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Perspective

Multiphase Chemistry under Nanoconfinement: An Electrochemical Perspective

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ABSTRACT: Most relevant systems of interest to modern chemists rarely consist of a single phase. Real-world problems that require a rigorous understanding of chemical reactivity in multiple phases include the development of wearable and implantable biosensors, efficient fuel cells, single cell metabolic characterization techniques, and solar energy conversion devices. Within all of these systems, confinement effects at the nanoscale influence the chemical reaction coordinate. Thus, a fundamental understanding of the nanoconfinement effects of chemistry in multiphase environments is paramount. Electrochemistry is inherently a multiphase measurement tool reporting on a charged species traversing a phase boundary. Over the past 50 years, electrochemistry has witnessed astounding growth. Subpicoampere current measurements are routine, as is the study of single molecules and nanoparticles. This Perspective focuses on three nanoelectrochemical techniques to study multiphase chemistry under nanoconfinement: stochastic collision electrochemistry, single nanodroplet electrochemistry, and nanopore electrochemistry.

Nature designs environments that are composed of multiple phases. For instance, molecules within single cells encounter a variety of solid and liquid phases. Thus, molecular interactions at phase boundaries are of great importance in understanding the fundamental tenets of life. Beyond the cellular level, multiphase systems are central to daily life and to human health. Emulsions, consisting of a dispersed oil phase in water, are ubiquitous in hair products, lotions, foods, and makeup. The development of wearable and implantable biosensors is contingent on understanding the interface between biology and the designed materials. Similar considerations are necessary for abiotic systems, where the development of new materials capable of converting sunlight into chemical bonds or electricity in wires depends on the precise engineering of the solid-state material and solution interface.

While these examples offer enticing applications, fundamental electrochemical measurements are likely at the heart of understanding reactivity in such complex environments. Electrochemistry has gained prominence in this line of inquiry, not only because the measurements are inherently at phase boundaries (i.e., the metal−electrolyte interface),[1] but also because few other techniques are as miniaturizable as electrochemical methods. However, even in electrochemistry, the understanding of interfacial complexity has been a centuries-long pursuit. Helmholtz correctly predicted the existence of a capacitance at an electrode−electrolyte interface in the 1870s, well before Arrhenius' salt dissociation theory. However, a fundamental understanding of this interface has eluded scientists.[2] Only within the past 50 years has an understanding started to emerge. These advances are largely driven by new measurement science tools as well as the miniaturization of such tools to the nanoscale, where chemical variations can be rigorously evaluated.[1−10]

Within the past few decades, scientists have become increasingly aware of the fact that chemical reactions at interfaces change under nanoconfinement.[11−14] This exciting observation has been validated by the use of various measurement science tools, including mass spectrometry,[15,16] nuclear magnetic resonance,[17] fluorescence spectroscopy,[18] sum-frequency scattering spectroscopy,[19] and electrochemistry.[20] These observations lead us to thought-provoking questions, such as do biochemical reactions proceed within a cell as they do in a beaker? Do chemical reactions that occur in the ocean proceed similarly in a droplet of mist created by crashing waves? Can the size of the container dictate the rate and product in the organic synthesis reactions? How do such observations translate to the abiotic origins of life, where chemical reactions of immense importance were thought to be thermodynamically unfavorable?[21]

New truths about nature can be unlocked when novel measurement tools become available. Over the past several decades, many groups have contributed to developing new electrochemical measurement tools to study complex chemistry in multiphase systems at the nanoscale.[22−25] In electrochemistry, the electrode−electrolyte interface is the bridge between the electrical conductor and ionic conductor. The chemical and physical transformation of matter exists on such an electrode−electrolyte interface, thus permitting the energy conversion. Remarkably, the dynamic structure and composi-

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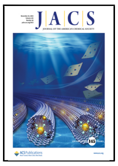

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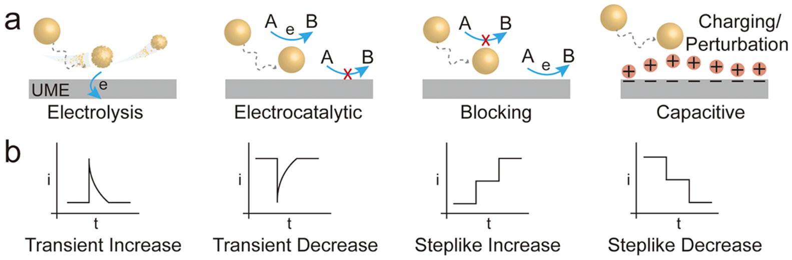

Figure 1. Schematic (a) and typical current responses (b) of stochastic collision electrochemistry, including electrolysis, electrocatalytic amplification, blocking, and capacitive collisions.

tion of the electrochemical interface controls the thermodynamics and kinetics of electrochemical reactions. There are significant efforts to geometrically confine the interface to a tiny space at the nanoscale to investigate and understand mass transport and charge transfer in multiphase electrochemistry.

There is a growing consensus that confining an interface can fundamentally change its chemical and physical features, enhancing the selectivity and the rates of electrochemical reactions. The development of nanoconfinement has led to advances in nanoelectrochemistry, permitting investigations into the stochasticity and heterogeneity of single entities such as single cells, single particles, and even single molecules. Drawing inspiration from living systems, diverse artificially nanoconfined systems serve as models that provide access to interface effects and to new truths of nature via electrochemical methods. In this Perspective, we largely discuss such new measurement science tools and their influence in understanding multiphase chemistry with a focus on nanoconfinement. We begin with a discussion of stochastic collision electrochemistry. These experiments have started to elucidate how chemistry (heterogeneous and homogeneous) changes under nanoconfinement. We then discuss performing electrochemistry in nanodroplets, a special type of stochastic electrochemistry that allows one to probe dynamic multiphase chemical processes at the nanoscale, one at a time. We end with a discussion of the nanopore-based electrochemical interface, the development of which has led to unprecedented sensitivity in measuring physicochemical properties of environments under nanoconfinement.

