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Two Aromatic Rings Coupled a Sulfur-Containing Group to Favor Protein Electron Transfer by Instantaneous Formations of $\pi\cdots S:\pi \leftrightarrow \pi:S\cdots\pi$ or $\pi\cdots\pi:S \leftrightarrow \pi:\pi\cdots S$ Five-Electron Bindings

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Abstract

The cooperative interactions among two aromatic rings with a S-containing group are described, which may participate in electron hole transport in proteins. Ab initio calculations reveal the possibility for the formations of the $\pi\cdots S:\pi \leftrightarrow \pi:S\cdots\pi$ and $\pi\cdots\pi:S \leftrightarrow \pi:\pi\cdots S$ five-electron bindings in the corresponding microsurrounding structures in proteins, both facilitating electron hole transport as efficient relay stations. The relay functionality of these two special structures comes from their low local ionization energies and proper binding energies, which varies with the different aromatic amino acids, S-containing residues, and the arrangements of the same aromatic rings according to the local microsurroundings in proteins.

INTRODUCTION

The transfer of an electron hole takes place in many biological processes^{1–9} and the anode regions of currently concerned biofuel cell.¹⁰ Therefore, how proteins efficiently transmit an electron hole to fulfill the fundamental biological movements has been widely investigated in the past few decades.^{11–18} The combination of hopping and superexchange mechanisms is

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Supporting Information The complete citation for ref 48 as well as the calculated molecular geometries, orbital characters, vertical ionization energies (IE_vs), binding energies (BEs), and ultraviolet spectra for all $\pi\cdots S:\pi \leftrightarrow \pi:S\cdots\pi$ or $\pi\cdots\pi:S \leftrightarrow \pi:\pi\cdots S$ bonding complexes and correlations among several quantities. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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employed to interpret long-range electron hole transport in proteins.^{19–23} Most long-range electron transports may be described by multistep electron-hopping processes with several electron stepping stones lying between the donors and acceptors.^{21,24–26} The stepping stones play a vital role in promoting electron transfer by transiently carrying charges. The electron is transferred between two shortest neighboring stepping stones via the superexchange mechanisms. Therefore, it is of great significance to explore the possible forms of stepping stones during the electron hole transport processes in proteins.

The basic feature of the stepping stones for hole transfer is low ionization potentials, which can capture and carry electron holes transiently. It is well-known that the ionization potential of tryptophan (Trp) residue is the lowest among the 20 natural amine acids. Therefore, it has been reported that the side chains of Trp residues can speed up electron transfer rate as relay intermediates of long-range electron transfer processes in many enzymes, including azurin,²⁵ ribonucleotide reductase,^{1,27} DNA photolyases,²⁸ Myoglobins,²⁹ MauG,³⁰ and so on. One notable case is that three Trp residues can form an electron transfer “wire” to facilitate electron hop in DNA photolyases.²⁸ Shih et al. found that the reduction potential of the intermediated Trp residue is 28 mV lower than that of the second valence rhenium (Re^{2+} complex), and the intervening Trp residue can facilitate electron transfer in a mutant *Pseudomonas aeruginosa* azurin.²⁵ Recently, Consani et al. discovered that the excited Tryptophan releases an electron to heme in myoglobins through ultraviolet two-dimensional spectroscopy.²⁹ In addition, it has been proposed that the side chains of tyrosine (Tyr) and cysteine (Cys) residues can also act as the relay stones of electron transfer in proteins. The driving forces come from the loss of the active protons (the protons link to the ring oxygen of Tyr and the sulfur of Cys) in the appropriate protein environments, which lowers the reduction potentials of these two residues. A remarkable example is the long-distance electron transfer process in the class I ribonucleotide reductase (RNR) involving four Tyr residues (Tyr122, Tyr365, Tyr731, and Tyr730) and a Cys residue (Cys439).^{1,8,31–33} Additionally, the Giese group examined electron transfer along a series of polypeptides and demonstrated that the existence of central aromatic amino acids can serve as “stepping stones” to support the electron hopping mechanism.^{26,34,35}

