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FEATURE ARTICLE

Peptides-assisted charge transfers in proteins: relay mechanism and its controllability

Yuxiang BU (✉)

Center for Modeling & Simulation Chemistry, Institute of Theoretical Chemistry, Shandong University, Jinan 250100, China

This feature article addresses several novel aspects regarding the peptide-mediated charge migrations, including: i) radical exchanges with tunable radical types (σ-radical versus π-radical) and electron-transfer (ET)-channel-tunable cooperative proton-coupled ET (PCET) mechanism, including hydrogen-atom transfer (HAT), single ET-channel PCET, double ET channel PCET, and channel-type-tunable (σ-channel versus π-channel) PCET; ii) hole hopping migration between the active groups in the side-chains and its controllability; iii) hole hopping through stepping-stones via a solvated "hole" form; and iv) electron hopping through positively charged groups as stepping-stones via a solvated electron state. In particular, the controllability of the ET channels (pathways and types) and solvated-"hole"/"electron"-based relay mechanisms are mainly mentioned. Clearly, this is an important addition to the well-documented mechanisms for charge migration in proteins. In view of the complexity of protein charge migration, further exploration on details of the stepping-stone-based relay mechanisms, by considering the properties and structures of the redox active centers, their intercalators, and the real surroundings, is still needed.

Keywords peptides-assisting charge migration, hole hopping mechanism, electron hopping mechanism, proton-coupled charge transfer, channel-tunable electron transfer

1 Introduction

The charge migration between cofactors in proteins is not only fundamental to some normal life processes, such as photo-synthesis, nitrogen fixation, aerobic respiration [1–7], but also associated with some damage/lesion processes, such as mutagenesis, carcinogenesis, and aging [8–10]. In normal functional processes, photo-induction or other energy stimuli may yield driving force for an actually functional behavior via charge separation with possible conformational change. Similarly, for the protein damage processes, exposure of proteins to light or ionizing radiation can also result in separated free hole or electron. In addition, the redox agents interacting with proteins may oxidize or reduce some groups of proteins, yielding charged motifs by getting or losing electrons or neutral radicals by cleaving chemical bonds. Further, these generated neutral radicals, cation radicals (holes), and excess electrons can migrate from the sites of their formation to other sites and even to a site far away from the sites of their formation, then realizing normal functional processes or causing unwanted lesions or damages. A survey of charge transfer characteristics reveals that transports of charges or radicals could be divided into two main categories: hole transfer (HOT) and electron transfer (ET). In general, charge transfer process accompanies proton transfer (PT) simultaneously, which may be mainly classified as a hydrogen atom transfer (HAT) [11–21] or as a more complicated proton-coupled ET (PCET) [17–30] process, with the latter further subdivided into several distinct types according to different reaction characteristics [17–22].

Although their exact mechanisms have been a source of controversy because of too complicated protein structures associated with the redox active sites, two mechanisms for charge migration between a donor and an acceptor are recognized: bridge-assisted superexchange (direct tunneling) and hopping. Both are supported by experimental evidence

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E-mail: byx@sdu.edu.cn

and theoretical calculations [31–35]. Some recent studies suggest that a hopping mechanism, which is now verified for charge migration in DNA [31,32], dominates superexchange in polypeptides or proteins [33–41]. In the hopping mechanism, the charge temporarily resides on a bridge for a short time (allowing for some nuclear relaxation if necessary) during its passage from one redox center to another. Thus, exploration of the structures and properties of such bridges becomes very important.