■ STOCHASTIC COLLISION ELECTROCHEMISTRY FOR HIGH-THROUGHPUT INTERFACIAL NANOELECTROCHEMISTRY

Investigating One Entity at a Time. In essence, an electrochemical reaction itself is a confined process. Almost all electrochemical processes occur within the electrical double layer (EDL) on the magnitude of nanoscale.[1] Consider the electrochemical reduction of hexacyanoferrate (III) to hexacyanoferrate (II) in an aqueous solution. The electron transfer at the electrode−electrolyte interface occurs via quantum mechanical tunneling between electrode and hexacyanoferrate (III), and this process must be located within 1−2 nm of the electrode surface.[26] The advent of an ultramicroelectrode (UME) is hugely important in understanding electrochemistry under the confinement. The UME is defined as a working electrode smaller than the scale of the diffusion layer, and its one dimension is smaller than 25 μm.[1] The unique properties of UME lie in the small time constant and low ohmic drops, which allow for quick convergence to a steady-state current after applying a potential. The tiny dimension gifts UME unexpected electrochemical properties including mass transport and electrode kinetics, supporting the extension of electrochemistry into ultrafast and precise nanoelectrochemical measurements.[27−29]

A ramification of an electrochemical tool with a UME is that the probe is only 1−10 times the size of the interesting/reactive entities. For similar reasons, nanoelectrodes are often employed when impacting particles are very small (1−100 nm) and the signal contribution is low. Stochastic collision electrochemistry, also termed as nanoimpact electrochemistry, developed to study the multiphase electrochemistry of single entities.[30−35] When an UME is placed in the dilute suspension of target entities, serial stochastic collisions of individual entities with the electrode−electrolyte interface generate current responses. According to the collision behaviors of single entities, we broadly classify the stochastic collision electrochemistry into four types, namely electrolysis collisions, electrocatalytic amplification collisions, blocking collisions, and capacitive collisions.[1] Figure 1a displays the electrolysis collisions that refers to the electro-oxidation or electroreduction of the redox-active entities, which causes the transient increase in *i*−*t* responses.[36−39] The dimensions, compositions, and concentrations of target entities can be determined by statistically analyzing the high-throughput current signals. The second type describes the collisions of electrocatalytically active NPs with the catalytically inert UME.[40−42] These collisions enable one to observe the enhanced current responses, where an electrochemical reaction occurs on the impacting particle once it is in electrical connection with the working electrode. The inelastic adsorption of individual NPs on the UME surface results in a steady-state increase of current. The elastic contact with UME will facilitate the observation of a series of transient current blips (<1 ms) as shown in Figure 1b. The third type is the blocking collision,[43−45] where random collisions or adsorptions of these electrically insulating objects will partially block the flux of redox-active species to the UME, leading to the transient or steplike decrease in the current magnitude. The last type is capacitive collisions that describe the disturbance of EDL by the dynamic arrival or departure of single entities, which could be used to characterize the potential of zero charge at the electrode−electrolyte interface.[46,47]

Applications in Transient Interfacial Chemistry. The confined effects have the ability to influence the transient interfacial process when the electrochemical measurements are performed at the nanoscale. Stochastic collision electrochemistry makes it possible to explore nonequilibrium interfacial electrochemistry, especially in the determination of electrode kinetics under nanoconfinement.[48,49] Figure 2a

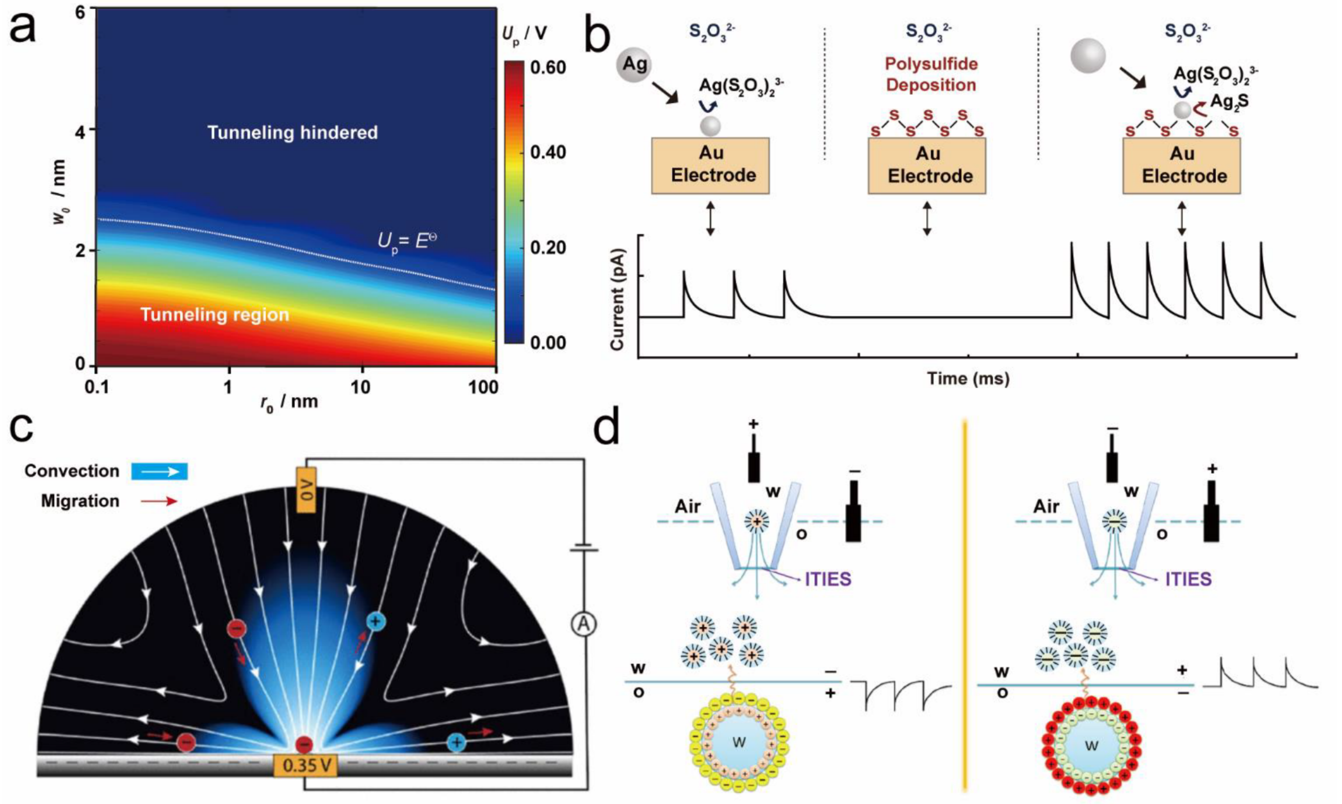

Figure 2. Stochastic collision electrochemistry based on a confined ultramicroelectrode (UME). (a) Investigation of dynamic potential distribution at the UME−electrolyte interface in electro-oxidation of individual Ag NPs. r_0, w_0, and U_p represent the radius, tunneling distance, and "feeling" potential of a single Ag NPs, respectively. Adapted with permission from ref 49. Copyright (2021) American Chemical Society. (b) Nanoconfined interface for profiling the transient interaction between a single Ag NP and Au UME. Adapted with permission from ref 50. Copyright (2021) American Chemical Society. (c) Controllable mass transport at the electrode−electrolyte interface in collision electrochemistry. Adapted with permission from ref 53. Copyright (2020) American Chemical Society. (d) The detection of single ionosomes enhanced by the charge transfer at the oil−water soft interface. Monitoring transient hydrated cation transfer at the confined interface between two immiscible electrolyte solutions (ITIES) (left) and hydrated anion transfer at the confined-ITIES by collision electrochemistry (right). Adapted with permission from ref 55. Copyright (2021) American Chemical Society.

