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Complete List of Authors:	Kraatz, Heinz-Bernhard; University of Toronto at Scarborough, Physical and Environmental Sciences Shah, Afzal; University of Toronto Scarborough, Department of Physical and Environmental Sciences Adhikari, Bimalendu; University of Toronto Scarborough, Department of Physical and Environmental Sciences Martic, Sanela; Oakland University, Chemistry Munir, Azeema; Quaid-i-Azam University, Chemistry Shahzad, Suniya; Quaid-i-Azam University, Chemistry Ahmad, Khurshid; Quaid-i-Azam University, Chemistry

Electron Transfer in Peptides

Afzal Shah*[a,b], Bimalendu Adhikari[a], Sanela Martic[c], Azeema Munir[b], Suniya Shahzad[b], Khurshid Ahmad[b] and Heinz-Bernhard Kraatz*[a]

[a]Department of Physical and Environmental Sciences, University of Toronto Scarborough, 1265 Military Trail, Toronto, M1C 1A4, Canada and Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

[b]Department of Chemistry, Quaid-i-Azam University, 45320, Islamabad, Pakistan

[c]Department of Chemistry, Oakland University, Rochester, MI, 48309, USA

*To whom correspondence should be addressed

e-mail: bernie.kraatz@utoronto.ca (Prof. Dr. Heinz-Bernhard Kraatz)

and afzals_qau@yahoo.com (Dr. Afzal Shah)

Abstract. In this review, we discuss the factors that influence electron transfer in peptides. We summarize experimental results from solution and surface studies and highlight the ongoing debate on the mechanistic aspects of this fundamental reaction. Here, we provide a balanced approach that remains agnostic and does not favor one mechanistic view over another. Support for a putative hopping mechanism in which an electron transfers in a stepwise manner is contrasted with experimental results that support electron tunneling or even some form of ballistic transfer or a pathway transfer for an electron between donor and acceptor sites. In some cases, experimental evidence suggests that a change in the electron transfer mechanism occurs as a result of donor-acceptor separation. However, this common understanding of the switch between tunneling and hopping as a function of chain length is not sufficient for explaining electron transfer in peptides. Apart from chain length, several other factors such as extent of secondary structure, backbone conformation, dipole orientation, the presence of special amino acids, hydrogen bonding, and the dynamic properties of a peptide also influence the rate and mode of electron transfer in peptides. Electron transfer plays a key role in physical, chemical and biological systems so its control is a fundamental task in bioelectrochemical systems, designing of peptide based sensors and molecular junctions. Therefore, this topic is at the heart of a number of biological and technological processes and thus remains of vital interest.

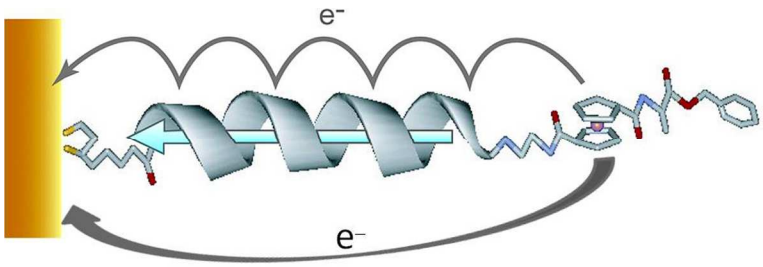
1. Introduction

Electron transfer (ET) to substantial molecular distances plays an important role in diverse metabolic cycles, oxidative phosphorylation, mechanism of radiation damaged DNA repair system, cellular signal transduction, enzymatic processes, photosynthesis and aerobic respiration.[1-3] Charge transport occurs through cell membrane and activates several cellular chemical events.[3] Through the transport of charge, information can be transferred in a protein chain over large distances. ET reactions among cofactors in proteins assist energy-conversion processes in living organisms.[4] While a large number of model peptide systems have been analyzed over the years in solution and chemically linked to surfaces, it has become apparent that the kinetics of the process are governed by molecular dynamics of the particular system and a range of experimental aspects, including the type of linker used in surface studies and the sequence of amino acids.[5] However, the definite role of these and other factors still demands further investigations in defining a clear mechanism.[6]

Up to date two discrete mechanisms are used to describe the ET process: 1) electron tunneling or superexchange and 2) electron hopping.[7-9] Tunneling is a coherent ET process as the bridge levels are not occupied due to high excitation gap between the donor states and bridge states. While hopping is an incoherent process in which electron occupies the levels of the bridging medium during its transport from donor to acceptor. Tunneling is an inherently quantum-mechanical process while hopping has features of classical mechanics. In a hopping mechanism, the peptide bridge not only electronically links the electron donor and acceptor but also involves its amino acids in oxidation and reduction thus offers relay stations/stepping stones

to the transport of electrons. The involvement of amino acid as redox-active intermediates renders the distant ET a multistep tunneling process (hopping process) in which the kinetics is faster in comparison to one long single-step electron transfer between the donor and acceptor.[10] The mechanism of ET changes as a function of donor-bridge-acceptor energetics. In case of tunneling, the donor is lower in energy than the molecular bridge and thus, the electron tunnels through the bridge to reach the acceptor. It has been proposed that hopping can occur when the donor is higher in energy than the bridging peptide and the electron hops between low energy sites from the donor to the acceptor.[8] A simplified model showing the difference between tunneling and a putative hopping ET mechanism is illustrated in **Scheme 1**.

A thorough understanding of the factors controlling ET mechanism is advantageous for the designing of molecular electronic devices,[11,12] interpretation of natural bioelectrochemical processes, use of peptides in molecular junctions[13,14] and bio-based sensors.[15,16] However, differences of opinion still exist about the mode of ET[17,18] as the mechanism is dictated not only by the commonly accepted chain length factor but also by the extent of secondary structure, dipole orientation, hydrogen bonding, oxidation potential, the presence of special amino acids and backbone conformation of peptides. Therefore, further investigations regarding a clear understanding of ET mechanism are pivotal for the use of peptides in molecular electronics applications. While a number of reviews on the mechanistic aspects of electron transfer in biomolecules have appeared,[3,7,19] the current review focuses on the factors that influence the electron transfer in peptide systems.



Scheme 1. Schematic view of electron transfer mechanism from an electron donor, in this case a Fc conjugate, to a surface by tunneling or by electron hopping between adjacent sites (reprinted with permission from ref[9]).

2. ET in peptides

Peptides, the building block of proteins perform several functions in living organisms. They work by joining electron acceptors and donors with each other, and facilitate redox reactions between them. The mechanism of electron transport in various peptides/proteins and the important factors which affect the rate of ET directly or indirectly are discussed here.