Although charge transfer phenomenon in proteins was recognized much earlier than that in DNA, up to now, knowledge regarding its mechanism for the former is still far more lacking than that about the latter. This fact could be attributed to more complicated protein structures. Perhaps, for many given redox proteins, the charge transfer directions are known, but the relevant details of the transfer mechanisms present large uncertainty. Different from DNA structures that are exhibited as quasi-one-dimensional alignment with various base-pair sequences and in which charge migrates along the DNA helix axis direction, proteins generally contain three types of structures: peptide chains (loops), helices, and tertiary structures (three dimensional). Basically, no well-stacked π-π interaction is available in proteins that are recognized to be dominant factor for facilitating charge migration along the DNA wire. The generated radicals, holes, and excess electrons can transport toward any directions via different mechanisms controlled by the peptide or protein structures. Thus, the transport of such a radical or a charge (a hole or an electron) is a complicated process influenced by a combination of energetics, electronic structures, and properties of the donor center, acceptor center, and possible bridges between them. It occurs over a broad distribution of energies, times, and spatial scales. The emergence of a complete picture of charge transports in proteins will require additional exploration of the structural, kinetic, and dynamic properties of proteins, especially the structures (linkers, stepping-stones, etc.) among possible charge donor-acceptor centers, but this feature article only offers insights into several novel elements of this challenge.

The diversity and some new characteristics of charge migrations in proteins are only summarized, relying on the original literatures for details, so that the focus can be on the basic biochemical issues. We herein combine experimental observations, theoretical predictions, and molecular dynamics simulations to address several novel aspects of the central features concerning charge transports in proteins: radical exchange with tunable radical types and ET channels, proton-regulated hole hopping migration, stepping-stones-based hole hopping migration, and stepping-stone-based electron hopping migration.

2 Methodology for calculations and simulations

Since this feature article aims at an overall analysis on some novel aspects of charge migrations in proteins on the basis of the recent progresses and the details for all relevant calculations, the modeling, and molecular dynamics simulations have been described elsewhere [42–46], methodologies are simply outlined here. Basically, in all calculations, the B3LYP (for the closed shell systems) or UB3LYP (for the open-shell ones) hybrid functional, which includes the Beck three-parameter exchange and the Lee, Yang, and Parr correction functionals [47,48], were employed in conjunction with different basis sets. In general, some modest basis sets (6-31G*, 6-31 + G*, and 6-311 + G* for relatively big molecules and 6-311 + + G** for small ones) were utilized to optimize the molecular geometries and to perform the harmonic vibrational analyses for confirming the nature of the corresponding stationary points (minima or transition states). To obtain more accurate results for energetics analyses, the relevant energy quantities were further determined via single-point calculations for all species at a large 6-311 + + G** basis set level and were also confirmed using MP2/6-311 + G* for some systems. In addition, binding energies between two fragments for the considered systems were determined with the basis set superposition error correction [49], and the restricted molecular orbital contours were used to display the orbital character. All calculations were carried out by using the Gaussian 03 suite of programs [50].

To obtain molecular dynamics information for the relevant cooperative ET/PT, *ab initio* molecular dynamics simulations were performed with the DMol^3 [51], as implemented in the Accelrys' Cerius2 package [52]. The DMol^3 calculations were done at the DFT level with the generalized gradient approximation (GGA) corrected-exchange potential of the BLYP [47,48,53], and a DND double numerical basis set augmented by a polarized function for heaven atoms. The energy tolerance in the self-consistent field calculations was set to 1.0×10^{-5} eV. The simulations were carried out in a canonical *NVT* ensemble, and temperature was kept constant (300 K) by using Massive GGM [54,55].

3 Radical transfer via proton-coupled channel-tunable electron transfers

One important structural element in proteins is the acylamide unit, such as in peptide bonds of various backbones, side-chains of residues (Asn and Gln), and active center molecules (Flavin, etc.). Besides, it is also found in DNA/RNA and many other biologic species [56–61]. Its radical in some

