Published in final edited form as:

J Phys Chem C Nanomater Interfaces. 2015 March 6; 119(13): 6998–7005. doi:10.1021/jp512628x.

A New Type of Electron Relay Station in Proteins: Three-Piece $S:\Pi:S \leftrightarrow S:\Pi:S$ Resonance Structure

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Abstract

A type of relay station for electron transfer in proteins, three-piece five-electron bonding, is introduced in this paper, which is also first proposed here. The ab initio calculations predict the formation of $S:\Pi:S \leftrightarrow S:\Pi:S$ resonance binding with an aromatic ring located in the middle of two sulfur-containing groups, which may participate in electron-hole transport in proteins. These special structures can lower the local ionization energies to capture electron holes efficiently and may be easily formed and broken because of their proper binding energies. In addition, the UV-vis spectra provide evidence of the formations of the three-piece five-electron binding. The cooperation of three adjacent pieces may be advantage to promote electron transfer a longer distance.

INTRODUCTION

Electron transfer (ET) plays a vital role in many biological processes, such as photosynthesis, cell respiration, DNA repair, and so on.^{1–9} To understand the exact pathway of ET in proteins for these biological processes, therefore, extensive investigations in

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ASSOCIATED CONTENT

Supporting Information

The complete citation for ref 51 as well as the calculated molecular geometries, orbital characters, vertical ionization energies (IE_v 's), binding energies (BEs), and ultraviolet spectra for all $S:\Pi:S \leftrightarrow S:\Pi:S$ bonding complexes and correlations among several quantities. This material is available free of charge via the Internet at <http://pubs.acs.org>

The authors declare no competing financial interest.

theory^{10–18} and experiment^{19–24} have been carried out in recent decades. On the basis of Marcus theory,¹ a one-step superexchange mechanism was proposed to explain the direct electron transfer from donor to acceptor, facilitated by intervening medium. In this mechanism, several factors were found to affect the kinetics of the ET, including peptide chain length, secondary structure, and hydrogen bonding.²⁵ The ET rate falls off exponentially with the donor–acceptor distance^{26–28} for the superexchange mechanism, a decreasing factor of 10 for the increase of 1.5–2.5 Å.^{29–33} Therefore, the single-step mechanism becomes unlikely for the large distance (10 Å or more).^{24,27,34–36} Therefore, a hopping mechanism was proposed to uncover efficient long-range ET in biological systems,^{24,35,37–41} which consists of a series of one-step superexchange electron tunneling processes. In the hopping mechanism, there are one or more relay stations, which can transiently carry electron or hole. Thus, the relay stations between donor and acceptor play an important role in the longrange ET in proteins. Therefore, much research has been carried out to interpret the relay stations.^{7,8,11,13,17,18,23,24,42–44} Aubert et al. proposed that tryptophan (Trp)^{7,43,44} and tyrosine (Tyr)³⁴ residues can act as relay stations in proteins. In addition, Wang et al. revealed that cysteine (Cys) and methionine (Met) can also function as relay stations for the ET through peptides.⁴²

The reason why Trp and Tyr can act as relay stations is that the corresponding ET reaction involves proton transfer from the side chain of Trp (or Tyr) to an adjacent functional group, and these two amino acids have appropriate redox potentials.^{34,43} However, in the studies of Wang et al., proton transfer does not occur during the ET process when Met acts as the relay station. The redox potentials of Met and Cys are high.⁴² These two sulfur-containing (S-containing) amino acids can facilitate electron transfer because the S atoms in the side chains can form two-center, three-electron bonds with the O atoms (N atoms) of the neighboring groups.^{42,45–49} The formation of this special three-electron bond can lower the location redox potential of the S-containing group. According to our previous work, the neighboring two atoms with the lone pair orbitals (lp) can form lp:lp three-electron bond, such as O:O and O:N,¹¹ which can also serve as relay stations for ET in proteins. In addition, we have proposed that the C-terminus of α -helices also can accelerate the rate of the long-range ET in proteins.¹³ More recently, our work has revealed that the neighboring aromatic rings can facilitate the side chains of Met or Cys residues to take part in ET processes by instantaneously forming lp: π multicenter three-electron (S: π) bonded stations in proteins.¹⁷ Monney et al.⁵⁰ confirmed the formation of this new type of S: π bonds by spectroscopic evidence in the next year.

Inspired by these studies^{42,45–48} and our previous works,^{11,13,17} we found a new type of special relay structures that have aromatic rings located between two S-containing groups (S-II-S, “II” denotes F, H, Y, or W for the side chain of Phe, His, Tyr, or Trp, respectively, “S” marks C or M for the side chain of Cys or Met) in proteins through carefully examining a series of protein crystal structures (some structures are shown in the Supporting Information), which can favor long-rang ET reactions in proteins. The ab initio calculations reveal that a special three-piece five-electron resonance bonding (S:II:S $\leftrightarrow$ S:II:S) may be formed according to the S- π -S structure, which can act as a relay station to facilitate the long-range ET in proteins with a lower local redox potential. This work reveals a new type

of relay stations for the long-range ET, which may provide a further understanding of the efficient ET processes in proteins.

