Peptide-Mediated Intramolecular Electron Transfer: Long-Range Distance Dependence

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I. Introduction

Electron transfer is one of the fundamental reactions in biological photosynthesis, respiration, and redox-mediated enzyme catalysis. Understanding the role of peptides and proteins in mediating long-range electron transfer has important physical, chemical, and biological implications.[1-5]

Intramolecular electron-transfer reactions, where electron transfer occurs between donor and acceptor sites separated by a synthetic peptide or protein fragment, have so far provided the most insight into the role of the peptide and protein in mediating electron transfer.

With use of proteins, a number of different intramolecular electron-transfer experiments have been carried out. These include protein-small molecule intramolecular electron-transfer studies where an electron-transfer protein is covalently modified with a redox reagent at a specific site,[6-17] protein-protein electron-transfer studies, where two different electron-transfer proteins are bound electrostatically or covalently prior to the electron-transfer step.[18-24] In both experiments, intramolecular electron transfer is initiated and measured using rapid kinetic techniques. While both of these kinds of experiments are biologically relevant to protein electron transfer and have their own merits, the disadvantage of the studies with proteins is that they are often limited in scope and are not easily amenable to the systematic changes needed to understand and control the *intra*molecular electron-transfer reactions.

With small molecule model systems, electron-transfer pathways in proteins can be tested by designing molecules that possess special features that simulate potential electron-transfer pathways in proteins. Pathways through peptide bonds, aromatic side chains, weak noncovalent hydrophobic interactions, hydrogen-bonding networks associated with α helices and β sheets and/or other secondary structural features that change the electronic structure and induce low-energy pathways across polypeptides can be designed into the synthetic systems and studied.

Before we describe the experiments in detail, a brief description of the theoretical framework that is necessary to understand some of the results will be introduced. For a more complete discussion of the theory, ref 5 should be consulted.

Electron-transfer theories predict that rates of intramolecular electron-transfer reactions (k_{et}) depend on the distance and driving force ($\Delta G°$) between the donor and acceptor sites, according to the following equations:[5,25,26]

$$k_{et} = \kappa_{el}\nu_n\kappa_n \quad (1)$$

$$\kappa_{el}\nu_n = 10^{13}\exp[-\beta(d - d_0)] \quad (2)$$

$$\kappa_n = \exp[-(\lambda + \Delta G°)^2/4\lambda RT] \quad (3)$$

The product $\kappa_{el}\nu_n$ in eq 1 describes the electronic interaction between the donor and acceptor sites, and the electronic factor β is related to the magnitude of this interaction. Equation 2 predicts that the rate of intramolecular electron transfer will decrease exponentially as the distance between the donor and acceptor, $d - d_0$, increases where d is the center-to-center distance between the donor and acceptor and d_0 is the close contact separation between these sites.

The term κ_n in eq 1 accounts for the reorganization energy (λ) for electron transfer with contributions from both the outer-sphere reorganization energy (λ_0) and the inner-sphere reorganization energy (λ_i). The λ_0 term provides a second contribution to the distance dependence of k_{et} as described for two separate spheres by the dielectric continuum model (eq 4) where a_1 and a_2

$$\lambda_0 = (\Delta e)^2(1/2a_1 + 1/2a_2 - 1/d)(1/D_{op} - 1/D_s) \quad (4)$$

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Michael Y. Ogawa received his B.A. from Oberlin College in 1980. After spending two years as a research technician in the Department of Anatomy at Case Western Reserve University, he received his Ph.D. in Inorganic Chemistry from Northwestern University (1987) under the direction of Prof. Brian M. Hoffman. He spent a postdoctoral year at The Rockefeller University with Prof. David Mauzerall before becoming an NIH postdoctoral fellow with Prof. Stephan Isied at Rutgers University. He is currently Assistant Professor of Chemistry and a Principal Member of the Center for Photochemical Sciences at Bowling Green State University.

are the radii for the acceptor–donor in the oxidized and reduced states, d is the separation between the donor–acceptor sites, and D_{op} and D_s are the optical and static dielectric constants of the solvent, respectively.

The inner-sphere reorganization energy is given by eq 5

$$\lambda_i = \tfrac{1}{2}\sum f_i(\Delta d_i)^2 \qquad (5)$$

where f_i are the individual force constants and Δd_i is the difference in bond length between the oxidized and reduced forms of the corresponding bonds.

According to eqs 1–3 the absolute reaction rate is dominated by electronic effects and/or the reorganization energy of the donor and acceptor. For a reaction with low driving force, the rate is determined by both electronic effects and the reorganization energy of the donor and acceptor, depending upon the driving force for the reaction ($\Delta G°$). While for a reaction with high driving force, especially when the driving force is of the same magnitude as the reorganization energy, the reaction rate is governed predominantly by electronic effects because the reorganization energy is compensated for by high driving force (eq 3). Therefore the electron-transfer studies in section IV will be discussed in two parts: complexes with high driving force and complexes with low driving force.

James F. Wishart was born in Detroit, MI, in 1958. He received his B.S. in Chemistry from the Massachusetts Institute of Technology in 1979. As a graduate student in Inorganic Chemistry (Ph.D. 1985) at Stanford University under the direction of Prof. Henry Taube, he was a recipient of a National Science Foundation Graduate Fellowship. He held postdoctoral appointments at Rutgers University with Prof. Stephan Isied and Kenneth Breslauer. In 1987 he joined the Chemistry Department of Brookhaven National Laboratory, where he is currently an Associate Chemist in the Radiation Chemistry Group. His interests include mechanistic studies of long-range electron-transfer reactions and electron-transfer pathways in proteins, the development of new accelerator systems for pulse radiolysis, and the application of high-pressure techniques to radiation chemistry.

*Intra*molecular electron transfer may or may not use the intervening bridge molecular orbitals to accomplish effective electronic coupling between the donor and acceptor. When the electron transfer proceeds directly from the edge of the donor to the edge of the acceptor by mechanisms *not involving the orbitals of the bridging peptide* it is referred to as a *through-space* (*or noncovalently linked*) *pathway*. Since all our studies are in aqueous solution, the phrase "through space" does not imply "through vacuum" since the pathway may involve solvent, ion pairing, and/or other noncovalent interactions. If on the other hand the orbitals of the bridging group assist in carrying the charge transfer between the donor and acceptor, the pathway is referred to as a *through-bond* pathway and the coupling between the donor and acceptor is therefore achieved through the orbitals of the bridging groups, in addition to other medium effects. In these cases the mechanisms of electron transfer have been discussed by a number of authors and is referred to as a superexchange mechanism.[27-30]

This article will review the work from our group and others on small molecule systems that have been designed and studied to explore long-range electron-transfer pathways available between a donor and an acceptor separated by a rigid peptide framework. The

role of the secondary structure of polyproline II in facilitating these mediations will also be explored.

II. Description of the Electron-Transfer Experiments

A. Characteristics of the Polyproline Bridge

In order to investigate the availability of long-range electron-transfer pathways across polypeptides, a series of peptide building blocks were covalently attached to transition metal ion donors and acceptors and their rates of *intra*molecular electron-transfer were measured.[2,31] Among the peptide bridging groups studied, the oligoproline building blocks proved to be the most desirable for systematic study of the distance dependence of long-range electron transfer.[2,31] The advantage of the oligoprolines over other naturally occurring amino acids and peptides is the early onset of secondary structure. This secondary structure imparts significant rigidity upon the spatial separation between the donor and acceptor. It has been demonstrated that the onset of secondary structure in oligoprolines begins at 3 to 4 proline residues, earlier than for other oligo amino acids. Two main secondary structures can be assumed by oligoprolines; and the propensity to form these structures can be manipulated by the choice of solvent and pH conditions.[31]

A detailed discussion of the conformations of oligoprolines and their related metal complexes is given in ref 2 and 31. Because of the importance of these conformations for determination of metal-to-metal distances in this paper, a few points will be reviewed here.