chemical or biologic surroundings has emerged as prominent redox-active cofactors and charge transfer intermediates in enzyme reactions or DNA/protein damage [62–66]. Nature employs the acylamide unit mainly to fulfill two criteria: (1) formation of an H-bonded network for protein helices and DNA base pairs and (2) possible participation in enzyme reactions [67–69]. Such a special unit has provided the possibility in binding bioactive metal ions at its carbonyl site [70–73] and releasing its proton in some abnormal physiologic conditions, such as oxidative lesions. Our recent studies have highlighted some special properties of the protons associated with the acylamide unit in oxidization or metal cation coupling cases [74–76]. An undoubted consequence upon single-electron oxidation of this unit is the release of a proton, yielding a N-dehydrogenated amide radical (σ-radical). Clearly, the generation of such an active radical is an important step in the protein lesion, and its interaction with other active sites may initialize a series of the sequent reactions, causing further protein damages through radical transfers. The exploration of the global potential energy surface reveals that there are three stable coupling modes for an amide radical with the other amide unit (Figure 1) [42]. Clearly, radical transfer may be realized by abstracting a hydrogen atom from another amide unit via a cyclic HAT mechanism with a six-membered cyclic configuration (Figure 1(a)) or a trans quasi-linear HAT mechanism (Figure 1(b)). However, interestingly, a seven-membered cyclic structure with abnormal C = O···O = C contact for the binding was also found, slightly over mode (a) and (b) by 3–5 kcal·mol^{-1}, as shown in Figure 1(c). This cyclic mode actually implicates a novel radical exchange pathway in which a proton and an electron may cooperatively transfer from one molecular fragment to another via two different channels. In contrast to the iminoxyl/oxime radical exchange reaction that also adopts a cyclic mode for PT/ET [22], the formation of such a cyclic structure requires an antielectronegativity rule ET from the more electronegative oxygen atom to the less electronegative nitrogen atom that is thermodynamically nonspontaneous (forbidden) for the radical fragment.

Further exploration of the transition state (TS) for the radical exchange via this cyclic pathway reveals that radical exchange between two moieties proceeds via a seven-center cyclic PCET mechanism that involves PT between the lone pairs of electrons on N centers, which is synchronous with ET from the doubly occupied n-orbital on O center of the amide unit to the singly occupied n-orbital on O of the amide radical through a two-center-three-electron channel. Actually, compared with the other two modes, this cyclic mode has a lower activation barrier (4.27 versus 10.3/12.3 kcal·mol^{-1}) and is more favorable for the PT/ET radical exchange. Two factors