COMPUTATIONAL DETAILS

To reveal the electron relay abilities of all possibly close S-II-S contacts, several high-resolution protein structures should be examined. According to the protein crystal structures, the S-II-S interactions are divided into three classes: simple models, one-chain models, and three-chain models. The simple models only include the side chains of Phe, His, Tyr, Trp, Cys, and Met (toluene for Phe, p-cresol for Tyr, 4-methylimidazole for His, 3-methylindole for the Trp, methanethiol for Cys, and dimethyl sulfide for Met), named $S:\pi:S$ (“:” indicates the two-electron bond and “.” denotes the three-electron bond), as shown in Scheme 1. In the one-chain models, one aromatic ring and two close S-containing side chains reside on a peptide chain, and the corresponding interaction structures are named as $Sxx:\Pi xx.Sxx$ (“ Sxx ” denotes Cys or Met, “ Πxx ” marks Phe, His, Tyr, and Trp, Scheme 1). The three-chain models are examined under two distinguishing situations. One is that the aromatic ring and two peptide units are included, whereas only the side chains of the two S-containing amino acids are retained, denoted by $S:\Pi xx.S$. The other is that the two S-containing groups are connected to the peptide chains while aromatic ring is included, named as $Sxx:\Pi.Sxx$ (Scheme 1).

All gas-phase calculations are carried out by using the Gaussian 09⁵¹ suite of programs. The M062X^{52,53} hybrid functional in conjunction with 6-31+G(d,p)^{54–57} basis set is utilized to optimize all geometries fully and to perform the harmonic vibrational analyses for confirming minima (all real frequencies). The singly occupied molecular orbitals (SOMO), highest doubly occupied molecular orbitals (HDMO), and second highest doubly occupied molecular orbitals (HDMO-1) (or other doubly occupied molecular orbitals under HDMO-1) are obtained from single-point calculations on the optimized structures using restricted open-shell M06-2X with 6-31+G(d,p) basis sets.

In an effort to explore the new functionality of the $S:\pi:S \leftrightarrow S:\pi:S$ structure (to take part in electron hole migration in proteins), the interactions of the three-piece system need to be detected with proper parameters including ionization energy (IE) and binding energy (BE, only for the simple models and three-chain models; there are two BE values for each system and the smaller one is employed), electron-transition spectrum, and so on. The BEs are calculated by subtracting basis set superposition errors (BSSEs) using the counterpoise approach.^{58,59} The adiabatic IE (IE_a) is the difference in energy between the $S:\pi:S$ complex (cation) and its corresponding closed-shell complex in their fully optimized states. In contrast, the vertical ionization energy (IE_v) is the energy difference between an $S:\pi:S$ complex (cation) and its corresponding closed-shell complex without change in structure (the latter has one more electron than the former). To explore the effect of protein polarizable environment on stabilities of the $S:\pi:S$ complexes, we carry out single-point calculations in two continuum solvents, including ether ($\epsilon = 4.335$) and water ($\epsilon = 78.36$) at the M06-2X/6-311++G(d,p)⁶⁰ levels of theory by means of the conductor-like polarizable continuum model (CPCM).^{61,62} The time-dependent density functional response theory (TD-DFT)⁶³ calculations are performed to determine the energy needed to excite an electron

from two doubly occupied bonding orbitals to the singly occupied antibonding orbital (σ/σ^*) of the $S:\pi:S$ complexes. The UV-vis spectra are calculated using the SWizard program, revision 5.0,^{64,65} using the Gaussian model. The width at half-height, $\Gamma_{1/2}$, is assumed to equal 1000 cm^{-1} . All these parameters are obtained by carrying out single-point calculations at the M06-2X/6-311++G(d,p)/M06-2X/6-31++G(d,p) levels of theory. Other data including the shortest distances, BEs, IE_v values, orbital characteristics, and correlations among several quantities for all structures are listed in the Supporting Information.

To further confirm that the interaction of an aromatic ring and two S-containing groups can effectively reduce the IE, the $M:F:M$ system is investigated using multistate density functional theory (MSDFT).^{66–68} Using block localized Kohn–Sham (BLKS) orbitals, MSDFT defines the electron hole to localize in a fragment or in two fragments in the MFM system on the basis of the optimized cation structure by the B3LYP method. According to the different positions of hole in $M:F:M$, there are four distinguishing states, including M^+-FM , $M-F^+-M$, MF^+-M , and MFM^+ , and these diabatic BLKS functions are defined as

$$\Phi_{M^2+}^{KLBS} = \hat{A} \{ \Psi_+^1(M^+) \Psi_0^2(MF) \} \quad (1)$$

$$\Phi_{F^1+}^{KLBS} = \hat{A} \{ \Psi_0^1(M) \Psi_+^1(F^+) \Psi_0^1(M) \} \quad (2)$$

$$\Phi_{MF^2+}^{KLBS} = \hat{A} \{ \Psi_+^2(MF^+) \Psi_0^1(M) \} \quad (3)$$

$$\Phi_{MFM^3+}^{KLBS} = \hat{A} \{ \Psi_+^3(MFM^+) \} \quad (4)$$

where M^+ (or F^+) indicates the hole resides on the corresponding M (or F) fragment, MF^+ and MFM^+ indicate the hole is delocalized over the two neighboring fragments and the three fragments, respectively, and FM shows that the neighboring M and F are united. The vertical ionization energy (IE_v) for every state is the energy difference between the corresponding cation state and the same closed-shell complex without change in structure.