The uniqueness of the oligoproline structural properties results from the presence of the five-membered-ring structure of the proline side chain which restricts rotation around the peptide bond, resulting in cis–trans conformational isomerism.[32-35] The interconversion between *trans*- and *cis*-prolylproline occurs with a half life of ~1–2 min at room temperature ($\Delta H^{\ddagger} \sim 20$ kcal/mol; $\Delta S^{\ddagger} \sim 0$ eu).[34] For high molecular weight oligomers several hours are required to complete this isomerism. The interconversion between the trans and cis isomers is known to be one of the slowest processes controlling conformational changes in peptides and proteins.[35]

Evidence for the trans versus cis structure in proline oligomers is best obtained from CD and NMR measurements.[36-38] Mandelkern and co-workers analyzed the conformation of poly-*l*-proline using ^1H and ^{13}C NMR and viscosity measurements.[38] Their analysis led to the conclusion that the majority (>97%) of the solution conformation of these polymers resemble the structure of *trans*-polyproline in the solid state. For a number of the metalloproline oligomers studied here, both CD and NMR measurements have been carried out in our laboratory, and *the predominant conformation of these metalloprolines in aqueous media has been shown to be the trans conformation* (>95%).[31]

Stryer et al. have studied oligoprolines (n = 5–12) by derivatizing their C and N termini with donor and acceptor chromophores.[39] Studies of energy transfer across polyproline in these oligomers showed that the efficiency of energy transfer decreases with increasing number of prolines, yielding a 50% transfer efficiency at 34.6 Å. This study also showed that the energy-transfer efficiency depends on $1/d^6$ where d is the distance between the ends of the oligoproline. These measurements were consistent with the oligoprolines being a spectroscopic ruler for defining the distance between a donor and an acceptor chromophore.

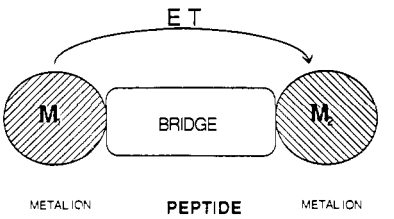


Figure 1. Donor–acceptor bridged complexes.

The crystal structures of tri- and tetraproline derivatives have been determined and found to be similar to that of *trans*-polyproline.[31,40,41] The structure of the oligomers and the trans polymer all show a left-handed helical structure with a repeat every three residues and a 3.1-Å translation per residue along the helical axis. Proline and hydroxyproline amino acids produce the rigid, rodlike fibrous proteins, such as collagen and other extracellular matrix proteins.

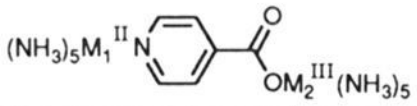
B. Characteristics of the Metal Ion Donors and Acceptors

Our studies have used transition-metal donor–acceptor complexes bound to oligoproline bridging peptides at the amine and carboxyl terminals (Figure 1).[2,31] Transition metal ion donors and acceptors have many advantages. By the choice of a donor–acceptor pair with a known driving force and reorganization energy, significant control of the rate of intramolecular electron transfer can be exercised. For example, the change in oxidation state of a metal ion can be accompanied by large reorganization energy and/or spin change—either of which can alter an intramolecular electron-transfer rate constant by many orders of magnitude.[31] The $(NH_3)_5Co^{III}(3d^6)$ species (and its reduced form, the high spin $(NH_3)_5Co^{II}(3d^7)$) has been used extensively as a transition-metal ion which can significantly slow down the rate of *intra*molecular electron transfer. On the other hand $(NH_3)_5Ru^{II}(4d^6)$ (or the corresponding $(NH_3)_5Ru^{III}(4d^5)$) and $(NH_3)_5Os^{II}(5d^6)$ (or the corresponding $(NH_3)_5Os^{III}(5d^5)$) are transition-metal donors and acceptors with very low inner-sphere reorganization energies, and electron-transfer reactions with these metal ions have much faster rates.

The choice of the spectator ligands around the metal donor–acceptor complexes can also be used to vary their reorganization energy. The electronic structure of the ligands can produce multiple oxidation states from which intramolecular electron transfer can proceed. The ruthenium bipyridines are examples of these, where in addition to the Ru^{II}/Ru^{III} oxidation states, ligand-centered reduced states can also be used to study intramolecular electron transfer. In these and related complexes with unsaturated ligands, intramolecular electron transfer can be studied for multiple oxidation states.

Table I clearly demonstrates how the intramolecular electron-transfer rate constant across the same bridge, isonicotinate, can change by more than *11* orders of magnitude with the use of different metal ammine donors and acceptors.[2] Such dramatic variation in the rate

TABLE I. Intramolecular Rates of Electron Transfer across the Same Bridge with Three Different Donor–Acceptor Metal Ion Pairs



$M_1^{II} \rightarrow M_2^{III}$	k_{obs}, s^{-1}	$M_1 - M_2$ distance, Å	$\Delta G°$, eV	ref
Os → Ru	$>5 \times 10^9$	9.0	−0.25	31
Os → Co	1.9×10^5	9.0	−0.15	57
Ru → Co	1.2×10^{-2}	9.0	+0.4	56

of intramolecular electron transfer is not possible with organic donors and acceptors which derive their reorganization energies from changes in C–C and C–H bond lengths.[43]

Quantitative estimates of both the inner- and outer-sphere reorganization energy for the donor and acceptor centers can be obtained from the free energy for the electron exchange for these centers. Detailed estimates for the intermolecular reorganization energies in several types of ruthenium complexes have been reported,[42] ranging from 2.1 eV for ruthenium(II/III) ammines to <0.8 eV for ruthenium bipyridines. For the cobalt ammine acceptor (e.g. $[Co(NH_3)_6]^{3+}$) an additional inner-sphere reorganization energy raises the overall reorganization energy to >3 eV.[65] For the intramolecular electron-transfer reaction at distances greater than the contact distance between the donor and acceptor the reorganization energy can be calculated (in some cases) from the temperature dependence of the rates of intramolecular electron transfer[63] (Section V).

C. Intramolecular Versus Intermolecular Electron-Transfer Reactions

In studying rates of *intra*molecular electron transfer in a series of closely related molecules it is important to eliminate interference from *inter*molecular reactions. This is done by conducting the electron-transfer experiments in very dilute solutions where the first-order *intra*molecular electron-transfer reactions can be distinguished from the second-order *inter*molecular reactions. A well-defined, stable chromophore at either the donor and/or the acceptor sites is necessary in order to monitor the *intra*molecular electron-transfer reaction at low concentrations and prevent interference from *inter*molecular reactions.

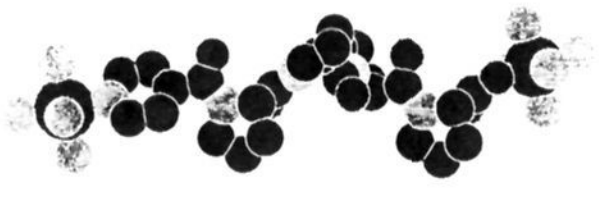
Complications can arise when there is a small amount of a conformer that can undergo fast intramolecular electron transfer by first undergoing electron exchange with the predominant conformer. In such cases the desired intramolecular electron transfer is studied at low concentration to eliminate this possibility. The electron exchange rate between the oxidized and reduced form of the donor molecule can be determined separately, in order to arrive at windows of time scales where interference from such an electron exchange is minimized. These complications usually arise in the longer members of the series such that they determine the distance limits and the time windows that intramolecular electron-transfer reactions can be studied.

For the proline donor–acceptor complexes where electron transfer occurs in time scales faster than 1 min, no cis–trans isomerization is expected to occur. At concentrations of 1–5 μM of the generated precursor complex, the rate of intramolecular electron transfer is significantly faster than any electron exchange between oligomers of different conformations. When the electron exchange occurs on the time scale of electron transfer, only a range of rates can be determined (Table II).

III. Methods for Measurement of Intramolecular Electron Transfer

A number of methods have been used to study rapid intramolecular electron transfer (e.g. NMR relaxation,

TABLE II. Intramolecular Electron Transfer Rates for the $[(NH_3)_5M^{II}L(Pro)_nM^{III}(NH_3)_5]^{4+}$, n = 0–4, Series

	n	M–M distance, Å	k_{et}, s^{-1} Os—Co	k_{et}, s^{-1} Os—Ru
	0	9.0	1.2×10^5	$>5 \times 10^9$
	1	12.3	2.7×10^2	3.1×10^6
	2	14.9	0.74	3.7×10^4
	3	18.1	0.04–0.09	3.2×10^2
	4	21.3	0.01–0.09	~50

EPR, Mossbauer); however, the most consistently used methods for studying rates of these reactions at time scales from subnanoseconds to minutes have been flash photolysis[44] and pulse radiolysis.[45] Pulse radiolysis is the more general technique since it does not have the constraint of requiring a long-lived excited state on either the donor or the acceptor.

