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Complex single-molecule and molecular scale entities in electrochemical environments: Mechanisms and challenges

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Abstract

Following a renaissance from the 1980s, electrochemistry has developed into sophisticated interdisciplinary science integrating solid-state and surface science and further, biological sciences. Most remarkably, even the single-molecule can now be addressed. Single-molecule electrochemistry covers transition metal complexes, organic redox molecules, fragile biomolecules, and molecular-scale hybrids between metallic nanoparticles and complex molecules, supported by new theoretical frames. We overview here selected areas of molecular scale electrochemistry. After a theoretical minimum, we address complex molecules in electron transfer, enzyme catalysis, and nanoparticle catalysis. Our focus is on issues not so much previously highlighted, such as competition between superexchange and sequential conduction, and resonance features in the transition between the two limits. Another aspect is coherent multi-electron transfer for large bias voltages often needed to drive enough current through solute molecular junctions. We note finally some single-molecule perspectives relating to DNA-based molecules and to spin transitions via chiral molecules.

1 | INTRODUCTION

Following a renaissance in the 1980s and 1990s, electrochemistry has moved to new levels reaching even a single molecule.^[1] Single-molecule electrochemistry extends to transition metal complexes,^[2] organic redox molecules,^[3] fragile biological macromolecules, such as metalloproteins^[4] and DNA-based molecules,^[5] and molecular-scale hybrids between nanoparticles (NPs) and electron transfer (ET) metalloproteins.^[6] Single-molecule

electrochemistry is paralleled by theoretical frames, rooted in evolving understanding of the electrochemical interface,^[7] and the fundamental electrochemical electron, proton/hydrogen atom, and atom group transfer process.^[8] Single-molecule technology under the coveted appellation molecular electronics are further-reaching perspectives.^[9] We overview here some areas underway to a new understanding of molecular-scale electrochemistry of complex chemical and biological entities. We address first a theoretical minimum relating to ET at

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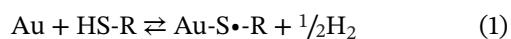
the electrochemical interface and in the in-situ electrochemical scanning tunneling microscopy (STM). We then discuss single-molecule entities that can be brought to do something, from ET to NP and enzyme catalysis.

2 | MOLECULAR SCALE ELECTROCHEMICAL SCIENCE

Nanoscience objects display novel size-dependent properties. Quantum mechanical phenomena such as electron tunneling are at the core, and physical laws such as the renowned Ohm's law take new forms. Metal and semiconductor nanostructures are also nanoscale electrochemistry objects. 2D and 3D graphene materials are other examples of non-traditional materials science^[10] in electrocatalysis, battery research, and (bio)fuel cells.^[11] Metalloenzymes and DNA are nanoscale bioelectrochemistry targets. Single-molecule electrochemistry is not as firmly established as single-molecule optics, which monitors truly single-molecule events, while single-molecule electrochemical STM monitors successive ET events.^[12] Single-molecule electrochemical ET events are, however, observed in collision electrochemistry,^[13] and electrochemistry can be combined with optical methods in single-event electrochemistry.^[12]

In-situ electrochemical STM and AFM,^[4a,14] offer two correlations, tunneling current/overpotential and current/bias voltage correlations. Ex-situ STM in air or vacuum only offers the latter.^[15] In-situ STM has become a powerful tool to map organic and inorganic molecules^[1,3b,16] and biomolecules such as redox (metallo)proteins and DNA.^[4b,5a,14,17] Conversion of in-situ STM currents to molecular structure requires strong theoretical support. In-situ STM has disclosed new ET phenomena, possibly a rationale for often observed very high current densities.^[14,18] Single-ET charging of metallic NPs,^[19] represent other single-entity phenomena. New electrode materials, with graphene-based interfaces^[10a,11a], perovskites,^[20] core-shell NPs,^[21] carbon nanotube,^[22] mixed-valence materials,^[23] and nanoporous electrodes^[24] have further become prominent.

Modified electrochemical surfaces, either the metallic surface itself as in nanoporous gold,^[24–25] or by self-assembled molecular monolayers (SAMs) have developed immensely.^[26] Surface spectroscopies (X-ray photoelectron spectroscopy (XPS), energy-dispersive spectroscopy (EDS), infrared spectroscopy (IR), and Raman), transmission and scanning electron microscopy, as well as STM/AFM, have enabled unprecedented structural resolution of thiol SAMs on Au-surfaces. Comprehensive studies have led to the adsorption process:



with sulfur bound as a thiyl radical, $\cdot\text{S}(0)$ ^[26b,c] in a strong van der Waals unit. The R-residues can be hydrophobic, hydrophilic, and electrostatically charged or neutral. $\cdot\text{S-R}$ SAMs, are therefore building blocks in tailoring surfaces for gentle binding of fragile biomolecules, and for catalytic and other purposes.^[14,27] Unless sterically hindered, adsorption is via mining of a surface gold atom, and sideways binding of two thiyl molecules, Figure 1. The bulky *tert*-butanethiol, 2-methyl-2-propanethiol is the only butanethiol binding solely on a flat surface.^[28] Packing is further determined by the Au-surface, illuminated by widely different packing of the amino acid cysteine on Au(111)-, Au(110)-, and Au(100)-surfaces, for which adsorption energies, structure, and molecular origin of STM contrasts have been mapped by ET theory and density functional theory (DFT).^[29]

3 | SINGLE-MOLECULE ELECTROCHEMISTRY AND IN-SITU STM OF COMPLEX MOLECULES

3.1 | Some core notions

Alkanethiol-based SAMs display prodigious binding modes,^[30] but are still simple molecules, although sharp capacitive peaks indicative of phase transitions are observed.^[31] Redox molecules that undergo chemical processes are what we denote as complex. The processes are simple ET as tunneling probes, including organic and inorganic redox molecules,^[2–3] enzyme-substrate,^[32] and inter-protein and protein-DNA interactions.^[4b,33] To this add quantum interference,^[34] statistical approaches,^[35] ionic liquid,^[3a,16b,36] and ionic atmosphere effects.^[14,37] Figure 2 shows an in-situ STM diagram of a redox molecule in a polar (aqueous, ionic liquid) medium, specifically reduction with negative bias (V_{bias}). The redox level is vacant at equilibrium, well above both Fermi levels, and superexchange prevails. As the overpotentials of the working electrode and tip are both shifted negatively, ET switches from superexchange to hopping, with the redox level temporarily populated. If coupling to the second electrode is weak, relaxation continues all the way across both Fermi levels, with renewed activation for the second step. If the coupling is strong, multiple ET continues until full relaxation.^[14,38]