RESULTS AND DISCUSSION

The Formation of $S:\pi:S \leftrightarrow S:\pi:S$ in the Simple Models

We inferred that there are 12 simple models ($S:\Pi:S$) among the four aromatic rings and two S-containing side chains. All possible 12 simple models are obtained by carrying out the M06-2X/6-31++G(d,p) optimizations, as shown in the Supporting Information. Here, we take $M:F:M$ as an example to reveal the essential properties of the $S:\Pi:S$ structures. Figure 1 shows the structure of $M:F:M$ and the plots of corresponding SOMO, HDMO, and HDMO-1. The distances between the aromatic ring and two S atoms are 2.98 and 2.98 Å, respectively, which are in agreement with the values in our previous work (2.89–2.91 Å).¹⁷ The distances are smaller than the neutral distances of 3.60 and 3.60 Å (Supporting Information), indicating a strong interaction among these three pieces at the cation state. The

BE (10.38 kcal/mol) of $M:F:M$ also confirms the strong interaction in $M:F:M$. In addition, the IE_v of $M:F:M$ is 7.00 eV, which is sharply lower than that of the monomer (8.64 eV for F or 8.69 eV for M). The IE_v value is comparable to the IE_v values of Trp (6.98 eV) and Tyr (7.82 eV) at the M06-2X/6-311++G(d,p)//M06-2X/6-31+G(d,p) level, two effective relay residues in proteins.^{6,7} All these values (short distances, BE, and lower IE_v) imply that there is a special interaction among the three fragments. As displayed in Figure 1, it is clear that SOMO is antibonding and delocalizes over the three fragments with an electron. On the contrary, HDMO and HDMO-1 are both bonding with two electrons, respectively. The plot of HDMO resides at the two methanethiols, and the plot of HDMO-1 delocalizes over the three fragments. The interactions of the three orbitals result in the formation of a special five-electron binding among the three fragments ($S:II:S \leftrightarrow S:II:S$ resonance binding), and the forming process is displayed in Figure 2. Each fragment, a toluene and two methanethiols, has a HOMO (highest occupied MO). When an electron hole moves into the three-fragment region, the interaction of three HOMOs generates three new molecular orbitals: an antibonding orbital (σ^*) and two bonding orbitals (σ_1 and σ_2). The association of these three new orbitals accounts for the generation of $S:II:S \leftrightarrow S:II:S$ resonance binding, which not only draws the three pieces close but also lowers the local ionization potential effectively. More importantly, the formation of $S:II:S \leftrightarrow S:II:S$ binding favors the electron hole moving to the region of the three close side chains. In addition, the moderately binding strength of the three fragments supports generation and separation of the $S:II:S \leftrightarrow S:II:S$ binding in proteins. The formation of $S:II:S \leftrightarrow S:II:S$ binding captures an electron hole, and then the separation of the close three pieces promotes the electron hole to move away. Therefore, it is reasonable to infer that the formation of $S:II:S \leftrightarrow S:II:S$ binding could enhance the rate of electron hole migration in proteins as an effective relay station.

Table 2 shows the values of IE_v 's for the four states of $M:F:M$ by carrying out the BLKS functions at the B3LYP/6-31+G(d) level of theory. The IE_v values of $M-F^+-M$ and M^+-FM are 8.19 and 7.96 eV, which are the largest among the four states of $M:F:M$. The IE_v value of MF^+-M (7.04 eV) is smaller than these of $M-F^+-M$ and M^+-FM . When the hole delocalizes over the three fragments, the IE_v of the system is the smallest among the four states. The IE_v value of MFM^+ is only 6.40 eV. These results indicate that the IE_v decreases with the increase in the size occupied by the hole. The hole delocalizing over the three electron-rich fragments can effectively reduce the energy of the system and can lead to the decrease of the IE_v of the system. Therefore, the cooperative action of the two S-containing groups with the inserting aromatic ring can effectively capture a hole in proteins.

In addition, TD-DFT calculations are carried out to analyze the electronic spectrum of $S:II:S \leftrightarrow S:II:S$ binding, which provides evidence of the existence of the five-electron binding. Figure 3 shows that there are two absorption peaks for $M:F:M$. The values are 1074.5 and 570.9 nm. The 1074.5 nm peak denotes an electron transition from HDMO to SOMO, and the 570.9 nm peak is from HDMO-1 to SOMO. It is clear that the oscillator strength of the 1074.5 nm peak is greatly larger than that of the 570.9 nm peak. This is contributed to the fact that the energy of HDMO is closer to SOMO compared with HDMO-1, supporting the electron transition from HDMO to SOMO. Therefore, these two electron transitions can indicate the formation of $S:II:S \leftrightarrow S:II:S$ binding. More importantly, the lower the values of the characteristic peaks for the $S:II:S \leftrightarrow S:II:S$

bindings, the stronger the relay ability for the S-II-S system is. However, there is no information about the structures of $S:II \cdot S \leftrightarrow S \cdot II:S$ complexes so far in the literature. Therefore, we also cannot find the spectral information on $S:II \cdot S \leftrightarrow S \cdot II:S$ complexes presented in the literature. Half of the $S:II \cdot S \leftrightarrow S \cdot II:S$ binding complexes, $S \cdot II$ three-electron bond, have been examined by experimental and theoretical methods. Glass and co-workers confirmed the formation of the $S \cdot II$ bond between a S-containing group and an aromatic ring through the effective synthetical technique.^{50,69} The characteristic spectra of $S \cdot II$ bond between the S atom and the phenyl ring are 550 and 705 nm. The 550 nm signal has a strong absorbing peak. TD-DFT calculations of our group indicate that the maximal absorbing peaks of $S \cdot II$ bond between the S atom and the phenyl ring are in the range of 583.1–673.9 nm depending on the different contact positions and distances, which are larger than the Glass's experimental value (550 nm). Therefore, our TD-DFT calculations only give the predicted values of the spectra for the $S:II \cdot S \leftrightarrow S \cdot II:S$ complexes, which may not be accurate values but can be an index of the formation of $:II \cdot S \leftrightarrow S \cdot II:S$ bindings.