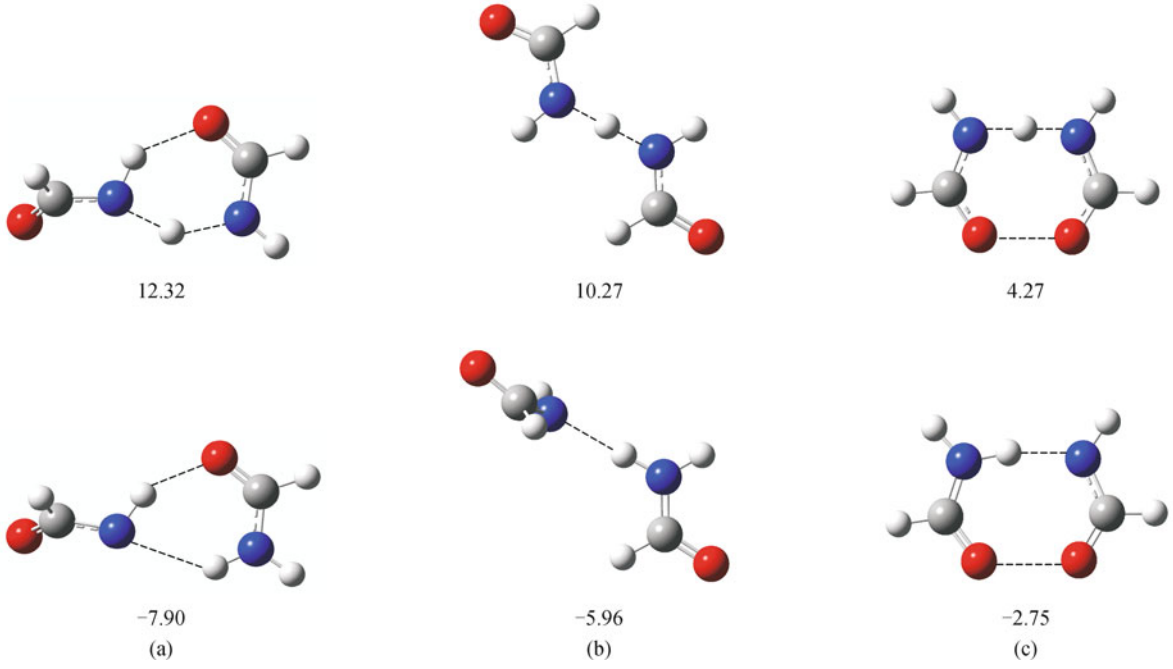

Figure 1 A schematic representation for three binding modes and their corresponding transition states of amide radical with the other amide unit [42]. The data (in kcal·mol^{-1}) are the corresponding binding energies (for the initial complexes) and activation barriers (for the transition states). The seven-membered cyclic initial structure (c) is energetically slightly higher than the other two structures ((a), (b)), but its activation energy is considerably smaller.

are recognized from the molecular orbital analyses for this observation. One is that there is a O···O "σ" bond associated by the next highest occupied molecular orbital (HOMO-1) for this cyclic mode TS, which plays a very important role in lowering the energy of the corresponding TS, and the other is the existence of a conjugative π bonding, Π_6 [23–30], over the molecular plane. As a generalized examination, similar investigations on a series of the amide…amide-radical derivatives with a similar cyclic structure reveal their similarities to the cyclic mode: a seven-center cyclic form of the O = C–N···H···N–C = O and similar hole distributions and also the same PT/ET radical-exchange mechanism. The substituents added to the N and C centers of the amide units may affect the planarity of the active centers, but they will hardly yield any effects on the seven-center cyclic PCET energetics.

Further examination on solvent effect using cluster model and bulk water by molecular dynamics simulation indicates a negligible effect of surrounding water molecules on the structure and energetics of the radical exchange pair, as mentioned in the previous work [42]. Quantum chemistry calculations reveal no water molecules by the side of the TS as a donor or acceptor of H-bonds directly linking with the TS structure. Water molecules can only form H-bonds with the TS structure at the "over" (to two N-H) and the "under" (to two O) zones (Figure 2). Further molecular dynamics simulation starting from the minimized configuration for 500ps with a statistic analysis on the whole dynamics process also proved this observation. Clearly, these observations indicate that the "over" and "under" zones are hydrophilic, while the "side" zone is hydrophobic. The statistics of the H-bonds formed at different zones over 100 snapshot structures extracted from the molecular dynamics simulation reveals that the number of the H-bonds formed at the "under" and "over" zones is predominant in the total number of the H-bonds of water molecules with TS structure (Figure 2) that formed. Therefore, it was concluded that water molecules can affect amide…amide-radical PT/ET mechanism through interaction with the N-H zone (over) and O···O zone (under), but the effect on energetics of the radical exchange is negligible.

However, it is more interesting that the Lewis acidic groups can yield considerable effect on the structure and energetics of the exchange pair. When different Lewis acidic groups, such as metal ions, ammonium (protonated Lys side-chain), guanidinum (protonated Arg side-chain), imidazolium (protonated His side-chain) groups, and their hydrates are bound to the two oxygen sites of the exchange pair (Figure 3), the PT/ET mechanism may significantly change. In addition to their inhibition to the PT/ET rate, these Lewis acids can effectively regulate the amide…amide-radical PT/ET cooperative mechanism to produce a single pathway HAT or a flexible ET-channel-tunable PCET mechanism. The regulation essentially originates from the change in the O···O bond strength in the TS, which is induced by the binding of the Lewis acidic groups. In general, the high-valent cation ions and those with large binding energies can promote HAT, and the low-valent cation ions and those with small binding energies favor PCET. Hydration may reduce the Lewis acidity of cations and thus favor PCET. Good correlations among the binding energies, barrier heights, spin density distributions, O···O contacts, and hydrated cation properties are found (Figure 4), which can be used to interpret transition in the PT/ET mechanism [42]. These findings regarding the modulation of the PT/ET pathway via hydrated cations may provide useful information for a greater understanding of PT/ET cooperative mechanisms, and it can be a possible method for switching conductance in nanoelectronic devices.