Pulse radiolysis has been used to measure rates of intramolecular electron transfer ranging from nanoseconds to 100 seconds. For very rapid reactions, nanosecond time scale and faster, flash photolysis is the most useful technique. Recently, flash photolysis involving electron-transfer quenching techniques has also been used to measure slow rates of intramolecular electron transfer.[11,46]

A comparison of the elementary steps for studying intramolecular electron transfer in pulse radiolysis and flash photolysis is best described by eqs 6 and 7.

pulse radiolysis

$$R^{\bullet} + \text{reactant} \rightarrow \text{precursor} \xrightarrow{k_{et}} \text{product} \quad (6)$$

flash photolysis

$$h\nu + \text{reactant} \rightarrow \text{precursor} \xrightarrow{k_{et}} \text{product} \quad (7)$$

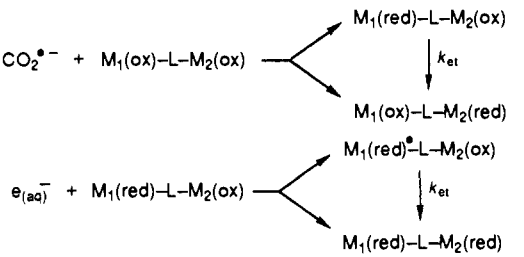
($R^{\bullet}$ = an oxidizing or reducing radical, $h\nu$ = light pulses)

In eq 6 a small amount of a radical is generated by pulse radiolysis in the presence of an excess of the fully oxidized (or fully reduced) species to be studied. The reaction of the radical with the reactant generates a nonequilibrium distribution of the precursor. The relaxation of this precursor to its equilibrium distribution, a rate that is governed by the driving force, reorganization energy, and electronic pathways, is then taken as the measure of the rate of intramolecular electron transfer from the donor site to the acceptor site.

For the very rapid reactions the limitation of the pulse radiolysis technique is in the pseudo-first-order reaction that the radical undergoes with the fully oxidized or fully reduced species to form the precursor complex (eq 6). The time scale for this reaction should be less than or at least in the range of the time scale for the intramolecular electron-transfer reaction. Variation of this time scale is helpful in extending the range of time scales of the pulse radiolysis study. Usually this is done by changing the concentration of the fully oxidized or fully reduced species to be studied. However limitations on either the solubility of the species or the rates of the *inter*molecular reactions that the donor–acceptor precursor complex can undergo limit the time window. The advantage of pulse radiolysis is that the precursor donor–acceptor complex can be generated by using either an oxidizing or a reducing radical.[47-50] The ability to study intramolecular electron transfer in a precursor which is generated by two different radicals undergoing different chemistries gives additional validity to the determination of the rate of intramolecular electron transfer.

In pulse radiolysis, examples of the types of chemistries used to generate the precursor complex are given in Scheme I. The carbon dioxide radical anion, $CO_2^{\bullet-}$, is generated pulse radiolytically from aqueous solutions by the reaction of $OH^{\bullet}$ with formate ion. When the aqueous electron was used, *tert*-butyl alcohol was added to the solution to scavenge $OH^{\bullet}$. Experiments with

SCHEME I



$CO_2^{\bullet-}$ can be conducted in acidic or basic media, while the aqueous electron can only be used in neutral or basic media.

In flash photolysis (eq 7) no limitation exists on the *inter*molecular reaction for the generation of the precursor complex, rather the upper limit on observable rates is defined by the width of the pulse of light used to initiate the reaction (eq 7). A long-lived excited state at the donor or acceptor site is required for studying the reaction. The generation of the excited state is carried out in very dilute solutions. With flash photolysis, rapid intramolecular electron-transfer reactions (nanosecond or picosecond timescale) can be observed if the electron-transfer step competes with the normal radiative or nonradiative decay channels of the light-sensitive chromophore. Limitations due to the mechanism of relaxation of the excited state, e.g. energy transfer rather than electron transfer, require additional experimentation to verify the nature of the excited-state reaction being studied. One advantage of using flash photolysis for studying *intra*molecular electron-transfer reactions is that under ideal conditions the rate of the photoinduced reaction, as well as the rate of the thermal back-reaction can be studied in the same donor–acceptor complex.

Other flash photolysis methods have also been used to measure thermal intramolecular electron-transfer reactions. This is accomplished when a long-lived excited-state molecule undergoes an *inter*molecular reaction to generate a nonequilibrium distribution of a precursor which undergoes thermal *intra*molecular electron transfer.[11,46] Such an approach is equivalent to pulse radiolysis (eq 6). In this approach, scavengers or quenchers are introduced to compete with the back reaction of the oxidized or reduced state resulting from the electron-transfer reaction of the excited-state molecule.

For flash photolysis studies there are a number of useful organic and inorganic chromophores that have long-lived excited states and have been shown to undergo photoinduced intramolecular electron transfer. Ruthenium and osmium bipyridines[51] and Re(bipy)-$(CO)_3L$[52-54] have excited states with lifetimes of hundreds of nanoseconds, while zinc porphyrins and other metalloporphyrins (Mg, Pd porphyrins)[55] have excited-state lifetimes that are in the millisecond time range.

IV. Intramolecular Electron Transfer across Polyproline Oligomers

This section will be divided into two parts: studies with donor–acceptor complexes having a low driving force ($-\Delta G^{\circ} < 0.5$ V) and studies with donor–acceptor complexes having a high driving force ($-\Delta G^{\circ} \geq 1$ V). This division makes it convenient for comparison of experimental results with the theories of electron

transfer. In all of the proline oligomers studied with transition metal ion donors and acceptors, the direction of electron transfer across the polyproline was always from the N-terminus to the C-terminus of the peptide.

A. Intramolecular Electron Transfer across Polyproline in Donor–Acceptor Complexes with Low Driving Force

A series of donor–acceptor complexes with bridging oligoproline ligands with metal ions attached to both the N and C peptide termini was synthesized, purified, and converted to the fully oxidized state.[56] A precursor complex was generated and the process of relaxation of the precursor complex to equilibrium, which is the intramolecular electron-transfer rate, was measured by monitoring the absorbance changes at either of the metal ion chromophores.

For the donor–acceptor series $[(OH_2)(NH_3)_4Ru^{II}i\text{-}(Pro)_nCo^{III}(NH_3)_5]$ ($Ru^{II}i(Pro)_nCo^{III}$) where i = isonicotinyl group, n = 0–4, the precursor was generated by using a small amount of a reducing agent, $(NH_3)_6Ru^{2+}$ or Eu^{2+}. In this series, the intramolecular

$$R + Ru^{III}i(Pro)_nCo^{III} \rightarrow Ru^{II}i(Pro)_nCo^{III} \xrightarrow{k_{et}} Ru^{III}i(Pro)_n + Co^{2+} \quad (8)$$

$R = (NH_3)_6Ru^{II}$ or Eu^{2+} $Ru^{III} = Ru^{III}(NH_3)_4(OH_2)$

$Co^{III} = Co^{III}(NH_3)_5$ i = isonicotinyl n = 0–4

electron-transfer reactions were found to be extremely slow occurring at time scales ranging from minutes to hours. The driving force for the reaction is $-\Delta G° \sim -0.5$ eV (i.e. the electron-transfer reaction is endoergic).[56,65] The electron-transfer reaction proceeds to completion, however, because of the rapid subsequent loss of NH_3 from the Co(II) product. For the n = 0–2 proline bridges in this series, a decrease in rate with distance was observed as expected when a peptide bridge separates the donor and acceptor metal ions. However, the electron-transfer rates for the longer bridges, $(Pro)_3$ and $(Pro)_4$, increased unexpectedly. The long time scale of these experiments allowed time for the equilibration of many forms of the electron-transfer complexes (multiple proline oligomers) prior to electron transfer. Therefore, the rapid rates observed for n = 3 and 4 prolines compared to n = 2 prolines were interpreted as rates corresponding to conformations where the donor and acceptor are in close proximity. While experiments on this slow time scale may be useful for probing the existence of different peptide conformational states, the distance dependence of the rate of electron transfer cannot be studied at these slow time scales because the multiple peptide conformations complicate the interpretation.