Similar analyses can be made for the other simple models, including $C:F \cdot C$, $C:F \cdot M$, $C:H \cdot C$, $C:H \cdot M$, $C:W \cdot C$, $C:W \cdot M$, $C:Y \cdot C$, $C:Y \cdot M$, $M:H \cdot M$, $M:W \cdot M$, and $M:Y \cdot M$. Their structures, frontier orbitals, and absorption spectrum information are displayed in the Supporting Information. The two shortest distances between the neighboring pieces ($d_{\min}$'s) are in the range of 2.90–3.35 Å, and the BE values range from 5.99 kcal/mol for $C:F \cdot M$ to 10.98 kcal/mol for $M:H \cdot M$. Analyzing the data in Table 1 shows that the BEs of $M:II \cdot M$ are generally bigger than that of $C:II \cdot C$. The IE_v values of all simple models are in the range of 6.43–7.24 eV, which are comparable to the two effective relay stations of Trp and Tyr as mentioned previously. The decreasing values of IE_v s range from 0.57 to 1.74 eV, as listed in Table 1. The absorption spectrum information is displayed in the Supporting Information. Similar to $M:F \cdot M$, there are two absorption peaks for every $S:II \cdot S$ binding, which correspond to electron transitions from HDMO and HDMO-1 to SOMO.

Influence of Peptide Chains on the Formations of $S:II \cdot S \leftrightarrow S \cdot II:S$

To elucidate the situation of one aromatic ring and two close S-containing groups all residing along the same peptide chain, all possible one-chain models ($Sxx:IIxx \cdot Sxx$) have been examined. Five one-chain models, including Cys:His $\cdot$ Cys, Cys:Tyr $\cdot$ Cys, Met:Phe $\cdot$ Met, Met:His $\cdot$ Met, and Met:Tyr $\cdot$ Met, are obtained by carrying out ab initio optimizations. The structures and corresponding MOs of Met:Phe $\cdot$ Met are shown in Figure 4, and the detailed information on other structures are in the Supporting Information. Just as the simple models mentioned earlier, the interactions among the ring and two neighboring S-groups of Met:Phe $\cdot$ Met form the $S:II \cdot S \leftrightarrow S \cdot II:S$ bindings. The corresponding three MOs are SOMO, HDMO, and HDMO-8 (the ninth HDMO), different from the SOMO, HDMO, and HDMO-1 for the corresponding simple model, $M:F \cdot M$. This result indicates that the presence of the peptide chain can modulate the energies of MOs. In addition, a part of HDMO-8 delocalizes over the peptide chain in Met:Phe $\cdot$ Met, decreasing the binding strength for $S:II \cdot S \leftrightarrow S \cdot II:S$ binding with respect to $M:F \cdot M$. The shortest distances between the aromatic ring and the two S atoms change from 2.98/2.98 Å in $M:F \cdot M$ to 2.96/3.23 Å in Met:Phe $\cdot$ Met, indicating that the presence of the peptide chain destroys the symmetry of the simple model. This structural change also confirms that the binding

strength of $S:II \cdot S \leftrightarrow S \cdot II:S$ in Met:Phe·Met is weaker than that in M:F·M. More importantly, the IE_v value of Met:Phe·Met is only 7.05 eV, which is sharply lower than the corresponding monomer (8.06 eV for His and 8.29 for Met). This significantly low IE_v indicates that the formation of the $S:II \cdot S \leftrightarrow S \cdot II:S$ binding among the neighboring Met-Phe-Met region can efficiently capture an electron hole. Similar analyses can be made for the other four one-chain models.

In addition, TD-DFT calculations reveal that the absorption spectra can also confirm the formations of the $S:II \cdot S \leftrightarrow S \cdot II:S$ bindings in $Sxx:IIxx \cdot Sxx$ systems. Compared with the corresponding simple models, the absorption peaks of one-chain models show red shifts, except Cys:His·Cys. The detailed analyses about absorption spectra of one-chain models are displayed in the Supporting Information.

Similar analyses are also applied to the three-chain model, and the details are in the Supporting Information. Figure 5 shows the structures of M:Phe·M with the corresponding SOMO, HDMO, and HDMO-4. It is clear that the $S:II \cdot S \leftrightarrow S \cdot II:S$ binding can be formed in the three-chain models. However, the presence of the peptide chain breaks the symmetry of the corresponding simple structure, and the distances between the middle aromatic ring and the two S atoms are 2.85 and 3.27 Å in M:Phe·M. The BE value of M:Phe·M is 9.54 kcal/mol, and the IE_v value is 6.77 eV, indicating that the neighboring M-Phe-M region may have the potential function of the relay station to promote the efficient transport of electron hole in proteins.