2.1 Effect of peptide chain length – Hopping versus Tunneling

The transport of electrons across large distances occurs naturally in biological systems. Electron transfer by tunneling takes place according to the Marcus theory[20] with ET rate constant (k_{et}) as exponential function of peptide chain length (k_{et} α $e^{-\beta r}$ where β and r represent decay constant and distance between donor and acceptor respectively).[21] While a sequential/hopping ET requires a suitable redox mediator[19] and its rate constant is a linear function of donor-acceptor distance.[22] Due to the exponential decrease of ET tunneling rate, this single step mechanism becomes less likely with increasing distance between the donor and acceptor. Once a peptide exceeds a certain chain length, a shallow distance dependence for k_{et} is observed, which is interpreted as a crossover from tunneling to a hopping mechanism.[23] Indeed such apparent changes in ET kinetics as a result of lengthening the donor-acceptor distance in peptide systems have been observed by several research groups.[19,22,23]

Polo *et al.* investigations of ET from donor to acceptor in solution employing oligopeptides of α-aminoisobutyric acid (Aib), which induces 3_{10}-helix formation, reveal that the lengthening of peptide chain by the addition of more α-amino acid units lowers the energy of the backbone and introduces new intramolecular bonds which act as ET shortcuts.[24] Thus, the exponential decrease in rate constant by increasing the chain length of peptides is compensated by the additional intramolecular bonds. Sisido and co-workers[25] also related the exponential decrease of ET rate constant to the increase in chain length (by addition of cyclohexyl glutamate residues) of the bridging medium separating pyrene as donor from nitrobenzene as acceptor. Xiao *et al.*[26] concluded the same result for ET reaction by monitoring tunneling currents of single molecule of non-helical cysteamine-$(Gly)_n$-Cys peptides (where n = 0-2). The large decay constant of 0.9 $Å^{-1}$ in these experiments offer evidence of tunneling mechanism in peptides of lengths less than 20 Å. Sek *et al.*[27] reported a similar tunneling behavior with a decay constant of 0.50 $Å^{-1}$ in 14-17-mer peptides of length greater than 20 Å, however, these peptides may tilt and come close to the surface with a distance of less than 20 Å. The currents of a series of α-helical peptides with 14-17 amino acids depicted in **Fig. 1** show a clear dependence on distance.

P14AA:
Cys(S-Acm)-Ala-Lys-(Glu-Ala-Ala-Ala-Lys)$_2$-Ala-NH-$(CH_2)_2$-SH
P15AA:
Cys(S-Acm)-Ala$_2$-Lys-(Glu-Ala-Ala-Ala-Lys)$_2$-Ala-NH-$(CH_2)_2$-SH
P16AA:
Cys(S-Acm)-Ala$_3$-Lys-(Glu-Ala-Ala-Ala-Lys)$_2$-Ala-NH-$(CH_2)_2$-SH
P17AA:
Cys(S-Acm)-Glu-Ala$_3$-Lys-(Glu-Ala-Ala-Ala-Lys)$_2$-Ala-NH-$(CH_2)_2$-SH

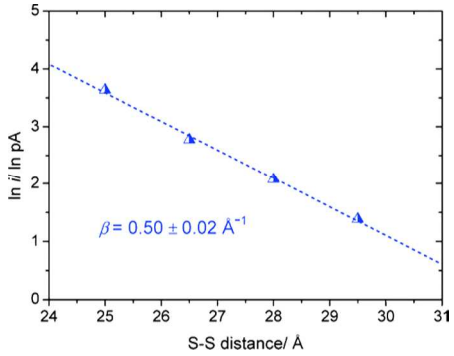


Fig. 1. The series of thiol-terminated α-helical peptides P14AA – P17AA having 14-17 amino acids using by Sek and coworkers in his electrochemical studies, in which the peptides have an increasing number of Ala residues. Shown is a plot of the current ln*i* as a function of the peptide length between the Cys-S and the C-terminal SH. Ala = alanine, Glu = glumatic acid, Lys =

lysine, Acm = acetamidomethyl (reprinted with permission from ref.[27], copyright 2006, American Chemical Society).

The mechanism of ET reactions of ferrocene (Fc) containing helical peptides of increasing chain length shown in **Fig. 2** were electrochemically investigated on gold surfaces (in aqueous 1M $HClO_4$ solution using Ag/AgCl as reference electrode).[28] The transfer of electron was found to occur even through the longest peptide (A64) of over 100 Å at a significant rate constant of 0.58 s^{-1}. The behavior of the semilog plot (Fig. 2B) indicates that the ET through the selected helical peptides is not occurring through conventional super-exchange mechanism, which should follow a linear distance dependency as shown by the dotted line. Hence, the roughly linear relationships of log of k_{et}^0 and $(k_{et}^0)^{-1/2}$ with film thickness suggests the involvement of hopping mode of ET between the amide group of peptides, which is supported by theoretical calculations. For 4-, 8- and 16-mer helical peptides, the ET is dominated by tunneling while for longer peptides of 24- and 32-mers, hopping mode dominates. The tunneling and hopping mechanisms are operating together and when the electron transfer length is in the range of the short distance, the tunneling mechanism prevails.

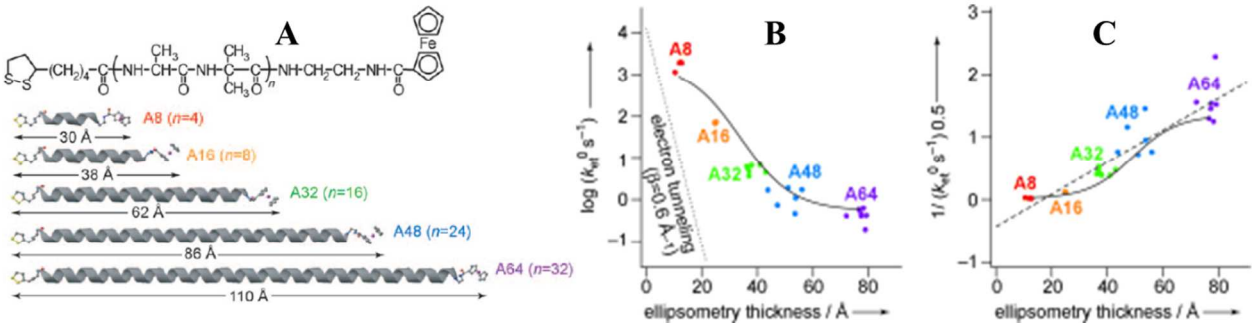
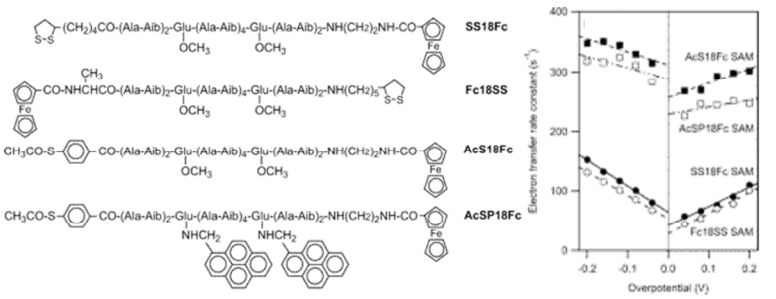


Fig. 2 (A) Helical peptide conjugates, possessing a C-terminal Fc redox label and an N-terminal disulfide for attaching to a gold surface. Distances between the S- and the Fc label are expressed in the ribbon diagram and range from 30 – 110 Å (B) Log of k_{et}^0 as a function of monolayer thickness. The experimental data are represented by colored filled circles, reference curve by the dotted line showing electron tunneling with a decay constant of 0.6 $Å^{-1}$, and the calculated result

based on tunneling and hopping mechanisms by solid line (C) Inverse of the square root of k_{et}^0 as a function of ellipsometry thickness. The dashed line represents linear fit and the solid line denotes the outcome of calculations based upon tunneling and hopping mechanisms. Here k_{et}^0 is taken as the sum of the tunneling and hopping ET rate constants, i.e., $k_{et}^0 = k_{tun} + k_{hop}$ (reprinted with permission from ref.[28], copyright 2010, John Wiley and Sons).