Charge transport in solid metal-molecule-metal junctions has evolved over several decades. The Landauer approach, which rests on high order quantum mechanical perturbation theory (Green's function frames), has been a primary frame for charge transmitting orbitals off-resonance the Fermi levels. This approach faces challenges, as a resonance between the three levels is approached. Charge transport then switches from

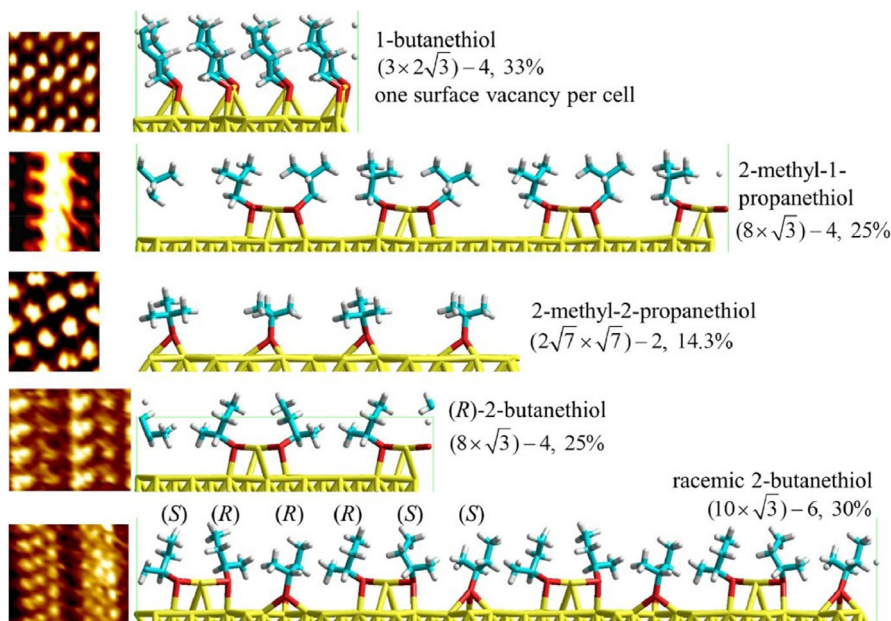


FIGURE 1 From top to bottom, binding of the four isomeric butanethiols on Au(111). Column to the left: high-resolution in-situ scanning tunneling microscopy (STM) images, on which the self-assembled molecular monolayers (SAM) interpretation is based^[27]

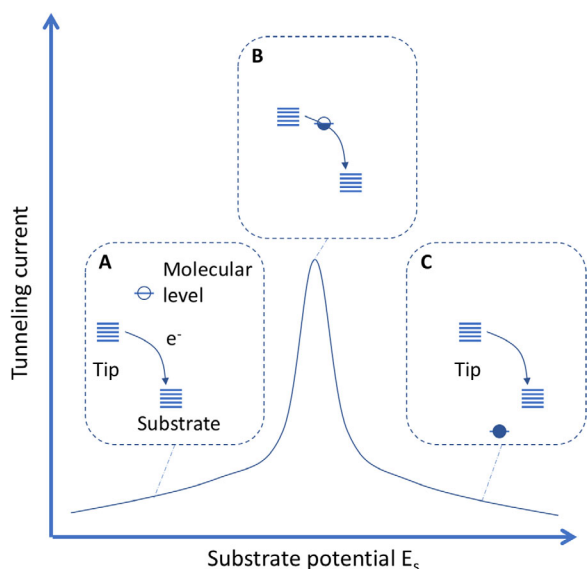


FIGURE 2 Tunneling current/overpotential correlation on the parallel variation of the substrate and tip potential^[2]

superexchange to electrochemical ET with a physical population of the intermediate molecular state(s) and strong electronic-vibrational coupling, crucial for solvated junctions. Such views were introduced 30 years ago,^[39] related concepts in fact much earlier.^[40]

3.2 | A theoretical minimum

Core notions of the rate constants, $W_{LR}(\eta)$, $W_{ML}(\eta)$ and $W_{RM}(\eta)$, and tunneling current, $j_{LR}(\eta)$ at given working

electrode overpotential (η) and tip/electrode bias voltage (V_{bias}) in two-step electron/hole transfer in molecular in-situ STM junctions can be summarized as^[14,38]:

$$W_{LR} \approx 2 \frac{W_{ML}W_{RM}}{W_{ML} + W_{RM}}$$

$$j(\eta) = en_{el}W_{LR}(\eta) \quad n_{el} \approx \frac{|eV_{bias}|}{\delta\varepsilon^*} \quad \delta\varepsilon^* \approx \frac{1}{\kappa_L\rho_L} + \frac{1}{\kappa_R\rho_R} \quad (2)$$

e is the electronic charge. The subscripts refer to the left (L) and right (R) electrodes, and to the molecule (M). $\rho_{L,R}$ are the densities of state and $\kappa_{L,R}$ (κ_{ML} or κ_{RM}) the electronic transmission coefficients. By Equation (2), the stronger the interaction between the molecule and the electrodes, or the faster electronic relaxation, the smaller $\delta\varepsilon^*$ and the larger the number of electrons transferred, n . Assuming linear response, and representing the Fermi distributions by step-functions,^[8,41]

$$W_{ML} = \frac{\omega_{eff}}{2\pi} \int_{-\infty}^0 \kappa_{ML}(\varepsilon)\rho_L(\varepsilon) \exp\left[-\frac{(\lambda_R - \varepsilon - \gamma eV_{bias} - \xi\eta)^2}{4\lambda k_B T}\right] d\varepsilon$$

$$W_{RM} = \frac{\omega_{eff}}{2\pi} \int_0^{\infty} \kappa_{RM}(\varepsilon)\rho_R(\varepsilon) \exp\left[-\frac{(\lambda_R - \varepsilon - \gamma eV_{bias} - \xi\eta)^2}{4\lambda k_B T}\right] d\varepsilon \quad (3)$$

Equation (3) applies to metal, semiconductor, and semimetal electrodes. λ_R is the nuclear reorganization free energy, ω_{eff} the effective frequency, k_B Boltzmann's constant, and T the temperature. ξ and γ represent the