shows that stochastic collision electrochemistry can investigate a dynamic potential distribution at the electrode−electrolyte interface confined by individual silver nanoparticles (Ag NPs).[49] A metal−solution−metal NP model is proposed by coupling the Butler−Volmer equation with Simmons theory to derive the "feeling" potential of single Ag NPs when diffusing into quantum electron tunneling region. The simulated two-dimensional contour map indicates that the geometric dimensions of Ag NPs readily affect the interfacial potential distributions, which is not revealed by the classic Gouy−Chapman−Stern theoretical framework. The collision responses can also be tuned by clever design of the involved interfaces. The efficiency of heterogeneous electron transfer at the Au UME−electrolyte interface is hindered owing to the stochasticity of large Ag NPs in dynamic collisions. However, by using a well-defined polysulfide modified Au UME, the interactions of diffusing Ag NPs at electrode (in the electron tunneling region) can be improved, as shown in Figure 2b.[50] The polysulfide layer acts as both an adhesive and preconcentrated reactive interface to effectively promote the electro-oxidation rate of Ag NPs, enabling the high-throughput characterization of NPs up to 100 nm by collision electrochemistry.

The rate of mass transport plays an important role in an electrochemical reaction, often limiting the electron transfer reaction rate at the solid−liquid interface.[51,52] While diffusion alone is often considered in mass transport processes, migration, and subsequent convection become more predominant under confinement. In such systems, the microenvironments created by all interfaces become an important consideration (e.g., zeta potential of electrode insulator). As shown in Figure 2c, finite element simulations are combined with collision electrochemistry to explore the dynamic behaviors of single particles.[53] The transient current, correlated microscopy, and simulated results indicate the electroosmotic flow as the form of convection makes the trajectories of single particles more complex, resulting in the bimodal current signals.[54] This also indicates that one can direct nanoparticles by tuning the electric field, the interfacial properties of the particles, or the electrode insulator. At the confined interface, fluid dynamics can be modulated to enhance the mass transport of individual particles at low supporting electrolyte ratios.[51−54] Collision electrochemistry can be further applied to investigate the fundamental charge transfer at a confined interface between two immiscible electrolyte solutions (ITIES).[55] The oil−water microinterface created by confining biphasic system at the tip of a micropipette. Figure 2d indicates that the electric field focused at the pipet orifice drives hydrated ion transfer, followed by the formation of individual well-dispersed ionosomes in the organic phase under the effect of electrostatic force. The formation of ionosomes is then spatially observed by the discrete ionic blips caused by the collision and fusion of individual ionosomes with the soft interface, indicating the electrochemical confinement provides an alternative platform to effectively achieve controlled emulsification by using a liquid−liquid interface. Nano- and micrometer scale water−oil biphasic systems and micropipettes are discussed in the following sections.

NANODROPLETS AS NANOCONFINEMENT REACTORS

How to Make Nanodroplets. Here, we consider nanodroplets to be liquid droplets with radii ranging from 10's to 1000's of nanometers. Nanodroplets can be found throughout nature, floating freely in the air of the atmosphere or trapped tightly in the cytosol of the cell. In this section, we focus on methods of forming nanodroplets suspended in an immiscible liquid, followed by a discussion of the electrochemical methods that can be employed to measure the reactivity of the nanodroplet-confined chemistry. These measurements can be performed on an array of nanodroplets or, with the highest analytical sensitivity, one nanodroplet at a time. Importantly, nanodroplet systems provide an accessible mimic for the compartments that build nature as well as a valuable platform for high-throughput measurements.

Emulsions are dispersions of nanodroplets through an immiscible liquid phase. Emulsions can be formed nearly spontaneously, taking advantage of the chemical potentials of the constituents (e.g., phase inversion composition/temperature methods)[56,57] or formed with high energy input by a mechanical device; including ultrasonication, high shear stirring, and high pressure homogenization.[58] Emulsions are typically thermodynamically unstable and reduce free energy by reducing the total interfacial area; demulsifying over time by droplet creaming, aggregation, and coalescence.[59] Surfactant molecules, nanoparticles, biopolymers are often added to stabilize the system.[60] When using an electrochemical detection, the stabilizer (i.e., emulsifier) needs careful consideration as the adsorption of the stabilizer to the liquid−liquid boundary can affect the size and charge of the suspended droplets[61] as well as the rate of electron/ion transfer.[62−66]

Instead of forming a dynamic distribution of suspended nanodroplets (i.e., an emulsion), single droplets can be formed one at a time with precise control over droplet dimensions. Microfluidic devices have been developed to create reproducible and stable nanodroplets for studies toward nanomedicine[67] and clinical diagnosis,[68] biosensing[69,70] and cell studies,[71] environmental analysis and treatment,[72] and chemical and nanomaterial synthesis.[73] Microfluidics work by carefully controlling fluid flow within nanochambers/channels. Often the analyte-containing fluid is pulsed into an immiscible carrier fluid, where analytes may be detected by a variety of techniques.[74] Electrochemistry is a common detection method in these systems, especially for point-of-care devices, due to the miniturizability, and cost-effective nature of the instrumentation.[75,76]

The literature covered in the remainder of this section uses ultrasonication methods to form the droplets. For ultrasonication methods, a mixture of immiscible solutions (typical volume/volume ratio is 10^3 continuous/dispersed phase) is exposed to ultrasonic sound waves (>20 kHz) in cycles, creating cavities in the liquid and resulting in emulsification.[77] Optical and fluorescence microscopy is limited by the diffraction limit of light which is a major challenge in characterizing the polydisperse nanodroplet systems; especially nanodroplet wetting.[78] Current methods to measure the distribution of nanodroplet size include dynamic light scattering, nanoparticle tracking analysis, and coulometry (i.e., electrolysis). Careful analysis of individual nanodroplet coulometry events can inform us about the size of the nanodroplet and its unique reactivity.

