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- Single-molecule electrochemistry by STM in aqueous and ionic liquid media
- *In situ* STM and electrochemistry of single redox metalloprotein molecules
- Molecular scale nanoparticle catalysis of simple electrochemical electron transfer processes
- Molecular scale tubes as local confinement for molecular charge transfer processes

Electrochemistry of single molecules and biomolecules, molecular scale nanostructures, and low-dimensional systems

An integrated experimental, theoretical, and computational approach

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Electrochemistry at ultra-small scales, where even the single molecule or biomolecule can be characterized and manipulated, is on the way to a consolidated status. At the same time molecular electrochemistry is expanding into other areas of sophisticated nano- and molecular scale systems including molecular scale metal and semiconductor nanoparticles (NPs) and other nanostructures, e.g. nanotubes, “nanoflowers” etc.. The new structures offer both new electronic properties and highly confined novel charge transfer environments.

1. Introduction

Chemical and biological sensing at ultra-small scales, and “molecular scale electronics” have been ultimate perspectives for single-molecule or single-entity (particles, tubes etc.) science^{1,2}. Molecular scale electrochemistry also discloses new properties or even phenomena different from macroscopic assemblies. The presence of two electrode surfaces in electrochemical *in situ* STM instead of a single electrode has for example disclosed new ET phenomena, possibly a rationale for often observed very high *in situ* STM current densities³⁻⁵. Molecular scale inorganic particles display single-ET charging in voltammetry⁶ and *in situ* tunneling spectroscopy (STS)⁷. Ionic liquid media are, further gaining importance,^{1,8,9} and “nanoimpacts”¹⁰ “hot” electrons and quantum dots¹¹, non-Gaussian solvent configurational fluctuations¹¹, and electronic spill-over^{13,14} are still other electrochemical single-entity phenomena. New electrode materials and electrode configurations are finally prominent in developing nanoelectrochemistry, with 2D and 3D graphene and graphene/NP hybrid materials^{15,16}, core-shell^{17,18} and Janus-like NPs¹⁹, 1D single carbon nanotubes²⁰, and nanoporous electrodes^{21,22} as examples.

The present short review addresses three areas in prodigious single-entity electrochemistry, all in development, and reflecting the authors' views: **(1)** Single-(bio)molecule structure and reactivity. **(2)** Molecular scale inorganic NPs. **(3)** Low-dimensional inorganic nanoscale structures (tubes, bent and twisted graphene sheets) with specific electronic properties and also serving as confinement for ET and other reactivity. In addition to overviewing experimental and theoretical achievements, efforts in molecular dynamics (MD) and quantum chemical density functional (DFT) simulations are addressed.

2. Single-molecule and -biomolecule electrochemistry, and *in situ* STM

Scanning tunneling and atomic force microscopy in aqueous electrolyte or ionic liquids under electrochemical control (*in situ* STM and AFM) has enabled approaching the ultimate limit of the single molecule in action, extending to single-molecule mapping of biomolecules such as metalloproteins and DNA-based molecules in natural environment²³⁻³⁰. Both non-covalent²⁸ and much stronger chemisorptive molecular wiring to the electrode and the (*in situ*) STM or AFM tip are feasible^{27,29,30}. Break-junction (B-J), and *i*(*t*) and *i*(*z*) methods (*i* the current density, *t* the time and *z* the distance) are other notions³¹. *In situ* STM enables recording **two** correlations, the (tunneling) current/bias $i_{\text{tunn}}/V_{\text{bias}}$ voltage correlation as in UHV/gas environment, and the current/overpotential i_{tunn}/η correlation (STS). The latter is reminiscent of electronic components with a gate electrode in addition to a source and a drain electrode.

2.1 Some conceptual frames of single-molecule electrochemistry

Following Tao's early work (1996)³² a considerable number of organic redox molecules and transition metal complexes in aqueous and ionic liquid media have been mapped to single-molecule resolution.^{1,23} A conceptual notion introduced early is the *in situ* STM/STS redox process as "hopping" with successive ET between tip and molecule, and between molecule and electrode^{3,33,34}. The two-step feature is apparent in the current density form

$$i(\eta; V_{\text{bias}}) = en \frac{k_{\text{tip},\text{mol}} k_{\text{electr},\text{mol}}}{k_{\text{mol},\text{tip}} + k_{\text{electr},\text{mol}}} \quad (1)$$