The ET rate of other Fc-labeled helical peptides consisting of alternating alanine (Ala) and Aib was also investigated on gold surface.[29] Here, the linkers significantly affected the kinetics of electron transfer due to local ET between gold and peptides, which may represent the rate-limiting step. The pyrenyl groups were too distant to allow direct transfer of electron and had little effect on rate of ET. The electron transfer rates for Fc oxidation at positive overpotentials and Fc^+ reduction at various negative overpotentials were also explored and on the basis of overpotentials of 0 V and extrapolation shown in **Fig. 3**, the k_{et} with values 42, 28, 257 and 229 s^{-1} was determined for the peptide films designated as: SS18Fc, Fc18SS, AcS18Fc, and AcSP18Fc, respectively.



Peptides	Estimated distance between Fc and Au	rate constant
SS18Fc and Fc18SS	43 Å	42 and 28 s^{-1}
AcS18Fc and AcSP18Fc	41 Å	257 and 229 s^{-1}

Fig. 3 Relationship of the electron transfer rate constant k_{et} with overpotential and distance between the Fc redox label and Au electrode. Structures of α-helical peptides studied are shown on the left (reprinted with permission from ref.[29] Copyright 2005, American Chemical Society).

Films prepared with pure Fc-peptide or mixed Fc-peptide/peptide exhibited similar ET rates suggesting the ET to occur between Fc group and Au electrode via a single peptide backbone rather than intermolecular transfer. In addition the ET rate was increased by changing methylene

chain with phenylene. However, the addition of pyrenyl group did not accelerate the rate of ET. The studies of Kimura on Fc-labeled peptides showed surprisingly low decay factor of 0.02-0.04 $Å^{-1}$ from the 16mer to 24mer, suggesting the bridge length dependence of ET rate to corroborate with a sequential mechanism. In such putative mechanism, the electron is suggested to occupy the LUMO of the peptide bridge followed by transfer to the acceptor site.[23] Additional studies by Kimura on Fc-terminated Aib-rich peptide films with a peptide length exceeding 20 Å, suggests that experimentally determined ET rates are 10^3–10^4 times larger than the theoretical rates. Kimura argues that the activation parameters in this system support ET by hopping.[28,30] In case of tunneling, the reorganization energy (energy needed for the nuclear rearrangements that accompany ET) for the Fc group is around 0.8 eV.[31] The activation energy for 100 Å α-helix was calculated to be about 0.2 eV. Activation energies from theoretically determined k_{et}^0 values at 298 and 323K were in agreement with the experimental values, which exclude ET by tunneling in peptides of length greater than 20 Å.[28]

The work of Brooksby *et al.*.[32] supports hopping mechanism as the results of their experiments reveal a decrease of decay constant to < 0.05 $Å^{-1}$ when the length of peptides exceeds 20 Å. Isied and co-workers[33] carried out radiolysis and photolysis experiments in solution on a donor and acceptor site where the two sites are separated by an oligoproline spacer of 0–9 residues and found that the value of β undergoes a transition from 1.4 to 0.18 $Å^{-1}$ when the donor–acceptor separation is over 20 Å. For long peptides, ET by a tunneling mechanism is possible only if they thermally adjust to a suitable conformation.[34] Theoretical studies show that conformational adjustments are necessary to direct biological long-range ET reactions.[35]

The investigations of self-assembled octadecapeptides carrying a Fc moiety facing the solvent side of the film on gold suggests that long range electron transfer over 40 Å follows a

hopping mechanism as shown in **Fig. 4** with amide groups in the helical peptide as hopping sites.[29] The Fc HOMO" and S "HOMO" are the localized highest occupied molecular orbitals on Fc moiety and sulphur atom respectively.

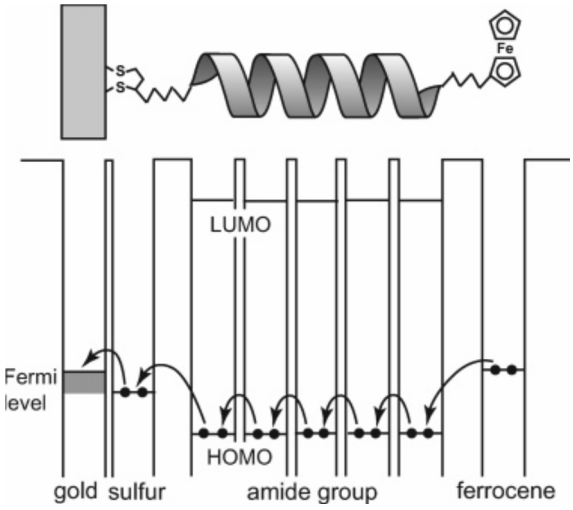
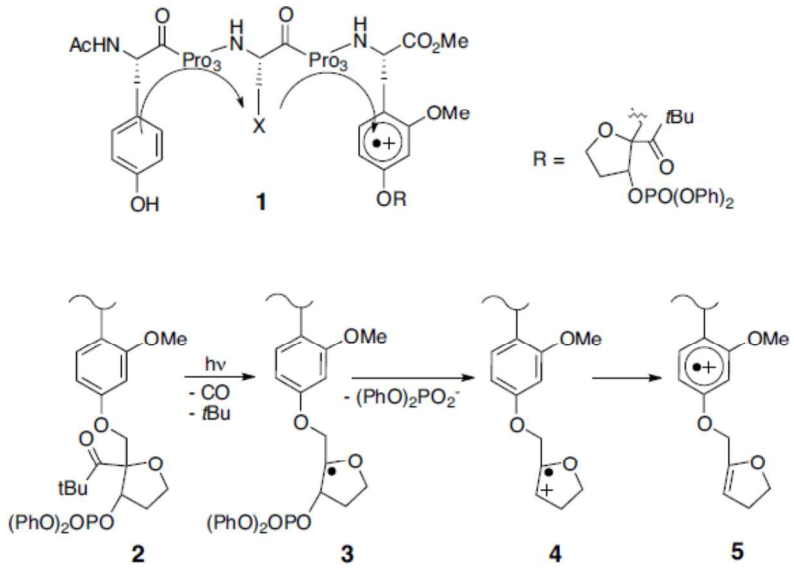


Fig. 4. View of the proposed energy diagram for long range ET by a putative hopping mechanism proposed by Kimura and coworkers (reprinted with permission from ref.[29] Copyright 2005, American Chemical Society).

The overall ET reaction from Fc to gold occurs in three steps (i) ET from the nearest amide group to gold (ii) electron hopping amidst the amide groups and (iii) ET to the nearest amide group from Fc moiety. The acceleration of ET by the substitution of methylene chain with a phenylene linker signifies that the overall ET rate is governed by the electron transfer through the linker. Chromophores insertion into the side chains did not pronouncedly affect the ET owing to their least suitable location for accelerating the rate determining step or supplementary hopping process with chromophores as hopping sites.[29] Abell and coworkers investigated the mechanism of ET in self-assembled monolayers (SAMs) of β-peptides containing a lipoic acid at N-terminus and a Fc group at C-terminus of peptide sequence $(\beta^3\text{Val-}\beta^3\text{Ala-}\beta^3\text{Leu})_n$ for n = 1, 2 (SSB_3Fc and SSB_6Fc). β-peptides consist of β-amino acids, which contain NH_2 group linked to the β-carbon in contrast to α-carbon in α-amino acids. The results of the group of Abell

experiments reveal a shallow dependence of ET rate on the electrode over potential, which is consistent with a hopping ET mechanism. The values of k_{et}^0 for SSB_3Fc and SSB_6Fc are 1200 and 2500 s^{-1}, respectively, which show slower ET than α-peptides of the same length.[32]