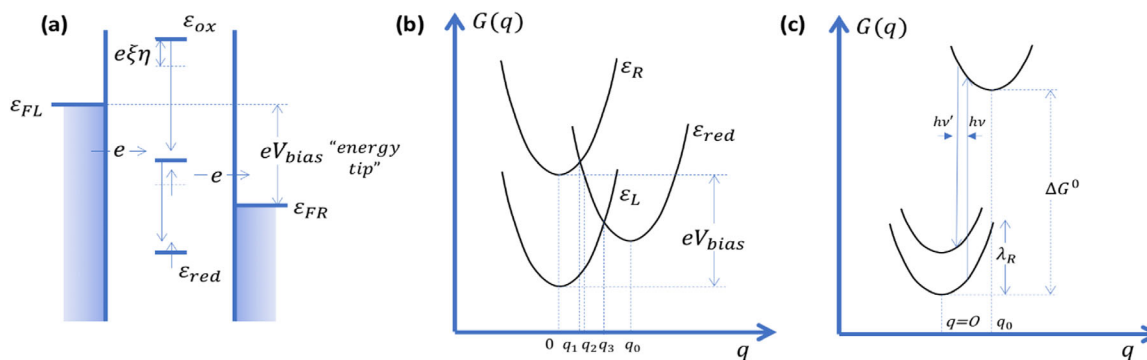


FIGURE 3 (a) Energy diagram representing two-step in-situ scanning tunneling microscopy (STM). (b) Potential (free) energy surfaces in two-step in-situ STM. (c) Optical analog in solute molecular resonance Raman scattering.^[39a,46]

overpotential and bias voltage at the molecular site. A difference from normal electrochemistry is thus that two potentials, η and V_{bias} here control the current.

In the weak-coupling, diabatic limit Equation (3) can be recast in terms of the Anderson-Newns chemisorption parameter, $\Delta_{ML}(\epsilon)$, of reactant level broadening^[42]:

$$\Delta_{ML}(\epsilon) = \pi \sum_k |V_{ML}(\epsilon)|^2 \delta(\epsilon) \rightarrow \pi |V_{ML}(\epsilon)|^2 \rho(\epsilon) \quad (4)$$

$V_{ML}(\epsilon)$ is the electronic coupling parameter, k numerates the electronic energy levels, and $\delta(\epsilon)$ is the delta-function. For electrode overpotentials, $|\eta| < \lambda_R$,

$$W_{ML}(\eta) \approx 4\pi \frac{\Delta}{\hbar} k_B T \sqrt{\frac{\pi}{\lambda_R k_B T}} \exp \left[-\frac{(\lambda_R - \gamma e V_{bias} - \xi e \eta)^2}{4\lambda_R k_B T} \right]; \quad 4\pi \frac{\Delta k_B T}{\hbar} \sqrt{\pi / (\lambda_R k_B T)} \ll 1 \quad (5)$$

where Δ is the $\Delta_{ML}(\epsilon)$ value near the Fermi level. The diabatic ET rate, Equation (5), is thus independent of the effective frequency. Equations (2) and (3) give symmetric current/overpotential correlations for symmetric junctions with a maximum at the equilibrium potential, $\eta = 0$. This expectation has met with some success, Section 4, but challenges remain:

- In-situ scanning tunneling spectroscopy (STS) of some complex molecules do not display a spectroscopic, but a sigmoidal correlation. A soft gating mode can account for such behavior.^[43] Equilibrium between oxidized and reduced probe molecules is an alternative:

$$\langle G \rangle = G_{red} + \frac{1}{1 + \exp \left[\frac{e\eta}{k_B T} \right]} (G_{ox} - G_{red}) \quad (6)$$

where G_{ox} , G_{red} , and $\langle G \rangle$ are the conductivities of the oxidized and reduced form, and of the average conductivity. Bridging spectroscopic and Nernstian behavior remains a challenge.

- Transition between hopping and superexchange is expected as the overpotential or bias voltage is scanned over wide enough ranges. It was recognized early that this transition involves entangled quantum features.^[44] Tao and associates provided experimental substance to such dual patterns.^[34a] Sowa and Marcus recently offered a formal frame, aiming at bridging two-step hopping with Landauer superexchange.^[45] The particular in-situ STM potential surface landscape, however, poses challenges, Figure 3,^[39a] notably with close relations to other three-level processes such as resonance Raman excitation profiles of solute molecules, Figure 3.^[46]
- Spin and Coulomb effects are other challenges that we note but do not presently discuss.
- The electrolyte itself imposes rectification,^[14,37] reflected in the correlated parameters ξ and γ , Equations (2) and (3).
- Large bias voltage is often needed to drive enough current. When $|eV_{bias}| > \lambda_R$ the reduced or oxidized molecular level after the first ET step is trapped between the electrode Fermi levels, rather than below (or above), Figure 3. The redox level then continues transmitting electrons, until further overpotential scanning takes the level out of the bias voltage window. The correlation then displays a plateau around the equilibrium potential, cf. Section 4
- Nuclear tunneling is incorporated straightforwardly. Sumi and associates studied, how quantized nuclear modes are reflected in STS.^[47] Nuclear tunneling is important when proton or hydrogen atom transfer is involved, single-molecule perspectives of which are discussed.^[48] Along such lines, electrochemical diamond plots have been introduced.^[14]

- A final challenge is the coupling between the molecule and the electrodes. Most theoretical approaches rest on the diabatic limit of the elementary ET steps. Weak interactions, however, entail small currents, illuminated by isomorphous Co- and Os-complexes^[2,49]. The former conducts poorly, the latter with striking amplification and other high-conductivity behavior. Attempts to incorporate the adiabatic limit into the tunneling conductivity of complex molecules are reported, with Medvedev's work of particular importance.^[50] A major challenge is that adiabatic ET not only implies transmission coefficients approaching unity but a fundamental change of the in-situ STM physics,^[38,50–51] all the way from weakly conducting individual ET steps to increasing coherence with only partial or no vibrational relaxation in the intermediate molecular electronic state.

4 | IN-SITU STM AND STS OF COMPLEX MOLECULES AND BIOMOLECULES

4.1 | Organic and inorganic redox molecules

Tao's study of Fe-protoporphyrin IX was the first case of single-molecule in-situ STS, showing a maximum around the equilibrium potential.^[16c] Other complex organic and inorganic molecules, with large on-off current ratios have followed.^[2,3,16d] Mechanical properties,^[52] solvent effects,^[16b,53] quantum interference,^[34] and stochastic effects,^[35] have also been addressed. The comprehensive studies of Nichols and associates on viologens, more recently on metalloporphyrins and polymetalates illuminate prodigious perspectives and challenges of these powerful approaches. Note that, 6V6 viologen between an Au tip and Au(111)-electrode surface via two 6-carbon thiy l linkers can here be compared with tetrathiafulvalene (6PTTF6).^[3b,c,31,54] STS of the rigid 6PTTF6 in aqueous electrolyte displays a sharp maximum, but the floppy 6V6 has a sigmoidal dependence. Gated ET via a torsional mode could reproduce the latter^[43] but as noted, sigmoidal correlations can also reflect equilibrated higher conductivity of oxidized than reduced 6V6, Equation (6). 6V6 in 1-butyl-3-methylimidazolium triflate displays, however, intriguingly a maximum. To elucidate this difference,^[54] we have initiated studies of the 6V6 electrochemical junction using quantum mechanical theory, classical molecular dynamics (MD) simulations, and DFT.^[55] Figure 4 reproduces qualitatively the solvent effect observed. The physical reason is a conspicuous difference in the solvent reorganization energy, 0.12 eV (water) vs. 0.45 eV (room temperature ionic liquid (RTIL)).

