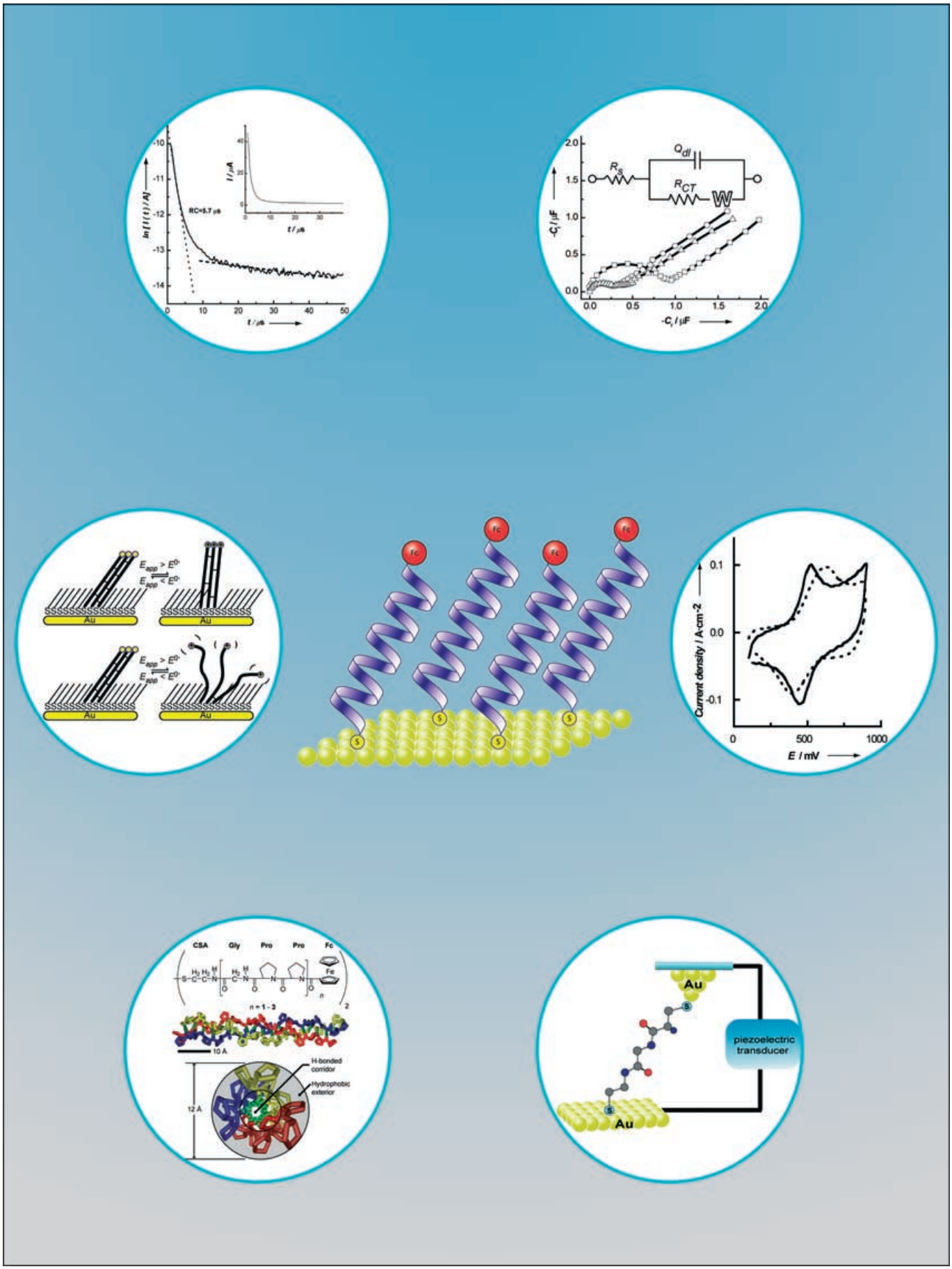

DOI: 10.1002/chem.200500143 *Chem. Eur. J.* **2005**, *11*, 5186 – 5194

Peptide Electron Transfer: More Questions than Answers

Yi-Tao Long, Erfan Abu-Irhayem, and Heinz-Bernhard Kraatz*[a]

Abstract: Nature has specifically designed proteins, as opposed to DNA, for electron transfer. There is no doubt about the electron transfer within proteins compared with the uncertain and continuing debate about charge transfer through DNA. However, the exact mechanism of electron transfer within peptide systems has been a source of controversy. Two different mechanisms for electron transfer between a donor and an acceptor, electron hopping and bridge-assisted superexchange, have been proposed, and are supported by experimental evidence and theoretical calculations. Several factors were found to affect the kinetics of this process, including peptide chain length, secondary structure and hydrogen bonding. Electrochemical measurements of surface-supported peptides have contributed significantly to the debate. Here we summarize the current approaches to the study of electron transfer in peptides with a focus on surface measurements and comment on these results in light of the current and often controversial debate on electron transfer mechanisms in peptides.

Keywords: electrochemistry · electron transfer · ferrocene · peptides · surfaces

Electron Transfer Studies of Peptides in Solution

In Nature, 20 common amino acids serve as the fundamental building blocks of functional peptides and eventually proteins. Understanding charge transfer, both electron transfer (ET) and hole transfer, processes in proteins is of fundamental importance to the unraveling of key biological processes. Experimentalists have two approaches to this problem: One group works on the protein itself and study its ET characteristics, while the other group works on readily constructed peptide model systems in order to gain insight into the "real thing".

Theoretical considerations by Schlag and co-workers suggest that peptides possess "near ideal conduction in the isolated state".[1a] Amongst the various mechanisms of ET, he suggested that charge transport in peptides is highly efficient and that it proceeds in a stepwise fashion.[1] Charge transfer is found to be a through-bond mechanism involving energetically accessible electronic states along the path of charge flow. Because of the complexity of peptides, the importance of individual amino acids in controlling ET is not yet understood in detail. More recently, the dynamic properties of protein folding have begun to attract attention. A quantum mechanical generalized master equation was used to treat protein folding processes ranging from picoseconds to a second or longer.[1b–d] Together with Petrov and May,[1f,g] a solid theoretical foundation was laid for a hopping model of ET in peptides, a mechanism, which is now recognized for charge transport in DNA,[2] but which is still controversial for peptides.

