4].

Development of miniaturised ITIES

Taylor and Girault introduced the concept of the miniaturised ITIES in 1986 by transferring tetraethylammonium ion (TEA+) from the organic phase to the aqueous phase through the interface formed at the 25 µm radius tip of pulled glass micropipettes 10. Afterwards several research groups have also reported their studies on micropipette-based ITIES 11, 18-20.

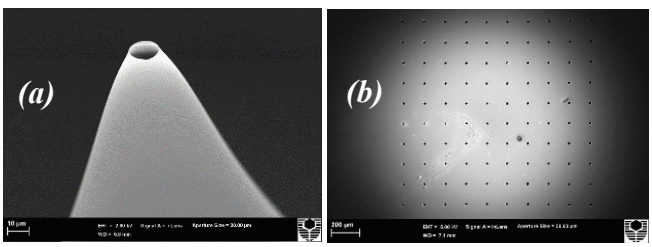

Fig. 3. (a) 100 pores of micro array glass membrane for micro ITIES and (b) micro pipette for creating a single micro ITIES.

In 1995 Beattie and co-workers [18] made thinner glass micropipettes of borosilicate and quartz materials by using an advanced pipette puller which solves the reproducibility problem of the tip geometry. Shao and Mirkin in 1998 developed a silanization process to change the hydrophilic glass pipette surface to hydrophobic, which makes the ITIES stable at the mouth of the micropipette [20]. Miniaturization research has been continued from the micrometre to the nanometre size. Nano-ITIES supported by glass pipettes in the same way as micro-ITIES are supported by micropipettes were introduced [21, 22].To get the better sensitivity micro-ITIES array were introducedwhich enhance the mass transfer at µITIES[23, 24]. Figure 3(a) and 3(b) shows a 100 pores micro array at glass membrane and a glass micropipette respectively.

Benefits of miniaturised ITIES

Miniaturisation of the ITIES from a macro-scale to a micro- or nano-scale offers some advantages with respect to the larger liquid-liquid interfaces. Double layer charging current and *IR* or Ohmic drop are very important to get the actual signal from the target species and crucial for kinetic parameters. The larger interface creates more charging current and more IR drop, which can inhibit obtaining the actual signal from the analyte. Miniaturisation of the ITIES results in very small currents generated at the ITIES which minimises the effects of Ohmic drop [15, 21, 25].

Furthermore, miniaturised ITIES enhance the diffusional mass transport rate, resulting in greater current densities and hence increase the sensitivity of the analytical response [21, 26-28].

Electrochemical setup

A typical cell setup with a pipette to form an ITIES at the tip of the pipette is shown in the Figure 4 (a). The organic electrolyte phase was introduced into the pipette which comes up to the tip and the organic reference solution (saturated BTPPACl in 10 mM LiCl) was

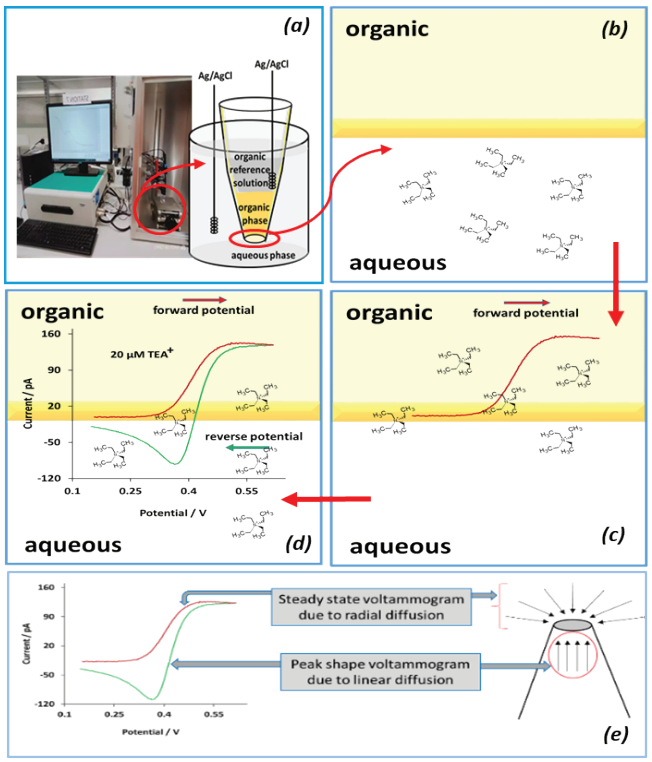

Fig. 4. (a) Electrochemical cell setup (b) interface at the tip of pipette (c) CV for forward potential (d) CV response for both forward and backward potential (e) diffusion pattern and their relative CV response at 46 µm radius pipette.