$k_{\text{tip},\text{mol}}$, $k_{\text{mol},\text{tip}}$, and $k_{\text{electr},\text{mol}}$ are the electrochemical rate constants, e the electronic charge, and n the number of electrons transferred in a single two-step STS event. *In situ* STS can be correlated with the electrochemical rate constants

$$k(\eta; V_{\text{bias}}) = \kappa_{\text{el}} \frac{\omega_{\text{eff}}}{2\pi} \exp \left\{ -\frac{[\lambda + e\eta(V_{\text{bias}}; \xi; \gamma)]^2}{4\lambda k_B T} \right\} \quad (2)$$

where k represents the rate constants in eq.(1), λ the reorganization free energy, κ_{el} the electronic transmission coefficient, ω_{eff} the effective vibrational frequency, k_B Boltzmann's constant, and T the temperature. ξ represents the electrode/molecule potential drop and γ the bias voltage drop at the site of the molecule. A central outcome is a current maximum at

$$\eta = \eta_{\text{max}} = \frac{1}{\xi} \left(\frac{1}{2} - \gamma \right) V_{\text{bias}} \quad (3)$$

η_{max} thus coincides with the equilibrium potential for symmetric tunneling junctions.

Eqs.(1)-(3) have framed molecular STS systems^{1,4,5,30,35} but has also disclosed limitations. Transition metal complexes and metalloproteins for which comparison with electrochemical rate constants is feasible thus show significantly higher single-molecule conductivity than expected from the macroscopic rate constants^{4,5,23,27}. Restricted solvent configurational fluctuations in the tunneling gap have been forwarded as one rationale⁷, which requires then attention to activationless ET. Coherent many-ET, $n \gg 1$ has also been suggested^{4,5,23}. Other features in need of attention are: (a) The electrode materials; (b) ionic liquid media and high

ionic strengths; (c) “quantum interference”³⁵; and (d) the transition between superexchange and “hopping” as the overpotential and bias voltage are varied.

2.2 Single-molecule *in situ* STM imaging and conductivity of redox metalloproteins

“Long-range” ET (LRET) in biological charge transfer is long recognized³⁶ LRET can refer to tunneling through the peptide frame between a metal centre and external reaction partners or electrode surfaces, with tunneling distances up to a couple of nanometers. LRET in larger protein complexes takes the form of multi-step “hopping”³⁶ but shorter-range tunneling is still a feature of each “hop”. *In situ* STM of horse heart cyt *c*³⁷ and horseradish peroxidase³⁸ were the first single-molecule metalloprotein *in situ* STM targets. Following the introduction of the blue copper protein *Pseudomonas aeruginosa* azurin as a robust *in situ* STM target^{27,39}, both much better resolved structural *in situ* STM and single-molecule *in situ* STS have been reported. Structural targets include the three major ET metalloprotein classes, the blue Cu-proteins^{2,3,22,27-30}, cytochromes^{40,41}, as well as a single Fe-S protein representative, *Pyrococcus furiosus* ferredoxin⁴². *In situ* STM and AFM of multi-centre *Achromobacter xylosoxidans* Cu-nitrite reductase (trimeric two-centre Cu-enzyme)⁴³ and several laccases is also reported^{44,45}.

Here we cannot overview the multitude of electrochemical single-molecule metalloprotein systems, but focus on some issues relating to our discussion in Section 2.1. We note first that in addition to high-resolution structural mapping, single-molecule *in situ* STS is reported for at least two ET proteins, *P. aeruginosa* azurin²⁸⁻³⁰ and the four- α helix bundle *E. coli* cyt *b*₅₆₂⁴. Both display a strong *in situ* STS feature around the equilibrium potential (on-off ratios up to an order of magnitude), eq.(3). The data accord with the multi-phonon two-step mechanism but prompt some observations. The azurin conductivity is quite close in the two cases of azurin binding to the Au(111)-surface via the disulfide bond, viz 2.5²⁹ and 3.3 nS³⁰, but notably lower, i.e. 0.4 nS for azurin non-covalently attached via an octanethiol SAM, according with weaker azurin-electrode coupling through the SAM²⁸. The latter data could be compared with electrochemical ET rate constants of $(0.5-1) \times 10^3 \text{ s}^{-1}$ (or higher). These would give about two orders of magnitude lower single-ET tunneling currents than observed. High currents are even more pronounced for cyt *b*₅₆₂ mutants with two oppositely located Cys residues inserted along either the long- or the short-axis. The conductivities vary only by a factor of two in spite of the distance difference and differently organized protein matter. The pattern accords with strongly adiabatic ET, $\kappa_{el} \rightarrow 1$, but leaves open a need for invoking other features such as single-molecule ET coherence.