In addition, the interactions of electron-rich neighboring groups can lower the localized reduction potentials, which also act as the relay stations to participate in electron hole transfer in proteins. It has been proposed that the two neighboring atoms with lone-pair orbitals may transiently form two-center three-electron bonds, including $\text{O} \cdot \text{O}$, $\text{O} \cdot \text{N}$, $\text{N} \cdot \text{N}$, $\text{S} \cdot \text{O}$, $\text{S} \cdot \text{S}$,^{36–39} and so on, to take part in long-distance electron transfer.⁴⁰ Likewise, the interactions of sulfur-containing (S-containing) groups with aromatic side chains can speed up the electron transfer rate by formations of $\text{S} \cdot \pi$ multicenter three-electron bonds.^{41–43} A similar result was validated by Class et al. that an aromatic ring approximately close to a S-containing group can facilitate the oxidation of a compound.^{44,45} In addition, $\pi-\pi$ interactions between two stacking aromatic rings can reduce the local ionization potential and readily capture an electron hole by the transient formations of $\pi \cdot \pi$ three-electron bonds to promote electron transport in proteins.^{46,47} These examples indicate that the relay stones may be formed between two electron-rich groups that are close during the electron transfer processes in proteins, implying the diversity of the relay stones. This diversity increases the

difficulty to explore accurate pathways of electron transfer in proteins. Therefore, great efforts should be made to investigate the possible relay stones in proteins.

Recently, Sachs and co-workers found that about 33% of all known protein structures contain Met S-aromatic structures, and the aromatic types change in different protein surroundings.⁴⁸ Similarly, we have also examined many protein structures and found that a S-containing group may synchronously interact with two aromatic rings. In the present work, we focus on elaborating two special types of relay stones for the protein electron hole transfer on the basis of a detailed examination of a series of protein crystal structures. In the first class, the structural element consists of π -S- π three-body five-electron (TB5E) binding (abbr. $\pi:S:\pi \leftrightarrow \pi:S:\pi$; S denotes S-containing fragment, including the side chains of methionine (Met) and Cys residues, and π indicates the side chains of aromatic residues, including phenylalanine (Phe), histidine (His), Tyr and Trp residues. “:” and “ $\leftrightarrow$ ” mark a three-electron bond and two-electron bond, respectively). The second structure type contains π - π -S TB5E binding, abbreviated as $\pi:\pi:S \leftrightarrow \pi:\pi:S$. The resonance of the TB5E Lewis structures can efficiently reduce the local ionization energies and promote the entry of an electron hole. Furthermore, the binding energies of these two types of relay stones are moderate, which means that the close three-body complexes can be destroyed (or separated) by the self-movements of proteins, facilitating the relay of electron hole in proteins. It is of fundamental importance to understand the mechanism by which proteins regulate the favorable structures to construct the efficient electron transfer pathway.^{12,15,21}

COMPUTATIONAL METHODS

A number of high-resolution protein structures have been examined to reveal that there are two interesting three-body structures: two aromatic rings with an inserting S-containing group (π -S- π) and two parallel aromatic rings with a side S-containing group (π - π -S). In this work, therefore, we mainly examine the electron relay function of π -S- π and π - π -S interacting structures. The π -S- π and π - π -S interactions are produced from different peptide chains or from the same peptide chain as cation radicals. To well address this issue, we included π -S- π and π - π -S cation interactions ranging from the simple to complex models. The interactions are divided into three classes: simple models, one-chain models, and two-chain models. The simple models only include the side chains of two aromatic residues and a S-containing residue named IISII and IIIS (“II” denotes F, H, Y, and W for the side chains of Phe, His, Tyr and Trp, respectively, ‘S’ represents C and M for the side chains of Cys and Met, respectively), as shown in Scheme 1. In a two-chain model, two aromatic rings link to a peptide chain, the third only remains an S-containing side chain, and the corresponding interaction structures are named XxxXxx-S (“Xxx” denotes Phe, His, Tyr, and Trp, and ‘S’ is C and M for the only side chains of Cys and Met, Scheme 1). The one-chain models represent that the three side chains on the same peptide chain, which are named XxxSxxXxx (“Xxx” denotes Phe, His, Tyr, and Trp, and “Sxx” denotes Cys and Met).

All gas-phase calculations are carried out by using the Gaussian 09⁴⁹ suite of programs. The UB3LYP^{50,51} hybrid functional in conjunction with the 6-31+G(d,p) basis set⁵²⁻⁵⁵ is utilized to optimize all geometries fully and to perform harmonic vibrational analyses for confirming minima (all real frequencies). For all the $\pi:S:\pi \leftrightarrow \pi:S:\pi$ and $\pi:\pi:S \leftrightarrow \pi:\pi:S$