CONCLUSION

Ab initio calculations reveal the possibility of formations of $S:II \cdot S \leftrightarrow S \cdot II:S$ resonance bondings, which may serve as relay stones of electron (hole) transfer in proteins. The interacted motif is that aromatic side chain is sandwiched between two S-containing amino acid residues at appropriate distances and arrangements. Two main reasons support these structures to participate in protein long-range ET. One is the interactions of these three electron-riched groups can lower the local IEs to capture electron hole. The other reason is that the BE values are in the range of 5.99–21.86 kcal/mol, which are moderate to support the formations and separations of $S:II \cdot S \leftrightarrow S \cdot II:S$ bondings. The formations and separations of these three-piece five-electron bindings may promote electron-hole transport in proteins. These findings may provide a further understanding of electron transfer pathway in proteins.^{70,71}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was financially supported by NSFC of China (21003162, 21273291), by the Fundamental Research Funds for the Central Universities (CDJZR14 22 55 01 and CQDXWL-2012-033), by the Chongqing Graduate Student Research Innovation Project (CYS14017), and by the National Institutes of Health (GM46736).

REFERENCES

1. Marcus RA, Sutin N. Electron Transfers in Chemistry and Biology. *Biochim. Biophys. Acta. Rev. Bioenerg.* 1985; 811:265–322.
2. Gray HB, Winkler JR. Electron Transfer in Proteins. *Annu. Rev. Biochem.* 1996; 65:537–561. [PubMed: 8811189]
3. Page CC, Moser CC, Chen X, Dutton PL. Natural Engineering Principles of Electron Tunnelling in Biological Oxidation-Reduction. *Nature.* 1999; 402:47–52. [PubMed: 10573417]
4. Yang H, Luo G, Karnchanaphanurach P, Louie TM, Rech I, Cova S, Xun L, Xie XS. Protein Conformational Dynamics Probed by Single-Molecule Electron Transfer. *Science.* 2003; 302:262–266. [PubMed: 14551431]
5. Prytkova TR, Kurnikov IV, Beratan DN. Coupling Coherence Distinguishes Structure Sensitivity in Protein Electron Transfer. *Science.* 2007; 315:622–625. [PubMed: 17272715]
6. Bollinger JM Jr. Biochemistry. Electron Relay in Proteins. *Science.* 2008; 320:1730–1731. [PubMed: 18583602]
7. Shih C, Museth AK, Abrahamsson M, Blanco-Rodriguez AM, Di Bilio AJ, Sudhamsu J, Crane BR, Ronayne KL, Towrie M, Vlcek A Jr, Richards JH, Winkler JR, Gray HB. Tryptophan-Accelerated Electron Flow through Proteins. *Science.* 2008; 320:1760–1762. [PubMed: 18583608]
8. Cordes M, Giese B. Electron Transfer in Peptides and Proteins. *Chem. Soc. Rev.* 2009; 38:892–901. [PubMed: 19421569]
9. Li J, Liu Z, Tan C, Guo X, Wang L, Sancar A, Zhong D. Dynamics and Mechanism of Repair of Ultraviolet-Induced (6-4) Photoproduct by Photolyase. *Nature.* 2010; 466:887–890. [PubMed: 20657578]
10. Jones ML, Kurnikov IV, Beratan DN. The Nature of Tunneling Pathway and Average Packing Density Models for Protein-Mediated Electron Transfer. *J. Phys. Chem. A.* 2002; 106:2002–2006.
11. Chen X, Zhang L, Wang Z, Li J, Wang W, Bu Y. Relay Stations for Electron Hole Migration in Peptides: Possibility for Formation of Three-Electron Bonds along Peptide Chains. *J. Phys. Chem. B.* 2008; 112:14302–14311. [PubMed: 18922032]
12. Beratan DN, Skourtis SS, Balabin IA, Balaeff A, Keinan S, Venkatramani R, Xiao D. Steering Electrons on Moving Pathways. *Acc. Chem. Res.* 2009; 42:1669–1678. [PubMed: 19645446]
13. Chen X, Zhang L, Zhang L, Sun W, Zhang Z, Liu H, Bu Y, Cukier RI. α -Helix C-Terminus Acting as a Relay to Mediate Long-Range Hole Migration in Proteins. *J. Phys. Chem. Lett.* 2010; 1:1637–1641.
14. Issa JB, Krogh-Jespersen K, Isied SS. Conformational Dependence of Electronic Coupling Across Peptide Bonds: A Ramachandran Map. *J. Phys. Chem. C.* 2010; 114:20809–20812.
15. Migliore A. Nonorthogonality Problem and Effective Electronic Coupling Calculation: Application to Charge Transfer in π -Stacks Relevant to Biochemistry and Molecular Electronics. *J. Chem. Theory Comput.* 2011; 7:1712–1725.
16. Voityuk AA. Long-Range Electron Transfer in Biomolecules. Tunneling or Hopping? *J. Phys. Chem. B.* 2011; 115:12202–12207. [PubMed: 21923189]
17. Chen X, Tao Y, Li J, Dai H, Sun W, Huang X, Wei Z. Aromatic Residues Regulating Electron Relay Ability of S-Containing Amino Acids by Formations of S: π Multicenter Three-Electron Bonds in Proteins. *J. Phys. Chem. C.* 2012; 116:19682–19688.
18. Sun W, Dai H, Tao Y, Xiao D, Zhang Y, Wei Z, Chen X. Potent Relay Stations for Electron Transfer in Proteins: π : π Three-Electron Bonds. *J. Phys. Chem. C.* 2013; 117:18325–18333.
19. Wierzbinski E, de Leon A, Yin X, Balaeff A, Davis KL, Rapireddy S, Venkatramani R, Keinan S, Ly DH, Madrid M, Beratan DN, Achim C, Waldeck DH. Effect of Backbone Flexibility on Charge Transfer Rates in Peptide Nucleic Acid Duplexes. *J. Am. Chem. Soc.* 2012; 134:9335–9342. [PubMed: 22548314]
20. Mandal HS, Kraatz H-B. Electron Transfer Mechanism in Helical Peptides. *J. Phys. Chem. Lett.* 2012; 3:709–713.
21. Lloveras V, Vidal-Gancedo J, Figueira-Duarte TM, Nierengarten JF, Novoa JJ, Mota F, Ventosa N, Rovira C, Veciana J. Tunneling versus Bopping in Mixed-Valence Oligo-*p*-phenylenevinylene