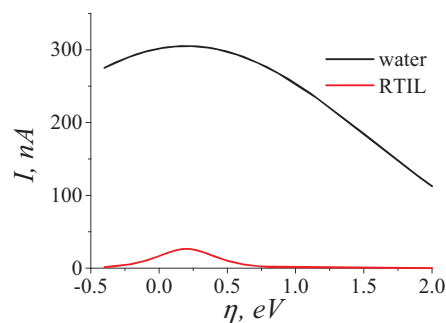


FIGURE 4 Computed current–voltage dependencies for electrochemical 6V6 junctions ($V_{bias} = 0.4$ eV, $C = 0.01$ M)^[55]

Presently we address two other aspects so far less in focus. Robust transition metal complexes, particularly Os-complexes of 2,2'-bipyridine and linking polypyridine have emerged as powerful in-situ STM/STS targets,^[2,49] Figure 5. The complexes show an STS maximum around the equilibrium potentials, with on-off ratios up to two orders of magnitude, following the bias voltage in accordance with Equations (2)–(5). The core Os-complex in ionic liquid illuminates another aspect. The broad central segment associated with the large bias voltage (0.7 V) reflects coherent electron transport until the current decays at still higher overpotentials, Section 3.2. Os-polypy complexes also offer a direct comparison between electrochemical ET and in-situ STS, concluding that several hundred electrons are transferred in a single adiabatic two-step in-situ STM event.

4.2 | Single-molecule bioelectrochemistry

Single-molecule in-situ STM was early brought to include large biomolecules.^[57] The now paradigmatic in-situ STM metalloprotein, the blue copper protein azurin, was introduced slightly later.^[4c,58] Studies now include broad mechanistic detail. (holo-, apo- and metal-substituted azurin, coherent versus two-step hopping, temperature, and kinetic isotope effects^[59]).

4.2.1 | Single-molecule in-situ STM of redox metalloproteins and metalloenzymes

P. aeruginosa azurin (Mw \approx 14,000 amu), introduced as an in-situ STM probe more than two decades ago^[58a–d] is the most comprehensively studied single-molecule redox metalloprotein. Strategies for this choice, Figure 6 are, first that the redox potential is comfortably accessible in both electrochemistry and in-situ STM. The β -sheet structure

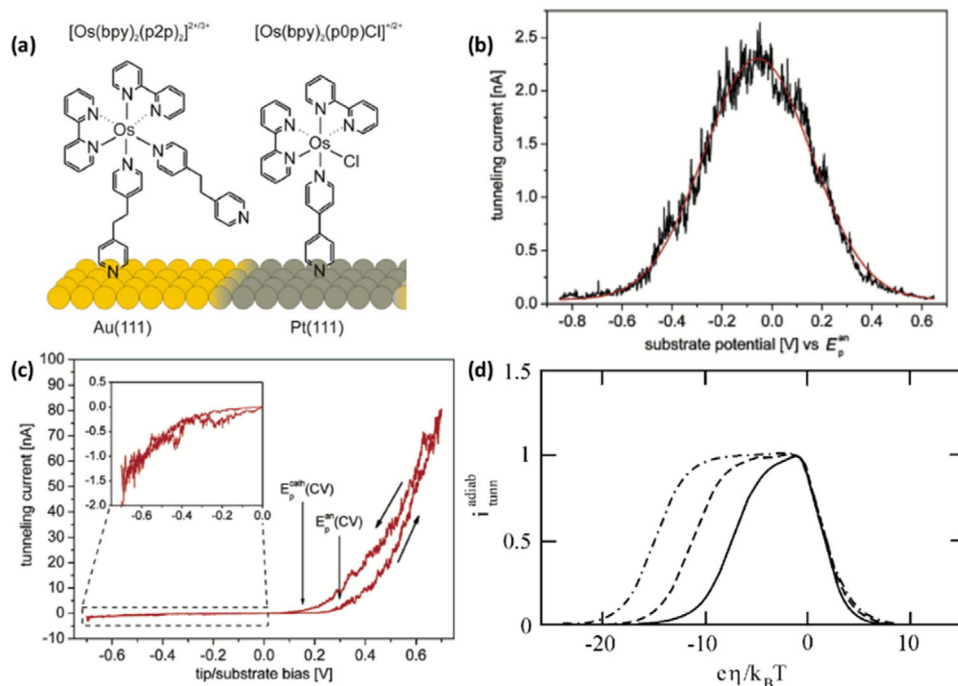


FIGURE 5 (a) Os-complexes on Au(111) and Pt(111). (b) Tunneling current/overpotential correlation in an ionic liquid. The broad peak is indicative of coherent electron transfer (ET) in an intermediate 0.5 V overpotential range. (c) Single-molecule rectification of the Os-complex. (d) Theoretical current/overpotential correlations at large bias voltages^[49,56]