The second issue that we address is the intramolecular ET channels in multi-centre redox metalloproteins illustrated by two cases, *A. xylosoxidans* CuNiR⁴³ and the two-heme protein *Pseudomonas stutzeri* cyt *c*₄ (Fig.1)^{40,41}. Focus is on the observation that binding of the protein to the electrode surface or binding of the enzyme substrate, here NO₂⁻ triggers conformational changes in the protein framework, opening intramolecular ET channels.

Fig.1

Cyt *c*₄ exchanges electrons in the ms-s time range with external reaction partners with no intramolecular ET between the two heme groups, Fig.1⁴⁰. On cyt *c*₄ binding to a SAM-modified Au(111)-electrode surface, in vertical orientation as verified by *in situ* STM, Fig.1 and cyclic voltammetry, an efficient channel opens with intramolecular ET in the microsecond range. A theoretical analysis could suggest reasons for this behavior⁴¹. The reorganization free energy and driving force are little affected by the binding, but the

transmission coefficient κ_{el} is exceedingly sensitive even to tiny structural changes. ET in the crystallographic structure is highly unfavorable, but small shifts of the heme planes, little costly in energy increase the transmission coefficient by orders of magnitude, Fig.1⁴¹.

Similar considerations apply to CuNiR⁴³. CuNiR, and many other enzymes mostly show no Faradaic electrochemistry, even though fast intramolecular ET (5-50 ms) between the Type I and Type II centres in solution has been detected⁴⁶. On NO₂⁻ substrate binding fast interfacial electrocatalysis of NO₂⁻ reduction via the now opened intramolecular ET channel, however, appears. Electrochemical AFM could show that channel opening is accompanied by 1 nm structural enzyme “swelling”⁴³. Features such as these have not been addressed before.

3. Single-entity electrochemistry of inorganic nanoparticles

Electrochemistry and electrocatalysis of metallic NPs has recently developed tremendously. We provide here a few observations for comparison with similar-size biomolecules and otherwise refer to recent reviews^{25,47,48}. Molecular scale noble metal (and core-shell) NPs are long known as electrocatalysts in fuel cell and other processes. Here we address AuNP catalysis of simple ET reactions. Reactant, product, and reaction intermediates in, say fuel cell processes are adsorbed on the NPs, and it is expected that changes in the surface electronic structures can result in catalytic effects compared with planar electrode surfaces. PdNPs, PtNPs and AuNPs are, however, also catalysts of simple electrochemical ET processes. Horse heart cyt *c* at Au(111)-surfaces modified by functionalized alkanethiol SAMs is a representative system, Fig.2⁴⁹. The standard rate constant at an undecanoic acid SAM modified Au(111)-surface is 4 s⁻¹. Linking a thioctic acid (TA) modified 3 nm AuNP between cyt *c* and the surface, the rate constant increases 20-fold. “Normal” molecular matter would entirely block the ET process on such a distance increase.

Fig.2

Understanding such phenomena is an opening research area. Chazalviel and Allongue introduced a model of a SAM-bound AuNP monolayer⁵¹, in which AuNPs form a “short-circuiting” catalytic metallic layer on top of the SAM. This model has been used to frame observed weak distance dependent ET rate constants via AuNPs adsorbed on functionalized alkanethiol modified polycrystalline Au-electrodes surfaces up to a SAM thickness of about 2 nm⁵². Another view is to focus on individual AuNPs and view the process as two-step, superexchange or hopping with consecutive ET between molecule and electrode via the AuNP^{13,49,53}. Key in the two-step view is the NP size. Small particles (≤ 2.5 nm) display discrete single-ET charging reminiscent of molecules^{6,7}, while the plasmonic electronic levels of larger NPs are continuous. In either superexchange or hopping efficient AuNP electronic overlap to either side is essential for facile LRET compared with planar metal surfaces. Size- and metal-dependent electronic density “spillover” of the kind studied for simple alkali metals⁵⁴ here be a core concept^{13,54}. Other rationales for the AuNP catalyzed ET rate enhancement including deformation of the electrode surface SAM are discussed elsewhere⁵⁵.

4. Two new electrode materials for molecular scale electrochemistry

4.1 Nanotubes as confinement for transport and charge transfer processes

“Nanotubes” represent extension from “0-D” NP to 1-D nanoscale structures. Nano- and picoampere cyclic and linear voltammetry of single-wall carbon nanotubes (SWCNT) has been reported⁵⁶⁻⁵⁹, and experimental nanoscale electrochemistry findings now warrant molecular level theoretical analysis. General principles of such analysis are formulated⁶⁰, and double layer effects specifically in the reduction of [Fe(CN)₆]^{3-/4-} and S₂O₈²⁻ at conducting

nanotubes modeled^{61,62} with intriguing expectations such as inverse Arrhenius behavior and disappearance of a “pit” in the current-voltage relations. Reactant – monoatomic metal (Ag, Au, Cu, Pt) nanowire orbital overlap for the $[\text{Fe}(\text{OH}_2)_6]^{3+/2+}$ and $[\text{Cr}(\text{OH}_2)_6]^{3+/2+}$ couples in aqueous solution has further been addressed by quantum mechanical theory⁶³. The electronic transmission coefficients were calculated and compared with Me(111)/water interfaces showing larger values for the nanowires at short distances, but significantly smaller values for larger distances. Lemay and associates⁶⁴ reported the first current/voltage analysis using theory for ET across metallic and semiconducting SWCNTs and scanning tunneling spectroscopy.