bonding complexes considered, B3LYP shows essentially no dependence on a change in the size and flexibility of the basis set. It is known that the B3LYP method does not include dispersion interaction and that it overestimates the delocalization of the electron hole due to self-interaction error.^{56,57} Therefore, to further verify the applicability of the B3LYP/6-31+G(d,p) method, the M062X⁵⁸/6-31+G(d,p) method is also carried out to examine all the models. The results indicate that binding energies for all the models obtained by the B3LYP method are smaller than those obtained by the M062X method and most of the correspondingly neutral π -S- π and π - π -S interacted structures can not be found using the B3LYP method, while they can be located using the M062X method. However, the distribution of electron hole for all the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S bonding complexes is in excellent agreement between the two methods. In addition, several structures of π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S bonding complexes are examined at the MP2/6-31+G(d,p) level of theory, which confirms that the B3LYP/6-31+G(d,p) method is suitable to explore the relay properties of the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S structures. Our main task, in this work, is to explore the relative relay abilities of the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S bonding complexes in proteins, but not the absolute structures of them. Although the B3LYP/6-31+G(d,p) value deviates from the value obtained at the CCSD(T)/cc-PVTZ,⁵⁹ the method still reveals the same changing orders in binding energies and ionization energies and is appropriate to investigate the relay abilities of the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S bonding complexes. Therefore, the B3LYP method is mainly used to analyze the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S binding radical cations in the present analyses.

In an effort to explore the electron relay functionalities of the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S in proteins, the interactions of two π -systems with a sandwiched or side S-containing group need to be detected with proper parameters including ionization energy (IE), binding energy (BE), ultraviolet (UV) spectrum, and so on. The adiabatic IE (IE_a) is the difference in energy between a π :S: $\pi \leftrightarrow \pi$:S: π (or π : π :S: $\leftrightarrow \pi$: π :S) bonding 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 a π :S: $\pi \leftrightarrow \pi$:S: π (or π : π :S: $\leftrightarrow \pi$: π :S) bonding complex (cation) and its corresponding closed-shell complex without change in structure (the latter has one more electron than the former). The BEs for the π :S: $\pi \leftrightarrow \pi$:S: π and π : π :S: $\leftrightarrow \pi$: π :S bonding complexes are calculated by subtracting basis set superposition errors (BSSEs) by means of the counterpoise approach.^{60,61} For a π :S: $\pi \leftrightarrow \pi$:S: π bonding complex, the BE is the energy difference between the optimized three-body complex and the sum of a aromatic side chain and remaining S- π two-body complex, using the structures in the corresponding π :S: $\pi \leftrightarrow \pi$:S: π binding complex. There are usually two different BEs for a π :S: $\pi \leftrightarrow \pi$:S: π bonding complex, and only the smaller (more negative) value is used in this paper. Similar calculations are carried out to obtain the BEs of the π : π :S: $\leftrightarrow \pi$: π :S bonding complexes. Time-dependent density functional theory (TDDFT)⁶² calculations are performed to determine the excitation energy for transferring an electron from a doubly occupied bonding orbital to the singly occupied antibonding orbital (σ/σ^*) for the π :S: $\pi \leftrightarrow \pi$:S: π or π : π :S: $\leftrightarrow \pi$: π :S complexes. All these properties are obtained by carrying out single-point calculations at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p)⁶³ and M06-2X/6-311+

+G(d,p)//M06-2X/6-31+G(d,p) levels. Other data including the shortest distances, BEs, EA_vs, EA_as, orbital characteristics, and correlations among several quantities for all structures are listed in the Supporting Information.

To further elucidate the origin that the interaction between two aromatic rings and one S-containing group can reduce the IE of system, the FMF complex is investigated using multistate density functional theory (MSDFT).^{64–66} Using block localized Kohn–Sham (BLKS) orbitals, MSDFT can be used to define the electron hole specific fragment or two fragments in the FMF system. In MSDFT analysis, the optimized cation structure is used along with the B3LYP density functionals. According to the different positions of hole in the FMF system, the (FMF)⁺ system is divided into four states, and the corresponding diabatic BLKS functions are defined as

$$\Psi_{F^2+}^{\text{KLBS}} = \hat{A} \left\{ \Omega_+^1 (F^+) \Omega_0^2 (MF) \right\} \quad (1)$$

$$\Psi_{M^1+}^{\text{KLBS}} = \hat{A} \left\{ \Omega_0^1 (F) \Omega_+^1 (M^+) \Omega_0^1 (F) \right\} \quad (2)$$

$$\Psi_{FM^2+}^{\text{KLBS}} = \hat{A} \left\{ \Omega_+^2 (FM^+) \Omega_0^1 (F) \right\} \quad (3)$$

$$\Psi_{FMF^3+}^{\text{KLBS}} = \hat{A} \left\{ \Omega_+^3 (FMF^+) \right\} \quad (4)$$

where F⁺ (or M⁺) indicates the hole position an F (or M) fragment, FM⁺ and FMF⁺ represent that the hole is delocalized over two neighboring fragments and all three fragments, respectively, and the notation MF specifies that the neighboring M and F are treated as a single fragment. 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

We have recently proposed that the close proximity of a S-containing and an aromatic residue in proteins can form special multicenter, three-electron bonds (S:·π) to facilitate hole migration.⁴² Combined with our recent study on the relay function of π:·π three-electron bonds⁴⁷ in proteins, we speculate that the interactions of two neighboring aromatic rings and an S-containing side chain (middle or side) may produce two special types of relay structures to participate in hole migration in proteins. We have confirmed this speculation through ab initio calculations.