One of the roles of peptides in living organism is to connect electron donors and acceptors and mediate ET between them. Based on this concept, Giese *et al.* developed an assay of radical cation of dialkoxyl phenylalanine as electron acceptor, tyrosine as electron donor and prolines as spacers for ET from donor to acceptor.[36] The electron acceptor of a precursor was produced by laser flash photolysis that yielded the desired aromatic cation radical as shown in **Scheme 2**(2→5).[36] The radical cation having oxidation potential less positive than proline was selected to avoid the oxidation of proline. Thus, in the presence of such a radical cation, proline acted as a medium and not as stepping stone of the ET process. Amino acids incorporated between the donors and acceptors were demonstrated to act as electron donor and convert to radical cations followed by subsequent gain of electron from the donor. With this assay, laser experiments were carried out and several amino acids, such as tryptophan, tyrosine, histidine, cysteine, cystine, and methionine were found to act as stepping stones for ET in peptides of chain length greater than 20 Å. The results of Giese *et al.* experiments also reveal that neighboring groups can stabilize the radical cation and control the ET rates in such a way that allow the ET between neighboring molecules. ET through peptides of chain length more than 20 Å cannot occur by a tunneling mechanism due to the energetically highly unfavorable oxidation of amide bonds. However, the presence of easily oxidizable groups as side chains facilitates ET through such peptides by a hopping mechanism.



Scheme 2. Giese's assay for the determination of charge propagation through peptides by site to site transfer or hopping (reprinted with permission from ref.[36]).

The secondary and tertiary structures are suggested to bring the hopping stations close together and thus highlight the significance of neighboring group effects. Another feature which the research team of Giese highlighted in peptides of different chain length is the control of ET via charged amino acids. Two positive charges at close proximity were generated and their strong columbic repulsion led to increased oxidation potential that resulted in a fast ET from the donor to acceptor. The experiments performed on charged amino acids demonstrated that conductance rate depends strongly on the direction of charge transport. The migration of positive charge in the direction of N-terminus led to protonation or N-deprotection which in turn caused to decrease the rate. However, the migration of charge away from N-terminus decreased coulomb repulsion and led to rate enhancement by tenfold. Interestingly, the Marcus and coulomb theory also supports this effect.[37]

A peptide consisting of tyrosine as donor, dialkoxyphenylalanine, a generator of electron and a 3rd residue having a side chain X acting as relay station was used as model peptide.[10,38]

Rigid proline bridges separating the three residues were used to reduce the effect of peptide conformation on the rate of ET. The donor and acceptor were separated to a distance of about 20 Å via a helical spacer (polyproline (PP) II).[38] Although proline sequences facilitate the ET but itself proline does not take part as a relay station due to the difficult oxidation of its side chain. In order to check which type of amino acid could act as a stepping stone, the ability of this system by varying the side chain X was utilized and its functionality was put to test by inserting trimethoxyphenylalanine. In fact, due to its facile redox behavior, trimethoxyphenylalanine acts as a relay station.[10] Alanine was also used as a relay amino acid but its oxidation is too difficult to act as stepping stone, thus, its ET follows long range single step mechanism. By exchanging the easily oxidizable relay amino acid trimethoxyphenylalanine with alanine (X = CH_3) the peptides comparison reveal that ET reaction comprising of two steps is faster than single-step ET by at least one order of magnitude.[10]

Maran and coworkers developed Aib-based peptide models in which peroxide and the phthalimide radical anion serve as electron acceptor and donor.[39] Maran observed an increase of the k_{et} with increasing number of Aib residues from 1–3 between the donor and acceptor. This inverse length dependence of the k_{et} was related to the rigidity of peptide due to the formation of intramolecular bonds, which increase the electronic coupling between the donor and the acceptor. This was also supported by theoretical calculations.[40] More support for the importance of peptides chain length and conformations comes from the work by Isied and coworkers, who demonstrated that distances between donors and acceptors and torsional angles within peptides are critical.[41]

2.2 Effect of structural modification and dynamics

Peptides can adopt different secondary structures[42] and the k_{et} is strongly affected by morphological changes of the peptide, causing potential changes in the ET mechanism.[43] Ashkenasy *et al.*[44] investigated the influence of peptide morphology on their electric conduction and found that conductance is strongly affected by a solvent controlled morphology, with a larger conduction for long and straight filaments, indicating that peptide design can potentially be applied to bio-electronic applications.

Schlag and coworkers explored the effect of structural modification on the transmission of charge from the C-terminus to the N-terminus of a peptide.[3] Their calculations (for the transfer of electron hole across a model dipeptide backbone) show that a barrier of about 0.4 eV must be overcome between the neighboring sites (see **Fig. 5**A and B). However, this large barrier cannot explain the efficient charge transfer in gas phase peptides and even in biological systems. The efficient charge transfer is suggested to control by the adjustment of Ramachandran angles by rotation of peptide to such an extent at which the distance between the carbonyl groups of neighboring amino acids remains about 2.8 Å (see **Fig. 5**C).[45] Detailed quantum mechanical calculations on pentaglycine have also shown that sequential ET depends on the alignment of the C=O groups of neighboring amino acids.[45] The rate of electron hole transfer is reduced by two orders of magnitude in aqueous system because water has been evidenced to produce a tight cavity around the peptide which impedes the ultra-fast angular motions of peptides.[46] Unlike aqueous system, the calculations show a higher ET in lipid environment.[3] Thus, according to these calculations the efficient ET in living organisms can be related to the presence of lipid environment.

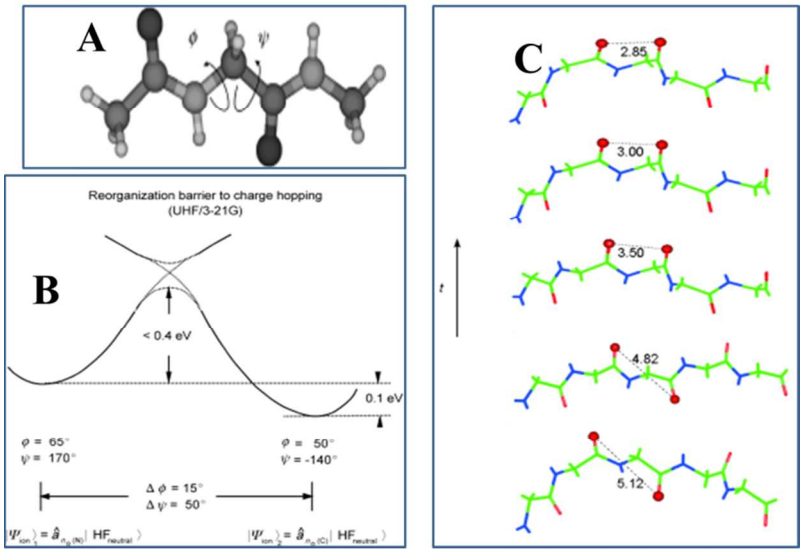


Fig. 5. (A) A model dipeptide showing the angles ψ and ϕ, (B) the energy barriers associated with charge transfer as a function of angular changes, and (C) schematic representations of angular changes and the associated variations in distances (given in Å) between adjacent CO groups (reprinted with permission from ref. [3]).