Several groups have been investigating the factors that control the rate of these processes using photophysical techniques and have analyzed their results using various methods, including Marcus–Hush theory of electron tunneling.[3] In a series of photophysical studies of well-behaved peptide model systems, it has become evident that the ET through the peptide spacer is greatly influenced by the separation between acceptor (A) and the donor (D), the nature of the peptide backbone, the amino acids sequence and the resulting flexibility.[4] However, the mechanistic interpretations for these observations are still highly controversial. Two major mechanisms are currently debated to rationalize the distance dependence of ET in peptide models: a bridge-assisted superexchange and an electron-hopping mechanisms. In the hoping mechanism, the electron temporarily resides on the bridge for a short time during its passing from one redox centre to the other, but in the superexchange, the conjugated bridge only serves as a medium to pass the electron between the donor and acceptor. In a superexchange mecha-

[a] Dr. Y.-T. Long, Dr. E. Abu-Irhayem, Prof. Dr. H.-B. Kraatz
Department of Chemistry
University of Saskatchewan
110 Science Place, Saskatoon
Saskatchewan, S7N 5C9 (Canada)
Fax: (+1) 306-966-4730
E-mail: kraatz@skyway.usask.ca

 DOI: 10.1002/chem.200500143

nism, the ET rate exhibits an exponentially distance dependence, whereas a linear distance relationship is expected for a hopping mechanism. Figure 1 shows the differences between the two mechanisms using a surface-supported peptide possessing an electron donating ferrocene group attached to the distal terminus of the peptide.

Hopping and superexchange mechanisms can both contribute in an electron-transfer system. For DNA, the currently accepted mechanism for the charge-transfer process is hole hopping in which the charge propagates down the double stranded DNA with the assistance of the π-stacked system.[5] While in DNA, specific sites (G) were identified as "hopping sites", the question arises as to which are these specific sites that may provide a finite residence time for the charge? It may be possible that charge may be able to reside in the amide group and "hop" from amide to amide, or that hops occur between specific amino acid groups that can accommodate charges, such as tyrosine or tryptophan. In fact, it should be asked: Is charge transfer in peptides independent of sequence and secondary structure? There are a number of studies making use of peptides with varying secondary structure and amino acid sequence. Peptides range from homooligomers, such as oligoprolines, oligoglycines, both of which have specific secondary structures, and peptides having α-helical or 3_{10}-helical structures (Figure 2). This has significant structural consequences, as this will change the separation between the donor and acceptor. The translational distance per residue changes from 1.50 Å for an α helix to 2.00 Å for a 3_{10} helix, to 3.12 Å for polyproline-II, to 3.1 Å for polyglycine-II.

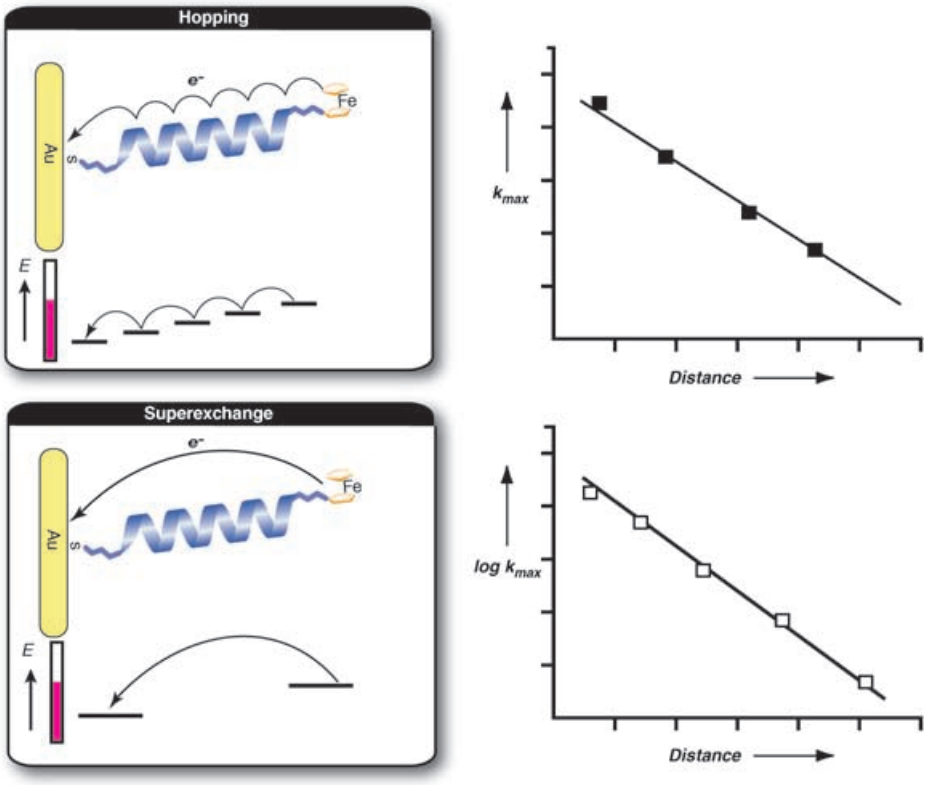

Figure 1. Comparison of the electron-transfer mechanism by hopping (above) and by superexchange (below). Please note the linear distance relationship of the electron transfer rate constant in case of the hopping mechanism and the exponential dependence for the superexchange mechanism.