Electrolyte structure and transport inside nanotubes are harder to address but in part understood. Chemical kinetics inside nanotubes is the next level of complexity but less understood. The structure of pure water inside SWCNTs was explored by X-ray diffraction and NMR techniques^{65,66} and by Molecular Dynamics (MD)⁶⁷ simulations successfully employed to hydrated ions^{68,69} and hydrated proton transport in the nanotubes⁷⁰⁻⁷², Fig.3. Nuclear quantum effects was incorporated using *ab initio* MD^{71,72} and path integral techniques⁷¹. CNT mobility of water molecules and hydrated protons is higher than in bulk solution, attributed to the ordered hydrogen bonds between water molecules in the CNT channels and weak interaction between water and the CNT walls. The first cationic coordination shells were found to be considerably less ordered in the nanotube than in bulk solution, but with only minor anion first coordination shell changes.

Fig.3

Understanding chemical *reactions* in confined nanotube space is highly challenging with potential applications, reviewed recently⁷³ with intriguing examples of electrochemical reactions. CNTs filled by electrolyte are also transport and charge transfer models for nanosize pores. Primary attention is given to catalytic effects with CNTs shown to modify the electronic catalyst properties.⁷⁴ Ion transport through single electrolyte filled CNTs was further probed using microfluidic devices on a silicon wafer⁷⁴⁻⁷⁷. Cations are preferentially transported, for example with fivefold ion diffusion enhancement in a 1.6 nm SWNT72 as compared with the other carbon nanotubes, scaling as $\text{Li}^+ > \text{K}^+ > \text{Cs}^+ > \text{Na}^+$ ⁷⁶. Similar effects were found for a vertically aligned MWCNT membrane⁷⁸. This might be understood taking into account the interplay between different factors: (1) specific water structure in a confined space where association of H_2O molecules plays an important role; (2) reduced hydration sheath of ions; (3) the size difference between cations and anions; and (4) coupling of ions to the hydrodynamic modes of water associates. Simulations at the molecular level are needed to gain a deeper insight into such challenging experimental observations.⁷⁶

Classical MD simulations of the kinetics of simple redox couples in nanopores have, finally been reported^{79,80} and framed by molecular ET theory. These computational results are, however, mutually contradictory. ET rate *enhancement* in nano-confined space⁸⁰, but a rate *decrease* compared with bulk solution⁷⁹, both based on MD has thus been concluded.

4.2 A note on graphene electrode materials

Even perfect graphene is attractive for electrochemistry of simple redox couples due to unique electronic properties (the Dirac point, nearly linear ascending and descending DOS near the Fermi level). Investigating such an electronic structure in current-voltage relations of adiabatic and diabatic ET processes is tempting and challenging. An experimental challenge is to fix and charge a graphene sheet. For example, if graphene resides on another electrode⁸¹,

does the latter then affect the graphene electronic structure? Graphene holds other promise as 2D-electrode materials, with catalytic properties attributed in the first place to defects, the role of which in ET processes is, however, poorly understood.

The kinetics of redox processes at the graphene edge (linear topological defect) is so far the most studied^{82,83}. The graphene edge activity can be understood from scanning electron spectroscopy, which discloses local electronic states below the Fermi level at *zigzag*-type⁸⁴, but not at *chair*-type graphene edges. Graphene sheet vacancies also results in local electronic states which makes the vacancies catalytically active⁸⁵. The rate constant of the FcMeOH/FcMeOH⁺ redox process was thus found to increase by two orders of magnitude on increasing the vacancy concentration to $5 \times 10^{12} \text{ cm}^{-2}$ (i.e. $\approx 2 \text{ nm}$ between the defects)⁸⁵. Oxidation of the graphene surface by dioxygen can be catalytically enhanced by nitrogen doping or by oxygen surface functionalities^{86,87}. For further discussion of the prodigious experimental, theoretical, and computational approaches relating to pure and applied properties of graphene and graphene composite materials, we refer to Refs.15 and 16 as representatives of a voluminous literature.