placed on the top of the organic phase. Then the pipette was immersed into the aqueous phase so that an ITIES formed at the tip of the pipette. As this was a miniaturized interface, so a two-electrode system was employed for this electrochemical cell. An Ag/AgCl or Ag electrode was in the aqueous solution and another Ag/AgCl electrode used in the organic reference solution. The micro-interface was polarised by imposing a potential difference between these two electrodes. The cell is described in the following scheme.

$$\mathrm{Ag}\left|\mathrm{AgCl}\right|\begin{matrix}\text{Sat'd BTPPACl}\\ \text{in 10 mM LiCl}\end{matrix}\Big|\begin{matrix}\text{10 mM BTPPATPBCl}\\ \text{in DCE}\end{matrix}\Big\|\begin{matrix}\text{x pM TEA in}\\ \text{10 mM LiCl}\end{matrix}\Big|\mathrm{AgCl}\left|\mathrm{Ag}\right.$$

Figure 4(c & d) shows a cyclic voltammetric (CV) response of tetraethyl ammonium ion (TEA) at micropipette interface and Figure 4 (e)describes how the CV response depends on diffusion modes.

II. Literature Review on Micro ITIES

Detection and characterization of inorganic ions

A vast range of inorganic ions has been investigated at the ITIES. Koryta[29] first reported on the facilitated ion transfer (FIT) of potassium and sodium ions at the ITIES by using ionophores DB18C6 (dibenzo-18-crown-6) and valinomycin, respectively, in the organic phase. That was a pioneering invention for a new path of ion selective sensors development using the ITIES. Osakai and co-workers reported on the development of K^+ ion-selective sensors based on FIT of K^+ at water/PVC membrane microinterfaces using DB18C6 [30]. Shao et al. also reported on FIT of K^+ at water/DCE nano-interface formed at nanopipettes [31]. Kinetic investigation for FIT of Cl^-, Br^-, NO_2^-, and $CH_3CO_2^-$ at micropipette supported water/DCE micro-interfaces has been investigated by Shao et al. using β-octafluoro-*meso*-octamethylcalix[4]pyrrole [32] and detection of ammonium ions was reported at the water/1,6-dichlorohexane micro-interface by a lipophilic cyclodextrin using CV, DPV, SWV [33]. Another investigation of a Cu^{2+} ion selective sensor development was reported at a liquid/organogel micro-interface [34]. For the last few decades, analytical application of the ITIES has been employed to investigate the maximum available inorganic cations and anions in environmental water samples [35]. Highly toxic hexachromic anions Cr(VI) was investigated across a microhole array-supported water/PVC-NPOE interface facilitated by Aliquat 336 to develop a simple and sensitive detection technique [36]. Radioactive uranyl (dioxouranium, UO_2^{2+}) was investigated by Ding et al. [37] across a water/DCE micro-interface using tributyl phosphate facilitator and they also calculated the Gibbs energy of transfer and the association constant of uranyl-tributyl phosphate complex.