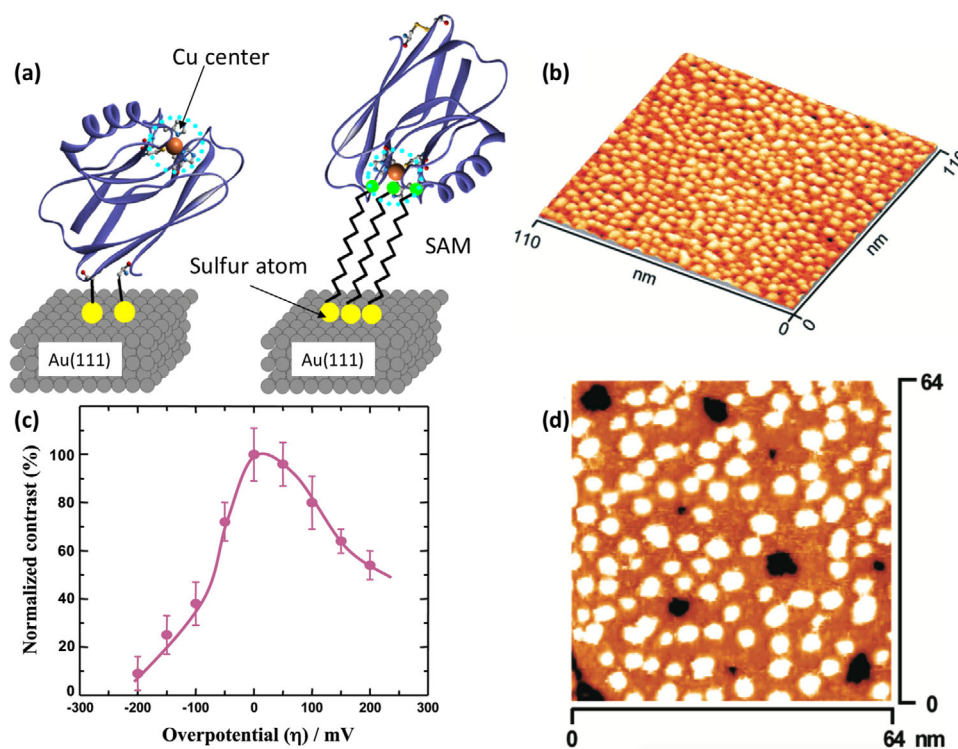


FIGURE 6 (a) *P. aeruginosa* azurin on Au(111), via the disulfide group, or via the hydrophobic patch around the Cu-center, on variable-length alkanethiol self-assembled molecular monolayers (SAMs). (c) Tunneling current/overpotential scanning tunneling spectroscopy (STS) of azurin on octanethiol SAM. In-situ scanning tunneling microscopy (STM) of azurin on bare Au(111) (b) and octanethiol SAM modified Au(111) (d)^[58b-d]

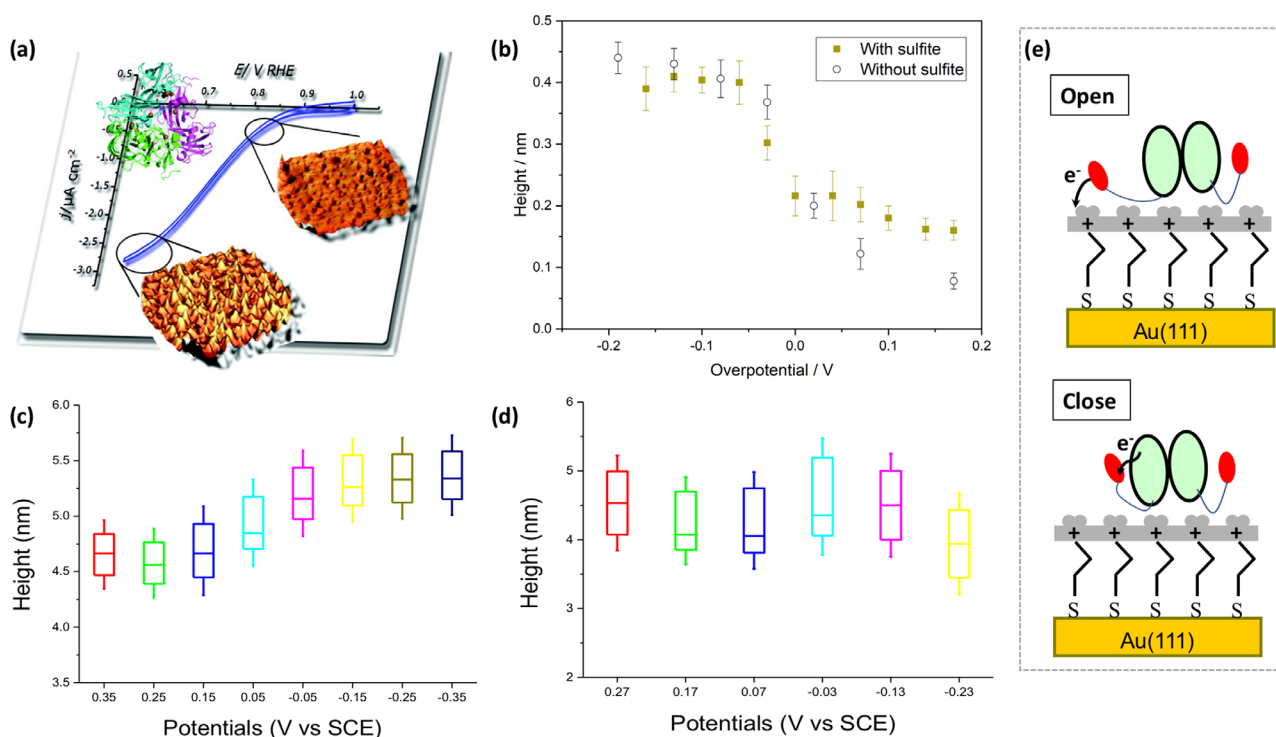


FIGURE 7 (a) Voltammetry and in-situ scanning tunneling microscopy (STM) of laccase (*Streptomyces coelicolor*). (b) Tunneling current/overpotential correlation of the Mo-enzyme hSO. Electrochemical AFM of CuNiR in the active (c) and resting-state (d). (e) Scheme of gated hSO electrocatalysis^[32,61,62]

is robust in biologically challenging STM and even XPS environments. Further, azurin holds two surface groups for Au-surface linking. One is disulfide for direct linking, the other one a hydrophobic patch around the Type 1 Cu-centre, suitable for gentle linking to hydrophobic thiol SAMs.^[58c] In-situ STS of azurin on variable-length thiol-SAMs displays a 10:1 on-off peak. Rigorous bandshape analysis requires attention to protein orientation, electrostatic potential distribution, ionic strength, and electronic coupling to the enclosing electrodes. Azurin also illuminates a recurrent issue. ET between the disulfide radicals generated by pulse radiolysis and the Cu-centre points to slow, millisecond intramolecular ET.^[58e] In-situ STM current densities, however, accord with much higher rates, indicative of adiabatic interfacial ET and according with strong in-situ STM contrasts, Figure 6.^[58c] This core metalloprotein has thus opened new areas of single-molecule bioelectrochemistry. As noted, ongoing activity relating e.g. to temperature dependence and phase transitions have disclosed other challenges.^[59b,c]

4.2.2 | Single-molecule metalloenzyme electrochemistry

In-situ STM extends to multi-center redox proteins, redox enzymes, and large protein and protein/DNA complexes.^[5a,17a,33,60] We focus here on two redox metal-

loenzyme classes. One is the blue copper enzymes, four-Cu laccase (Lc), and two-Cu nitrite reductase (CuNiR), Figure 7. A representative of the other class is the molybdenum enzyme human sulfite oxidase (hSO).