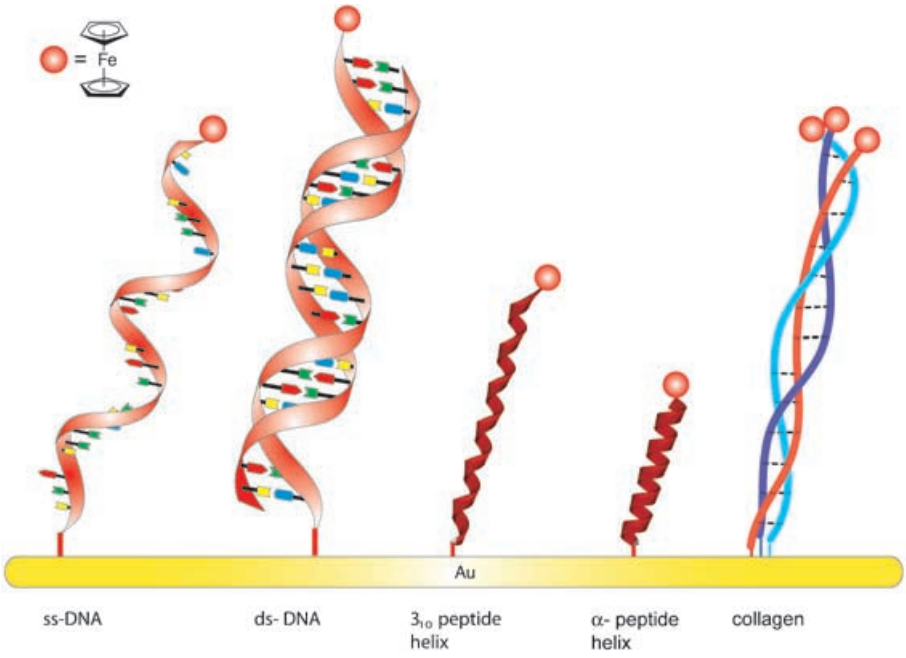

Figure 2. Schematic view of ferrocene modified single-stranded (ss)- and double-stranded (ds)-DNA, and a helical, 3_{10}-helical and a collagen-like peptide on gold surfaces.

Isied, one of the pioneers of peptide ET, and his co-workers recently reported a series of peptide-bridged diruthenium systems in which the length of the oligoproline spacer

was varied (Figure 3).[6] Using radiolysis for longer oligoprolines (n = 3–9), he was able generate $[(bpy)_2Ru^{II}(L^{\bullet})\text{-}Pro_n\text{-}apyRu^{III}(NH_3)_5]^{4+}$ from the oligoproline precursor and avoid major contributions from solvent reorganization, working in an activationless regime. For the shorter oligoproline spacers, the ET rate constants were determined by comparing the decay of the excited state emission from $[(bpy)_2Ru^{II}(L^{*})\text{-}Pro_n\text{-}apyRu^{III}(NH_3)_5]^{5+}$ and from the mononuclear Ru complex $[(bpy)_2Ru^{II}(L^{\bullet})\text{-}Pro_n\text{-}OH]^{2+}$. His results indicate a transition in mechanism of the ET from "predominantly electron exchange to predominantly electron hopping".[6] These experimental results agree with theoretical considerations by Petrov and May.[1f,g]

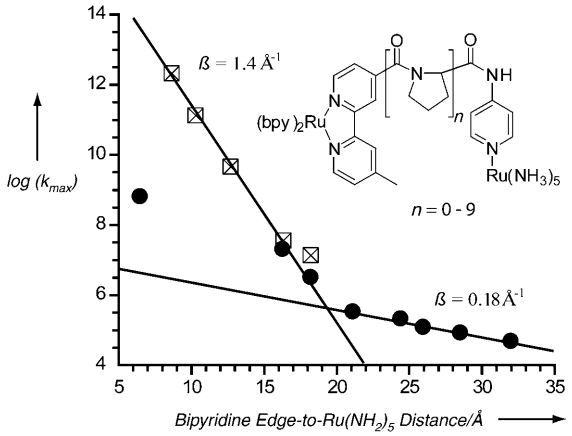

Figure 3. Plot of logk_{max} (radiolysis: ●, $k_{1,max}$; and photolysis: □, $k_{2,max}$), versus the distance from the edge of Isied's oligoproline conjugates (redrawn from ref. [6])

Newton, Isied and co-workers also reported a theoretical study providing a rationale for differences in electron-transfer kinetics between peptides of various secondary structural motifs.[7] Using idealized structural elements, Isied presents a model that rationalizes the differences in electron-transfer kinetics for various secondary peptide structures which they conclude are due to the differences in the direction and magnitude of the peptide dipolement and changes in the electronic coupling between the donor and acceptor group $|H_{AD}|$. Isied's results show that there are significant differences between α- and polyproline-II helices and extended β-strand-like structures. Electronic coupling will be higher for the helical structures compared with the strand-like structure, resulting in faster electron transfer in helices. Although, the partial double bonding character of the peptide bond is important in this context, peptides do not provide a completely conjugated pathway, as for example polyolefins. This difference manifests itself also in a lower electron transfer ability of peptides, compared with π-conjugated chains. In the grand scheme of things, the electron transfer ability in peptides, as measured by β, is comparable to alkyl chains and is about 1 Å^{-1}. Other molecules, such as DNA (β=0.2–0.9 Å^{-1}), polyolefins (β = 0.2–0.6 Å^{-1}), and oligo(*p*-phenylene vinylene) (β = ≈0.01 Å^{-1}), exhibit a significantly higher electron transfer ability.[8]

However, recent results on the solution electrochemistry of aminoisobutyric (Aib)-homooligomers linked to a *p*-cyanobenzamide or a phthalimide donor clearly provide a different picture of the mechanism of the ET process. In these systems, Maran was able to probe the ET from the donor to the C-terminal peroxide, which is reductively cleaved into an alcoholate and a *tert*-butoxide radical.[9] Aib-rich peptides are known to form a stable 3_{10} helix (helix of three amino acids per turn with a translational distance of 2.00 Å per residue and 10-membered hydrogen-bonding rings) in solution which possesses intramolecular C=O···H-N hydrogen bonding. The number of hydrogen bonds increases with the length of the peptide. Also, earlier work showed that the redox potential shows a dependence on the number of intramolecular hydrogen bonds in these peptide conjugates.[10] Maran found that the ET rate exhibits only a weak distance dependence. In some cases, in which phthalimide was used as the donor, the rate even appeared to increase with distance! In order to increase the driving force and to favor a hopping mechanism, the energy gap was increased by attaching a *p*-cyanobenzamide donor to the N-terminal side of the peptide. Importantly the ET rates in both systems exhibit only a smaller than expected distance dependence (Figure 4). Maran rationalized his results invoking a superexchange mechanism in which the bridge is intimately involved and presents evidence from variable temperature electrochemical experiments which suggest that a hopping mechanism is not operational in these systems. It has to be pointed out that although both groups studied helical peptides, Isied's systems cannot engage in inter- or intramolecular hydrogen bonding whereas Maran's Aib systems engage in strong intramolecular hydrogen bonding. This raises the