In order to increase the rate of electron transfer across the same bridging oligoprolines, the $(OH_2)(NH_3)_4Ru^{II}$ was replaced by the $(NH_3)_5Os^{II}$ to form the $[(NH_3)_5Os^{II}i(Pro)_nCo^{III}(NH_3)_5]$ series (where i = isonicotinyl group), which will be referred to as $Os^{II}i\text{-}(Pro)_nCo^{III}$. The change in the donor from Ru(II) to Os(II) increased the driving force for the electron-transfer reaction to $-\Delta G° \sim +0.15$ V and correspondingly increased the rate of intramolecular electron transfer.[57]

Intramolecular electron-transfer rates were studied using pulse radiolysis techniques by the reaction of a small amount of the reducing $CO_2^{\bullet-}$ radical (from the reaction of hydroxyl radical with sodium formate) with at least a 10-fold excess of the oxidized sample (eq 9).

$$CO_2^{\bullet-} + Os^{III}i(Pro)_nCo^{III} \rightarrow CO_2 + Os^{II}i(Pro)_nCo^{III} \xrightarrow{k_{et}} Os^{III}i(Pro)_n + Co^{2+} \quad (9)$$

$Os^{III} = Os^{III}(NH_3)_5$ $Co^{III} = Co^{III}(NH_3)_5$

i = isonicotinyl n = 0–4

Table II shows the corresponding rates. At the faster time scales in this series (seconds to milliseconds), electron transfer is observed unencumbered by conformational changes of the bridging ligand because cis–trans isomerism occurs on the 1–2-minute time scale. In this $Os^{II}i(Pro)_nCo^{III}$ series, the rates of electron transfer rapidly decrease with distance for n = 0–2 prolines, while for n = 3, 4 prolines, the rates of electron transfer decrease less than for n = 0–2 prolines. This raises the possibility that different conformational forms of the bridging peptide may still be equilibrating by $Os^{II/III}$ self-exchange at this time scale.

In order to make the electron-transfer reaction proceed at faster time scales, a new series using the same polyproline bridging ligands was prepared, where the acceptor, $(NH_3)_5Co^{III}$, was replaced with a $(NH_3)_5Ru^{III}$ acceptor.[31] The intramolecular electron-transfer rates (eq 10) were measured. The driving force of the

$$CO_2^{\bullet-} + Os^{III}i(Pro)_nRu^{III} \rightarrow CO_2 + Os^{II}i(Pro)_nRu^{III} \xrightarrow{k_{et}} Os^{III}i(Pro)_nRu^{II} \quad (10)$$

$Os^{III} = Os^{III}(NH_3)_5$ $Ru^{III} = Ru^{III}(NH_3)_5$

i = isonicotinyl n = 0–4

electron-transfer reaction in this new $Os^{II}i(Pro)_nRu^{III}$ series ($-\Delta G° \sim +0.25$ eV) was not much larger than as in the earlier $Os^{II}i(Pro)_nCo^{III}$ series ($-\Delta G° \sim +0.15$ eV), but the reorganization energy was decreased. As expected, the intramolecular electron-transfer rates for this $Os^{II}i(Pro)_nRu^{III}$ series[31] (Table II) are substantially faster than in the $Os^{II}i(Pro)_nCo^{III}$ series. The intramolecular electron transfer rates for this $Os^{II}i(Pro)_nRu^{III}$ series[31] are much more rapid than the isomerization time of the bridging peptide ($t_{1/2} \sim 1$ min). Moreover, the studies were conducted at low concentration where electron exchange between any $Os^{II/III}$ conformers is slower than the observed intramolecular electron transfer.[31] The electron-transfer rates decreased as expected for n = 0–3 prolines when additional proline residues were introduced into the bridging ligand (Table II).

One of the unexpected results for the $Os^{II}i(Pro)_nRu^{III}$ series was the intramolecular rate observed for n = 4 prolines, $k \sim 50$ s^{-1} at metal-to-metal distances approaching 21 Å, is *significantly faster* than what was expected on the basis of an extrapolation of the rates for the previous three members of the series. However, electron-transfer studies on this series could not be extended beyond n = 4 prolines because the *inter*molecular electron-transfer rate interferes with the *intra*molecular electron-transfer reaction even at the lower concentration.[56]

In order to pursue the reason for the unexpected increase in rate for n = 4 prolines in the $Os^{III}i(Pro)_nRu^{III}$ series, two new series of complexes were designed, where the rate of electron transfer was further optimized by increasing the driving force. These series of complexes

where intramolecular electron transfer occurs at a high driving force will be discussed in the following section.

B. Intramolecular Electron Transfer in Donor–Acceptor Complexes with High Driving Force

By using ruthenium polypyridine complexes as donors or acceptors, a series of molecules can be prepared where intramolecular electron transfer across the polyproline bridging peptides occurs with a high driving force ($-\Delta G° \geq 1$ eV). In addition to high driving force, the total reorganization energy for the electron-transfer process is reduced with the ruthenium polypyridine donors and/or acceptors,[42] and therefore more rapid rates are expected.

To obtain complexes with high driving force, the $\{(bpy)_2Ru^{II}L\}$ group, where bpy = 2,2′-bipyridine and L = 4-carboxy-4′-methyl-2,2′-bipyridine ligand, was covalently linked to the N-terminus of the proline peptide.[2,58,59] The $(NH_3)_5Co^{III}$ group was attached to the C-terminus of the prolylproline. In the $[(bpy)_2Ru^{II}L(Pro)_nCo^{III}(NH_3)_5]$ series, the aqueous electron was used to generate a ligand-centered radical donor state, $\{(bpy)_2Ru^{II}L\}^{•-}$. Intramolecular electron-

$$e^-_{aq} + (bpy)_2Ru^{II}L(Pro)_nCo^{III} \rightarrow \{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III} \xrightarrow{k_{et}} (bpy)_2Ru^{II}L(Pro)_n + Co^{2+} \quad (11)$$

$Co^{III} = Co^{III}(NH_3)_5$ bpy = 2,2′-bipyridine
L = 4-carboxy-4′-methyl-2,2′-bipyridine
n = 1–6

transfer rates from $\{(bpy)_2Ru^{II}L\}^{•-}$[60] to the Co(III) acceptor were measured for proline bridges from n = 1–6 (eq 11). In this series, very rapid reactions were observed, such that for n = 1 proline only an estimate of the rate, $k > 5 \times 10^8$ s^{-1}, could be obtained using pulse radiolysis techniques.

The rates obtained for intramolecular electron transfer for the $[\{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III}(NH_3)_5]$ series (referred to as $\{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III}$) are shown in Table III and Figure 2. For the short distances, n = 1–3 prolines, the change in rate with distance is similar to that for the $Os^{II}i(Pro)_nRu^{III}$ series studied earlier. For the longer distances starting with n = 4 prolines, a very small change in the electron-transfer rate is observed as the number of prolines increases. The rates observed for 4–6 prolines are much faster than expected by extrapolation from shorter distances. A similar observation was made earlier for n = 4 prolines in the $Os^{II}i(Pro)_nRu^{III}$ series. However, since that series could not be extended beyond n = 4 prolines, no conclusion could be reached as to whether the deviation of the observed rate, 50 s^{-1}, from the expected rate, ~3 s^{-1}, was an anomaly or part of a general trend. Now in the $\{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III}$ series, the slow rate of decrease with the increasing number of prolines has been observed for three separate bridges; n = 4–6 prolines. Furthermore, because of the high driving force for the reaction, the rates observed for the $\{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III}$ series were significantly faster than for the corresponding $Os^{II}i(Pro)_4Ru^{III}$ series. The $\{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III}$ series could not be extended beyond six prolines due to interference of intermolecular reactions at the lowest practical concentration of 2 μM and the reaction of $\{(bpy)_2Ru^{II}L\}^{•}$ with $^{•}CH_2(CH_3)_2COH$ (generated by scavenging OH$^{•}$ with *tert*-butyl alcohol).[61]

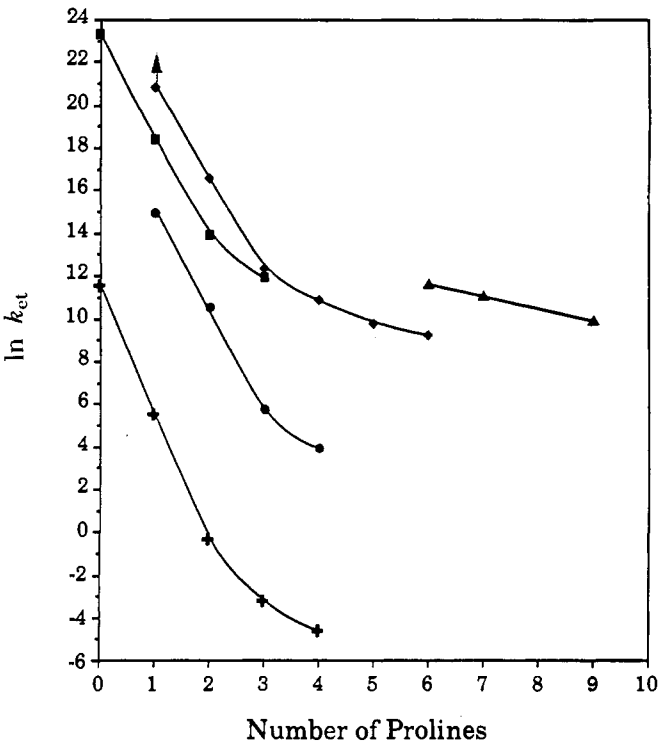


Figure 2. Rates of intramolecular electron transfer across five series of oligoproline donor–acceptor complexes: ▲, $[\{(bpy)_2Ru^{II}L\}^{•}(Pro)_napyRu^{III}(NH_3)_5]^{4+}$; ◆, $[\{(bpy)_2Ru^{II}L\}^{•}(Pro)_nCo^{III}(NH_3)_5]^{3+}$; ■, $[(bpy)_2Ru^{II*}L(Pro)_nCo^{III}(NH_3)_5]^{4+}$; ●, $[(NH_3)_5Os^{II}i(Pro)_nRu^{III}(NH_3)_5]^{4+}$; +, $[(NH_3)_5Os^{II}i(Pro)_nCo^{III}(NH_3)_5]^{4+}$.