π:S:π↔π:S:π Five-Electron Bindings

This type of three-body structure can be formed between two parallel aromatic rings of two amino acids associated with an inserting S-containing group (the side chain of Met or Cys). Figure 1 shows a typical example (FMF) of these three-body structures with the

corresponding frontier orbitals. The shortest distances between the S atom of dimethylsulfide (CH_3SCH_3) and the two aromatic rings (two toluene) are 3.20 Å and 3.16 Å at the B3LYP/6-31+G(d,p) level, respectively, which are shorter than the usual van der Waals separation of ~3.4 Å.⁶⁷ These short distances indicate that the S atom strongly interacts with the two aromatic rings. With the inclusion of dispersion energies, the shortest distances at the MP2/6-31+G(d,p) level are 3.07 Å and 3.04 Å for the two types of complexes, respectively, which are shorter than the results of the B3LYP/6-31+G(d,p) optimization. Therefore, the MP2 method also supports the presence of strong interactions among the three groups, and the decrease in the distances indicates that the interaction energies at the MP2 method are larger than those from the B3LYP method. The following molecular orbital analysis also confirms this conclusion. The SOMO of FMF is delocalized over the three fragments and is of antibonding character, indicating that the electron hole delocalizes over the three fragments. Furthermore, both HDMO and HDMO-3 also are delocalized over the three fragments, as shown in Figure 1. Therefore, the interaction of SOMO, HDMO and HDMO-3 produces a special TB5E binding ($\pi^*:\text{S}:\pi \leftrightarrow \pi:\text{S}:\pi^*$). More importantly, the formation of this $\pi^*:\text{S}:\pi \leftrightarrow \pi:\text{S}:\pi^*$ binding results in a lowering in IE in this local region. The predicted value of IE_v for FMF is only 6.84 eV, which is significantly smaller than that of any monomer of the two functional groups (8.48 eV for toluene and 8.59 eV for dimethylsulfide) and also lower than the corresponding F:F (7.68 eV)⁴⁷ and S:F (ca. 7.15 eV)⁴² dimers. In addition, the BE for this TB5E structure is 8.1 kcal/mol, which moderately favors the formation of the $\pi^*:\text{S}:\pi \leftrightarrow \pi:\text{S}:\pi^*$ binding structure and facilitates hole transport through this local complex. The separation of this three-body five-electron structure promotes the hole to continue transport. Orbital interactions favoring the formation of the $\pi^*:\text{S}:\pi \leftrightarrow \pi:\text{S}:\pi^*$ binding is shown in Figure 2. When a hole moves through a three-body region, their highest occupied molecular orbitals (HOMOs) (three isolated monomers have three HOMOs) may interact with each other to generate three new molecular orbitals (MOs) delocalized over the three fragments. Two of them bond (1σ and 2σ) below the lowest HOMO among the three monomers in energy and are occupied by two electrons. The third is an antibonding orbital (σ^*) with an electron with an energy above the highest HOMO among three monomers in energy. The delocalization of these three new MOs help facilitate hole migration as a special relay station in proteins.

To further characterize hole delocalization, BLKS calculations were carried out for the four states of FMF at the B3LYP/6-31+G(d) level of theory. It is interesting to notice that the computed IE_v s decrease with increase in the area occupied by the hole, as shown in Table 1. The IE_v is the largest for the case of the hole residing in a single fragment. The IE_v s of F^+-MF and $\text{F}-\text{M}^+-\text{F}$ are 8.30 and 7.70 eV, respectively (Table 2). When the hole is delocalized over two neighboring fragments, the IE_v is reduced (The IE_v of FM^+-F is 7.13 eV). When the hole delocalizes over the three fragments, the IE_v is the lowest. The IE_v of FMF^+ is only 6.75 eV. These results further conform that the resonance delocalization of three electron-rich fragments can effectively reduce the IE of the whole system. The computed resonance energy from the dimer-localized cation radical to the delocalized trimer species is 0.38 eV, and the electronic coupling between FM^+-F and $\text{F}-\text{FM}^+$ is 30.47 meV.