Metalloenzymes often show no voltammetry of their own, but strong electrocatalytic signals as the substrate is added. In CuNiR and Lc electrons are let in at the type 1 center, and out towards dioxygen or nitrite reduction at the Type 2/3 or Type 2 center, via direct links connecting the Type 1 and Type 2 or type 2/3 centers. In-situ STM offers single-molecule clues.^[32,61] Single-molecule resolution of CuNiR is achieved only when NO_2^- is present as if NO_2^- triggers conductivity. The same applies for Lc, which shows high conductivity when O_2 -substrate is reduced, but is completely transparent when no O_2 reduction occurs, Figure 7. Electrochemical AFM discloses substantial CuNiR swelling from the resting to the active state, Figure 7.^[61] Such changes transmit to the Cu-centers showing that even small conformational reorganization triggers fast intramolecular and interfacial ET.

hSO on ω -amino octanethiol SAM modified Au(111)-electrodes also gives single-molecule in-situ STM.^[62] The Moco center with high electronic density is potentially a strong in-situ STM target. As for the blue copper enzymes, the substrate is a small molecule, sulfite, not itself detectable by STM, but which can trigger enzyme electronic changes. In-situ STM discloses 2%–5% coverage of molecular scale contrasts with a clear transition from low

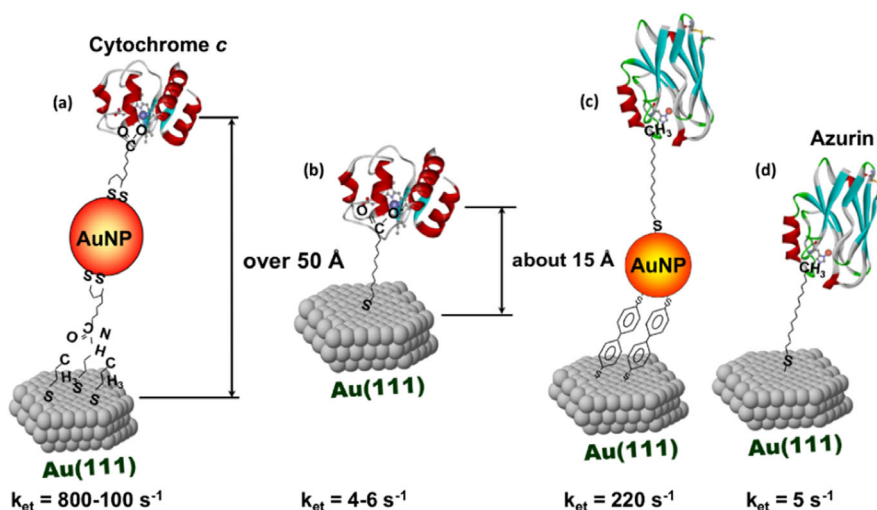


FIGURE 8 (a,b) Interfacial electron transfer (ET) of horse heart cytochrome *c* via a 3 nm coated AuNP and directly at a self-assembled molecular monolayer (SAM)-covered Au(111)-electrode. (c,d) Similar configurations for the blue copper protein azurin^[6]

conduction at high potentials to high conduction at low potentials. In-situ STS is sigmoidal, as noted indicative of either Nernstian equilibration or gated tunneling.^[62] The closed/open mechanism could favor the latter. Another challenge is that in-situ STM/STS in the absence and presence of sulfite is virtually indistinguishable. This suggests that enzyme activity is not directly monitored as for the blue Cu-enzymes, but a sulfite independent tunneling process through the two enzyme domains.

4.3 | Molecular scale NP/molecular hybrids

SAM-protected metallic NPs range from targets in molecular electronics, to biomolecular marking and electrocatalysis.^[63] AuNPs are core targets, but other metals, alloys, and core-shell NPs have attracted attention. AuNPs are targets in experimental and theoretical studies.^[53] Note that, 1–2 nm coated AuNPs display single-ET charging^[64] fading out above about 2.5 nm, that is, the size of large transition metal complexes.

NP catalysis where small molecules strongly adsorb has been framed by electronic structure computations.^[65] Electrocatalysis by protected AuNPs, as for transition metal complexes, quinones, metalloproteins, and enzymes^[53] are, however, quite different. In spite of ET distance extension up to several nm, more than an order of magnitude rate increase is observed. Similarly extended molecular matter would entirely close ET. There is presently no obvious single physical origin of the rate enhancement. The complexity of the electrochemical interface is presently beyond computational capacity. In a recent study, we explored, whether a single gold molecular scale nanocluster (AuC) could be a catalytic

center, with a focus on the ET reactivity of the AuC surface structural elements towards a ferrocene probe, Fc. A recurrent issue is further, whether ET via the NP would be by superexchange, or sequential, fully relaxed ET.^[53]

Figure 8 shows two electrode/AuNP/probe systems.^[6] Insertion of a 3 nm coated AuNP enhances the rate constant more than an order of magnitude. Figure 9 shows the model used, with electrode, Au_{*n*}C (*n* = 13–147), Fc probe, and dielectric solvent. We combined notions of electronic spillover, i.e. whether the AuC electronic density expands further than from a planar Au-surface, with molecular ET theory.^[53] In superexchange electronic AuC levels couple purely electronically levels around the electrode Fermi level to the redox level. Rate enhancement is either by energy resonance between the electrode and the AuC levels or by the enhanced electronic overlap between molecule and AuC compared with molecule and electrode. Enhancement by sequential ET is only by stronger overlap with the AuC than with the planar electrode. We notice^[53]:

- Two-step hopping via electronically populated AuC prevails over superexchange. Crudely, AuC-mediated two-step ET reduces to a rate-determining short single-step ET in the former, while superexchange involves about twice as long ET distance.
- The AuC/molecule transmission coefficient is highly sensitive to the AuC size (Au₁₃-Au₁₄₇) and to face, ridge, and so forth surface structures. The Au(100) facet gives by far the most facile ET and is the only structural element that can exceed ET rates at planar Au(111). Notably, ET selectivity is more conspicuous at longer distances.
- The AuC electronic densities of states display discreteness up to the largest AuC addressed, Au₁₄₇, Figure 10, giving Lorentzian-like rather than sigmoidal