The proposed atomistic bifunctional model offers an explanation to the transport of charge by a mechanism involving the twisting of peptides to a conformation of lowest energy barrier followed by femtosecond charge transfer. The traditional models of chemical kinetics fail in offering explanation to such distant ET in biological systems due to large number of eigenstates and associated extremely large phase space. Any local energy is either lost before reaching the far end or take longer time for the reaction to occur in peptides of more than two or three residues.[47] The model suggested by McConnell also considers the coupling of all available states as a necessary condition for lowering the potential barrier for efficient ET.[48] The research team of Beratan and Onuchic proposed a more complex theoretical model, which takes into account the coupling through covalent bonds, H-bonds and through space contacts.[49] In their pathway model, the effect of secondary structure and dynamics are taken into consideration and electron transfer rates are predicted that match experimental findings. The results of Maran and

coworkers experiments also support pathway model.[24] More support comes from the Guallar and coworkers[50] who evaluated the electronic coupling between donor and acceptor (bridged by oligopeptides) by extensive quantum chemical and molecular dynamics calculations.

Most interestingly, a study of the two peptides PCB-β3Val-β3Ala-β3Leu-$NHC(CH_3)_2OOtBu$ and PCB-$(\beta3Val\text{-}\beta3Ala\text{-}\beta3Leu)_2$-$NHC(CH_3)_2OOtBu$[51] give different electron transfer characteristics and calculations support the involvement of the amide groups in the ET process. The ET rates with values ~2600 and 10 s^{-1} corresponding to hopping and superexchange mechanism were determined for the above mentioned beta peptides respectively. The prominent difference in rates and mechanism of ET can be related to the fact that the former adopts a 14-helix conformation while the latter a poorly defined secondary structure.

2.3 Effect of hydrogen bonding

Hydrogen bonding plays a significant role in modifying the ET mechanism of peptides. The switching of ET mechanism observed in several synthetic peptides of α-aminoisobutyric acids has been related to hydrogen bonding.[52] **Fig**. **6**a shows a plot of log k_{app}, the apparent ET rate constant, and distance between Fc to N terminus and features a prominent change in slope after three Aib units. A steeper slope for small peptides (0-2 residues) with a higher attenuation constant suggests a super-exchange mechanism while longer peptides (n=3–5 residues) displaying a shallow slope (see **Fig**. 6b) supports hopping mechanism.[52]

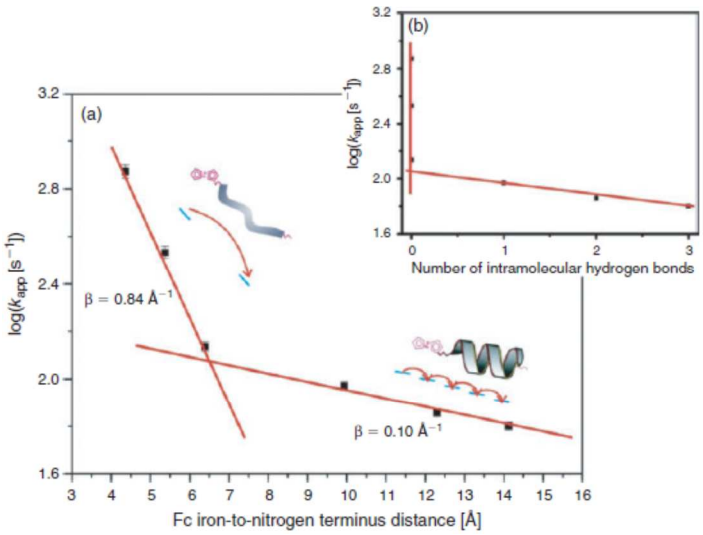
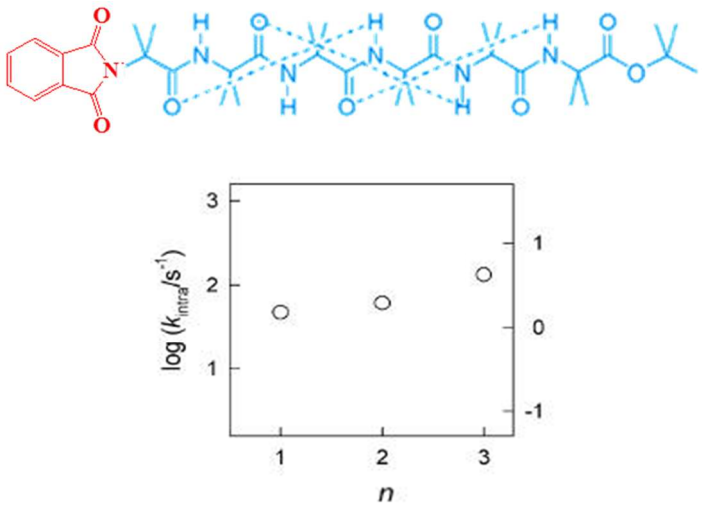


Fig. 6. (a) Transition in mechanism using a series of oligomers (0-5) of α-aminoisobutyric acids, (b) k_{app} dependence on the number of intramolecular hydrogen bonds (reprinted with permission from ref.[52]).

The shorter peptides with n = 0-2 cannot adopt a well-defined secondary structure while peptides of longer chain length (n=3–5) adopt a helical conformation due to intramolecular hydrogen bonding. Therefore, the mechanism of ET switches from superexchange to hopping on transitioning from ill-defined shorter peptides to intramolecular hydrogen bonded well defined longer peptides. The authors supported the crossing over of mechanism by computational studies which showed the helical conformation adaptability of even two residues containing peptide. Thus, on the basis of both experimental and theoretical studies it is concluded that the mechanism of ET in peptides is controlled mainly by secondary structure rather than the commonly accepted chain length factor. Interestingly Maran and coworkers found the ET rate of oligopeptides of Aib to increase with increasing number of spacer amino acids from one to three between the donor and acceptor.[24] Importantly, authors argue that the experimental findings are the result of H-bonding interactions which provide a more efficient pathway for electron transfer (**Scheme 3**).



Scheme 3. Chemical structure of Aib-oligopeptide showing H-bonding interactions between residues by dashed lines and plot of intramolecular ET rate constant as a function of number of intramolecular hydrogen bonds (reprinted with permission from ref. [24]).

A transition of ET from tunneling to hopping mechanism in peptide nucleic acid (PNA) and oligoprolines has also been predicted by theoretical calculations.[53] However, hopping mechanism is improbable because of the high energy barrier for transferring an electron to the LUMO of the bridge where donor-acceptor distances are small.[54] Abell *et al.* offered electrochemical evidence about the dependence of ET mechanism on the secondary structure and concomitant intramolecular hydrogen bonding in peptides.[55] This explanation is in line with theoretical studies that relates greater number of intramolecular hydrogen bonding with effective donor-acceptor electronic coupling.[56-58]

Protein backbone can serve as effective molecular wires along which electrons tunnel between its redox sites.[1] In fact it has been shown that in certain protein based ET systems, the electron tunneling occurs along polypeptide strands with tunneling jumps through hydrogen bonds.[59]

The work by Kraatz and coworkers also support this finding. In their work, oligoprolines and collagen-mimics employs while collagen is not involved in biological electron transfer, it is

an ideal model system for studying H-bonding in peptides and electron transfer since from a molecular dynamics point of view, the system is expected to be more rigid. A comparison of collagen mimics, capable of H-bonding, with oligoprolines that are unable to engage in H-bonding interactions, shows higher ET rates for the H-bonded collagen mimics than the structurally related oligoprolines. For longer collagen mimics of the composition Fc-CO-(Pro-Hyp-Gly)$_n$-Cys(n=4,6 - 9), which form a H-bonded collagen-like triple helix, the ET kinetics shows a shallow distance dependence with a decay constant of 0.05 Å^{-1} (**Fig. 7**).[60]