- Polychlorinated Bis(triphenylmethyl) Radical Anions. *J. Am. Chem. Soc.* 2011; 133:5818–5833. [PubMed: 21446654]
22. Donoli A, Marcuzzo V, Moretto A, Toniolo C, Cardena R, Bisello A, Santi S. Charge Mapping in 3_{10} -Helical Peptide Chains by Oxidation of the Terminal Ferrocenyl Group. *Org. Lett.* 2011; 13:1282–1285. [PubMed: 21341757]
23. Wittekindt C, Schwarz M, Friedrich T, Koslowski T. Aromatic Amino Acids as Stepping Stones in Charge Transfer in Respiratory Complex I: An Unusual Mechanism Deduced from Atomistic Theory and Bioinformatics. *J. Am. Chem. Soc.* 2009; 131:8134–8140. [PubMed: 19507904]
24. Malak RA, Gao Z, Wishart JF, Isied SS. Long-Range Electron Transfer Across Peptide Bridges: The Transition from Electron Superexchange to Hopping. *J. Am. Chem. Soc.* 2004; 126:13888–13889. [PubMed: 15506726]
25. Long YT, Abu-Irhayem E, Kraatz HB. Peptide Electron Transfer: More Questions than Answers. *Chem.—Eur. J.* 2005; 11:5186–5194. [PubMed: 15977279]
26. Marcus RA. Electron Transfer Reactions in Chemistry: Theory and Experiment (Nobel Lecture). *Angew. Chem., Int. Ed.* 1993; 32:1111–1121.
27. Mayo S, Ellis W, Crutchley R, Gray H. Long-Range Electron Transfer in Heme Proteins. *Science.* 1986; 233:948–952. [PubMed: 3016897]
28. Hopfield JJ. Electron Transfer Between Biological Molecules by Thermally Activated Tunneling. *Proc. Natl. Acad. Sci. U.S.A.* 1974; 71:3640–3644. [PubMed: 16592178]
29. Winkler JR, Gray HB. Electron Tunneling in Proteins: Role of the Intervening Medium. *J. Biol. Inorg. Chem.* 1997; 2:399–404.
30. Williams RJP. The Medium in Electron Transfer Proteins. *J. Biol. Inorg. Chem.* 1997; 2:373–377.
31. Skourtis SS, Beratan DN. High and Low Resolution Theories of Protein Electron Transfer. *J. Biol. Inorg. Chem.* 1997; 2:378–386.
32. Moser CC, Page CC, Chen X, Dutton PL. Biological Electron Tunneling through Native Protein Media. *J. Biol. Inorg. Chem.* 1997; 2:393–398.
33. Farver O, Pecht I. The Role of the Medium in Long-Range Electron Transfer. *J. Biol. Inorg. Chem.* 1997; 2:387–392.
34. Stubbe J, Nocera DG, Yee CS, Chang MC. Radical Initiation in the Class I Ribonucleotide Reductase: Long-Range Proton-Coupled Electron Transfer? *Chem. Rev.* 2003; 103:2167–2201. [PubMed: 12797828]
35. Morita T, Kimura S. Long-Range Electron Transfer over 4 nm Governed by an Inelastic Hopping Mechanism in Self-Assembled Monolayers of Helical Peptides. *J. Am. Chem. Soc.* 2003; 125:8732–8733. [PubMed: 12862461]
36. Winkler JR, Malmström BG, Gray HB. Rapid Electron Injection into Multisite Metalloproteins: Intramolecular Electron Transfer in Cytochrome Oxidase. *Biophys. Chem.* 1995; 54:199–209. [PubMed: 7749059]
37. Horsley JR, Yu J, Moore KE, Shapter JG, Abell AD. Unraveling the Interplay of Backbone Rigidity and Electron Rich Side-Chains on Electron Transfer in Peptides: The Realization of Tunable Molecular Wires. *J. Am. Chem. Soc.* 2014; 136:12479–12488. [PubMed: 25122122]
38. Meggers E, Kusch D, Spichty M, Wille U, Giese B. Electron Transfer Through DNA in the Course of Radical-Induced Strand Cleavage. *Angew. Chem., Int. Ed.* 1998; 37:460–462.
39. Jortner J, Bixon M, Langenbacher T, Michel-Beyerle ME. Charge Transfer and Transport in DNA. *Proc. Natl. Acad. Sci. U.S.A.* 1998; 95:12759–12765. [PubMed: 9788986]
40. Colton IJ, Anderson JR, Gao J, Chapman RG, Isaacs L, Whitesides GM. Formation of Protein Charge Ladders by Acylation of Amino Groups on Proteins. *J. Am. Chem. Soc.* 1997; 119:12701–12709.
41. Melvin T, Botchway S, Parker AW, O'Neill P. Migration of Photoinduced Oxidative Damage in Models for DNA. *J. Chem. Soc. Chem. Commun.* 1995:653–654.
42. Wang M, Gao J, Muller P, Giese B. Electron Transfer in Peptides with Cysteine and Methionine as Relay Amino Acids. *Angew. Chem., Int. Ed.* 2009; 48:4232–4234.
43. Aubert C, Vos MH, Mathis P, Eker AP, Brettel K. Intraprotein Radical Transfer During Photoactivation of DNA Photolyase. *Nature.* 2000; 405:586–590. [PubMed: 10850720]