In addition to the position variation of the ET channels (N-H···N versus O···O pathway) in the radical exchange process mentioned above, the Lewis acidic groups can also regulate the states of the transferring electron and transfer channel types (σ-channel versus π-channel), presenting other

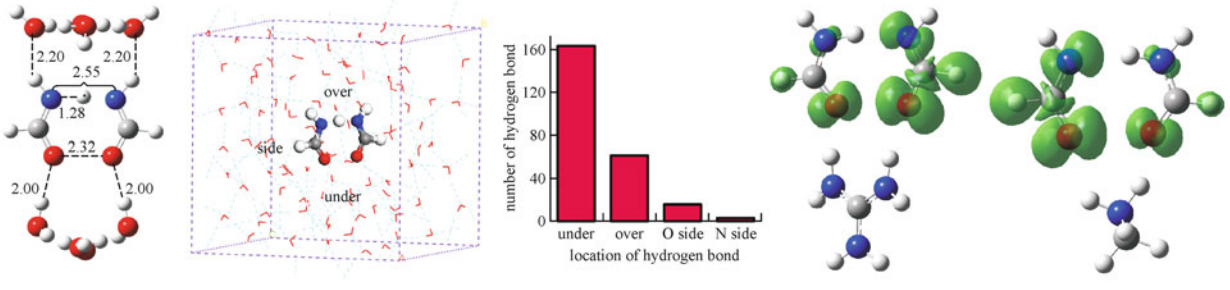

Figure 2 Cluster and molecular dynamics simulation models for solvation effect of radical exchange pair and cation binding model [42]. From left to right: Cluster model for DFT calculations; Snapshot of (amide···amide-radical + 95 H_2O) system in which H-bonds are shown in blue broken lines and waters in red; The statistics of H-bonds around the core coupling pair; and Guanidinum/ammonium-affected spin density distributions of the radical exchange pair.

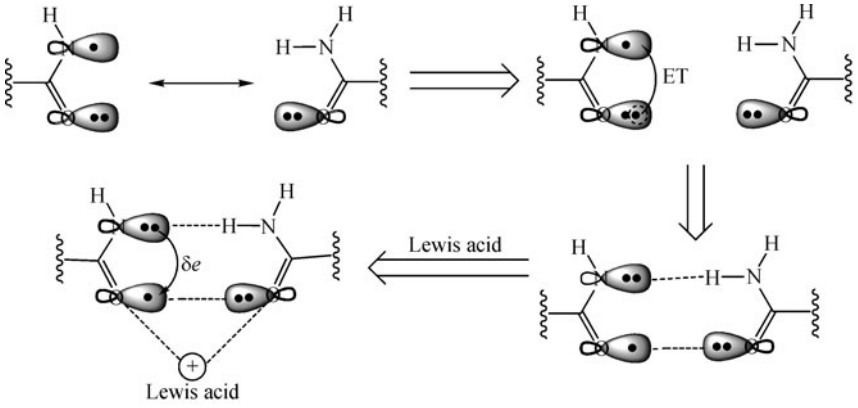

Figure 3 A schematic representation of binding mechanism between an amide radical and an amide unit, requiring an anti-electronegativity-rule ET in forming cyclic structure in which two moieties are bound together by a N···H-N H-bond and a three-electron bond. Binding of a Lewis acid to the O···O site can result in feedback of a part of electron (δe), and the feedback amount depends on the acidity of the attached Lewis acid.