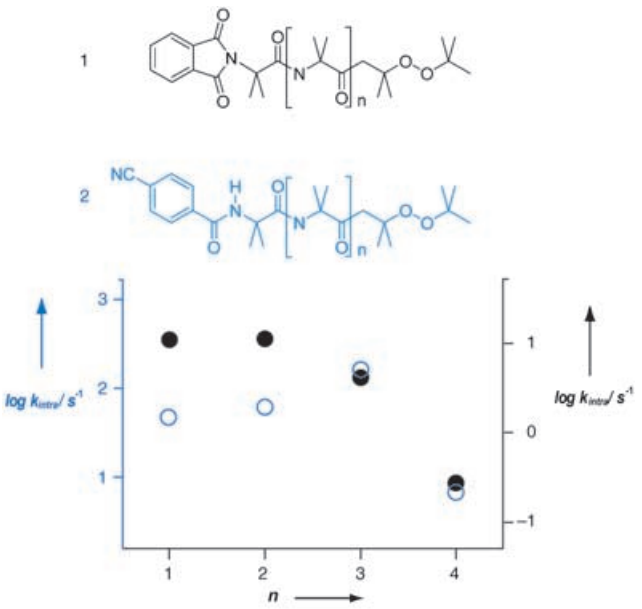

Figure 4. Dependence of the intramolecular ET rate constants for compounds *p*-cyanobenzamide substituted oligopeptides (blue, left scale) and phthalimide substituted oligopeptides (black, right scale) on the number of intramolecular hydrogen bonds. Redrawn from ref. [9].

question as to whether hydrogen bonding does indeed affect the ET mechanism in peptides.

The charge and the dipole of the peptide also play an important role in the electron transfer. The dipole of an α helix (about 3.5 D per amino acid residue) generates an electrostatic filed along the helix axis of $10^9\,V\,m^{-2}$, producing an effective positive charge at the amino end and an effective negative charge at the carboxyl terminus, each having a magnitude of 0.8×10^{-19} C. Fox and Galoppini demonstrated the effect of the electric field generated by the helix dipole on ET in Aib-rich α-helical peptides.[11] Other than the effects from secondary structure (e.g. α helix and β sheet), dipole and hydrogen bonding, the solvent has also a marked influence on the study of the electron transfer. Meyer and co-workers[12] showed that the redox-separated state formed with 33–96% efficiency depending on the solvent in the helical oligoproline system. The rate constant for back-ET is also solvent dependent.

Electron Transfer Studies of Peptides on Surfaces

Over the past few years, electrochemical studies of peptides immobilized on surfaces have become a viable alternative for the study of ET processes. This approach is particularly interesting in that it may minimize the conformational freedom the peptide has in a two dimensional quasicrystalline arrangement. Our work began by constructing redox active peptides that can be attached to a gold surface making use of ferrocene (Fc) labeled constructs.[13] With the help of Fc-COOBt,[14] a stoichiometric ferrocenoylation agent prepared from ferrocene carboxylic acid and 1-hydroxy-1,2,3-benzotriazole, it is possible to prepare a series of Fc-peptide conjugates by solid- and solution-phase peptide coupling. These Fc-labeled peptides are readily immobilized onto a gold surface by using the cystamine (CSA) disulfides. Other sulfur containing groups, such as lipoic acid and thiols can also be used to heterogenize the peptides on gold. The resulting films are in many cases well-ordered and their structure can be probed with reflectance-absorbance infrared spectroscopy, making it possible to experimentally determine the tilt angle of the peptide axis with respect to the surface. Tilt angles for most of the helical peptides are in the range of 30–55° with respect to the surface normal. The ability to form tightly packed surfaces depends on the length of the peptides and presumably their structure. Short peptides form loosely packed films that show a large degree of inhomogeneity within the film and that have up to 15% vacant gold sites. By contrast, longer peptides form well-ordered films.[15] Electrochemical techniques, such as cyclic voltammetry (CV), chronoamperometry (CA) and electrochemical impedance spectroscopy (EIS) are used to study the ET kinetics in these films and to obtain parameters, ranging from the molecular footprint of the ferrocene–peptide conjugates on the surface to the interfacial resistance exerted by the film on the ET process.

Bilewicz and co-workers[16a] studied the effect of increasing the glycine spacer from two to six in Fc–oligoglycine cystamine films anchored to a gold electrode. The oligoglycines from Gly_2 up to Gly_5 adopt a β-sheet-like polyglycine-I structure, while the Gly_6 chain forms the polyglycine-II helix (translational distance per residue 3.1 Å). The peptides were separated from each other by alkylthiols which prevented intermolecular hydrogen-bonding interactions. As expected, these peptides display a one-electron redox chemistry due to the Fc group. In addition, a decrease in k_{ET} was observed upon increasing the number of Gly residues in the peptide (Figure 5). These changes were attributed to potential changes in the secondary structure of oligoglycine chain, from β sheet to a helical polyglycine-II structure. But importantly, a change in mechanism from a bridge-assisted superexchange to electron hopping could not be ruled out. In this context, Kimura's work is critical. He found a weak linear distance dependence for ET and postulated that a hopping mechanism is present in helical Fc-labeled peptides.[17] The question arises as to the exact nature of the hopping mechanism. Does the electron have a finite residence time? If so, can experiments be devised that allow the hopping mechanism to be establish unequivocally. Therefore, it is important to point out that in the case, where a hopping pathway is provided, as is in the case of helical peptides incorporating non-natural amino acids containing a naphthyl residue in the side chain, the ET appears to occur via electron hopping.[18]

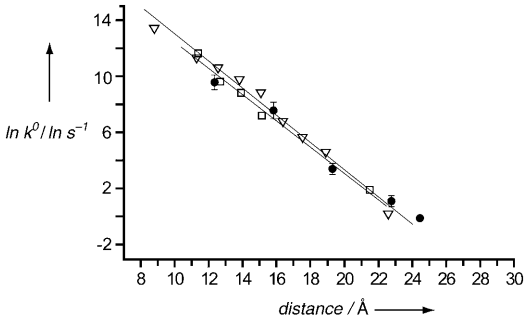

Figure 5. Plot of $\ln k^0$ vs the length of the spacer separating the ferrocene from the electrode surface. The data obtained by Chidsey and co-workers[16b,c] (▽, $FcCOO(CH_2)_nSH$; n = 5–15, 18) and Creager et al.[16d] (□, $FcCONH(CH_2)_nSH$, n = 7–10, 15) for alkanethiolate monolayers with tethered ferrocene redox centers are shown for comparison (●, $FcCO(NHCH_2CO)_nNH(CH_2)_2SH$, n = 2–6). Solid lines represents linear fits to distance dependences for *n*-alkanethiolate monolayers. The decay constant for the alkyl chains is about 1.2 per atom. Redrawn from ref. [16a].