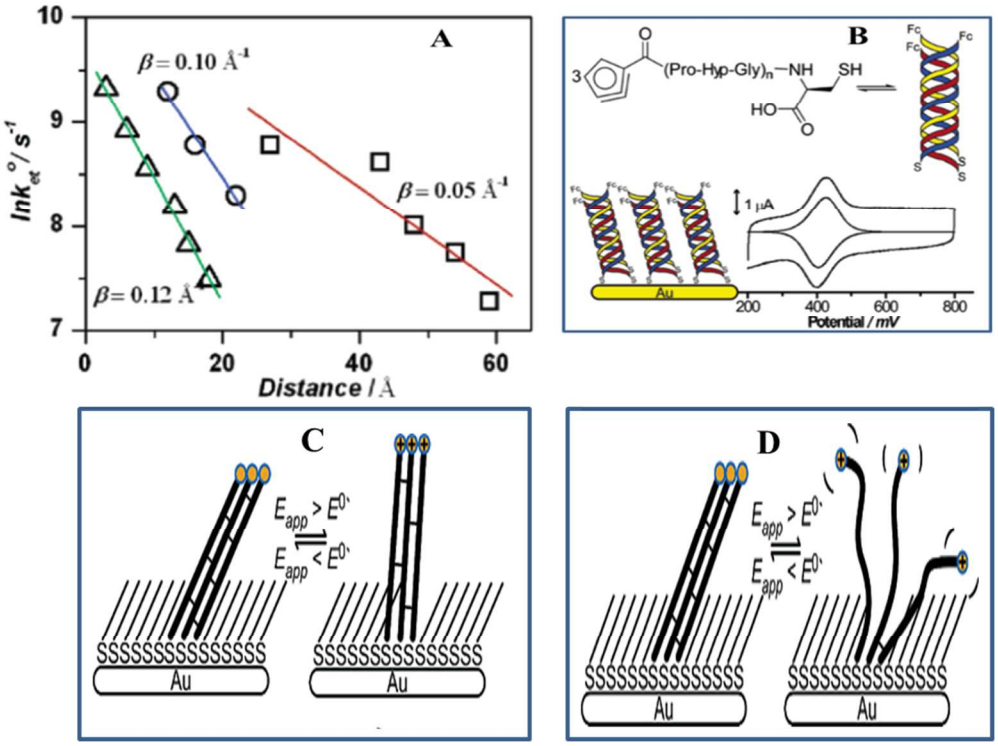


Fig. 7. (A) Dependence of electron-transfer rate constants on the film thickness for oligoprolines (Δ), the Pro-Pro-Gly repeat unit containing collagen mimics (O), and long collagens with a Pro-Hyp-Gly repeat (□). (B) Chemical structures of Fc-labeled collagen models and monolayer formation on a gold surface. CV (raw and background subtracted simulated data) of a film of Fc-peptide 1 on a gold microelectrode at a scan rate of 100 mV s^{-1} in a 2 M $NaClO_4$ aqueous solution. The potential is reported vs a Ag/AgCl reference electrode (C) Schematic of the H-bonded assembly in response to an applied potential. (D) The oxidation of the Fc group forces the shearing of some of the H-bonds because the Fc+ is electrostatically pushed away from the positive bias placed on the electrode. (b) The oxidation of the Fc to Fc+ produces enough electrostatic repulsion to drive the Fc+ headgroups away from one another, resulting in the

fraying of some of the H-bonds at the top of the film (reprinted with permission from ref.[60], copyright 2007, American Chemical Society).

But in these Fc-labeled systems, one has to be mindful that oxidation installs three Fc^+ in close proximity causing electrostatic repulsion, which results in a significant distortion of the system. In earlier work on the related collagen-like system FcCO-(Pro-Pro-Gly)n, it was shown that intramolecular H-bonding in the structure is greatly affected by the electrochemical experiment.[61] Oxidation causes electrostatic repulsion between adjacent Fc^+ groups resulting in the movement of the entire surface-bound molecule. This involves breathing motions of the H-bonding network and rocking motion of the individual peptide strands, which give rise to an observable deuterium isotope effect for the electron transfer step.

2.4 Effect of dipole moment

The dipole moment is considered to have accelerating effect on electron transfer if oriented in the direction of electric field.[62] Several researchers have demonstrated that the rate of ET changes with the direction of dipole moment.[63] Giese and his group investigated the influence of dipole moment on rate of charge transport in peptides[64] by generating a radical cation by laser flash photolysis and observed ET rate constant of 3.5×10^4 s^{-1} in polyproline II-helix having positive dipole end at the C-terminal end of amino acids. They determined rate constant of 3×10^6 s^{-1} after incorporation of the radical cation in α-helical peptides having negative dipole end at the C-terminus. Thus, the reaction rate of α-helical peptide is two orders of magnitude higher than that of the respective cation of the polyproline II-helical peptide, supporting the direction of dipole moment to have a significant effect on the rate of ET. However, in sharp contrast to Giese *et al.* the results of Kimura *et al.*[29] experiments conducted on various Fc-labeled peptides show that the dipole moment has no effect on electron transfer rates. They found that E^o values are

independent of the dipole directions and nearly the same in all cases (about 0.45 V). Their experiments demonstrate the linker to have a significant effect on the ET rate of peptides.

Dipole moments also modify the ET even if they do not cause a change from single-step to multi-step.[65] Change in conformation leads to the change in overall dipole moment. Consequently a rate difference between opposite directions of the ET ought to be observed if the peptide has an overall dipole moment alongside its backbone. The studies of ET in both directions along the peptide having α-helical conformation reveal that the rates in the direction C-terminus → N- terminus are 5–27 times faster than those in the opposite direction, i.e., N-terminus → C-terminus (depending on the solvent.[66,67] These studies are in agreement with earlier work by Fox and Gallopini.[68]

When the helix conformations are denaturized, they transform into random coils and show similar values of ET for both sides of the denaturized peptide backbone (**Fig. 8**).[67, 68]

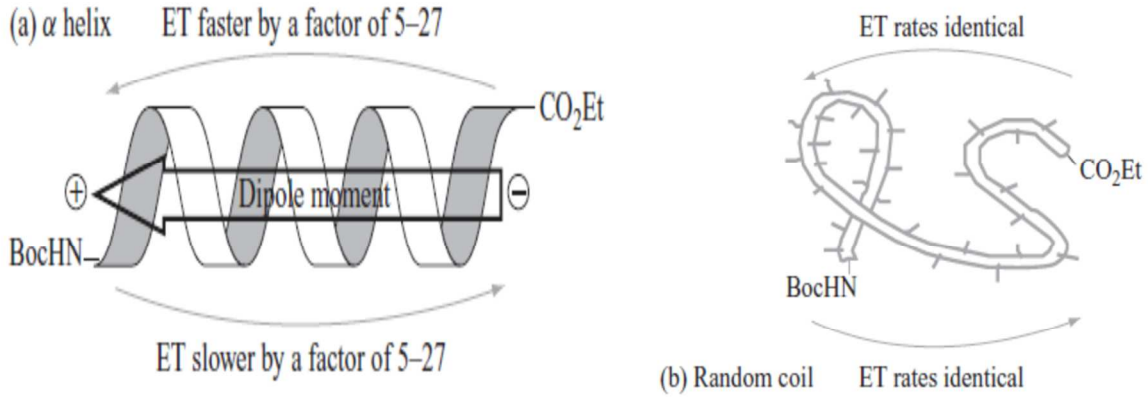


Fig. 8. Dependence of ET rates on conformation of peptides (a) in an α-helical conformation, the rate of ET depends on the direction of overall dipole moment (b) For a random coil conformation of a denaturized α-helical peptide, no difference in the ET rates was found independent of the direction of electron transfer (reprinted with permission from ref.[67]).