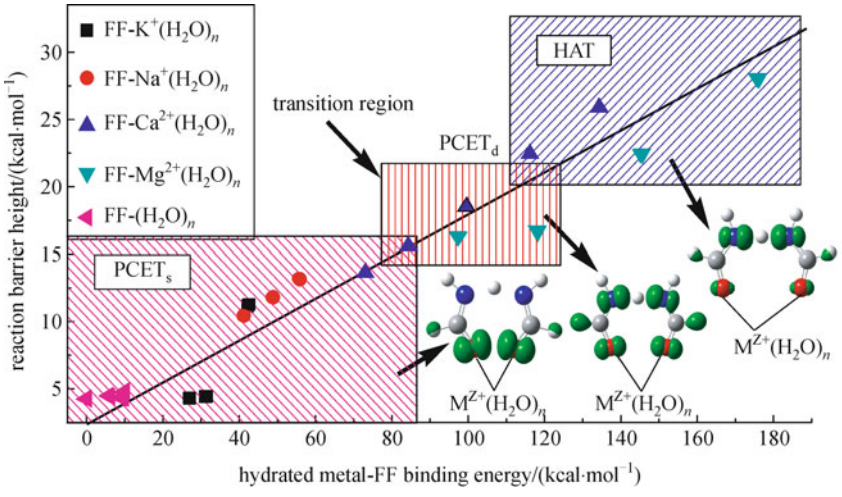

Figure 4 The linear correlation between the binding energies (ΔE_b) and the barrier heights (ΔE_a). Three regions may be recognized for PT/ET, as assisted by different cations and their hydrates [42]. The upper box (blue) is the HAT region, the lower (pink) is the single-ET channel PCET ($PCET_s$) region with $PT_{N\leftrightarrow N}$ and $ET_{O\leftrightarrow O}$, while the middle (orange) is the transition region in which ETs occur via two channels at the N↔N and O↔O vectors, respectively ($PCET_d$).

unique PCET mechanisms (proton-coupled σ-electron σ-channel transfer ($PC^{\sigma}E^{\sigma}T$), proton-coupled σ-electron π-channel transfer ($PC^{\sigma}E^{\pi}T$), proton-coupled π-electron σ-channel transfer ($PC^{\pi}E^{\sigma}T$), and proton-coupled π-electron π-channel transfer ($PC^{\pi}E^{\pi}T$)) [43].

Expanding an amide unit by some conjugated rings can result to many amide- or imide-containing species or groups that are active centers with different radical types upon oxidization or dehydrogenation in proteins or also present many potential biologic or microelectronic applications, such as Flavin, Perylenediimide derivatives, *etc*. In particular, Flavin and its derivatives exhibit tunable radical states that dehydrogenated oxidized-type Flavin and its derivatives are σ-radicals, while their cation radicals are of π-type. However, the reduced Flavin behaves as π-type radicals for both its dehydrogenated and cation radical forms. For other group-fused imides, their dehydrogenated radicals and cation radicals (oxidized) present a diversity of radical types (π-type versus σ-type), subject to the structures and properties of their fused groups. Thus, it is predictable that the radical exchanges among these molecules and groups could exhibit as various PCET formalisms, as shown in Figure 5 [43].