Earlier work on helical Fc–oligoprolines carried in dichloromethane,[4c] where the oligoprolines are unable to form intra- or interstand hydrogen-bonding patterns, show significant "through-bond" contributions to the ET. Collagen-like peptides can engage in interstrand hydrogen bonding and are structurally related to the oligoprolines. The simple (Pro-Pro-Gly) repeat unit was chosen as a starting point. Each single peptide strand adopts a left-handed polyproline-II structure. Three peptide strands assemble into a

supramolecular right-handed triple helical structure by forming inter-peptide hydrogen bonds between the amide NH of each glycine residue with the carbonyl groups of the proline residues on adjacent peptide strands, as illustrated in Figure 6. The net result is that hydrogen bonding occurs on the interior of the triple helix providing, for longer peptides, a hydrogen-bonded corridor on the interior with all aliphatic residues pointing towards the exterior of the triple helix.[19] Using these Fc–collagen model conjugates, we hoped to understand the role of interstrand hydrogen bonding in the ET mechanism. It was expected that if a hopping mechanism involves hopping from amide to amide, as suggested by Kimura for α-helical systems,[17] a change of the conditions such as deuteration and temperature in a hydrogen-bonded system such as collagen models, should be measurable by electrochemical techniques. A collagen-like structure provides a well-defined framework to probe the role of H-bonded peptide assemblies in ET reactions.

The solution structures of the Fc–collagen models were evaluated by using circular dichroism spectroscopy (CD) and nanopore measurements. The CD measurements show that the longer collagen models with three repeats are strongly hydrogen bonded and exist in the collagen conformation. These results were confirmed by measurements of the ion flow through an α-hemolysine nanopore with a pore dimension of 1.5 nm (see Figure 7). Molecular transits cause blockage of the ion current, which is related to the size of the peptide passing through the pore.[20]

Films of the Fc–collagen model peptides were formed on Au microelectrodes. The peptides displayed a strong hydrogen bonding in the film. Furthermore, with increasing length of the peptide spacer, the film thickness increases. Our electrochemical measurements by CV and CA in H_2O and D_2O, allowed us to evaluate the ET kinetics (see Figure 8).[21] A linear and shallow distance dependence of k_{ET} on film thickness was found. Furthermore, our ET studies in D_2O show that the ET rates are slower and a kinetic isotope effect (KIE) of 1.2 to 1.6 was observed. This is an important finding since KIE were not observed for ET in peptide models before. In terms of mechanistic insight, we suggested that ET via the peptide spacer proceeds according to Jortner's thermally induced hopping (TIH) mechanism. This is also in line with Kimura's proposal of electron hopping from amide to amide.[17] However, our results also suggest electron entrainment in the hydrogen bonded Fc–peptide conjugate that is to say that ET must proceed along the hydrogen-bonded interface. Additional studies are currently underway to evaluate the effect of sequence in peptide assemblies that are significantly longer. In work presented by Kimura, Bilewicz and from our own work, a significant issue arises that is

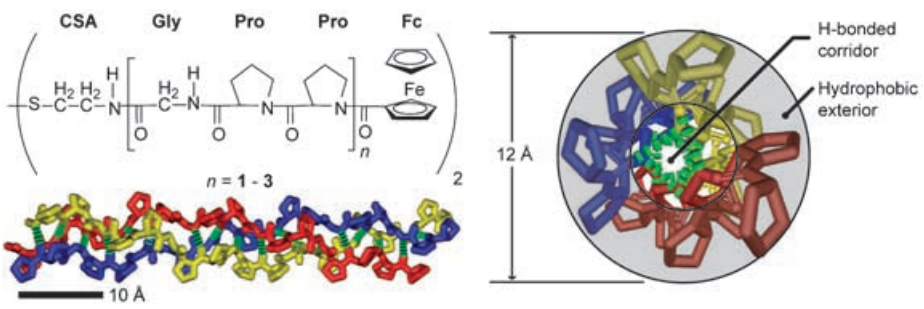

Figure 6. Chemical structure of Fc-collagen models having a Pro-Pro-Gly repeat and a schematic view of the supramolecular coiled-coil structure adopted by a Pro-Pro-Gly repeat unit taken from the solid-state structure. The helix pitch is 10 Å; on the right is given a view down the helical core showing the hydrogen-bonded corridor and the arrangement of the hydrophobic residue towards the exterior of the helical structure. Redrawn from ref. [21].

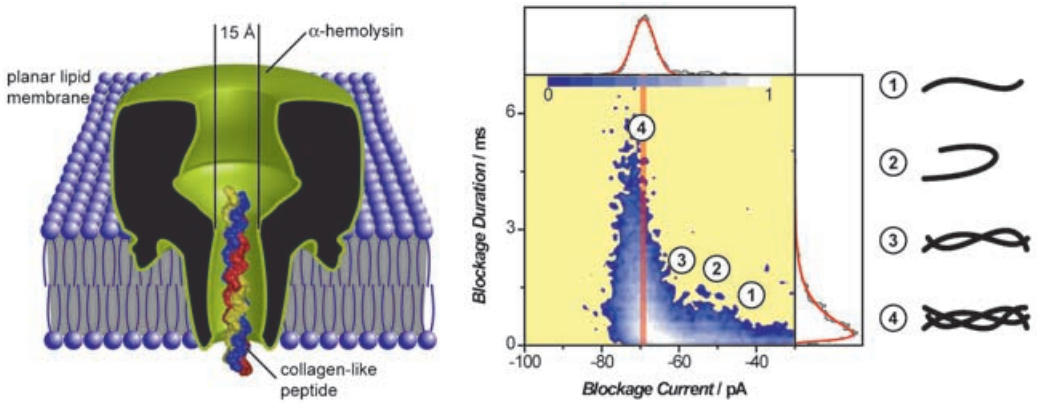

Figure 7. Left: Representation of the α-hemolysin pore inserted into a planar lipid bilayer with a linear collagen-like peptide passing through the 1.5 nm diameter pore. Right: Contour plots of current transients of $[Fc\text{-}(Pro\text{-}Pro\text{-}Gly)_3\text{-}CSA]_2$. The horizontal and vertical red lines represent cross-sections of the contour plots. Each horizontal cross-section was fit to a Gaussian distribution, and each vertical cross-section was fit to a double exponential function. $[Fc\text{-}(Pro\text{-}Pro\text{-}Gly)_3\text{-}CSA]_2$ has a i_{block} distribution positioned at −75.4(0.2) pA with a $w_{1/2}$ of 6.2 pA, and the t_{block} distribution is described by lifetimes of 33(5) μs and 591(17) μs. Bin widths used: Current blockage 0.5 pA and blockage duration 0.025 ms. (right): Values in parentheses are the standard deviations. Reproduced from ref. [20] with permission of the American Chemical Society, 2004.