44. Aubert C, Mathis P, Eker APM, Brettel K. Intraprotein Electron Transfer between Tyrosine and Tryptophan in DNA Photolyase from *Anacystis Nidulans*. *Proc. Natl. Acad. Sci. U.S.A.* 1999; 96:5423–5427. [PubMed: 10318899]
45. Giese B, Wang M, Gao J, Stoltz M, Muller P, Graber M. Electron Relay Race in Peptides. *J. Org. Chem.* 2009; 74:3621–3625. [PubMed: 19344128]
46. Fourré I, Bergès J. Structural and Topological Characterization of the Three-Electron Bond: The SO Radicals. *J. Phys. Chem. A.* 2004; 108:898–906.
47. Brunelle P, Rauk A. One-Electron Oxidation of Methionine in Peptide Environments: The Effect of Three-Electron Bonding on the Reduction Potential of the Radical Cation. *J. Phys. Chem. A.* 2004; 108:11032–11041.
48. Schoneich C, Pogocki D, Hug GL, Bobrowski K. Free Radical Reactions of Methionine in Peptides: Mechanisms Relevant to β -Amyloid Oxidation and Alzheimer's Disease. *J. Am. Chem. Soc.* 2003; 125:13700–13713. [PubMed: 14599209]
49. Champagne MH, Mullins MW, Colson AO, Sevilla MD. Electron Spin Resonance Evidence for intra- and intermolecular $\sigma\sigma^*$ Bonding in Methionine Radicals: Relative Stabilities of S-Cl, S-Br, S-N, and S-S Three-Electron Bonds. *J. Phys. Chem.* 1991; 95:6487–6493.
50. Monney NPA, Bally T, Bhagavathy GS, Glass RS. Spectroscopic Evidence for a New Type of Bonding between a Thioether Radical Cation and a Phenyl Group. *Org. Lett.* 2013; 15:4932–4935. [PubMed: 24059648]
51. Frisch, MJ.; Trucks, GW.; Schlegel, HB., et al. Gaussian 09, revision D.01. Wallingford, CT: Gaussian, Inc.; 2013.
52. Zhao Y, Truhlar DG. Exploring the Limit of Accuracy of the Global Hybrid Meta Density Functional for Main-Group Thermochemistry, Kinetics, and Noncovalent Interactions. *J. Chem. Theory Comput.* 2008; 4:1849–1868.
53. Zhao Y, Truhlar DG. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* 2008; 120:215–241.
54. Frisch MJ, Pople JA, Binkley JS. Self-Consistent Molecular Orbital Methods 25. Supplementary Functions for Gaussian Basis Sets. *J. Chem. Phys.* 1984; 80:3265–3269.
55. Clark T, Chandrasekhar J, Spitznagel GW, Schleyer PV. Efficient Diffuse Function-Augmented Basis Sets for Anion Calculations. III. The 3-21+G Basis Set for First-Row Elements, Li-F. *J. Comput. Chem.* 1983; 4:294–301.
56. McLean AD, Chandler GS. Contracted Gaussian Basis Sets for Molecular Calculations. I. Second Row Atoms, Z=11–18. *J. Chem. Phys.* 1980; 72:5639–5648.
57. Krishnan R, Binkley JS, Seeger R, Pople JA. Self-Consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* 1980; 72:650–654.
58. van Duijneveldt FB, van Duijneveldt-van de Rijdt JGCM, van Lenthe JH. State of the Art in Counterpoise Theory. *Chem. Rev.* 1994; 94:1873–1885.
59. Boys SF, Bernardi F. The Calculation of Small Molecular Interactions by the Differences of Separate Total Energies. Some Procedures with Reduced Errors. *Mol. Phys.* 1970; 19:553–566.
60. Kendall RA, Dunning TH, Harrison RJ. Electron Affinities of the First-Row Atoms Revisited. Systematic Basis Sets and Wave Functions. *J. Chem. Phys.* 1992; 96:6796–6806.
61. Cossi M, Rega N, Scalmani G, Barone V. Energies, Structures, and Electronic Properties of Molecules in Solution with the C-PCM Solvation Model. *J. Comput. Chem.* 2003; 24:669–681. [PubMed: 12666158]
62. Barone V, Cossi M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *J. Phys. Chem. A.* 1998; 102:1995–2001.
63. Casida ME, Jamorski C, Casida KC, Salahub DR. Molecular Excitation Energies to High-Lying Bound States from Time-Dependent Density-Functional Response Theory: Characterization and Correction of the Time-Dependent Local Density Approximation Ionization Threshold. *J. Chem. Phys.* 1998; 108:4439–4449.
64. Gorelsky, SI. SWizard program. Ottawa, Canada: University of Ottawa; 2013. <http://www.sg-chem.net/>.