How to Study Nanodroplets Electrochemically. Stochastic collision electrochemistry (described in detail above) monitors real-time collisions of nanoparticles with the electrode surface and can measure individual things if the electrode is small enough such that the signal change from the single object is resolvable.[72,73] Collisions of nanodroplets can be observed by amperometry (current−time), voltammetry (current−potential), and open circuit potentiometry (potential−time). The majority of these experiments are performed amperometrically (measuring current over time), which will be the focus in this perspective. Single nanodroplet collision events are detected using ultramicroelectrodes ($r = 10^{-6}$ m) or nanoelectrodes ($r < 10^{-6}$ m). Ensembles of micro- and nanodroplets can be studied by using macroelectrodes. Here, we will only cover "reactor" experiments, where the contents of the nanodroplet are electrochemically active. Current blockade experiments for insulating particles, including nanodroplets, have previously have been covered.[79]

Amperometric and voltammetric experiments monitor the current and set or scan the electrode potential, respectively. Electrochemistry is fundamentally quantitative in that the measured current (charge per second) can be attributed to the moles of electrons passed to the electrode. Nanodroplets can be individually sized if one knows the concentration of electroactive species and number of electrons that participate in the heterogeneous oxidation/reduction of that species. When a nanodroplet irreversibly adsorbs to an ultramicroelectrode surface that is biased at a potential sufficient to oxidize/reduce the confined analyte, the analyte is totally consumed and the volume can be backed out using Faraday's law,

$$Q = nFMV \tag{1}$$

where Q is the total charge passed, n is the number of electrons, F is Faraday's constant (96485 C/mol), and M is the molarity of the electroactive species (mol/nanodroplet volume), and V is the volume of the nanodroplet. Essentially, these nanodroplets can be considered subfemtoliter electrolysis cells, where the total conversion of analyte (oxidized to reduced species or vice versa) can be accomplished in seconds or less. Performing electrolysis in low dielectric media under bulk conditions can be difficult due to the resistivity of the solvent. Using nanodroplets, one is able to quickly (in principle, submillisecond[80]) electrolyze with 100% conversion in a resistive solvent by passing low currents. Nanodroplet solvents, including nitrobenzene,[81] benzene,[82] toluene,[83] dichloroethane,[84] and cyclohexane[82] have all been explored for simple electrolysis reactions. Additionally, the exponential decay after the initial peak current has been fit using bulk electrolysis theory to back out the contact radius (i.e., effective electrode radius),[81,82] using

$$i(t) = i_0 e^{-\left(\frac{mA}{V}\right)t} \tag{2}$$

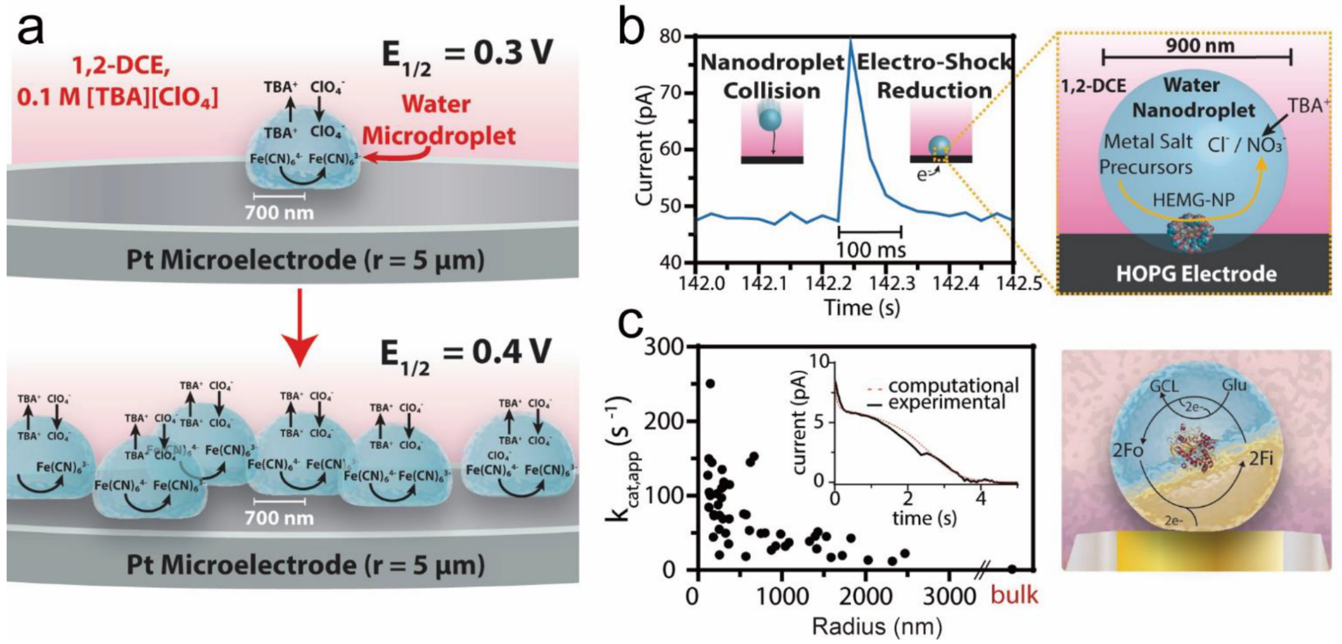

Figure 3. (a) Schematic illustrating the dependence on the number of adsorbed aqueous nanodroplets and the 100 mV shift in $E_{1/2}$ for the $Fe(CN)_6^{3-/4-}$ couple. Adapted with permission from ref 95. Copyright (2020) American Chemical Society. (b) Collision transient for nanodroplet-mediated electrodeposition, where the amperometric signal reports on the reduction of metal salt precursors contained in a single nanodroplet. The metals are fully (>98%) reduced within 100 ms. The inset shows the disordered codeposition of various metal precursors and charge balance by the transfer of TBA+ across the oil−water interface. The right of this panel shows a schematic of the electroreduction. Adapted with permission from ref 99. Copyright (2019) Springer Nature. (c) Plot relating the apparent rate constant ($k_{cat,app}$) to the size of nanodroplet ($N = 50$). The inset shows an example of a background-subtracted amperometric transient for a nanodroplet ($r = 611$ nm) collision containing 5 mM ferrocyanide, 75 mM glucose, and 0.5 mM FADGDH. The overlaid red dashed line illustrates the computation. The right side of this panel shows a schematic of the enzymatic reaction. Adapted from ref 20. Copyright (2021) with permission from Proceedings of the National Academy of Sciences USA.

where $i(t)$ describes the current at any time, i_0 describes the initial current (either the measured peak current or the calculated mass transfer-limited current to an inlaid disk), m is the mass transfer coefficient (often taken as mass transfer to an inlaid disk), A is the contact area between the droplet and electrode, V is the droplet volume, derived from eq 1 above, and t is time. The calculated contact radii are typically on the order of single to tens of nanometers for droplets with radii 100−2000 nm.

One important aspect of these experiments is that electroneutrality must be maintained, requiring ions to transfer from one phase to the other to allow electron transfer. This can be accomplished by the transfer of a redox species[85−88] or added salts.[85] As such, to ensure that the reaction is confined to the nanodroplet phase, special care must be taken to ensure reactants and products are soluble in only one phase.