Detection and characterization of drug molecules

Liquid/liquid interfaces have been employed as a powerful electrochemical platform for the detection and characterization of drug molecules. Arrigan and his group investigated propranolol, which is a cationic β-receptorblocking drug, in artificial saliva. They employed ion-transfer voltammetry based on arrays of microinterfacesformed at the mouths of silicon micropores between artificial saliva and an organogel phase [38]. They got a LOD of 20 nM byapplying differential pulse stripping voltammetry (DPSV) including a preconcentration step. They also investigated the effect of bovine serum albumin on propranolol sensing in the artificial serum matrix when using the same technique [39]. Pereira et al. monitored the electrochemical behavior of anticancer drug daunorubicin (DNR) in both neutral and ionic forms at the water/DCH micro-interface array by imposing CV and differential pulse voltammetry (DPV). Protonated ractopamine, which is a β-agonist drug, was investigated in artificial serum based on a water / DCH micro-interface array using voltammetric techniques. A LOD of 0.1 μM was successfully achieved by employing stripping voltammetry, which is suitable for real samples as well [40]. HyeJin Lee and her group reported the development of a microscale-ITIES sensor for determining the anticancer drug topotecan in biological samples at a microhole supported water/polyvinyl chloride-2-nitrophenyloctyl ether (PVC-NPOE) gel interface [41]. Very recently, for the first time, the ionizable drug diclofenac has been detected and characterized at water/1,6-dichlorohexane microinterface based on microporous silicon nitride membrane using CV and DPV [42]. Poltorak and his group [43] investigated the electrochemical behavior of four fluoroquinolone antibiotics (ciprofloxacin, enrofloxacin, marbofloxacin and ofloxacin) at both macro and micro supported water / DCE interface using ion–transfer voltammetry (ITV). They detected all of the molecules within the available potential window where cipofloxacine is the most hydrophilic compound among all four. They calculated range of thermodynamic and kinetic parameters as well as the LOD, which is around 1 μM. Herzog and his group [44] reported on the proton assisted transfer of an herbicide, ametryn, at a single μITIES as a function of pH. Depending on the pH of the aqueous phase, they observed direct ion transfer as well as proton assisted transfer.

Kataky and Lopes reported [45] the detection of drug enantiomers of ephedrine at a μITIES based on a micropipette, where a cyclodextrin chiral selector was used in the organic phase as a facilitator to transfer the protonated enantiomers. A significant differences of their transfer potentials was recorded, although the difference in association constants of the ephedrinium enantiomers with the cyclodextrin was very small. Lopes and Kataky[46] further investigated interactions of chiral drugs (S)-propranolol and (R)-propranolol with the protein α(1)-acid-glycoprotein at a μITIES formed with a micropipette by employing CV and DPV. In this

case, the current response for the transfer of ions decreases differently for the two enantiomers of the drug because of the protein interaction, which makes it possible to calculate the association constants of each enantiomer with the protein [46].

The electrochemical behavior of vitamin B1 at a pipette-based water / nitrobenzene micro-interface was investigated by Huang et al. [47] using stripping voltammetry and enabled to reach a detection limit of 4.6 μM. They also applied potential step chronoamperometry to study the ion transfer process and observed a steady-state current obtained after 15 seconds of the potential step. This observation is important because for applying stripping voltammetry, the pre-electrolysis time need to be set at least 15 seconds. Mono-, di- and tri-adenosine phosphates play an important role in energy metabolism in living systems. Qian et al. [48] investigated their properties at water / 1,2-dichloroethane micro-interface array facilitated by an ionophore N-(2-[bis-(2-(4-tert-butylbenzoyl)-aminoethyl)-amino]ethyl)-t-butylbenzamide and observed distinct ion transfer potentials.

Electrochemical behavior of proteins at the ITIES

Amemiya and colleagues in 2003 [49] reported for the first time about the phase transfer of the biological polypeptide protamine at micropipette-based water / 1,2-dichloroethane interface. Protamine is a highly charged macromolecule with 30 amino acids and its isoelectric point (pI) > 12. This charge transfer analysis confirms that each protamine carries at least 20 positive charges at the isoelectric point or lower pH or at physiological pH. This investigation at the ITIES provided a basis for amperometric sensor development for biological macromolecules [49]. Amemiya and coworkers[50] further investigated protamine at water / 1,2-dichloroethane micro-interface by adding dinonylnaphthalenesulfonate (DNNS) as an ionophore in the organic phase. The diffusion coefficient of protamine and its ionised charge were calculated for this interfacial charge transfer process and were in good agreement with previously determined values.