A pathway model through quantum calculations was used to expound the influence of peptide conformations on the rate of ET. The results reveal that rate is influenced by the charge of ions

attached to the systems[69] and the direction of ET process validates the significant control of dipole moment.[70]

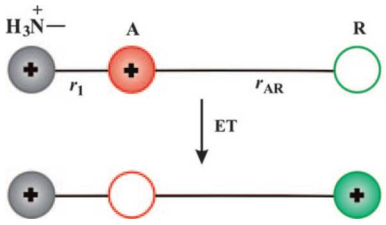
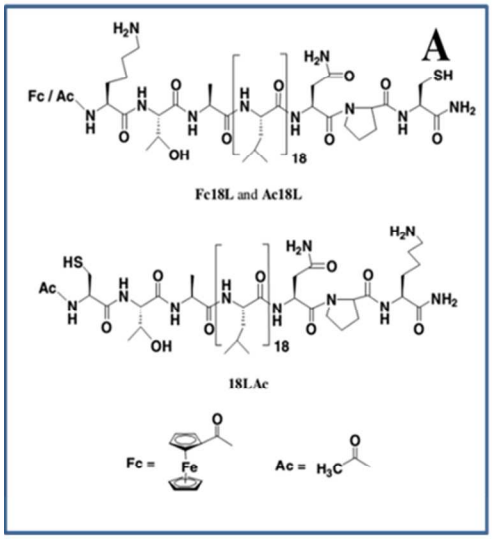


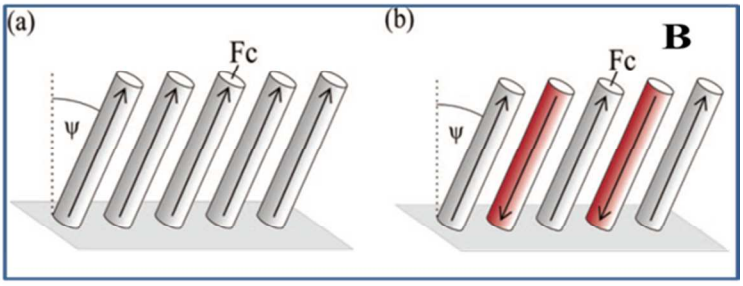
Fig. 9. Representation of an electron transfer chain in a peptide system with A as an electron acceptor and R as relay amino acid (reprinted with permission from ref [72]).

In polyproline systems adopting a PPII helix, the PPI helix has a high conformational stability and remains unchanged in the temperature range of 20 - 80°C.[71] Each of the triproline spacers in a PPII helix corresponds to a distance of 10 Å, consequently acting as a medium for ET and put a distance between the acceptor and the donor. The same system was further experimented to test the effect of ammonium group on ET processes between and through peptides. The rates of the protonated amino group either slowed down or accelerated the intermolecular ET between peptides. The reason for the change in rate is the difference of coulomb energies between the charges. The rate of electron transfer decreased when the positive charge is located nearer to the electron donor (tyrosine) which donates a proton while being oxidized. On the contrary if the ammonium group is in the locale of positively charged electron acceptor the rate increases. For example in the peptide shown in **Fig. 9**, the two positively charged ions are in close vicinity before the ET step and afterwards far away from each other. The coulomb energies of the charges affect the standard free energy and activation energy. In this case the linear dependence of activation energy on standard free energy could be observed.[72] In another model peptide, the ET rates showed dependence on the direction along the peptide backbone with amino acids as relay stations in a stepwise ET process.[67] The secondary structure of peptides influences the ET

radically. In α- and 3_{10}-helices the carbonyl groups point from N-terminal to the C-terminal end of the peptide and display dipole moments which escalate with the lengths of the helices. Consequently it could happen that such large dipole moments reduce the reduction potential of the C-terminal amide groups so that they can act as relay stations. [66]

The Kraatz group investigated the effect of dipole on ET through α-helical peptides by attaching the Fc redox group to the N-terminal side of a leucine-rich peptide.[73] Two unlabeled peptides were used as diluents but the diluents differ in the way they attach to the surface and the direction of the peptide dipole. While the diluent Ac18L attaches to the Au surface in the same fashion as Fc18L giving rise to a film having all peptide dipoles aligned, the diluent 18LAc will attach to the surface with the peptide dipole aligned in the opposite direction. The study focuses on two films containing 5% Fc18L. One film was formed from 5% Fc18L and Ac18L, and one film was formed from 5% Fc18L and equimolar amounts of Ac18L and 18LAc (47.5% each). Electrochemical results show that the film in which the Fc-peptide is embedded with all dipoles aligned exhibits more rapid electron transfer kinetics, compared to the film with opposite dipole alignment. However, it has to be added that in this experiment, the two films have different behaviour in the electric field gradient, pointing to differences in the dynamic properties of the two films, and in this case they appear to be connected. This makes impossible to separate the role of the dipole and the dynamic properties of the film. In order to gain more insight, combined SPR-electrochemical studies by Zhou and Kraatz on these films showed that Film1 possesses a more dynamic behaviour as a potential is applied.[73] This in turn may have important consequences for the electron transfer process in these films, suggesting that the Fc group is highly dynamic and that electron transfer may not be controlled as efficiently as thought by formation of a molecular film.





Dipole moment / D			k_{et} / s^{-1}	
18LAc	Ac18L	Fc18L	Film 1	Film 2
87.10	92.77	87.12	$1.2(5) \times 10^{-2}$	$1.5(3) \times 10^{-3}$

Scheme 4. (A) Molecular structures of the peptides Fc18L, Ac18L and 18Lac. (B) Schematic diagram of: Film1, composed of 5% Fc18L and 95% Ac18L (a) and Film2 composed of 5% Fc18L, equimolar amounts of Ac18L and 18LAc (b), showing the direction of the dipole moments of the a-helical peptides on gold surface. Table shows the dependence of electron transfer rate constant on film composition and concomitant dipole moment (reprinted with permission from ref. [5,73]).

One also has to be mindful of potential anion effects that may cloud the interpretation of electrochemical electron transfer experiments. While this has not been explored for longer peptide that adopt any secondary structure, studies were reported for very short Fc-containing systems, in which the film properties are strongly affected by the nature of the counter ion present in solution. [74]

In a recent study, Maran and coworkers[75] reported the effect of the orientation of peptide conjugated dipole moment on the electrochemical behaviors of fullerene-peptide-radical systems as shown in the **Fig. 10**.