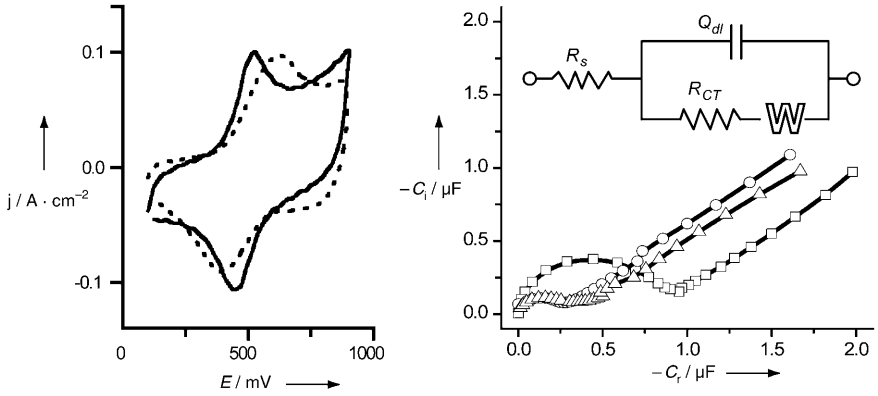

Figure 8. Left: CVs of a film of $[Fc\text{-}(Pro\text{-}Pro\text{-}Gly)_3\text{-}CSA]_2$ on gold in H_2O (——) and D_2O (-----) at a scan rate of 500 V s^{-1} in 2 M $NaClO_4$, Pt counter electrode vs Ag/AgCl reference; right: Impedance data shown in the complex capacitance plane for $[Fc\text{-}(Pro\text{-}Pro\text{-}Gly)\text{-}CSA]_2$ ○, $[Fc\text{-}(Pro\text{-}Pro\text{-}Gly)_2\text{-}CSA]_2$ △, and $[Fc\text{-}(Pro\text{-}Pro\text{-}Gly)_3\text{-}CSA]_2$ □. Equivalent Circuit for fitting hexanethiol-diluted Fc-peptide cystamine films. R_S = solution resistance; Q_{dl} = CPE of double layer capacitance, R_{CT} = charge transfer resistance; W = Warburg diffusion element (at an applied bias voltage of $E^{0'}$ vs Ag/AgCl for the Fc group and ac amplitude of 5 mV rms in 2 M $NaClO_4$ at room temperature, from 100 kHz to 1 Hz). Reproduced from ref. [21] with permission of the American Chemical Society, 2004.

linked to the coupling of electron transfer to molecular motion. The time scale of the electron movement from the Fc to the gold surface through the peptide spacer in all current electrochemical experiments is in the millisecond time scale, which is slower than the movement of small functional groups.[22] Thus, it can be speculated that at least in the case of the hydrogen-bonded Fc–collagen models, movements of the entire molecule, such as breathing motions of the hydrogen-bonding network or rocking motions of the individual Fc–peptide strands, could be responsible for the observed isotope effect. Thus the role of molecular dynamics needs to be evaluated thoroughly. It was shown for example by Kawatsu and Yamato that the nuclear dynamics contributes to the ET rate significantly.[23] Similarly, Onuchic and co-workers[24] have demonstrated the influence of hydrogen bonds in azurin using molecular dynamics calculations (MD). In the Fc–peptide conjugates described here, we can assume that MD is playing an important role in determining the exact mechanistic pathway. However, in the absence of detailed molecular dynamics calculations, this remains an open and unanswered question.

In recent single molecule studies, Tao and co-workers[25] were able to measure the current–potential characteristics of individual peptide molecules. Using Gly-containing peptides with an increasing number of Gly residues with cysteamine linkages at the C- and N-terminus of the peptide, Tao was able to create individual molecular junctions between a gold electrode and a second gold electrode that was moved in an out of the peptide solution (CSA-Cys, CSA-Gly-Cys, Cys-Gly-Cys, and CSA-Gly-Gly-Cys). The process was controlled by a feed-back loop that drove the electrode into contact with the gold surface. Once the contact was established, a feedback loop activated a piezoelectric transducer to pull the electrode out of contact (Figure 9, left). Basically, the number of the molecular junctions could be counted by the number of steps in the conductance between the two electrodes. Significant pH dependence is observed for only the peptide having a free COOH group.

Using this method, the current–potential (i–V) characteristics of each of the Gly-containing peptides, as a function of pH, were measured and a significant pH dependence on the conductance (G) was observed. Importantly, the conductance (G) of the peptides versus length (L) can be described by $G = A\exp(-bL)$ (with $A = 0.15G_0$ and $b = 1.1 \pm 0.1$ per carbon or nitrogen atom) (see Figure 9, right). This Figure also contains data for alkanethiols of comparable lengths ($A = 0.65G_0$ and $b = 1.0 \pm 0.1$ per carbon). Tao's findings are perfectly consistent with a coherent tunneling process.

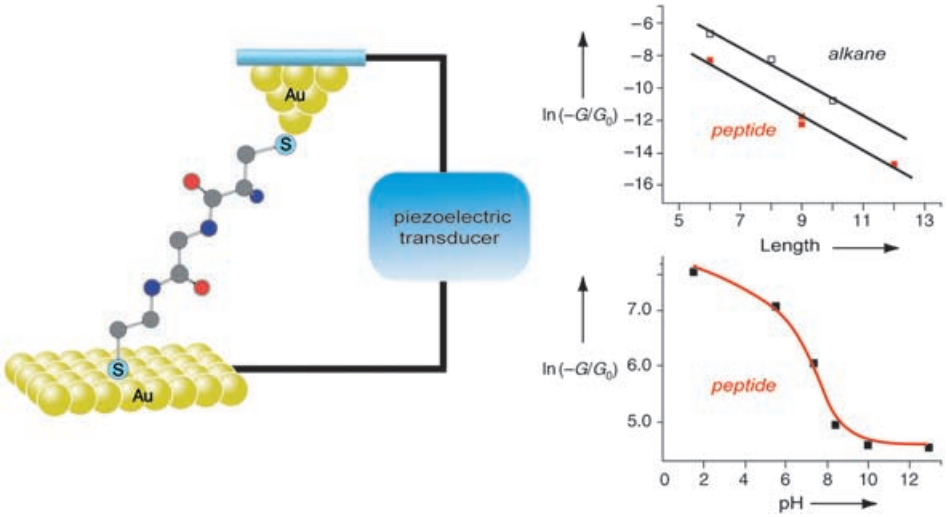

Figure 9. Illustration of a molecular peptide junction formed by separating two electrodes controlled by piezoelectric transducer. Plot of the ln$G$ vs peptide length (number of carbon or nitrogen atoms in the peptides). b_N is obtained from the linear fit. For comparison, the data for alkanedithiols are also plotted; (top right) Conductance vs pH for Cys-Gly-Cys (bottom right). Redrawn from ref. [25].