The rapid rate measured for n = 6 prolines in the $\{(bpy)_2Ru^{II}L\}^{•-}(Pro)_nCo^{III}$ series suggested that if the reorganization energy associated with the $Co^{III}(NH_3)_5$ acceptor could be decreased, faster rates should be observed. Therefore the $(NH_3)_5Co^{III}$ acceptor was replaced with the $[(NH_3)_5Ru^{III}apy]$ group (where apy = 4-aminopyridine), an acceptor with a much lower reorganization energy to form the series $[\{(bpy)_2Ru^{II}L\}^{•}(Pro)_napyRu^{III}(NH_3)_5]$.

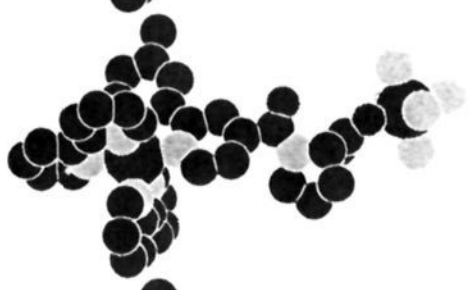
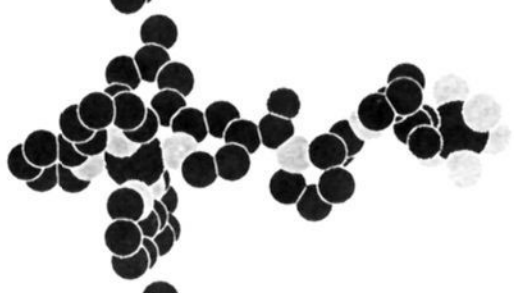
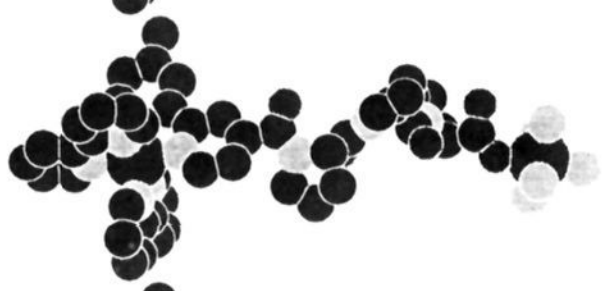
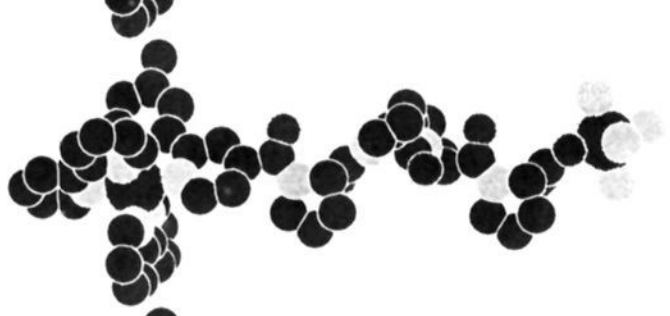
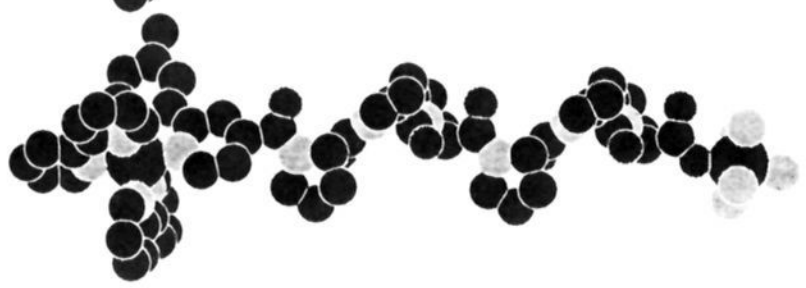
A new series of donor–acceptor molecules, the $[\{(bpy)_2Ru^{II}L\}^{•}(Pro)_napyRu^{III}(NH_3)_5]$ (referred to as the $\{(bpy)_2Ru^{II}L\}^{•}(Pro)_napyRu^{III}$ series), with proline bridges n = 6, 7, 9 was synthesized and studied.[59] In the

$$e^-_{aq} + (bpy)_2Ru^{II}L(Pro)_napyRu^{III} \rightarrow \{(bpy)_2Ru^{II}L\}^{•}(Pro)_napyRu^{III} \xrightarrow{k_{et}} (bpy)_2Ru^{II}L(Pro)_napyRu^{II} \quad (12)$$

$apyRu^{III} = (4\text{-aminopyridine})Ru^{III}(NH_3)_5$
L= 4-carboxy-4′-methyl-2,2′-bipyridine
n = 6–9

$\{(bpy)_2Ru^{II}L\}^{•}(Pro)_napyRu^{III}$ series, the high driving force is maintained ($-\Delta G° \sim 1.5$ V), but the reorganization energy is reduced, resulting in more rapid rates. The accessibility of Ru^{II} and Ru^{III} states for both the donor and acceptor, as well as the $\{(bpy)_2Ru^{II}L\}^{•}$ radical state, allows the study of the electron-transfer reaction from a $\{(bpy)_2Ru^{II}L\}^{•}$ donor to an $[apyRu^{III}(NH_3)_5]$ acceptor and from a $[apyRu^{II}(NH_3)_5]$ donor to a $[(bpy)_2Ru^{III}L]$ acceptor. By using pulse radiolysis conditions, the rates of intramolecular electron transfer where an electron is transferred from the $\{(bpy)_2Ru^{II}L\}^{•}$

TABLE III. Rates of Intramolecular Electron Transfer across the Polyprolines $[(bpy)_2Ru^{II}L(Pro)_nCo^{III}(NH_3)_5]^{4+}$, n = 0–6, Series[c]

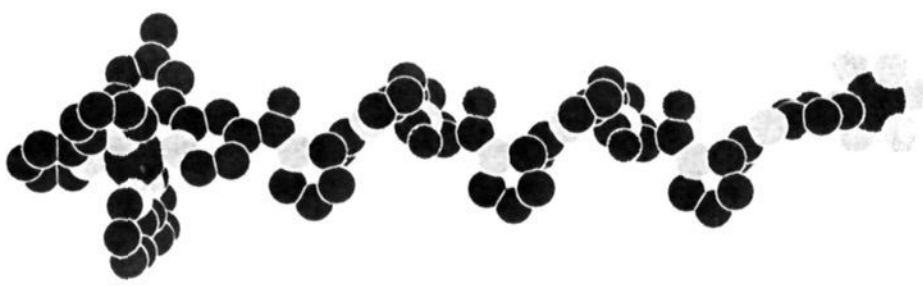
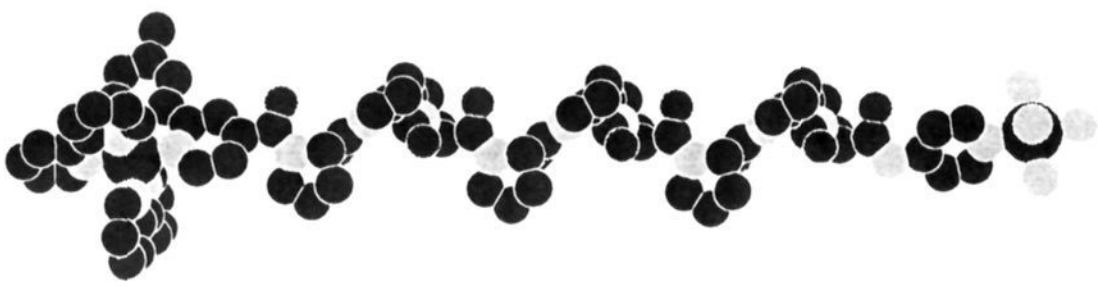
	n	M–M distance, Å	$[(bpy)_2Ru^{II}L]^{\bullet}$: k_{et},[a] s^{-1} (25 °C)	$[(bpy)_2Ru^{II}L]^{*}$: k_{et},[b] s^{-1} (20 °C)
	0	9.0	–	1.3×10^{10}
	1	12.2	$>5 \times 10^{8}$	1.0×10^{8}
	2	14.8	1.6×10^{7}	1.1×10^{6}
	3	18.1	2.3×10^{5}	1.5×10^{5}
	4	21.3	5.1×10^{4}	
	5	24.1	1.8×10^{4}	
	6	27.3	9.8×10^{3}	