5. Some perspectives

Electrochemistry of single molecular scale entities covers highly diverse targets, developed as new research over the last decade. Entities include single small molecules such as alkanethiols, and large biological molecules such as metalloproteins and DNA based molecules. Interfacial electrochemical single-entity ET also covers a prodigious range of inorganic particle, wire, rod, “flower”, layer etc. structures all the way from “0D” via 1D and 2D, to 3D structures, structurally and functionally understood to different degrees. We have focused on interplay between advanced experimental studies, quantum mechanical charge transfer theory, and quantum and computational chemistry, and selected for discussion of three single-entity system classes. Electrochemistry of single *molecules* seems best understood, much due to increasing use of the scanning probe microscopies, in situ STM and AFM. Structural and functional mapping have reached high resolution, but we have also noted unresolved challenges, such as conformational changes on electrochemical adsorption of large biomolecules, and often very high tunneling current densities (per molecule).

Functional Au-, Pt- and core-shell NPs are used biomedically, in catalysis, electrochemical sensing, and in fuel cells. Controlled NP synthesis is established, but high-resolution structural properties, say of thiol-protected AuNPs, and understanding of the Au-S bond⁸⁸ is only now offering firmer basis and rational routes towards AuNPs in real use. Fundamentals of metallic NPs are far from understood, but the electrochemistry of composite nanowires, nanorods, nanoflowers, and single CNTs, offer even greater challenges. Mere atomic intercalation changes drastically the electronic CNT structure and reactivity. Electrochemistry of single nanowires, nanorods, and nanoflowers, and experimental and computational probing of electrochemical reactivity inside nanotubes is thus only just beginning,

With single-entity electrochemistry moving, entirely new systems of interest for electrochemical and in situ STM/AFM single-entity probing may appear. One new area could be electrical, optoelectronic, and magnetic properties of layered perovskites⁸⁹. Surfaces of these 2D materials could be locally, using spintronics notions and magnetic STM/AFM tips. A second area is molecular magnets. These are engineered building blocks of strongly magnetic transition metal or rare earth complexes, which can be hierarchically fine-tuned into magnetic materials⁹⁰. Local electrochemical STM/AFM probing of molecular magnets would support exciting new materials science, and more specifically address often overlooked spin

effects in elementary ET processes. The developments in NP applications demonstrate what can be achieved by interdisciplinary research that includes quantum chemical calculations, experimentation and modern microfabrication¹⁴. Progress in the new areas will equally depend on such interplay.

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Fig. 1

Pseudomonas stutzeri cyt c_4 (PDP code 1EPT). Top left: Crystal structure to show the high-potential C- (red, positively charged) and low-potential N-domain (blue, negatively charged) and the equilibrium orientation of the two heme groups. These are bound by a strong H-bond, but orientation and distance are unfavourable for fast intramolecular ET. Top middle: Cyt c_4 immobilized via the C-domain on a Au(111)-electrode surface modified by a (negatively charged) ω -decanoic SAM. Top right: In situ STM image showing that vertical cyt c_4 orientation on the SAM modified surface prevails. Bottom left and right: Two cyt c_4 structures to illustrate conformational fluctuations needed for facile intramolecular ET. To the left is the equilibrium structure. To the right the hydrogen bond between the heme groups is broken (at low energy cost) and the heme planes brought closer towards better electronic overlap, strongly facilitating intramolecular ET. Adapted from Refs.40 and 41.

Fig. 2

Illustration of AuNP catalysis of interfacial electrochemical ET. Top left: Horse heart cyt *c* electrostatically attached to a 11-mercaptoundecanoic acid SAM (negatively charged,) via the positively charged surface domain around the heme group. Top right: Cyt *c* electrostatically attached to a 3 nm thioctic acid (two Au-S links per TA molecule) protected AuNP in turn covalently linked to a Au(111)-electrode surface via a mixed cysteamine/1-propanethiol SAM. The > 20-fold rate constant increase is indicated. Bottom: Illustration of interfacial ET via a dithiol SAM modified AuNP. One probing molecule, $[\text{Ru}(\text{NH}_3)_6]^{2+/3+}$ reacts by outer sphere ET, the other one, Ferrocene $^{0/+}$ by inner sphere ET. Adapted from Refs. 13 and 49.

Fig. 3

Schematic views of structure and reactivity of a metal nanowire and a water-filled tube. Top: Electron transfer from a charged metal nanowire to an external molecular electron acceptor, here a hexa-aqua transition metal complex. Bottom: Water molecules inside a (10, 7) single-walled carbon nanotube as derived from preliminary MD simulations at 300K in progress.