The pH influence was rationalized by the charge on the peptide spacers changing the tunneling barrier and thus the conductance of the spacer material. Why are Tao's results different from Bilewicz' results on oligoglycines, who suggested that ET proceeds by electron hopping. Clearly Tao's results on short Gly spacers indicate tunneling and not hopping? The solution to this problem is length.

Epilogue

Although several groups have made seminal contributions to our understanding of the ET properties in peptides, they are far from being understood. Theory has provided some important insights into this fundamental process.[1] The state of the art investigation for ET of surface-bound molecules was recently reviewed.[3] Some experimental results on ET in peptides appear to suggest that a hopping mechanism dominates over a superexchange, while others suggest that the mechanism is strongly dependent on the length of the peptide, its structure or even may depend on the presence of specific side chains.

One important question has to be asked: Why do electrochemical measurements of peptides assembled into films and monolayers give results that are so different from the observations made by single molecule measurements or in solution? There are two possible answers: a) Tao's peptides are short peptides and he may be in the tunneling region rather than Isied's hopping regime which would be operational only for longer peptides; b) a more intriguing and potentially controversial answer lies in the presence of possible intermolecular interaction that peptides may undergo on surfaces. These interactions can be proximity effects, hydrophobic interactions or maybe even intermolecular hydrogen bonding. In work on Fc–glycines and Fc–collagen models, the peptides were separated by alkylthiols. Although this should prevent lateral electronic communication between the redox centers, it is clear that surface electrochemical measurements probe the colligative properties of the peptide film rather than the electron-transfer characteristics of individual molecules. At the present time the jury is still out on what effects are responsible for these different results. Even more tantalizing is the variety of secondary structures for peptides, each of which offers a different hydrogen-bonding pattern and different translational distances. Can it be expected that ET processes follow the same mechanism in peptides of different amino acid sequences and different secondary structures?

However, measurements in the solid state, on surfaces and in molecular junctions, are critical. Detailed structural knowledge is crucial for the interpretation of the kinetic data. To some degree, the detailed knowledge of charge transfer in double-stranded DNA is due to the well defined and well behaved structure it adopts in solution and on the surface. For peptides, the situation is significantly more complex. The flexibility of peptides, their ability to adopt various stable secondary structures and to interact with each other on the surface complicates the issue. Although, experimentally the tilt angles of the peptides and the film thicknesses are readily accessible structural quantities, a more detailed structural analysis is important, since differences in the secondary structure of the peptide may profoundly influence its electronic properties, as was demonstrated for the series of oligoglycines, which appear to undergo a length dependent transformation from a β sheet to a helical oligoglycine-II structure.

The exploration and application of peptide conjugates in molecular electronics has only begun, aided largely by the ease of preparation of peptide conjugates by solid- or solution-phase synthesis. The inherent ability of peptides to engage in specific interactions with each other, with other biomolecules, such as proteins and DNA, and with metal ions is a key feature that we are only now beginning to explore. The molecular recognition processes potentially may allow gating of signal transduction through the interaction of the peptide with other biomolecules. Furthermore, peptide–metal ion interactions can be tailored and made specific for sensing applications. In addition, the interaction with metals may allow to fine tune the electronic properties of the peptide surfaces for a particular application.

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council of Canada. H.B.K. is the Canada Research Chair for Biomaterials. The authors also thank Dr. T. C. Sutherland for useful discussions.

[1] a) S.-Y. Sheu, E. W. Schlag, D.-Y. Yang, H. L. Selzle, *J. Phys. Chem. A* **2001**, *105*, 6353–6361; b) S.-Y. Sheu, D.-Y. Yang, H. L. Selzle, E. W. Schlag, *J. Phys. Chem. A* **2002**, *106*, 9390–9396; c) E. W. Schlag, D.-Y. Yang, S.-Y. Sheu, H. L. Selzle, S. H. Lin, P. M. Rentzepis, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9849–9854; d) R. Weinkauf, P. Schanen, A. Metsala, E.-W. Schlag, M. Buergle, H. Kessler, *J. Phys. Chem.* **1996**, *100*, 18567–18585; e) E. W. Schlag, S.-Y. Sheu, D.-Y. Yang, H. L. Selzle, S. H. Lin, *J. Phys. Chem. B* **2000**, *104*, 7790–7794; f) E. G. Petrov, Y. V. Shevchenko, V. May, *Chem. Phys.* **2003**, *288*, 269–279; g) E. G. Petrov, Y. V. Shevchenko, V. I. Teslenko, V. May, *J. Chem. Phys.* **2001**, *115*, 7107–7122.

[2] a) M. Bixon, J. Jortner, *J. Am. Chem. Soc.* **2001**, *123*, 12556–12567; b) M. Bixon, B. Giese, S. Wessely, T. Langenbacher, M. E. Michel-Beyerle, J. Jortner, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 11713–11716; c) P. T. Henderson, D. Jones, G. Hampikian, Y. Z. Kan, G. B. Schuster, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 8353–8358; d) R. N. Barnett, C. L. Cleveland, A. Joy, U. Landman, G. B. Schuster, *Science* **2001**, *294*, 567–571.

[3] For the most recent discussion, see: D. M. Adams, L. Brus, C. E. D. Chidsey, S. Creager, C. Creutz, C. R. Kagan, P. V. Kamat, M. Lieberman, S. Lindsay, R. A. Marcus, R. M. Metzger, M. E. Michel-Beyerle, J. R. Miller, M. D. Newton, D. R. Rolison, O. Sankey, K. S. Schanze, J. Yardley, X. Zhu, *J. Phys. Chem. B* **2003**, *107*, 6668–6697; see also: S. F. Nelsen, R. F. Ismagilov, D. A. Trieber II, *Science* **1997**, *278*, 846–849.