Scanlon et al.[51] investigated the behavior of two biological macromolecules namely insulin and hen-egg-white lysozyme (HEWL) at water / organogel μITIES formed on an array of solid-state micropores in a membrane. They reported that these bio-macromolecules go through an interfacial adsorption in the aqueous side which facilitated the transfer of anions from organic phase to the adsorbed protein layer on the aqueous side, whereas the tetraethylammonium cation (TEA^+) followed a simple ion transfer mechanism [51]. The behavior of myoglobin was also observed at an array of aqueous / PVC-gelled 1,6-dichlorohexane micro-interfaces by applying CV [52]. This analysis also followed the previous one [51], where myoglobin absorbed at the aqueous side of the interface to facilitate the transfer of the organic phase anions through the interface. However, the reverse process was desorption controlled, confirmed by the voltammetric scan rate of the reverse peak current. As like all other proteins, in this case also pH plays a vital role to detect the myoglobin [52]. Alvarez de Eulate and Arrigan[53] studied HEWL at an array of μITIES and were able to detect 0.03 μM by applying adsorptive stripping voltammetry, which is more than 10 times lower than the previous HEWL detection at the ITIES by CV [51]. These findings provided a new analytical platform for the label-free detection of protein.

Enzyme-catalyzed reaction

The products or substrates from enzyme-catalyzed reaction can be detected at the ITIES which creates a new dimension for harnessing the biological selectivity of enzymes for bioanalytical process. Pereira et al. [54] developed an amperometric glucose biosensor based on facilitated proton transfer across a gellified microITIES. The protons are generated from the dissociation of gluconic acid, which is a product of the oxidation of glucose by oxygen catalysed by the enzyme glucose oxidase. Lee and coworkers[55, 56] also reported the detection of organophosphate pesticides paraoxon, parathion and methyl parathion at a microhole-based water/organogel interface by a facilitated proton transfer mechanism. In this case, the enzyme organophosphorous hydrolase was added as a reagent in the organic phase which produced protons by hydrolyses with the target analytes and these were subsequently detected by ion transfer voltammetry or amperometry. Akter and Arrigan[57] investigated a label-free nonredox electrochemical detection of the cancer protein biomarker PSMA (prostate specific membrane antigen) at the μITIES array based on assisted proton transfer voltammetry without use of antibodies. The LOD by applying SWV (square wave voltammetry) was 3.5 pM, which was lower than the reported values [58-61]. Recently Zannah and Arriganreported label free detection of catalase (CAT) enzyme at liquid/liquid micro interface array [62]. An electroanalytical signal has been found when the aqueous phase pH was lower than the isoelectric point of CAT, proving its electroactivity at the μITIES. CVs of CAT in artificial serum also demonstrated the feasibility of μITIES to detect such large molecules in the presence of various ionic species. The calculated LOD was 3.5 nM, which is lower than that for other proteins reported to date, which further manifested the suitability of L/L μinterface array in practical applications (e.g., biosensor development).

DNA detection

DNA detection and characterization is one of the challenging approaches in analytical chemistry. In 1998, Horrocks and Mirkin reported that micropipets provide a simple ion transfer technique for the electrochemical determination of DNA by its binding with non-redox-active cations, where the cation was taken in the organic phase present inside the pipet and DNA (oligonucleotides) were added to the aqueous phase.

The cation transfers to the aqueous phase was controlled and facilitated by the DNA present in the aqueous phase [63]. The interaction of high molecular DNA with drug molecules daunorubicin and dopamine was investigated at water/1,6-dichlorohexane (DCH) microarray interface by Ribeiro et al. in 2015 [64]. Felisilda and Arrigan[65] investigated a synthetic oligonucleotide thrombin-binding aptamer (TBA, 15-mer) at liquid / organogelμITIES interface array. TBA was detected in the presence of cetyltrimethylammonium (CTA^+) in both aqueous and organogel phases. By employing CV, the limit of detection (LOD) of TBA reached down to 0.11 μM.