The thermodynamics of ion transfer (i.e., hydrophilicity/lipophilicity of ions) between a single toluene nanodroplet and the aqueous continuous phase has been calculated by using fast scan cyclic voltammetry and Fourier-transformed sinusoidal voltammetry.[84] We also note that nanodroplet collisions can also be detected at a polarized/polarizable liquid−liquid interface,[89] instead of a polarized liquid−microelectrode interface, and has been demonstrated with amperometry, voltammetry, and potentiometry.[89−93]

How Electrochemistry Can Be Used to Elucidate the Influence of Nanoconfinement. While many groups have developed the means to study reactions within nanodroplets, there are very few electrochemical studies aimed at determining if reactivity is different in the nanodroplet compared to its bulk, continuous counterpart.

An array of millions of nanodroplets adsorbed onto a macroelectrode allows access to reactivity occurring in the three-phase microenvironment that is formed at the oil−water−electrode (surface area is increased ∼10^3 compared to a macrodroplet of the same volume).[78,94] Figure 3a illustrates that compared to the heterogeneous voltammetry in the continuous solution, the half-wave potential ($E_{1/2}$) for the $[Fe(CN)_6]^{3-/4-}$ redox couple in nanodroplets was observed to be +100 mV, and dependent on the number of droplets on the electrode surface. It was also observed in this system that a second peak in the voltammetry was present when tetrabutylammonium cations were available complex with $[Fe(CN)_6]^{3-}$, allowing for solvation in organic solutions and the heterogeneous reduction in the dichloroethane phase between the nanodroplets.[95]

In addition to new insights into chemistry at the three-phase boundaries of nanodroplets, we also see advantages in the rapid electrolysis for the species inside. By loading nanodroplets with a metal precursor salts, one can electrodeposit a nanoparticle upon collision with a biased electrode, and gain control the nanoparticle size, morphology, roughness and coverage.[96−98] As shown in Figure 3b, the small nature of the nanodroplet allows electrolysis of metal precursor salts to occur on the order of a few tens of milliseconds. These concepts were used to electrosynthesize high entropy metallic nanoparticles with equimolar amounts of eight different metals.[99] The growth kinetics of single nanoparticles in these tiny reactors was measured by nucleation and growth models.

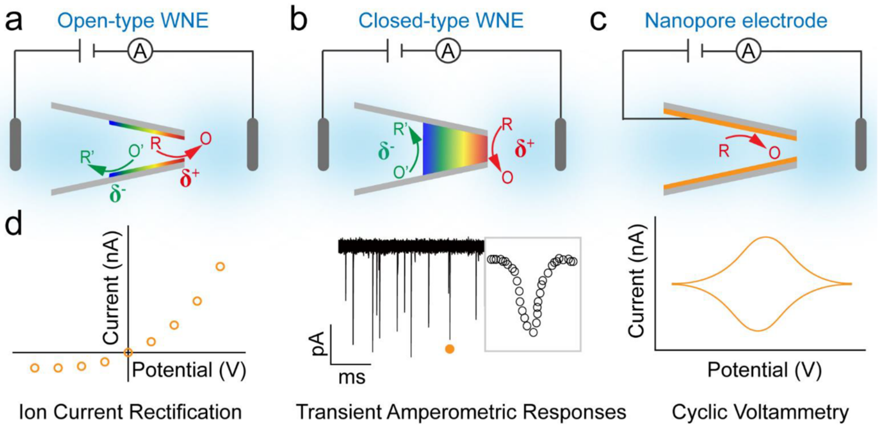

Figure 4. Schematic diagram of nanopore-based electrodes. (a) Charge transfer in open-type wireless nanopore electrodes (WNE). A couple of electrochemical reactions occur at two extremities of the conductive layer under the driving voltage. (b) Closed-type WNE for bipolar electrochemistry at the multiphase interface. The opening tip of nanopipette is filled with conductive material. (c) Schematic representation of nanoelectrochemistry confined within nanopore electrodes. The voltage is directly applied at the conductive layer of electrode, driving the electrochemical oxidation or the electrochemical reduction of redox species. (d) The multidimensional electrochemical readouts of nanopore-based electrodes.

Here, the heterogeneous growth rate constants did not have a dependence on the size of their container,[100] and future studies should be aimed at elucidating if this finding is generalizable to unimolecular/heterogeneous reactions.[101]

There is considerable literature where a nanodroplet is loaded with a well-behaved electron mediator, and the collision responses are used to study the size and mass transfer of nanodroplets. However, the nanodroplet composition can be chosen such that they can also act as model carriers for important species, like oxygen, which can be directly detected by the heterogeneous reduction.[102] It is also possible to use rapid nanodroplet electrolysis to create and maintain an electrocatalyst. This was demonstrated in 2015 by Compton's group, who used the heterogeneous reduction of Vitamin B_{12} in nanodroplets to catalyze oxygen reduction.[103] By using an electrocatalyst, the measured current can report on the kinetics of the chemical reaction if the heterogeneous redox reaction is not rate-limiting. Here, one was able to approximate an average k_{cat} for nanodroplets containing dehalogenation reactions catalyzed by Vitamin B_{12}.[104]

Ultimately, these nanodroplets can be simple mimics for cells or components within cells; and the reactivity in these confined geometries can help elucidate new truths of nature. A simple biological system can be created by trapping an enzyme, substrate, or cofactor in an aqueous nanodroplet. The stochastic nanoelectrochemical method allows one to probe the entire nanodroplet distribution of the emulsion, one droplet at a time, while rigorously accounting for the size of each impacting container (i.e., coulometry). If the enzymatic cofactor is redox-active, it can be electrochemically generated when the nanodroplet contacts the biased electrode. Thus, it is possible to track the enzymatic reaction from the start (presence of the cofactor) to the finish (depletion of the substrate). This method allowed for the observation of an apparent rate constant that is 2 orders of magnitude larger in a nanodroplet compared to bulk. Figure 3c shows a typical electrochemical transient from a catalytic collision event. The limiting current response is used to calculate the turnover kinetics and is plotted versus the droplet radius. It is shown that the rate constant is inversely related to the nanodroplet size for confined glucose dehydrogenase enzymes,[20] an observation that has been seen experimentally using a fluorogenic reaction[18,105] and theoretically by implicating interfacial stabilization of the transition states,[106,107] anisotropy or conformation.[108]