The B3LYP/6-31+G(d,p) calculations located seven simple structures for the $\pi^*:\text{S}:\pi \leftrightarrow \pi:\text{S}:\pi^*$ bindings, including FCF, FMF, FMH, FCY, FMY, YCY and WMW (the

details are in the Supporting Information). As illustrated above, analogous analysis can be made for the other six $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures. The IE_{v} s of all the $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures are in the range of 6.42–7.02 eV, and the corresponding BEs change from 5.8 to 10.9 kcal/mol.

The TD-DFT calculations confirmed the formations of the $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ bindings. There are two distinct absorption peaks to reflect electron transitions from the two doubly occupied MOs to the SOMO [$(1\sigma)^2 \rightarrow (\sigma^*)^1$ and $(2\sigma)^2 \rightarrow (\sigma^*)^1$]. The maximal absorption spectrum (λ_{max}) of FmF is 1061.5 nm with a high oscillator strength ($f = 0.2576$), which arises from the electron transition from HDMO [$(2\sigma)^2$] to SOMO [$(\sigma^*)^1$]. Additionally, the absorption peak at 687.6 nm with a low oscillator strength (0.0243) represents electron transition from HDMO-3 [$(1\sigma)^2$] to SOMO [$(\sigma^*)^1$]. In addition, the TD-DFT calculations reveal that the electron transition energies of this kind of $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ binding change with the different aromatic rings and lone pair groups as well as the distances separating the three fragments. Figure 3 compiles the absorption spectra of seven $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures, including FCF, FMF, FMH, FCY, FMY, YCY, and WMW. It should be noted that the λ_{max} values of these seven complexes change from 1031.0 to 2171.5 nm, and the corresponding increasing order is FCF (1031.0 nm) < FMF (1061.5 nm) < FMH (1089.1 nm) < FCY (1418.5 nm) < FMY (1426.2 nm) < YCY (1972.2 nm) < WMW (2171.5 nm), as listed in Table S7. As mentioned above, the λ_{max} values reflect electron transition from $(2\sigma)^2$ to $(\sigma^*)^1$. The change in maximal absorption spectra indicates the diversity of the $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures in proteins. A careful analysis reveals that three factors play critical roles in the change in red shift from FCF to WMW. The most important factor is the sizes of the two aromatic rings in the $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures. Greater aromatic rings can provide a more delocalized electron hole, causing a red shift of the λ_{max} values. The total area of two aromatic rings increases in order of FMH < FCF = FMF < FCY = FMY < YCY < WMW, in good accord with the changing order of the λ_{max} . The second is the distance of the two aromatic rings in the $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures. A longer distance between two aromatic rings can induce a red shift in the λ_{max} . The shortest distances between the two rings of the seven $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures are in the increasing order of FCF (6.31 Å) < FMF (6.36 Å) < FMH (6.37 Å) < FMY (6.56 Å) < FCY (6.60 Å) < YCY (6.98 Å) < WMW (7.11 Å), consistent with the red-shift order. The third is the relative orientation of the two aromatic rings. A parallel structure can cause a blue shift in λ_{max} , and, conversely, a twisting structure may result in a red shift. As mentioned above, FMH and FMY are the two special cases. Although the aromatic area of FMH is the smallest among the seven $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures, the λ_{max} is not the smallest. Similarly, the shortest distance (6.56 Å) of FMY is smaller than that (6.60 Å) of FCY. However, the λ_{max} (1426.2 nm) of FMY is larger than that (1418.5 nm) of FCY. In both cases, the two aromatic rings in FMH and FMY are contorted. Therefore, these three main factors make the λ_{max} values increase from FCF to WMW. A similar analysis can be made for the changing tendency in the $(1\sigma)^2 \rightarrow (\sigma^*)^1$ electron transitions of the seven $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ structures.

There is no experimental information about the structures and the corresponding spectra of the $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ complex. Therefore, we cannot compare the computed absorption spectra with the corresponding experimental results. However, the absorption spectra of the analogously weak interaction structures, such as $\text{S} \cdot \pi$, $\text{S} \cdot \text{S}$, $\text{S} \cdot \text{N}$, and $\text{S} \cdot \text{O}$ three-electron

bonds, have been intensively examined by theoretical and experimental methods in the past 30 years. Our previous work⁴² predicted that the $\lambda_{\max}$ of the $S:\pi$ bindings formed between an S-containing group and the aromatic side chain of Phe are in the range of 580–675 nm, roughly consistent with the experimental value of Monney et al. (550 nm).⁴⁵ In addition, our group also showed that the values of absorption spectra for the $S:\pi$ three-electron bonds are mainly in the range of 370–416 nm, which are in agreement with the experimental values of 385 nm⁶⁸ and 390 nm.³⁸ All these indicate that TD-DFT calculations can reliably predict the spectra information for the $\pi:S:\pi\leftrightarrow\pi:S:\pi$ weak interactions. At least TD-DFT calculations can yield the correct trends in energy changes. For example, the experimental values of $S:\pi$, $S:\pi$, $S:\pi$, and $S:\pi$ three-electron bonds are 385 nm, 400 nm, 475 nm,⁶⁸ and 550 nm,⁴⁵ respectively, which increase with the inter-fragment distance. This trend is consistent with the change in the computed $\lambda_{\max}$ with increased size of the two aromatic rings in the $\pi:S:\pi\leftrightarrow\pi:S:\pi$ structures.