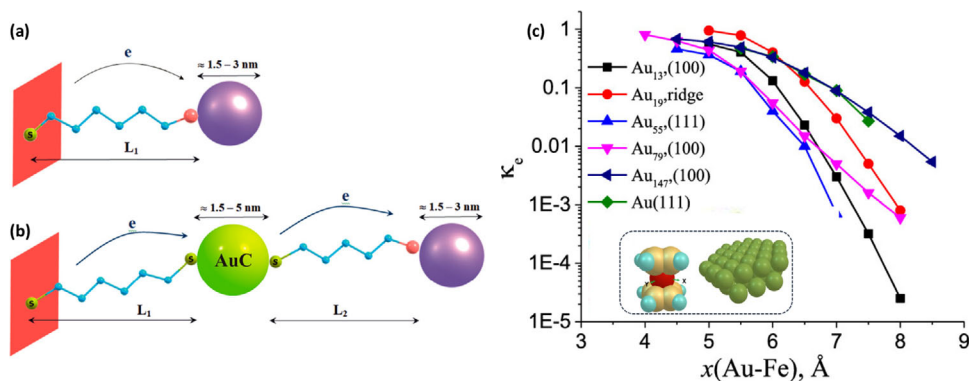


FIGURE 9 (a) A redox molecule (purple sphere) linked to an electrode surface via a bifunctional alkanethiol linker. Linking groups are represented by the small spheres. (b) The molecule is linked via an AuC. (c) Electronic transmission coefficient (χ_e) versus Au–Fe separation for electron transfer (ET) between solute Fc^+/Fc and the prevailing surface sites of five different-size AuCs, as well as the planar Au(111) surface. Inset of (c): Space-filling model of Fc and a two-layer $\text{Au}_{54}(27 + 27)$ cluster to mimic the Au(111) surface^[53]

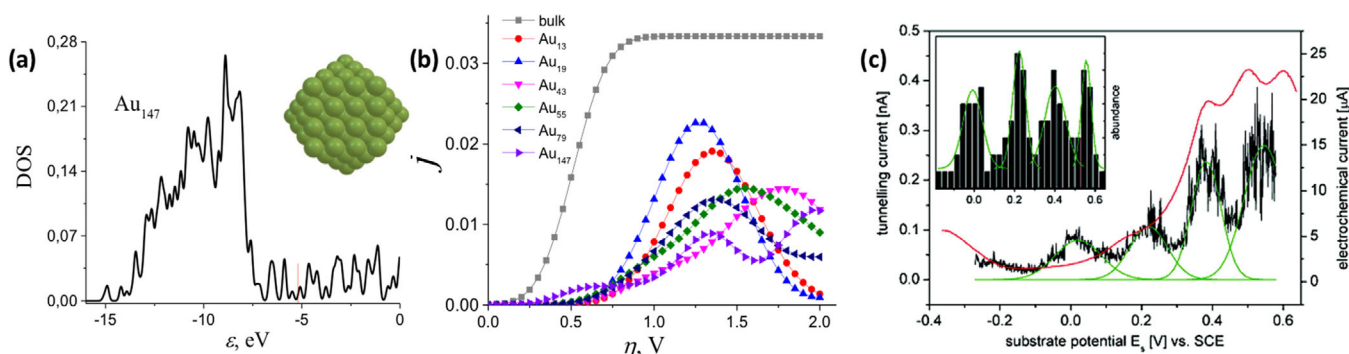


FIGURE 10 (a) Density of states, Au_{147}C . (b) Computed current/overpotential correlations for electron transfer (ET) between variable-size AuCs and Fc.^[53] (c) Recorded tunneling current/overpotential correlation for a coated Au_{145}C ^[19b]

current/overpotential correlations as for macroscopic electrodes, with new experimental challenges.

- SAM coating was addressed by incorporating a single $\text{S}(\text{CH}_2)_6$ molecular linker between Au_{147}C and Fc. Such a superexchange channel was found to be fully competitive.

The study offers insight into AuC catalysis of simple electrochemical ET, but the conclusions are fraught with limitations associated with AuC size and SAM coating. Plasmon theory and focus on collective AuC array properties, might suggest other routes.^[66]

5 | SOME PERSPECTIVES

Molecular scale, single-entity electrochemistry has evolved impressively over the last few years. We have here overviewed selected areas focused on complex redox molecules and metalloenzymes, and on AuNP/molecular hybrids mapped to single-entity resolution. We noted the powerful electrochemical in-situ STM potential, supported by first principle DFT, and by phenomenological

approaches, to which detailed modeling can be added as warranted. We conclude by noting some challenges and cautiously, how to meet them.

5.1 | Computational challenges and the electrochemical interface

The electrochemical interface and the fundamental electrochemical ET process are understood in considerable microscopic detail, but theoretical and computational challenges remain. Particularly this applies to in-situ STM with two surfaces and overlapping double layers. The electrolyte itself then poses unresolved challenges, for example, regarding the potential distribution in the tunneling gap.^[14,37] The spatial confinement can also impose freezing of solvent configurational fluctuations, operating as tunneling barrier indentations or sites for electron hopping. Resolution of such issues is warranted in new data interpretation.

Reliable estimation of transmission coefficients remains a complex problem. A key quantity is the coupling parameter, Equation (4). The surface can be modeled either by

a cluster,^[42] or in solid-state physics terms. Marcus and associates used a tight-binding approach.^[67] Constrained DFT^[68] enables preparing different localized electronic states. Behara and Dupuis^[69] recently developed a scheme for the coupling parameter for periodically extended redox systems. Finally, for heterogeneous ET we have to deal with complex reaction paths, which strictly speaking cannot be described by normal Landau-Zener theory.^[8] A Monte Carlo approach to overcome this challenge was used.^[70]

Another challenge is reliable estimations of the solvent reorganization free energy λ_R . Rough estimates based on dielectric continuum theories are sometimes adequate but frequently fail for spatially confined reaction layers. MD instead offers reasonably accurate λ_R .^[71] The microscopic structure of the reaction layer is of special interest, by affecting significantly reactant molecular conformation and orientation, as well as the distance of closest approach. Molecular-level insight is presently largely by classical MD^[72], but progress was attained recently by ab initio MD of metal/water interfaces.^[73] This method is very promising and free from classical force field drawbacks, but still restricted to small ensembles and short simulation times.

Another computational challenge was addressed by Nørskov and associates, who developed modeling of multi-step electrocatalytic processes.^[74] Their approach rests on calculating Gibbs' free energies for each reaction step, with the overpotential introduced formally as a "computational hydrogen electrode". The approach has met with qualitative success, but hardly describes fully the real mechanism of complex electrocatalytic processes, which call for estimations of the energy barriers of ET and chemical steps. Reliable calculations of the activation barriers are significantly more complex than Gibbs' free energy estimations and remain as major challenges.