■ MULTIPHASE INTERFACIAL CHEMISTRY UNDER THE NANOPORE CONFINEMENT

How to Make Nanopore Electrodes. Nanopores refer to geometrical structures with a nanometer-sized opening, which offer well-defined nanoconfined spaces to accommodate single entities, including single cells, single particles, and single molecules. This confinement can affect the ion/molecular transport and molecular interactions.[109−113] Here, nanopore-based electrodes are defined as a subset of nanoelectrodes in which the inner walls of nanopores are modified with a layer of conductive materials (e.g., gold, silver, carbon, conductive polymer) or the inner channels of nanopores are filled with conductive materials. Figure 4a−c shows the typical nanopore-based electrodes including open-type wireless nanopore electrodes (WNEs), close-type WNEs, and nanopore electrodes, respectively. Coupling electrochemical multiphase interface with such nanopore confinement enables the observation of unique nanoelectrode kinetics and transient mass transport at the nanoscale by multidimensional electrochemical readouts including chronopotentiometry responses, amperometry signals, and cyclic voltammetry.[114−117]

Nanopipettes with an orifice on the scale of tens to hundreds of nanometers are the most commonly used substrates for the fabrication of single nanopore-based electrodes. Chemical etching is a traditional method to generate a nanopipette. Alternatively, laser-assisted pulling methods have been developed to reduce the production cost and fabrication time.[118] Here, the laser applies local heat to soften the middle of a glass or quartz capillary, which is followed by mechanically pulling capillary into two newly prepared pipettes.[119] Recently, these physical pulling strategies have become widely available. Careful control over fabrication parameters, including heating level, pulling force, pulling time, and the size of laser spot enables the geometry of nanopipettes to be precisely adjusted to certain pore size, taper length, and cone angle.[120] To further shape nanopipettes with high precision, advanced nano-

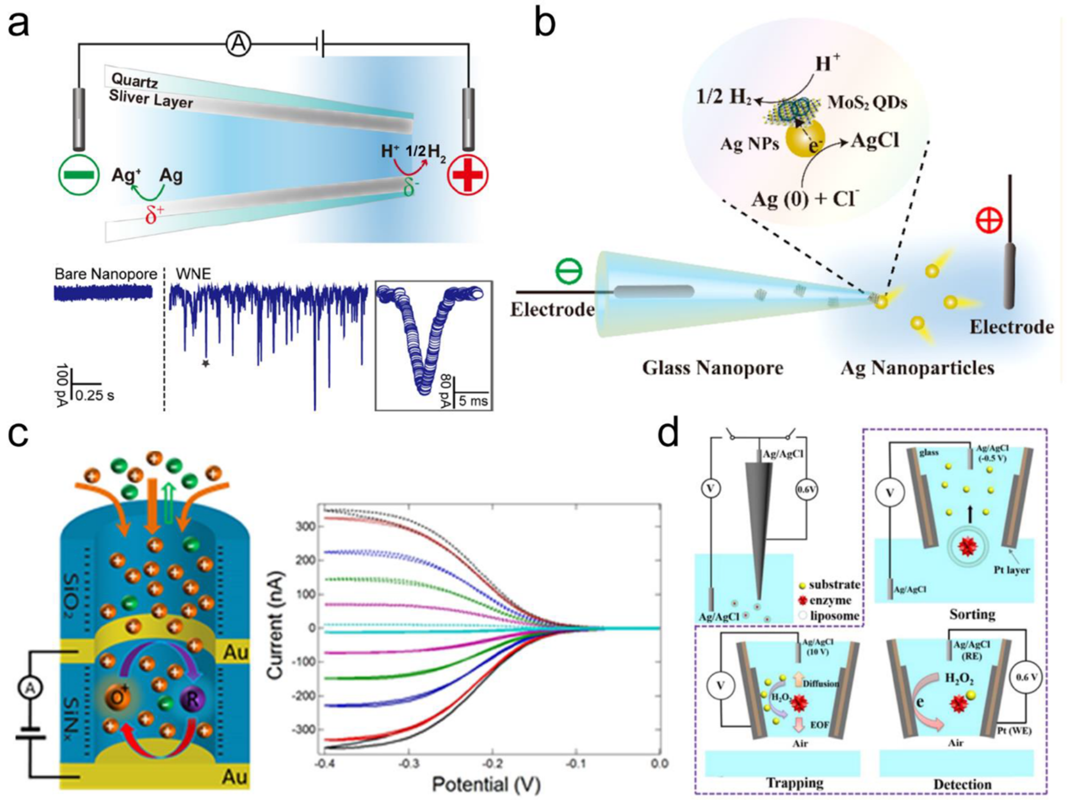

Figure 5. Enhanced electron transfer and mass transport under nanopore-based electrode confinements. (a) Ag wireless nanopore electrodes (WNE) for single-molecule and ion measurements based on bipolar electrochemistry. The sensing illustration by open-type WNE (top), and the recording ionic blips (bottom). Adapted with permission from ref 132. Copyright (2017) American Chemical Society. (b) Three-phase interface (metal−liquid−gas) on a single Ag nanoparticle electrode for the *operando* investigation of hydrogen evolution reaction at the single particle level. Adapted with permission from ref 134. Copyright (2019) American Chemical Society. (c) Amplified current by electromigration and ion accumulation effects in nanopore electrode arrays (NEA). The schematic diagram shows the configuration of NEA (left) and cyclic voltammograms of $Ru(NH_3)_6^{3+}$ in the presence of a supporting electrolyte with different concentrations (right). Adapted with permission from ref 140. Copyright (2016) American Chemical Society. (d) Schematic setup showing the nanopore electrode-based single cell analysis by using electroosmotic to balance the diffusion within the nanoconfinements. Adapted with permission from ref 141. Copyright (2022) American Chemical Society.

technologies such as focused ion beam (FIB) milling and electron beam irradiation are applied to the shrinkage of opening tips.[121,122]

For the fabrication of nanopore-based electrodes, a thin layer of conductive material functionalizes the inner wall of the prepared nanopipette. Chemical vapor deposition is often used to modify the quartz of the pipet's inner wall with a conductive carbon layer, forming a hallow carbon nanopore electrode with an open path for solution through the middle.[123−127] For the preparation of open-type WNE, physical vapor deposition can achieve the modification of the inner wall of nanopipettes with a nanothick metal layer.[120] The nanosized open path can confine and control ions and molecules near the electrode surface to form a multiphase interface (Figure 4a). In addition to nanopore-based electrodes with an open pass, closed-type WNEs are created by filling the opening tip of nanopipette with metal nanomaterials via chemical and electrochemical reduction (Figure 4b).[120] "Nanopore electrodes" are shown in Figure 4c, where the potential is directly applied on the conductive layer at the inner wall of nanopipettes. The number of nanopore-based electrodes could also be scaled up to form nanopore electrode arrays by FIB milling or nanosphere lithography with subsequent reactive ion etching.[128]