Furthermore, our calculations revealed that the $\pi:S:\pi\leftrightarrow\pi:S:\pi$ resonance structures can also be formed on the same peptide chain (one-chain models), as shown in Figure 4 and the Supporting Information. It should be noted that the presence of peptide chains can reduce the stabilizations of the three-part $\pi:S:\pi\leftrightarrow\pi:S:\pi$ binding structures. For the case of PheCysPhe, the shortest distances between the middle S atom of Cys and the aromatic rings of two Phe are 3.38 and 3.54 Å, respectively, which are larger than those in the corresponding monomer models (3.15 and 3.16 Å in FCF). The longer distances among the three side chains imply that the binding strength of the $\pi:S:\pi\leftrightarrow\pi:S:\pi$ configuration becomes weaker. The distributions and interactions of the corresponding frontier MOs also support the formation of the $\pi:S:\pi\leftrightarrow\pi:S:\pi$ binding. As shown in Figure 4, SOMO, HDMO, and HDMO-3 not only mainly reside in the three side chains but also partially delocalize over the peptide chain. The latter diminishes the binding strength of $\pi:S:\pi\leftrightarrow\pi:S:\pi$ resonance. However, the formation of $\pi:S:\pi\leftrightarrow\pi:S:\pi$ binding can decrease the IP_v of the Phe-Cys-Phe region. The calculated value of IP_v of PheCysPhe is 7.42 eV, which is lower than the IP_v of any monomer (7.71 eV for Cys and 8.92 eV for Phe). Similar analyses can be made for the other one-chain models. It should be clarified that the $\pi:S:\pi\leftrightarrow\pi:S:\pi$ bindings can not be formed among all the cases of three neighbor residues residing in the same main chains because of steric hindrances. A representative example is the case of a middle Met interaction with two neighboring Phe, as shown in Figure 5. The S atom of Met is easily close to one side aromatic ring and produces an $S:\pi$ three-electron bond.⁴² If the middle S-containing group moves to the other aromatic ring, a new $S:\pi$ three-electron bond is formed. Therefore, it is clear that the switching of the middle S-containing side chain between the two aromatic rings can facilitate the electron hole transfer from one aromatic ring to the other aromatic ring in the PheMetPhe case.

$\pi:\pi:S\leftrightarrow\pi:S$ Five-Electron Bindings

In this section, we mainly examine the relay function of an S-containing side chain attaching to two nearly parallel aromatic rings from one side in proteins. A representative example is the side chain of Cys interaction with two side chains of Phe at the one-electron oxidation state, named FFC, as shown in Figure 6. The plot of SOMO indicates that the electron hole entirely delocalizes over the three fragments with an antibonding feature. In addition, two

doubly occupied MOs, HDMO and HDMO-2, are also distributed over the three residues. However, the plot of HDMO displays a bonding link between the two aromatic rings, and the plot of HDMO-2 shows the bonding characteristic to connect the three parts. Then, the combination of SOMO, HDMO, and HDMO-2 generates a special π - π -S five-electron binding ($\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$). The orbital interaction diagram for a $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ resonance is shown in Figure 2B. When the neighboring three electron-rich fragments, two nearly parallel aromatic rings and a S-containing group, approach each other during the hole transfer processes in proteins, the system readily releases an electron, and the three highest occupied MOs of three fragments are hybridized to produce three new MOs (SOMO and two doubly occupied MOs). The association of the antibonding SOMO and the two bonding HDMOs creates the special $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ resonance to connect the three parts as a whole. The shortest distances between the two neighboring parts in FFC are 3.31 and 3.28 Å, and the corresponding binding energy is 7.0 kcal/mol. More importantly, the IE_v of FFC is 7.29 eV, which is significantly lower than the IE_v of any of the monomers (8.80 eV for toluene and 9.45 eV for methanethiol). These results indicate that the interactions among the two parallel aromatic side chains of Phes and the side chain of Cys may capture a hole to facilitate electron transport in proteins by the formation of the $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ binding. Similar analyses can be made for the other IIIS systems, including FFM, FYM, FWM, HFC, YFC, and YFM (the details are in the Supporting Information). The IE_{vs} of these IIIS systems are in the range of 6.39–7.29 eV, which are all lower than these of the corresponding monomers and are compared with the IE_v of the side chain of Trp (7.15 eV), an effective relay station in proteins.