5.2 | New molecular scale single-entity materials science

We noted Au-, Pt- and core-shell NPs as molecular-scale single-entity targets, used biomedically, in catalysis, electrochemical sensing, and in fuel cells.^[63] PdNPs, PtNPs, and AuNPs also catalyze (bio)electrochemical ET processes.^[53] Nanoporous metals are in focus as new electrode materials with interesting properties^[24] and offer reactive molecular-scale surface sites for bioelectrochemical enzyme binding. Molecular scale single-entities of other materials than gold (and other electronically soft metals) are reaching comparably established levels.^[10a,b,11a,75] With a better understanding of the electronic structural differences between metal, semiconductor, and semimetal electrode materials,^[76] new theoret-

ical efforts at ET processes on these electrode materials are warranted, relating to bulk surfaces, low-dimensional forms, and molecular-scale structures. Even pristine graphene is attractive due to its unique electronic properties (the Dirac point, and near linearly ascending and descending densities of states around the Fermi level).^[77]

The atomic thickness of graphene can modulate the reactivity of electrochemical interfaces. Single-layer graphene was explored as a semitransparent barrier for the hydrogen evolution reaction on copper.^[10c] A Cu/graphene interface showed intermediate activity compared to Cu (more active) and graphene separately (less active), suggesting electronic semi-transparency, in which Cu participates partially in the reaction despite residing underneath the graphene layer. A gold underlayer also significantly facilitates ET on graphene^[78] according most straightforwardly with hybridization of the graphene orbitals with wave functions of the metal support. Other ET mechanisms based on superexchange via graphene could be forwarded. Layered perovskites,^[79] metal-organic-frameworks,^[80] and molecular magnetic materials^[81] smarter than graphene offer novel probes for spintronics notions and magnetic STM/AFM.

Nanopores constitute other spatially confined ET environment. Electrolytes in conducting single-wall carbon nanotubes (CNT) are valuable models for ultrathin cylindrical pores in metal electrodes. The strong dielectric anisotropy in such systems is frequently treated in terms of radial (*rad*) and axial (*ax*) dielectric constants, ϵ_{rad} and ϵ_{ax} . Based on classical MD simulations these quantities show intriguing behavior: ϵ_{rad} decreases with decreasing CNT diameter, whereas ϵ_{ax} increases,^[82] leading to highly non-trivial electrostatics. ET across a conducting CNT for the $\text{Fe}^{3+/2+}$ couple inside the tubes is also reported.^[82b] MD simulations show that the smaller the nanotube diameter, d_{CNT} the faster ET, mainly due to decreasing solvent reorganization free energy, λ_R attributed to frustrated solvation, especially for Fe^{2+} . A lower λ_R is most conspicuous in the region $0.8 \text{ nm} < d_{\text{CNT}} < 2 \text{ nm}$, where the Fe^{2+} coordination number is reduced from 6 to 4. The dipole reorientation τ_L time decreases notably when $d_{\text{CNT}} < 2 \text{ nm}$ but remains nearly constant ($\approx 6 \text{ ps}$) for wider nanotubes. As $1/\tau_L$ is a crude estimate of the effective frequency, this is an additional factor favoring accelerated adiabatic ET in narrow CNTs.

Considerable progress in experimental studies of molecular diffusion in ultra-narrow carbon nanotubes has finally been reported.^[83] Most experiments are based on nanofluidic devices where a 1.5–1.6 nm SWCNT (length ca, $20 \mu\text{m}$) spans a barrier separating electrolyte reservoirs. Note that 1–2 orders of magnitude ion transport rate enhancement compared with solution bulk was observed. Redox species confined within carbon nanotubes (or other

ultra-narrow channels) can in fact be expected soon to be probed by cyclic voltammetry in mixed diffusion/kinetic regimes, and nanofluidics to become new hard-core concepts in forthcoming prototype electrochemical cells.

5.3 | From single molecules to macroscopic assemblies

The core of nanoscience is the transition between the single molecular-scale entity and macroscopic, thermodynamic assemblies. As in other single-entity science, single-molecule electrochemical properties fluctuate in space and time. Each entity adsorbs slightly differently from its neighbors, transfers electrons slightly differently, and so forth, reflected in distributions of in-situ STM peak conductances and imaging contrasts of individual molecules (as opposed to crystalline lattices). As the transition from the single entity proceeds towards macroscopic assemblies or over long times, single-molecule dynamics are averaged out, and macroscopic behavior takes over. Molecular scale stochasticity is encountered in a variety of electrochemical phenomena overviewed recently,^[84] for example collision electrochemistry, electrodeposition, ionic conductivity through nanopores, ion intercalation into battery materials, and fundamentals of electrochemical and photoelectrochemical redox processes. The $I(t)$ in-situ STM mode introduced by Haiss et al.^[85] supported by stochastic models^[86] is an early such example.

Current fluctuations rooted in random electronic population and depopulation (telegraphic noise) were reported early for solid-state junctions^[87] and electrochemical polyaniline oxidation and reduction.^[88] Sub-ms current fluctuations become apparent as the transition potential is approached. In a recent study, Li et al. introduced a novel approach to stochastic versus bulk molecular conductivity, using a better-defined target system, ferrocene in acetonitrile solution bound to Au(111) and an Au-tip by variable-length alkanethiol linkers.^[35] The data report average sigmoidal in-situ STS as for viologen in aqueous solution and polyoxometallates in ionic liquid. Subtle single-molecule overpotential dependent tunneling current fluctuations are, however, apparent close to the equilibrium potential. The study illuminates strikingly transition from single-molecule to macroscopic patterns, which is exactly the heart of nanoscience.

6 | CONCLUSION

We note finally, first that outstanding, but in due time tractable challenges, are correlations between electron density transfer and electron spin transfer (spintronics). This is long recognized in nuclear magnetic resonance

spectroscopy of paramagnetic redox metalloproteins,^[89] but now on the way to new prominence for example from conductivity studies of DNA probes with chiral centers.^[90] STM with magnetic enclosing substrate and tip could add to the evolution of this new single-entity electrochemical science. Secondly, pure and redox-modified DNA-based molecules offer other single-molecule in-situ STM challenges. Conductivity by electron or hole hopping accords well with photoinduced charge transfer, but not immediately with much lower energy thermal charge transfer.^[91] However, thermal fluctuations both in the energetics of potential hopping centers and in superexchange (tunneling) barriers are long known to induce pronounced conductivity enhancement.^[92] Such views are now being rediscovered under appellations such as flickering resonance in molecular conductivity of DNA duplexes and quadruplexes^[93] and how these differ from redox metalloproteins.^[94]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not Applicable

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