[a] Pulse radiolysis technique. [b] Flash photolysis technique. [c] bpy = 2,2′-bipyridine; L = 4-carboxy-4′-methyl-2,2′-bipyridine.

donor to the $[apyRu^{III}(NH_3)_5]$ acceptor were studied for n = 6, 7, 9 proline bridges. The rates observed are shown in Table IV. The same weak dependence of the electron-transfer rate on the number of prolines was observed in this series (Figure 2) as in the previous $\{(bpy)_2Ru^{II}L\}^{\bullet}(Pro)_nCo^{III}$ series. The absolute value of the rates was higher than those of the corresponding $\{(bpy)_2Ru^{II}L\}^{\bullet}(Pro)_nCo^{III}$ series reflecting mainly the decrease in reorganizational energy at the $[apyRu^{III}(NH_3)_5]$ acceptor site. The rate measured for the complex with n = 9 prolines represents the longest distance that intramolecular electron transfer has ever been observed across synthetic peptides (30 Å of peptide bridges).

In order to measure the rates of intramolecular electron transfer at very short proline distances n = 0–1 for the $(bpy)_2Ru^{II}*L(Pro)_nCo^{III}$ series, flash photolysis techniques were used to measure the electron-transfer

TABLE IV. Rates of Intramolecular Electron Transfer across the Polyprolines $[(bpy)_2Ru^{II}L(Pro)_napyRu^{III}(NH_3)_5]^{4+}$, n = 6–9, Series[a]

	n	M—M distance, Å	k_{et}, s^{-1}
	6	31.6	1.1×10^5
	7	34.5	6.4×10^4
	8	–	–
	9	40.8	2.0×10^4

[a] bpy = 2,2′-bipyridine, L = 4-carboxy-4′-methyl-2,2′-bipyridine, apy = 4-aminopyridine.

rates, because the available pulse radiolysis technique was not rapid enough.[62] In this flash photolysis study

$$h\nu + (bpy)_2Ru^{II}L(Pro)_nCo^{III} \rightarrow (bpy)_2Ru^{II*}L(Pro)_nCo^{III} \xrightarrow{k_{et}} (bpy)_2Ru^{III}L(Pro)_n + Co^{2+} \quad (13)$$

$Co^{III} = Co^{III}(NH_3)_5$ bpy = 2,2′-bipyridine
L = 4-carboxy-4′-methyl-2,2′-bipyridine
n= 0–3

the electron is transferred from the excited state of the $(bpy)_2Ru^{II*}L$ donor to the $Co^{III}(NH_3)_5$ acceptor. This $(bpy)_2Ru^{II*}L$ excited state is a weaker reducing agent, $E°$ = –0.8 V, than the $\{(bpy)_2Ru^{II}L\}^•$ donor, $E°$ = –1.2 V vs NHE, used in the pulse radiolysis studies. Table III shows the rates measured for n = 0–3 prolines. The rates for the photoinduced reactions are slightly slower than the corresponding rates obtained with pulse radiolysis with $\{(bpy)_2Ru^{II}L\}^•$ as a donor. However in both series, a rapid decrease in rate between n = 0–2 prolines was observed. The flash photolysis study could not be extended beyond n = 3 prolines because the rate of the intramolecular electron-transfer reaction becomes too slow to compete with the intrinsic rate of the excited state decay.

V. Activation Parameters for Long-Range Intramolecular Electron Transfer

There are two principal causes for changes in the rates of intramolecular electron transfer with distance: the electronic factor and the distance dependence of the outer-sphere reorganization energy (eq 2).[26,66] The electronic factor, which decays with distance, is determined by the interaction between the donor, bridge, and acceptor. This decay has always been assumed to be exponential with distance, having a β-value characteristic of the system (eq 2). For the $Os^{II}i(Pro)_nRu^{III}$ series, because the reaction was studied in aqueous solution, a substantial part of the decrease of rate with distance can be accounted for as an increase in the outer-sphere reorganization energy as the distance between the donor and acceptor is increased.[63] Other studies of distance dependence of rates of electron transfer in low dielectric media are not expected to show a large contribution of the outer-sphere reorganization energy to the distance dependence.[67–69]

The importance of correcting for the distance dependence of the outer-sphere reorganization energy was demonstrated in a related study of photoinduced electron transfer with one and two proline bridging groups which was conducted in methanol.[72] A different distance dependence for electron-transfer rates was ob-

TABLE V. Activation Parameters for Five Series of Oligoproline Donor-Acceptor Complexes

complex	number of Prolines	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
$[(NH_3)_5Os^{II}i(Pro)_nCo^{III}(NH_3)_5]^{4+}$			
	0	10.2	0
	1	11.7	-8
	2	12.7	-16
	3	12.4	-22
	4	11.5	-25
$[(NH_3)_5Os^{II}i(Pro)_nRu^{III}(NH_3)_5]^{4+}$			
	0	-	-
	1	4.2	-15
	2	5.9	-19
	3	7.4	-23
	4	-	-
$[\{(bpy)_2Ru^{II}L\}^{*}(Pro)_nCo^{III}(NH_3)_5]^{3+}$			
	1	-	-
	2	6.0	-5.6
	3	9.3	-2.4
	4	9.4	-5.4
	5	8.9	-9.0
	6	9.1	-9.4
$[(bpy)_2Ru^{II*}L(Pro)_nCo^{III}(NH_3)_5]^{4+}$			
	0	-	-
	1	0.4	-20
	2	1.8	-25
	3	2.1	-28
$[\{(bpy)_2Ru^{II}L\}^{*}(Pro)_napyRu^{III}(NH_3)_5]^{4+}$			
	6	5.6	-16.7
	7	5.1	-19.4
	9	-	-

served in methanol than was observed in aqueous solution. However, after correction for the difference in the reorganizational effects, the electronic factor calculated for the two studies was found to be similar.

In order to separate the dependence of the rate of intramolecular electron transfer on reorganizational energy from that of the electronic effects, a plot using a rearranged form of the transition-state expression (eq 14) can be used.[63,66] In this equation the rate of elec-

$$\ln k_{et} + \Delta H^{\ddagger}/RT = \ln[\kappa_{el}(kT/h)] + \Delta S^{\ddagger}/R \qquad (14)$$

tron transfer is corrected for the reorganization enthalpy at a specific distance (reorganization entropy is neglected), and the temperature-independent $\Delta S^{\ddagger}/R$, which is related to the electronic factor, can be obtained.

There are several underlying assumptions which must be satisfied in order for eq 14 to be valid. These are discussed in ref 63. It suffices here to say that the donor and acceptor need to be similar in structure, charge type, and hydrophobicity in order to eliminate thermodynamic temperature dependencies that are different in the donor and in the acceptor. The series $[(NH_3)_5M_1^{II}i(Pro)_nM_2^{III}(NH_3)_5]$[31,57] where M_1/M_2 = Os/Co and Os/Ru and the series $[OH_2(NH_3)_4Ru^{II}i(Pro)_nCo^{III}(NH_3)_5]$ satisfy the assumptions needed for the separation of the reorganization energy from the electronic effects[63,64] in eq 14. In these series, the reorganization energy can be calculated directly by assuming that the reorganization energy, λ, is as shown in eq 15. where $\Delta H^{\ddagger}$ is the activation enthalpy and ΔH°

$$\lambda = 4(\Delta H^{\ddagger} - \Delta H^{\circ}/2) \qquad (15)$$

is assumed to be equal to ΔG°, the driving force for the reaction. From the activation enthalpies and driving force provided in Table V, calculation of the reorganization energy is possible.

The $\{(bpy)_2Ru^{II}L\}^{*}(Pro)_nCo^{III}$ and the $\{(bpy)_2Ru^{II}L\}^{*}(Pro)_nRu^{III}$ series do not satisfy the requirements for separating the reorganization energy from the electronic effects. This is mainly due to the hydrophobic and hydrophilic nature of the donor and the acceptor. In such cases the activation enthalpy cannot be directly related to the reorganizational energy. In these series, the temperature dependence was studied only for qualitative comparison within the series.