To gain additional insights, the electron transition spectra of these $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ bindings are obtained by carrying out TDB3LYP calculations. Again, there are two characteristic absorption peaks for a special $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ binding, as displayed in Figure 7. One absorption peak comes from the electron transition from HDMO [$(2\sigma)^2$] to SOMO [$(\sigma^*)^1$] with a strong oscillator strength. The other peak is generated from the electron transition from HDMO- n [$n = 1$ or 2 , $(1\sigma)^2$] to SOMO [$(\sigma^*)^1$] with a weak oscillator strength. However, the two characteristic absorption peaks are changed with the different aromatic rings and S-containing group in the π - π -S complexes. Figure 7 displays the absorption spectra of six $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ structures, including FFC, FFM, FYM, HFC, YFC, and YFM. The λ_{max} values of the strong absorption peaks for the six complexes are in the range of 1395.7–2158.8 nm and the corresponding increasing order is HFC (1395.7 nm) < FFC (1443.5 nm) < FFM (1674.6 nm) < YFC (1887.2 nm) < FYM (1949.5 nm) < YFM (2158.8 nm). The red shift from HFC to YFM may be attributed to three main factors. The most important factor is the size of the two aromatic rings in the $\pi \cdot \pi : S \leftrightarrow \pi : \pi \cdot S$ structures. Larger aromatic rings can provide more distribution space for the electron hole, causing increases of the λ_{max} values, similar to the above $\pi S \pi$ systems. The total area of two aromatic rings increases in order of HFC < FFC = FFM < YFC = FYM = YFM, which follows the increasing order of the λ_{max} . The second is the effect of the different S-containing groups. It is clear that the λ_{max} of FFM is larger than that of FFC, as well as the YFC and YFM pair. This can be attributed to the fact that the electron-donating ability of M is stronger than that of C, causing HDMO-2 (1σ) to mainly reside in the M and the close aromatic ring (Figure 6). This distribution lowers the energy of 1σ and pushes 2σ to be

higher in energy. Therefore, the gap between (2σ) and (σ^*) is reduced and the gap between (1σ) and (σ^*) is raised when C is replaced by M for the same two-aromatic rings in the $\pi:\pi:S \leftrightarrow \pi:\pi:S$ structures. Therefore, for FFM, the transition energy from (2σ) to (σ^*) is red-shifted, and the transition energy from (1σ) to (σ^*) is blue-shifted with respect to FFC. The third is the influence of the relative position of two aromatic rings in the $\pi:\pi:S \leftrightarrow \pi:\pi:S$ structures. For example, the $\lambda_{\max}$ of FYM (1949.5 nm) is lower than that of YFM (2158.8 nm). This is because the electron affinity of F is larger than that of Y. For all the $\pi\pi S$ systems, the plots of HDMOs mainly distribute over the two end parts. Therefore, HDMO of FYM is lower than that of YFM in energy, which causes the blue-shift of electron transition from HDMO to SOMO for FYM with respect to YFM. In summary, these three main factors make the $\lambda_{\max}$ values increase from HFC to YFM.

Similar to the $\pi S \pi$ systems, the presence of peptide chains also supports the formations of $\pi:\pi:S \leftrightarrow \pi:\pi:S$ resonance bindings. The details can be found in Supporting Information.

CONCLUSION

The present work provides a systematic analysis of the formations of the $\pi:S:\pi \leftrightarrow \pi:S:\pi$ and $\pi:\pi:S \leftrightarrow \pi:\pi:S$ resonance bindings in proteins by carrying out electronic structure calculations. The results indicate that the cooperative interactions of the three electron-rich groups in close proximity (two aromatic rings and a S-containing group) can efficiently lower the local ionization potential to capture a hole by the formation of $\pi:S:\pi \leftrightarrow \pi:S:\pi$ or $\pi:\pi:S \leftrightarrow \pi:\pi:S$ binding. The moderate binding strengths of the $\pi:S:\pi \leftrightarrow \pi:S:\pi$ or $\pi:\pi:S \leftrightarrow \pi:\pi:S$ structures not only support the generations of these weak interaction complexes but also facilitate the separations of them induced by the self-movement of proteins, which is in favor of the transfer of hole in proteins. TD-DFT calculations reveal that there are two characteristic peaks for the $\pi:S:\pi \leftrightarrow \pi:S:\pi$ (or $\pi:\pi:S \leftrightarrow \pi:\pi:S$) binding, which reflect electron transitions of $(2\sigma)^2 \rightarrow (\sigma^*)^1$ and $(1\sigma)^2 \rightarrow (\sigma^*)^1$. The results of this study may open up new avenues to explore the microcosmic electron transfer paths during the dynamic processes of proteins. The cooperative interactions among several electron-rich neighboring fragments may exclusively promote protein electron hole transfer by the instantaneous formations of the fascinating three-body (two-body) multi-center five-electron (three-electron)^{41,47} binding structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Schematic Representations of Simple Models, One-Chain Models, and Two-Chain Models for the Considered Three-Body Five-Electron Bindings

Figure 1.