Carbohydrate detection

Heparin is a highly sulphated polydisperse mixture of carbohydrates and widely used as a blood anticoagulant. Amemiya and coworkersreported on the behavior and detection of heparin at 1,2-DCE / water (blood plasma) micro-interfaces formed at the tip of a micropipette [66]. In that study, different quaternary ammoniums were used as cationic ionophores to figure out the structural requirements for heparin-ionophore complex formation. They found that complexation with octadecyltrimethylammonium cations was the best for low detection limits. This was also the first time to study using direct blood samples at the ITIES to investigate the biomedical utility of ion-transfer voltammetry [66]. Voltammetric extraction of heparin with a new ionophore 1-[4-(dioctadecylcarbamoyl)butyl]guanidiniumacross 1,2-dichloroethane / water single micro-interface at a pipette tip was investigated by Amemiya and co-workers[67]. They found that the heparin molecule can strongly bind with more than one ionophore to become electrochemically neutral and then this highly lipophilic heparin complex becomes extractable into the nonpolar organic phase.Felisilda et al. [68] investigated two sulphated polysaccharide fucoidansat an array of μITIES where the organic electrolyte phase was gellified. CV experiments showed that the detection process follows an adsorption process when scanned to negative potentials, while it gave a desorption peak on the reverse scan. By applying adsorptive stripping voltammetry (AdSV), they found a LOD of 1.8 μg mL^{-1} for *U. pinnatifida*fucoidan in aqueous phase of 10 mM NaOH and 2.3 μg mL^{-1} in synthetic urine. Felisilda et al. [69] also investigated the electrochemical characterization of sucrose octasulfate (SOS) utilizing voltammetry at a liquid / organogel μITIES array. They found that the detection of SOS depends on the organic cations present in the organic phase. The LOD of SOS was found 0.036 μM with tridodecylmethylammonium ($TDMA^+$) organic phase cation using AdSV.

Neurotransmitters

Shen and her group[70] reported the ion transfer of neurotransmitters and neuromodulators, namely acetylcholine (ACh), serotonin (5-HT), and tryptamine (T), across the DCE/water interface by CV and amperometry. This qualitative and quantitative detection for both electrochemically non-redox (ACh) and redox active neurotransmitters (5-HT and T) with nanopipette-based ITIES makes a strong base for sensor probes. Another neurotransmitter,dopamine (DA), has been well studiedby Arrigan et al. [71] as well as by Shao's group at microITIES[72]. However Shen and her group [73] reported dopamine transfer across the nanopipette based the 1,2-DCE/water interface facilitated by dibenzo-18-crown-6 ionophore (DB18C6). Shen and her group [74] developed a new method to detect gamma-aminobutyric (GABA) at a nano-ITIES pipette electrode at biological pH 7.0 by pH modulation from the oil phase. They added octanoic acid (OA) to the organic phase 1,2-dichloroethane inside the pipette whereas GABA was in the aqueous phase. GABA was detected upto 22.4 μM by CV. They also confirmed that neither the protons from the OA nor the OA itself come out from the oil phase. Wang et al. [75] reported on the liquid/liquid interface microsensor (LLIM) to monitor the redox-inactive neurochemical choline at cerebrospinal fluid /DCE interface. Choline gave an excellent response in the LLIM with detection limit 0.37 μM.

Use as SECM probes

Scanning electrochemical microscopy (SECM) with the tip of a micro- or nano- pipette has become a useful scanning probe technique for quantitative monitoring of chemical reactivity [76] as well as enabling the imaging of the electrochemical properties of a surface or interface with an ion. Currently SECM has become a powerful method for chemists to investigate electrochemical process happening in living cells [77, 78]. Bard et al. [79] reported that the tip of a micropipet-supported ITIES can act as a SECM probe to detect silver ions and explore Ag^+ toxicity in living cells. By adding calixarene-based Ag^+ ionophore (IV) into the pipette containing the DCE organic phase, they constructed a Ag^+-selective SECM tip. They monitored the Ag^+ concentration by imaging of the uptake and efflux of Ag^+ by SECM approach curves on living fibroblast cells, which opens a new mode to study cell metabolism, drug delivery and toxicity evaluation by SECM. Shao et al. [80] reported their kinetic analysis of K^+ transfer facilitated by DB18C6 across the water/DCE nano-interface using SECM with a nanopipette tip. Mirkin et al. [81] also reported on their nanopipette ITIES based SECM investigation to characterize rapid ion transfer, as well as information about tip geometry. Shen et al. [82] reported on the high resolution imaging of ion transport through single nanopores by SECM with a 17 nm radius pipette supported ITIES to study the permeability of porous nanocrystalline silicon membranes.

III. Conclusion

It has been seen that, although the electrochemistry at liquid/liquid interfaces is a comparatively new technique, but it has bloomed in lots of research areas, because of its versatile applications and suitability. Especially, the miniaturized

ITIES brought a new dimension in research by overcoming the limitations of the larger interfaces. Research in this field is expanding rapidly and there are many opportunities to develop by integrating with other techniques as well.

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