VI. Electron-Transfer Pathways in Proline Oligomers

Throughout the series of metal donor–acceptor complexes from $n = 0$ to $n = 9$ prolines, the rates of intramolecular electron transfer across proline oligomers vary by more than 10 orders of magnitude.[31,57-59,62] Within each series, the driving force and reorganizational energy and distance between the donor and acceptor determine the absolute value of the rates. For the same donor and acceptor in a series, the differences in rates can also vary by as much as 10^8 times. This is ascribed to electronic factors and the variation in the outer-sphere reorganizational energy.

Figure 2 is a plot of ln k (k is the rate of intramolecular electron transfer) versus the number of proline residues separating the donor and acceptor. The number of prolines is synonomous with a fixed distance of 3.1 Å per residue (shortest through-space distance) or 4.2 Å per residue (through-bond distance), because of the rigidity of the oligoproline structure.[2] At short distances (n = 0–3), the change in rate with distance (the slope of the plot) is relatively constant throughout the series, regardless of the absolute rate measured.

Figure 2 also shows a significant change in behavior occurs between $n = 3$ and $n = 4$ prolines in these systems. This seems to be a general trend across all the series studied. The metal-to-metal distance for $n = 4$ prolines is approximately 21 Å. At these long distances measurement of intramolecular electron-transfer rates is not possible in some of the series of donor–acceptor complexes studied because of the interference from other reactions. However, when the donor and acceptor are chosen such that there is a high driving force and/or a low reorganizational energy, measurement of the rate of intramolecular electron transfer becomes possible. This has been accomplished in two series where $\{(bpy)_2Ru^{II}L\}^{*}$ has been used as the donor and $^{-}Co^{III}(NH_3)_5$ or $[apyRu^{III}(NH_3)_5]$ has been used as the acceptor. In this series of compounds a much weaker change of rate with distance is observed for n = 4, 5, 6 with $^{-}Co^{III}(NH_3)_5$ as the acceptor and n = 6, 7, 9 with $[apyRu^{III}(NH_3)_5]$ as the acceptor. For the $n = 9$ compound, the longest separation between a donor and acceptor in a series, a rate constant $k = 2.0 \times 10^4$ s^{-1} is observed at metal-to-metal distances approaching 40 Å.

Before introducing the possible interpretations for the two different rate domains in Figure 2, a separation of the distance dependence of the reorganization energy for these systems from the electronic effects, which gives rise to the pathways, should be discussed. In the metal ammine systems this has been done.[63,64] The results for n = 0–3 show that more than half of the distance de-

pendence can be accounted for from reorganizational effects. For the long distances (n = 4–9 prolines) only a weak change of rate with distance is observed. Models predict that the outer-sphere contribution to the reorganization energy approaches a constant value at long distances; the outer-sphere term (eq 4) therefore does not contribute to the distance dependence of the observed rates.

Turning now to the electronic effects, several interpretations can be made for the two domains of rate variation with bridge length that are observed for these oligoproline donor–acceptor complexes (Figure 2). Each interpretation includes a combination of coupling mechanisms to account for the observed rates.

The first interpretation is a *through-space* pathway which operates at short distances n = 1–3, resulting in large decreases in rate with distance. At longer distances, $n \geq 3$–4 prolines, the *through-space* pathway quickly drops off and a new *through-bond* pathway dominates (a pathway which directly involves the orbitals of the bridging peptide). Extrapolation of the rates for the *through-bond* pathway (by extrapolating the weak slope in Figure 2 to zero prolines) shows that the rate for the *through-bond* pathway is lower than the rate for the corresponding *through-space* pathway by several orders of magnitude.

The second interpretation involves two *through-bond* pathways: one for the short distances n = 1–3 and one for the long distances n = 4–6. For the long distances the onset of secondary structure in the polyproline bridge for $n \geq 3$–4 prolines results in a lower amide $n \rightarrow \pi^*$ absorption band. This energy shift is indeed observed in the absorbance and CD spectra of the proline oligomers. These lower energy orbitals can contribute to a more efficient *through-bond* pathway, thus accounting for the change in distance dependence for the longer series (n = 4–9).

A third possible interpretation to account for the weak change of rate with distance for n = 4–6 prolines involves a combination of a through-bond pathway for n = 1–3 and the participation of water molecules bound to the helical bridging peptide for the n = 4–9. Water molecules surrounding the prolines can connect between the proline residues n, and $n + 3$ in the helices *through nonbonded interactions* starting with $n \geq 3$–4 prolines and short circuit the long *through-bond* pathway around the polyproline covalent bonds. These nonbonded interactions will have to be more favorable than a lengthy through-bond pathway in order to produce a weaker slope for the longer oligoproline series (n = 4–9). In order to differentiate the solvent stabilized pathway from the other pathways, more experiments where the solvent is changed from water to deuterium oxide should provide useful information.

A fourth interpretation can involve parts of the first and third interpretations where a *through-space* transfer for n = 1–3 and solvent participation for n = 4–9 are invoked. In this case electron transfer will be proceeding without mediation of peptide orbitals.

The recent analysis of Creutz, Sutin, and co-workers[64] for the proline series with metal ammine donors and acceptors favors a *through-bond* pathways at least for n = 0–3 prolines. For the longer oligomers n = 4–9 prolines, more work is being done to understand the observed weak dependence of the rate on distance.

VII. Related Studies of Peptide-Mediated Electron Transfer

During the last five years a number of studies of donor–acceptor molecules with peptide-bridging ligands have appeared, including two studies using the polyproline-bridging ligands discussed in this review. In this section the results from these related studies will be presented and discussed in light of the model that we have presented.

Schanze and co-workers studied a series of oligoprolines with n = 0–4 proline residues using both organic and inorganic donor–acceptor molecules.[72-74] Two series of complexes were studied. The first series were molecules of the type $(bpy)_2Ru^*(5\text{-AP})(Pro)_nQ$ where $(bpy)_2Ru(5\text{-AP})$, (5-AP = 5-amino-1,10 phenanthroline) and Q = *p*-benzoquinone were used as donors and acceptors, respectively.[73] Photoinduced intramolecular electron transfer from the excited state of the ruthenium donor to the quinone acceptor was studied in five separate molecules with n = 0–4 prolines. The studies were carried out in organic solvents because of the limited solubility of the complexes in water. Under such conditions, the *cis-/trans*-proline isomerization equilibrium is shifted toward a higher percentage of the cis isomer than in water, resulting in multiple bridge conformations. The kinetics of intramolecular electron transfer obtained from the emission decay of the excited state were therefore multiphasic, especially at the longer distances. The efficiency of electron transfer falls as the number of proline spacers increases; however, quantitative determination of the rate of electron transfer on distance is not possible because of the multiexponential kinetics displayed by some of the molecules. This behavior is attributed to a number of slowly equilibrating isomers of the peptide bridges in the methylene chloride solvent. Overall, a substantial decrease in electron transfer rates (>5,000 fold) was observed as four prolines were introduced between the donor and acceptor.

In a later study $(bpy)Re^{I*}(CO)_3$ and 4-(dimethylamino)benzoate (DMAB) were used as donor and acceptor to synthesize three molecules of the type $[(bpy)Re^{I}(CO)_3pyXNH(Pro)_nDMAB]$ with n = 0–2 prolines.[73] These molecules proved to be more amenable to quantitative study of the rates of intramolecular electron transfer and their temperature dependence. A sharp decrease in rate with distance was observed for these three molecules ($\beta = 1.0 \pm 0.1$). Although this study was conducted in methanol, a comparison of the temperature-independent part of the rate constant $\Delta S^*/R$ was found to be similar to that in the $Os^{II}i\text{-}(Pro)_nRu^{III}$ systems[31] studied earlier. The magnitude of the decrease in rate with distance in the $Os^{II}i\text{-}(Pro)_nRu^{III}$ system was larger, but the distance dependence of the electronic coupling is similar in the $Os^{II}i(Pro)_nRu^{III}$ and Re/DMAB donor–acceptor systems since it is a characteristic of the proline bridge. Schanze's recent results in methanol at short distances are in agreement with the aqueous results for the bimetallic complexes with very short prolines described in this paper. The differences in the absolute rates and temperature dependence of the two studies are mainly due to differences in the driving force and reorganization energy of the different donor–acceptor sites and solvents used.

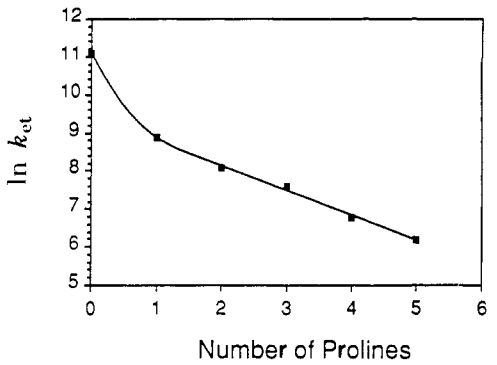


Figure 3. Rates of intramolecular electron transfer in Tyr-(Pro)$_n$Trp, n = 1–5 prolines.