Interaction of two aromatic rings with an inserting S-containing fragment (FmF) and the corresponding singly occupied molecular orbital (SOMO), the highest doubly occupied molecular orbital (HDMO), and HDMO-3. The numbers are the shortest distances for the neighboring groups. The boldfaced numbers are obtained at the B3LYP/6-31+G(d,p) level, and the italic numbers are at the MP2/6-31+G(d,p) level.

Figure 2. Illustration of orbital interactions in the $\pi : \cdot S : \pi \leftrightarrow \pi : S : \cdot \pi$ and $\pi : \cdot \pi : S \leftrightarrow \pi : \pi : \cdot S$ five-electron binding complexes.

Figure 3.

Two characteristic bands [$(1\sigma)^2 \rightarrow (\sigma^*)^1$ and $(2\sigma)^2 \rightarrow (\sigma^*)^1$] of the seven $\pi:S:\pi \leftrightarrow \pi:S:\pi$ structures. The changing trend of the maximal absorption spectrum ($\lambda_{\max}$) reflects the discrepancies of the three-fragment five-electron structures.

Figure 4.

$\Pi \cdot S : \pi \leftrightarrow \pi : S \cdot \pi$ five-electron bindings formed among two aromatic side chains and an inserting S-containing side chains on the same peptide chain.

Figure 5.

Two structures of PheMetPhe with the corresponding occupied molecular orbitals, which display the interactions among the three side chains.

Figure 6. Structures of FFC and FFM and the corresponding singly occupied molecular orbitals (SOMOs) and two doubly occupied molecular orbitals (HDMO-2s) obtained at the B3LYP/6-311++G(d,p) theory of level.

Figure 7.

Two characteristic peaks $[(1\sigma)^2 \rightarrow (\sigma^*)^1]$ and $(2\sigma)^2 \rightarrow (\sigma^*)^1$ of the seven $\pi:\pi:S \leftrightarrow \pi:\pi:S$ structures. The changing trend of the maximal absorption spectrum ($\lambda_{\max}$) reflects the discrepancies of the π - π -S five-electron structures.

Table 1

Shortest Distances (d_{short}), Binding Energies (BEs), Vertical Ionization Energies (IE_{vs}) and Decreasing Values (IE_{vs}) of IE_{vs} for the Simple Models of $\pi \cdot \text{S} : \pi \leftrightarrow \pi : \text{S} \cdot \pi$ and $\pi \cdot \pi : \text{S} \leftrightarrow \pi : \pi \cdot \text{S}$ Binding Complexes Obtained at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p) Level of Theory

B3LYP	WMW	FMH	FMY	FMF	YCY	FCY	FCF
d_{short} (Å)	3.56/3.56	3.34/3.03	3.22/3.34	3.20/3.16	3.43/3.55	3.26/3.34	3.16/3.15
BE (kcal/mol)	10.9	6.2	5.8	8.1	10.9	6.6	10.2
IE_{v} (eV)	6.46	6.66	6.75	6.86	6.98	6.99	7.04
IE_{v} (eV)	0.53	0.41	0.48	0.56	0.50	0.43	0.67

B3LYP	FFC	FFM	FWM	FYM	HFC	YFC	YFM
d_{short} (Å)	3.31/3.28	3.42/3.18	3.71/3.25	3.50/3.38	3.29/3.37	3.38/3.46	3.49/3.49
BE (kcal/mol)	7.0	12.0	6.5	8.5	5.1	4.6	8.2
IE_{v} (eV)	7.29	7.07	6.39	6.91	7.07	7.16	7.00
IE_{v} (eV)	1.51	1.63	0.76	1.25	1.44	1.00	1.16

Table 2

Vertical Ionization Energies (IE_v s) for the Four Different States of FMF by Carrying out the Block Localized Kohn–Sham (BLKS) Orbitals at the B3LYP/6-31+G(d) Level of Theory

	F^+-MF	$F-M^+-F$	FM^+-F	FMF^+
IE_v (eV)	8.30	7.70	7.13	6.75