Multidimensional Readouts by Nanopore Electrochemistry. The double life of nanopore-based electrodes provides not only diverse electrochemical interfaces to investigate the electron transfer but also access to versatile nanoconfined environments, where fluid flow can be studied at the single molecule level. In practice, the tip radii and cone angles of nanopore-based electrodes can be determined via electron microscopies. Electrochemical methods are also practical strategies to characterize the features of electrodes (e.g., surface charge, electrochemical activity, and surface area). Here, we focus on characterization by the ionic response and faradaic current. Nanopore-based electrodes such as open-type WNEs and nanopore electrodes feature a nanosized channel which allows for directed fluidic flow under conditions of a concentration gradient, electric field, or external force. Ion current rectification (ICR) as a phenomenon is readily perceived by tapered electrodes. Figure 4d illustrates the ICR response that refers to the asymmetric potential-dependent rate of the ion fluxes through the electrode orifice, giving rise to a nonohmic ion current−voltage response when sweeping the potential difference between two Ag/AgCl electrodes. The fundamental study of ICR of nanopore-based electrodes is based on the pioneering work of Bard and co-workers who published the ICR response in a quartz nanopipette with 20 nm radius orifice.[129] The asymmetry in either the spatial distribution of surface charge or geometry allows the formation of an asymmetric EDL at the electrode−electrolyte interface.

As a consequence, this gives rise to the depletion and accumulation of ions at opposite polarized potentials within the nanopore-based electrodes. The characteristic thickness of EDL or Debye length at a planar surface can be used to elucidate the effect of EDL on the ion movement in electrode confinements, which is given by[129]

$$\delta = (2n^0 z^2 e^2 / \epsilon \epsilon^0 kT)^{-1/2} \tag{3}$$

where n^0 is the concentration of species of charge z in a phase with dielectric constant ϵ. T is the absolute temperature, e is the electronic charge, ϵ^0 is the vacuum permittivity, and k is the Boltzmann constant. The ICR is more pronounced when the orifice dimension of electrode is comparable to the thickness of EDL. This allows for a significant nonlinear ion current−voltage plot. The thickness of EDL can be precisely controlled by adjusting the ionic strength or the geometrical dimension of the tip region of nanopore electrodes. As shown in Figure 4d, the electron transfer process at the multiphase interface of nanopore-based electrodes can also be monitored by recording faradaic responses (e.g., cyclic voltammetry, transient amperometric responses).[125,130]

Multiphase Electrochemistry Confined in the Nanopores. With the boom of single entity nanoelectrochemistry, nanopore-based electrodes have been employed to explore electron and mass transfer under nanoconfinement. Nanopore confinement in the nanopore facilitates bipolar electrochemistry at the electrode interface, allowing half reactions to occur at two electrode extremities.[120,125,130] Based on this, WNE are able to probe multiphase electrochemistry at the microscale.[120] The voltage applied at two driving Ag/AgCl electrodes (E_{dri}) results in the anodic and cathodic overpotentials at the two poles of WNE, respectively. The magnitude of overpotential and the fraction of E_{dri} dropping across the WNE are determined by the length of WNE (l_{wne}) and the magnitude of E_{dri} as follows,[131]

$$\Delta E_{\text{wne}} = E_{\text{dri}}\left(\frac{l_{\text{wne}}}{l_{\text{total}}}\right) \tag{4}$$

where l_{total} is the distance between two driving electrodes. Importantly, two poles of WNE are oriented in the opposite polarity of the Ag/AgCl electrodes.[131] While many interesting bipolar electrochemical studies have been presented in recent decades, the majority of bipolar experiments are carried out either at the micrometer scale or under a high driving voltage.[131] In the case of WNE, almost all of the driving voltage is focused at the WNE tip. Therefore, the tapered geometry allows a high overpotential drop between the two poles of the WNE, driving coupled electrochemical reactions in the nanoconfined space.

Open-type WNE for conducting bipolar electrochemistry has been designed to explore the kinetics of single nanobubble nucleation at the three phases boundary.[132,133] Figure 5a is an illustration showing the schematic of single hydrogen bubble measurements via WNE.[132] In this case, the three-dimensional asymmetric geometry results in high overpotential across the silver WNE, driving the hydrogen evolution reaction (HER) and electrochemical oxidation of a silver layer at the cathodic and anodic poles, respectively. The formation of single hydrogen nanobubbles appears as high-throughput spikes in the amperometric i−t curve. This nanobubble-amplified transient ion current strategy is further expanded to monitor heterogeneous electron transfer in single living cells.[133] Additionally, the focused electrical potential at the nanopipette tip can drive bipolar electrochemistry on a single nanoparticle.[134−137] Three-phase interface (metal−liquid−gas) is formed when HER is catalyzed by MoS_2 quantum dots as shown in Figure 5b.[134] This geometrically well-defined single nanoparticle electrode shows the potential in *operando*, a particle-by-particle investigation of the structure−activity relationship of single nanocatalysts.

In traditional macroscopic three-electrode cell configurations, the mass transport of redox-active species in bulk solution largely occurs by diffusion, which takes place from high to low concentration. In addition to diffusional transport, electromigration and convectional transport are especially important in nanopore electrochemistry.[138−140] In nanopore-based electrode confinements, the EDL overlap exhibits when the Debye length at the solid−liquid interface is comparable to the radius of nanopore electrodes, and electromigration contributes to the mass transport. It has been reported that in the absence of supporting electrolyte, an enormous current enhancement as large as 2000-fold is observed which arises from the ion migration and ion accumulation within the ring-risk nanopore electrode arrays (Figure 5c),[139,140] providing an additional current amplification method for ultrasensitive nanoelectrochemical measurements. Indeed, the enhancement of mass transport by electroosmotic flow has been used to achieve single cell measurements, as shown in Figure 5d.[141] Electroosmotic flow describes the motion of liquid under an applied voltage. The authors used electroosmotic flow to balance the diffusion at the tip of electrodes, enabling the trapping of low-abundance enzymes within the electrode−electrolyte interface. Accumulated hydrogen peroxide, the byproduct produced by the trapped enzyme, undergoes electro-oxidation to generate transient resistive pulses.