[4] a) Y. J. Zheng, M. A. Case, J. F. Wishart, G. L. McLendon, *J. Phys. Chem. B* **2003**, *107*, 7288–7292; b) M. Sisido, S. Hoshino, H. Kusano, M. Kuragaki, M. Makino, H. Sasaki, T. A. Smith, K. P. Ghiggino, *J. Phys. Chem. B* **2001**, *105*, 10407–10415; c) M. M. Galka, H. B. Kraatz, *ChemPhysChem* **2002**, *3*, 356–359; d) S. S.

Isied, M. Y. Ogawa, J. F. Wishart, *Chem. Rev.* **1992**, *92*, 381–394; e) A. K. Mishra, R. Chandrasekar, M. Faraggi, M. H. Klapper, *J. Am. Chem. Soc.* **1994**, *116*, 1414–1422.
[5] a) B. Giese, *Annu. Rev. Biochem.* **2002**, *71*, 51–70; b) B. Giese, *Top. Curr. Chem.* **2004**, *236*, 27–44; c) M. A. O'Neill, J. K. Barton, *J. Am. Chem. Soc.* **2004**, *126*, 13234–13235; d) M. A. O'Neill, J. K. Barton, *J. Am. Chem. Soc.* **2004**, *126*, 11471–11483.
[6] R. A. Malak, Z. Gao, J. F. Wishart, S. S. Isied, *J. Am. Chem. Soc.* **2004**, *126*, 13888–13889.
[7] Y. K. Shin, M. D. Newton, S. S. Isied, *J. Am. Chem. Soc.* **2003**, *125*, 3722–3732.
[8] a) B. W. Davis, A. W. Svec, A. M. Ratner, R. M. Wasielewski, *Nature* **1998**, *396*, 60–63; b) F. Giacalone, J. L. Segura, N. Martin, D. M. Guldi, *J. Am. Chem. Soc.* **2004**, *126*, 5340–5341.
[9] F. Polo, S. Antonello, F. Formaggio, C. Toniolo, F. Maran, *J. Am. Chem. Soc.* **2005**, *127*, 492–493.
[10] S. Antonello, F. Formaggio, A. Moretto, C. Toniolo, F. Maran, *J. Am. Chem. Soc.* **2003**, *125*, 2874–2875.
[11] E. Galoppini, M. A. Fox, *J. Am. Chem. Soc.* **1996**, *118*, 2299–2300.
[12] D. R. Striplin, S. Y. Reece, D. G. McCafferty, C. G. Wall, D. A. Friesen, B. W. Erickson, T. J. Meyer, *J. Am. Chem. Soc.* **2004**, *126*, 5282–5291.
[13] a) H.-B. Kraatz, D. M. Leek, A. Houmam, G. D. Enright, J. Lusztyk, D. D. M. Wayner, *J. Organomet. Chem.* **1999**, *589*, 38–49; b) M. V. Baker, H.-B. Kraatz, J. W. Quail, *New J. Chem.* **2001**, *25*, 427–433; c) Y. Xu, P. Saweczko, H. B. Kraatz, *J. Organomet. Chem.* **2001**, *637–639*, 335–342; d) P. Saweczko, G. D. Enright, H. B. Kraatz, *Inorg. Chem.* **2001**, *40*, 4409–4419; e) I. Bediako-Amoa, R. Silerova, H. B. Kraatz, *Chem. Commun.* **2002**, 2430–2431.
[14] H.-B. Kraatz, J. Lusztyk, G. D. Enright, *Inorg. Chem.* **1997**, *36*, 2400–2405.
[15] I. Bediako-Amoa, T. C. Sutherland, C.-Z. Li, R. Silerova, H. B. Kraatz, *J. Phys. Chem. B* **2004**, *108*, 704–714.
[16] a) S. Sek, A. Sepiol, A. Tolak, A. Misicka, R. Bilewicz, *J. Phys. Chem. B* **2004**, *108*, 8102–8105; b) C. E. D. Chidsey, *Science* **1991**, *251*, 919; c) D. B. Robinson, C. E. D Chidsey, *J. Phys. Chem. B* **2002**, *106*, 10706; d) K. Weber, L. Hockett, S. E. Creager, *J. Phys. Chem. B* **1997**, *101*, 8286.
[17] T. Morita, S. Kimura, *J. Am. Chem. Soc.* **2003**, *125*, 8732–8733.
[18] K. Yanagisawa, T. Morita, S. Kimura, *J. Am. Chem. Soc.* **2004**, *126*, 12780–12781.
[19] a) K. H. Mayo, *Biopolymers* **1996**, *40*, 359–370; b) R. Z. Kramer, L. Vitagliano, J. Bella, R. Berisio, L. Mazzarella, B. Brodsky, A. Zagari, H. M. Berman, *J. Mol. Biol.* **1998**, *280*, 623–638.
[20] T. C. Sutherland, Y.-T. Long, R.-I. Stefureac, I. Bediako-Amoa, H.-B. Kraatz, J. S. Lee, *Nano Lett.* **2004**, *4*, 1273–1277.
[21] H.-B. Kraatz, I. Bediako-Amoa, S. H. Gyepi-Garbrah, T. C. Sutherland, *J. Phys. Chem. B* **2004**, *108*, 20164–20172.
[22] a) S. Spoerlein, H. Carstens, H. Satzger, C. Renner, R. Behrendt, L. Moroder, P. Tavan, W. Zinth, J. Wachtveitl, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 7998–8002; b) K. H. Mayo, V. A. Daragan, D. Idiyatullin, I. Nesmelova, *J. Magn. Reson.* **2000**, *146*, 188–195.
[23] a) T. Kawatsu, T. Kakitani, T. Yamato, *J. Phys. Chem. B* **2002**, *106*, 11356–11366; b) T. Kawatsu, T. Kakitani, T. Yamato, *J. Phys. Chem. B* **2002**, *106*, 5068–5074.
[24] C. Kobayashi, K. Baldridge, J. N. Onuchic, *J. Chem. Phys.* **2003**, *119*, 3550–3558.
[25] X. Xiao, B. Xu, N. Tao, *J. Am. Chem. Soc.* **2004**, *126*, 5370–5371.

Published online: June 24, 2005