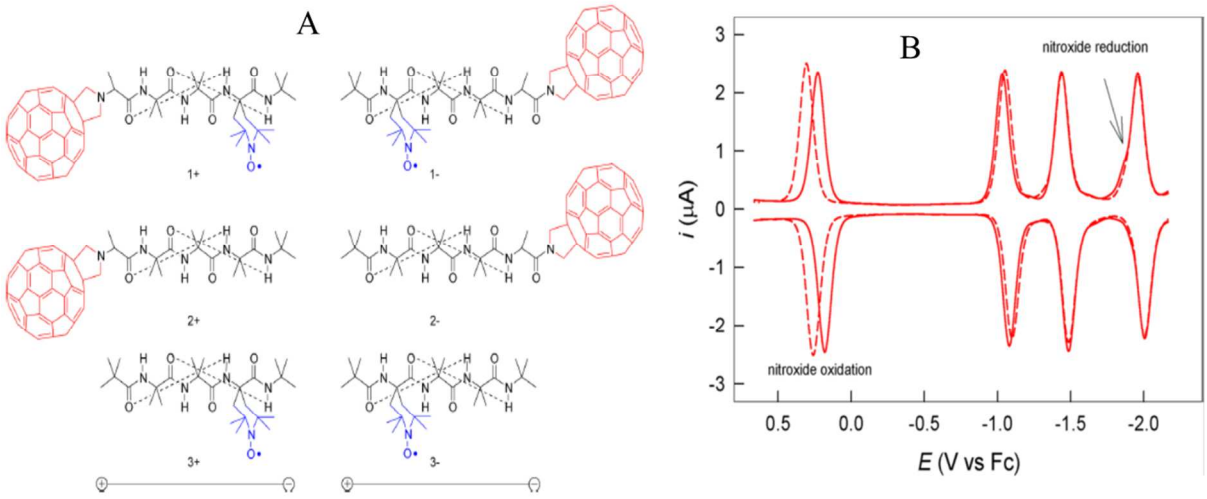


Fig. 10. (A) Structures of electron transfer chain comprised of fullerene-peptide-NO-radical conjugates. Dotted lines represent H-bonding interactions between Aib-residues and (B) electrochemical study showing the differential pulse voltammograms of conjugate 1+ (solid line) and of conjugate 1− (dotted line) (reprinted with permission from ref. [75]).

For this purpose, they conjugated C_{60} fullerene and nitroxide radical to a rigid 3_{10}-helical peptide, which has a strong molecular dipole. Electrochemical studies reveal that the dipole moment of the helix significantly affects the formal potentials of both electroactive groups, fullerene and nitroxide. Interestingly, R_2-NO oxidation in conjugate 1+ is easier than that of conjugate 1− by 80 mV. The nitroxide group of 1+ is on the negative side of the peptide dipole that may facilitate its oxidation, suggesting the consistency of $E°$ shift with the direction of the dipole moment effect. CV analysis of peptides 3+ and 3− showed a potential difference of 90 mV, which demonstrates that the $E°$ shift does not depend on the presence of the fullerene moiety but only on the difference in orientation of the peptide dipole moment. FT-IR and NMR studies provided evidence of folded helical structures and highlighted a strong effect of the orientation of peptide on the spectral patterns, indicating a specific interaction of one of the helical orientations of peptide with the fullerene C_{60} moiety.

2.5 Effect of oxidation potential

Stepping stones of low oxidation potential can facilitate ET through peptides. Quantum chemical calculations and electrochemical experiments show that the radical cation linked to the C-terminal of an α-/3_{10}-helical peptide injects a positive charge in the adjacent amide group.[76] The direction and dipole moments of α- and 3_{10}-helices cause to lower the reduction potentials at the C-terminal end of the amide groups and thus make them as stepping stones for a hopping ET processes.[62,64,76] The results of Kimura *et al.* also give clues about the ET through amide groups.[30] However, quantum chemical calculations puts a limit on the oxidation potential of electron acceptor and demands this potential to be high enough to warrant the oxidation of amide groups of α-helices which could consequently act as relay stations of multistep ET reaction. On the basis of results obtained from experiments by Giese *et al.*[64] separating a radical cation from electron donor by polyproline, it can be concluded that a boost in ET rate is possible by any factor which could increase the negative charge on the amide groups and thus lower their oxidation potential for facile electron abstraction.

3. Summary and Outlook

Despite a multitude of experimental results, the exact mechanism of how an electron transfers from a donor to an acceptor site in peptides remains a hotly debated topic. Essentially, distance relationships are probed, which are then interpreted mechanistically. On one side of the debate is the group that favors a hopping mechanism. A shallow distance dependence suggests that an electron hops between adjacent sites. This mechanism appears to find some support in calculations but to date there is no experimental evidence that an electron can access the peptide backbone. A general peptide, in the absence of special amino acids such as Tyr or Trp, displays

no noteworthy Faradaic electrochemistry and low lying HOMO or LUMO levels appear not to be available for redox process. For electron transfer, there is no evidence that supports the presence of an electron residing on the peptide backbone. On the other side of the debate are those that favour a single step tunneling mechanism. It is important to keep in mind that there are three experimental communities attempting to address this issue. Studies involving photophysical methodologies, surface-supported peptides electrochemically, and scanning tunneling methods in many cases provide results that appear contradictory when used to interpret them mechanistically. If the studies to date have demonstrated anything than it is that peptide conformations are important and the dynamic properties of peptides cannot be overlooked. Peptides are molecules and their dynamics are influenced by the experimental conditions. Clearly this is an important factor that will need to be included in any interpretation of electron transfer processes to provide a definitive answer to this ongoing issue.

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Biographies:

Heinz-Bernhard Kraatz (Ph.D. 1993, U. Calgary) is a Professor of Chemistry and Head of the Department of Physical and Environmental Sciences at the University of Toronto Scarborough. Awards include the PetroCanada Young Innovator Award, the Florence Bucke Science Prize, the Canadian Research Chair in Biomaterials, and the Award in Pure or Applied Inorganic Chemistry from the Canadian Society for Chemistry. His research is focused on the design of surface-supported bioconjugates, biosensors, and bio(nano)materials, including the self-assembly and materials properties of redox-active peptides.

Dr. Afzal Shah is assistant professor in Quaid-i-Azam University of Pakistan. He earned his Ph.D. (physical chemistry) in 2010 under the supervision of Prof. Rumana Qureshi. His Ph.D. was sponsored by Higher Education Commission of Pakistan. Currently his is doing post-doctoral research with Prof. Kraatz in the University of Toronto. His research interests include the elucidation of electrode reaction mechanism of biologically important molecules, development of sensitive voltammetric methods for the detection of environmental toxins and designing of new synthetic routes for the preparation of green surfactants.

Bimalendu Adhikari obtained his PhD in 2012 under the supervision of Prof. Arindam Banerjee at the Indian Association for the Cultivation of Science, India. Currently, he is a post-doctoral fellow at the University of Toronto, Canada with Prof. Heinz-Bernhard Kraatz. His research interests include supramolecular chemistry, gels, peptides, ferrocene, electrochemistry and nanomaterials.

Sanela Martic obtained her Ph.D. 2009, Queen's University, under the supervision of Prof. Suning Wang and co-supervision of Prof. Gang Wu. After postdoctoral work in in the Kraatz group at the University of Western Ontario and University of Toronto, she accepted a faculty position at Oakland University (Michigan, USA), where she is currently an assistant professor of chemistry. Her research interests are in the area of bioanalysis of neurodegeneration biomarkers and peptide and protein assembly toward biomaterials.

Azeema Munir is a PhD scholar in the Physical Chemistry section of Quaid-i-Azam University, Islamabad, Pakistan. She received her M.Phil

degree from the same university in 2013. The main field of her research is surface assisted pH dependent electron transfer reactions of long chain organic molecules.

Suniya Shahzad received a M.Phil in Physical Chemistry from Quaid-i-Azam University, Islamabad, Pakistan, in 2013. She is currently doing her PhD at the same University. Her research is focused on the electron transfer mechanism in DNA and PNA.