Several studies of intramolecular electron transfer in small flexible peptides have been carried out using pulse radiolysis. Hoffman et al. studied a series of molecules, $[(NH_3)_5Co^{III}(Gly)_n(NB)]$, n = 0–2, where $(NH_3)_5Co^{III}$ acts as an electron acceptor and p-nitrobenzoic acid (NB) is an electron donor.[75,76] Rate constants of 2.6×10^3, 5.8×10^3, and 1.5×10^3 s^{-1} for n = 0, 1, 2 glycines, respectively, were obtained. In this study, the dipeptide bridging group undergoes more rapid intramolecular electron transfer than the amino acid bridged complex. A *through-space* mechanism, not involving the glycine bridge, where the p-nitrophenyl group comes in close proximity to the Co(III) center, was used to interpret these results.

In another related study, Prutz and Land studied intramolecular electron transfer across glycine residues in small molecules of the type Trp(Gly)$_n$Tyr, n = 0–3.[77-80] Here 0–3 glycine residues separated the tryptophan (Trp) from the tyrosine (Tyr) residue. These investigators found that the azide radical $N_3^{\bullet}$ (generated from the reaction of hydroxyl radical with N_3^-) preferentially attacked the Trp side chain to generate the Trp radical (Trp$^{\bullet}$). The resulting Trp radical, Trp$^{\bullet}$, accepts an electron from the Tyr side chain creating a Tyr radical, Tyr$^{\bullet}$, which can undergo further reactions. In these studies the electron-transfer rate decreased between n = 0–2 glycines, but the rate increased for n = 3 glycines. This again seems to be consistent with a *through-space* mechanism for the n = 3 glycines, where the orbitals of the bridge do not participate in the electron-transfer process. A comparison of the results for the Trp(Gly)$_n$Tyr studies (n = 0–3) and those of $[(NH_3)_5Co(Gly)_n(NB)]$ (n = 0–2) show that in these flexible systems the nature of the donor and the acceptor binding to the bridging ligand can alter the mechanism of intramolecular electron transfer. Furthermore, in the $[(NH_3)_5Co(Gly)_n(NB)]$ series the direction of electron-transfer reaction is from the N-terminus to the C-terminus of the peptide, while in the Trp(Gly)$_n$Tyr series, the direction of the electron transfer is from the C-terminus to the N-terminus of the peptide. Both of these effects could account for the unexpected *increase* in rate as the peptide bridge is lengthened.

Recently the use of Trp and Tyr as donor and acceptor to study intramolecular electron transfer across peptides has been extended to an extensive series of rigid proline polypeptides of the type Tyr(Pro)$_n$Trp.[81,82] The direction of electron transfer in this series is from the N-terminus to the C-terminus of the bridging proline. In another series, Trp(Pro)$_n$Tyr, where the direction of electron transfer through the peptide is from the C-terminus to the N-terminus, a different slope for distance dependence is observed. The driving force for all these electron-transfer reactions is very small (E° < 0.1 V). The results for the Tyr(Pro)$_n$Trp series in this study can be compared to our studies, since the direction of electron transfer in these molecules and those in Figure 3 are both from the N-terminus to the C-terminus of the peptide. Figure 3 shows a plot of ln k (k is the intramolecular electron transfer rate) versus the number of proline spacer groups in these molecules. As seen in Figure 3 the slope changes at n = 1 proline. This change in slope can be interpreted as a change in the mechanism of electron transfer between n = 0 and n = 1–5 prolines. As the number of prolines increased from n = 1 to n = 5, a modest decrease in the rate of intramolecular electron transfer is observed, only ~ 100-fold. This weak decrease in rate with distance was attributed to a mechanism that makes use of the proline orbitals.

In comparing these results (Figure 3) with our study (Figure 2), a more rapid onset of the weak slope at n = 1 proline is observed for Tyr(Pro)$_n$Trp, compared to our study where the change in slope occurs between n = 3, 4 prolines. A slow decrease in rate is observed in both studies at the long distances (≥4 prolines). The major difference between the two studies is the nature of the donor and acceptor and their mode of bonding to the proline bridge. In the studies using Tyr/Trp as donor–acceptor, additional methylene groups separate the proline residue from the donor and acceptor groups which can give rise to the behavior observed. The transition-metal donors and acceptors provide a wider range of driving forces, reorganizational energies, and distances than the organic donors and acceptors. Furthermore with the transition-metal donors and acceptors the intramolecular electron transfer reaction is free from interference from other side reactions such as the further reactivity of the Tyr$^{\bullet}$ and its deprotonation after the electron-transfer reaction is completed. The conclusion from comparing these two studies is that the nature of the donor–acceptor and its covalent bonding to the bridging peptide can alter the mechanism and the distance dependence of the rate of intramolecular electron transfer.

In a series of papers Sisido and co-workers examined the role of the α helix in mediating long-range electron-transfer reactions.[83-85] They incorporated a specific amino acid sequence into an α-helical-forming polypeptide and studied the rate of intramolecular electron transfer across this sequence. They used the (dimethylamino)phenyl (dmaPhe), D, group as donor and the pyrenylalanine (pyrAla), A, group as acceptor in compounds of the type (GluOBzl)$_m$dmaPhe(Ala)$_n$pyrAla(GluOBzl)$_4$ from m = 38, 45. The number of alanines separating the donor and acceptor groups varied between n = 0–2 alanines. The incorporation of these short peptides into α-helical-forming polypeptides resulted in molecules that are separated by 5.4, 9.4, and 5.5 Å edge to edge. The rate of electron transfer measured for n = 0 and n = 2 alanines was very similar, ~2×10^7 s^{-1} at −20 °C in trimethyl phosphate. However, for n = 1 alanine, the rate constant was 7×10^5 s^{-1}. The authors interpret these results to imply strong

through-space interaction between the chromophores, dominating any weaker through bond coupling in the $n = 2$ peptide.

Kuki and co-workers have studied the effect of a heavy atom on the acceleration of intersystem crossing between two chromophores separated by an α-helical peptide which is rich in aminoisobutyric acid (Aib).[86,87] Presumably the transmission of the heavy atom effect of a *p*-bromophenylalanine group to a distal naphthalene group occurs through noncovalent or through-bond coupling mediated by the bridged peptide. The heavy bromo atom is expected to exert its influence by accelerating the rate of intersystem crossing in the naphthalene group. This results in an acceleration of the quenching of the naphthalene excited singlet state.

Four peptides were synthesized: two dipeptides and two octapeptides. One dipeptide was attached to the side chains of β-(1′-naphthyl)-*l*-alanine and *p*-bromophenylalanine, and a second dipeptide was attached to β-(1′-naphthyl)-*l*-alanine and the phenylalanine side chains as a control. The corresponding octapeptide (AcAibAibβ-(1′-naphthyl)AibAibPhe(Br)$(Aib)_3$NHMe) was synthesized, where an aromatic naphthyl side chain is substituted at amino acid residue 3 and a bromo-Phe at amino acid residue 6. A second octapeptide identical to the first, but without the bromo substituent, was studied as a control. These Aib-containing octapeptides were chosen because of their propensity to form an α-helical structure.

The fluorescence quenching behavior of the bromo dimer and the bromo octamer showed that quenching is twice as effective in the octamer as in the dimer, although the side chains in the octamer are separated by 13 σ bonds compared to only 7 σ bonds in the dimer (adjacent residues). The conclusion for this system was that the *through-bond* interaction is less effective than *through noncovalent* interactions. In this helical peptide nonbonding interactions play a dominant role in accelerating the rate of intersystem crossing of the naphthalene chromophores.

VIII. Concluding Remarks

The experiments described here for the oligoproline donor–acceptor complexes demonstrate that rapid rates of electron transfer, occurring in the microsecond timescale, can be measured at donor–acceptor separations of 35–40 Å. Intramolecular electron-transfer rates at such long distances have not been observed before. The studies presented show that by changing the driving force and reorganization energy and the nature of the donor and acceptor, intramolecular electron-transfer rates can be measured at these long distances. Although most of the studies completed thus far use oligoproline bridging groups, the lessons drawn from these studies should make their extension to nonproline ligands feasible. Additional electron-transfer pathways in other protein secondary structure such as α helices and β sheets are candidates for future studies. Further exploration of rates of electron transfer at these long distances is more elaborate model systems should lead to a much better understanding of pathways in electron-transfer proteins.

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