■ CONCLUSIONS AND OUTLOOK

A century ago, the concept of measuring picoampere currents was unimaginable. Over the past century, electrochemistry has grown immensely as a measurement science tool. Measuring such low currents has now provided pathways to study the electrochemistry of single atoms, molecules, and nanoparticles. What remains the most significant question is the nature of the interface.[142] Recently, however, more complex, real-world multiphase systems have been studied with electrochemistry. Such studies have elucidated the ion transfer properties and reaction acceleration in very tiny volumes. Electrochemistry also addresses nanoscopic heterogeneities with ever-smaller nanoelectrodes. One topic of great interest that was not discussed here is scanning electrochemical cell microscopy.[143−145]

The work presented in this perspective highlights the power of high-throughput nanoelectrochemistry toward the *operando*/*in situ* characterization of dynamic interfacial processes. We believe that over the next decade, electrochemistry will witness a rapid growth of understanding in multiphase chemistry, importantly for environments under nanoconfinement. The ability of nanoelectrochemistry to directly investigate the charge transfer and mass transport at the single entity level provides insight into the transient interchange of chemical and electrical energy at the nanoconfined interface. Yet it is difficult to surmise from a single amperogram the physicochemical properties of solution species without correlated microscopy and spectroscopy. Therefore, the combination of nanoelectrochemical techniques and ultrafast spectroscopy/microscopy will produce a comprehensive picture of structure−activity relationships of single entities. A combination of techniques will also further elucidate new truths of nature in the molecular and electronic dimensions. For example, electrochemistry based on UME collisions could be coupled with liquid-cell transmission electron microscopy[146,147] to reveal molecular information, dynamic structural and compositional evolution of individual nanocrystals during electrochemical reaction in real-time. That said, the more techniques that are observing the same phenomenon, the further that phenomenon is from reality. This "observer effect" was popularized by Heisenberg, who recognized that to make a measurement, one must alter the state of what is measured. Careful efforts to understand the impact of each measurement tool on the system must be taken.

Finite element simulations based on continuum models are now commonly employed as the widely used computational method of choice in nanoelectrochemistry. However, the multiphase electrochemical process under nanoconfinement is nonequilibrium and discontinuous. Thus, it remains necessary to enhance the theoretical nanoelectrochemistry by building intricate bridges among density functional theory, molecular dynamics modeling, and finite element modeling. The emergence of artificial intelligence in analytical chemistry will also certainly accelerate the progression of advanced theoretical simulation and assist multidimensional analysis to precisely offer the detailed information on multiphase interface in chemical/physical processes.

The cutting-edge single entity nanoelectrochemistry is the most promising technique to advance the real-world applications of confined interfaces in the field of energy conversion and precision medicine. We hope a wearable and portable eHealth system based on the nanopore interface array chips could be designed for point-of-care testing of diseases, empowering patients with real-time single molecule diagnostic platform with high sensitivity and selectivity. Also, UME arrays can be developed for large-scale energy generation, conversion, and storage with high efficiency by taking advantage of the mass transfer properties.

Here, we focused on the studies of electron transfer events in multiphase microenvironments, as measured by electrochemical methods. However, these results have implications that are of uniting interest among nearly all scientific disciplines. Analytical chemists, who are focused on making these measurements possible, have developed a myriad of techniques to probe physical and chemical transformations in and around confined reactors. Of particular interest is the measurement of the accelerated reaction rates. The highest apparent acceleration factors (10^4−10^6) reported are for systems of highly charged microdroplets (air−water or mixed solvent interface) generated by electrospray, where the product formation is measured by mass spectrometry.[148] Here the act of creating droplets that will eventually ionize the chemical constituents changes the system quite a lot, and comparison to atmospheric/environmental chemistry is an important collaboration toward the discovery of the origin of life.[21]

Fluorescence microcopy has been used to observe accelerated rates occurring in an oil droplet−water emulsion.[18] In that study, the authors note an inverse relationship between the apparent forward rate (and K_{eq}) and droplet size ($\geq 8\ \mu$m) with a 45-fold enhancement that could be explained by interfacial adsorption. The results of this simple chemical equilibrium find parallels in biochemical studies, where the stability of proteins and biochemical catalysis are routinely studied in subcellular-sized reactors.[17,108] It also finds applications in synthetic/materials chemistry where confinement can tune mass transport, enhance electron-transfer rates, and alter the stability/dispersion of a material to improve electrochemical performance.[149]

In recent years, vibrational sum-frequency generation spectroscopy has become a powerful tool to measure kinetics at phase boundaries, including an accelerated photooxidation reaction occurring water−air interface.[150] Verlet's work also elucidates the solvated electron at such a boundary. These observations have led to detailed explorations into the microdroplet boundary and the electric field/species that may be stabilized in this extreme microenvironment.[151,152] It has become clear that physical properties at the intersection of two immiscible dielectric media (e.g., $\varepsilon_{water} = 80$, $\varepsilon_{air} = 1$) must not mimic conditions in the deep center of a liquid phase. Computational chemists have performed simulations (i.e., reactive force field model of water, ReaxFF/C-GeM) of the air−water interface for spherical microdroplets that demonstrate that electric field alignments along free O−H bonds at the surface are ∼16 MV/cm larger and have an order of magnitude higher distribution compared to O−H bonds in bulk water.[21,153]

While advances in nanoconfinement measurements are a budding field for analytical chemists, the observation that organic reactions could proceed differently in the presence of a phase boundary has been well established. Sharpless described hydrophobic reactions that were accelerated when water was stirred into the organic solution in 2005[107] (but there were reports of such phenomena in the 1980s) and Marcus provided a theoretical framework that relied on the hydrogen bonding between phases.[106] As scientists reach the nanoscale, these individual studies mark advances in fundamental understanding within disciplines, including chemistry and biology. However, taken together, the amalgam can provide governing principles that may ultimately put the recipe for life at our fingertips. Synergy across disciplines is the ultimate requirement of this work.

In this Perspective, we have shown that multiphase chemistry, especially under nanoconfinement, challenges fundamental chemistry concepts. These environments are of great importance in nature, where molecules constantly interact with multiple phases during the reaction progress. Many biological processes take place within crowded environments constructed of many interfaces. Advanced nanoelectrochemical techniques, known for their high spatiotemporal resolution, offer a powerful means to investigate transient interfacial processes within these biological confinements. As a result, one can uncover the dynamic behaviors exhibited by single biomolecules and the unique reactivity in complex biological systems. Furthermore, chemists are becoming more aware of variations in reactivity and capitalizing on chemistry in small volumes for synthetic purposes. Studying such interfaces under nanoconfinement can elucidate new and surprising chemistry, providing answers to the following enticing questions: Why are chemical reactions accelerated under nanoconfinement? Can regioselectivity be influenced due to nanoconfinement? How do the kinetics and colligative properties change under nanoconfinement? What role did nanoconfinement play in the genesis of life? The development of new measurement tools is fueling the discovery in this area. Nanoconfinement controlled multiphase chemistry offers an exciting new chemical frontier that holds great potential for new knowledge.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

EDL, electric double layer; UME, ultramicroelectrode; NP, nanoparticle; ITIES, immiscible electrolyte solutions; $E_{1/2}$, half-wave potential; WNE, wireless nanopore electrode; ICR, ion current rectification; FIB, focused ion beam.

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