65. Gorelsky SI, Lever ABP. Electronic structure and spectra of ruthenium diimine complexes by density functional theory and INDO/S. Comparison of the two methods. *J. Organomet. Chem.* 2001; 635:187–196.
66. Song L, Gao J. On the Construction of Diabatic and Adiabatic Potential Energy Surfaces Based on Ab Initio Valence Bond Theory. *J. Phys. Chem. A.* 2008; 112:12925–12935. [PubMed: 18828577]
67. Song L, Mo Y, Gao J. An Effective Hamiltonian Molecular Orbital-Valence Bond (MOVB) Approach for Chemical Reactions as Applied to the Nucleophilic Substitution Reaction of Hydrosulfide Ion and Chloromethane. *J. Chem. Theory Comput.* 2009; 5:174–185. [PubMed: 20047006]
68. Cembran A, Song L, Mo Y, Gao J. Block-Localized Density Functional Theory (BLDFT), Diabatic Coupling, and Their Use in Valence Bond Theory for Representing Reactive Potential Energy Surfaces. *J. Chem. Theory Comput.* 2009; 5:2702–2716. [PubMed: 20228960]
69. Chung WJ, Ammam M, Gruhn NE, Nichol GS, Singh WP, Wilson GS, Glass RS. Interactions of Arenes and Thioethers Resulting in Facilitated Oxidation. *Org. Lett.* 2009; 11:397–400. [PubMed: 19102660]
70. Monney NP-A, Bally T, Giese B. Proline as a charge stabilizing amino acid in peptide radical cations. *J. Phys. Org. Chem.* 2015
71. Hendon C, Carbery DR, Walsh A. Three-Electron Two-Centred Bonds and the Stabilisation of Cationic Sulfur Radicals. *J. Phys. Org. Chem.* 2014; 5:1390–1395.

Figure 1. Structure of $M:F:M$ with the corresponding singly occupied molecular orbitals (SOMO), highest doubly occupied molecular orbitals (HDMO), and second highest doubly occupied molecular (HDMO-1).

Figure 2. Sketch map of the MOs of three fragments that linearly combine to new MOs resulting in the formation of $\text{S}:\text{II}:\cdot\text{S} \leftrightarrow \text{S}:\cdot\text{II}:\text{S}$ five-electron binding.

Figure 3. Maximal absorption spectrum (λ_{max}) and the corresponding oscillator strengths (f) of M:F:M system.

Figure 4.
Structure of Met:Phe...Met with the corresponding SOMO, HDMO, and HDMO-8.

Figure 5.
Structure and the corresponding SOMO, HOMO, and HOMO-4 of M:Phe...M.

simple models

one-chain models

three-chain models

Scheme 1.

Schematic Representation of Simple Models, One-Chain Models, and Three-Chain Models for All the Considered $S:\Pi::S \leftrightarrow S:\Pi::S$ Bonded Radical Cations

Shortest Distances between Aromatic Ring and Two Neighboring S-Atoms ($d_{\min}$, Å), Difference between Two Distances ($d_{\min}$, Å), Binding Energies (BEs), Vertical Ionization Energies (IE_v , eV), and Decreasing Values of IE_v (IE_v , eV) for All the Structures

Table 1

	C:F:M	C:H:M	C:Y:C	C:W:C	M:F:M	M:H:M	M:Y:M	M:W:M
$d_{\min}$ (Å)	2.97/2.95	2.99/2.99	3.35/3.33	3.22/3.28	2.98/2.98	3.11/2.90	2.99/2.99	3.25/3.15
$d_{\min}$ (Å)	0.02	0	0.02	0.06	0	0.21	0	0.1
BE (kcal/mol)	8.49	10.66	8.23	8.42	10.38	10.98	9.69	9.56
IE_v (eV)	7.21	7.02	7.24	6.78	7.00	6.73	6.84	6.43
IE_v (eV)	1.43	1.09	0.66	0.57	1.64	1.38	1.06	0.92
	C:F:M	C:H:M	C:Y:M	C:W:M	C:Tyr:C	M:Phe:M	M:His:M	M:Tyr:M
$d_{\min}$ (Å)	3.40/2.67	3.28/2.72	3.35/2.85	3.35/2.97	3.26/3.07	3.27/2.85	2.65/3.28	3.18/2.80
$d_{\min}$ (Å)	0.73	0.56	0.5	0.38	0.19	0.42	0.63	0.38
BE(kcal/mol)	5.99	7.68	6.67	7.82	8.54	9.54	9.20	8.49
IE_v (eV)	6.90	6.60	6.91	6.48	6.97	6.77	6.37	6.47
IE_v (eV)	1.74	1.51	0.99	0.87	0.85	1.28	1.69	1.35
	M:Trp:M	Cys:H:Cys	Cys:Y:Cys	Cys:His:Cys	Cys:Tyr:Cys	Met:Phe:Met	Met:His:Met	Met:Tyr:Met
$d_{\min}$ (Å)	3.02/3.17	3.00/3.25	3.26/3.21	2.78/3.41	3.20/3.46	3.23/2.96	2.74/3.42	2.83/3.26
$d_{\min}$ (Å)	0.15	0.25	0.05	0.63	0.26	0.27	0.68	0.43
BE (kcal/mol)	13.25	21.86	15.54					
IE_v (eV)	6.20	6.44	6.76	6.79	7.18	7.05	7.00	6.75
IE_v (eV)	0.68	1.67	1.14	1.27	0.64	1.00	1.06	1.07

Table 2

Vertical Ionization Energies (IE_v 's) for the Four Different States of $M:F^+M$ by Carrying Out Constrained DFT Calculations with Block Localized Kohn–Sham (BLKS) Orbitals at the B3LYP/6-31+G(d) Level of Theory

	M-F⁺-M	M⁺-FM	MF⁺-M	MF⁺M
IE_v (eV)	8.19	7.96	7.04	6.40