4 Proton-regulated hole hopping migration

Similar to the hopping model in DNA, in which specific sites (Guanine and Guanine runs) with low ionization potentials (IP) are identified as “hopping sites”; recent progress reveals

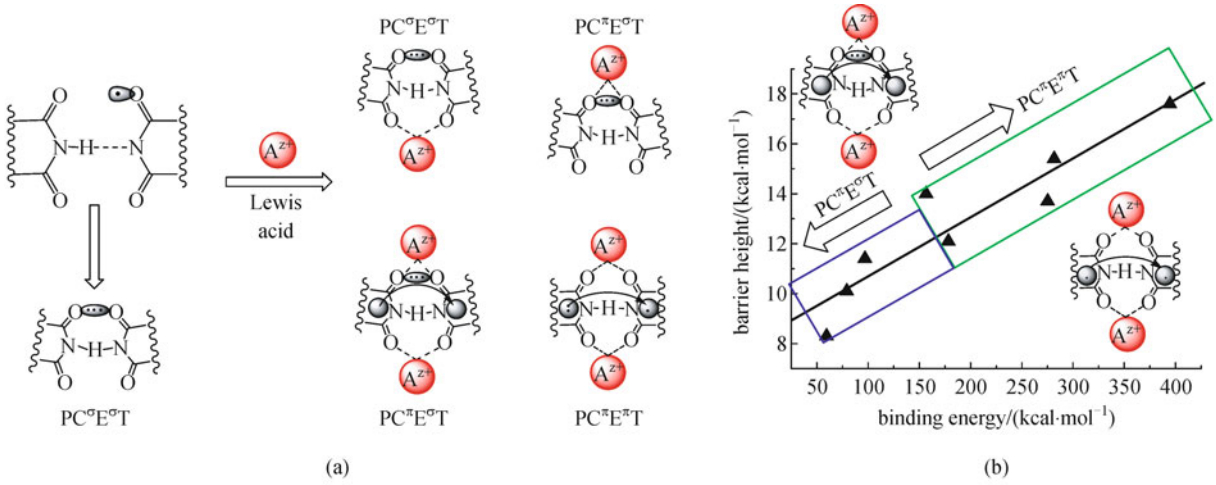

Figure 5 (a) A schematic representation for various PCET types which depend on the asymmetric structural effect and the Lewis acidity of the positively charged groups. (b)A nearly linear correlation between the binding energies and the reaction barrier heights for a double hydrated metal ion complexes (taking imide…imide-radical + $2A^{z+}$ as a model) and the PCET mechanism type transition subject to the Lewis acidity of the regulating groups [43].

that amino acids can serve as semiconductor relay elements to facilitate charge migration [31–41,44–46,77,78], suggesting a novel pathway for long-range charge migration in proteins, a charge relay mechanism. As it is well-known, some amino acids, such as aromatic Tyr, Trp, and His, and S-containing Cys and Met have lower IPs and thus are susceptible to loss of an electron from their aromatic rings and thio-groups. This property implies a possibility for them as stepping-stones for hole hopping migrations [33–35]. Clearly, a detailed exploration on the role and possibility of amino acids or helical structures between the redox centers in mediating hole migration in proteins may help us in a deep understanding of charge transport mechanism.

In general, ET and HOT are undistinguishable for a short-range transfer, but for long-range migration, both of them may behave differently, depending on the structures and properties of the intervening groups or media between two redox active sites, and thus, this could be recognized from each other. Undoubtedly, the existence of the easily ionized side-chain groups with high HOMO level between the active sites may facilitate hole migration via a stepping-stone mechanism, while that of positively electrostatic groups with low LUMO (the lowest unoccupied molecular orbital) facilitates electron hopping migration.

However, too many examples exist up to now for this peptide-mediating charge transfer event to be mentioned here. In this part, we employ two usual amino acid residues (Tyr and Trp) as modeling active sites to elucidate how they mediate charge migration because they are two vital redox residues in many redox processes in native biologic systems. Their mediating intramolecular or intermolecular charge transfers are involved more generally in radical enzymes and in ET proteins and thus have important physical, chemical, and biologic implications [79–81]. For example, i) in the R2 subunit of *E. coli* ribonucleotide reductase, there are two ET steps (Trp48→Tyr122$^{\bullet+}$ and then Tyr356→Trp48 in this a 35 Å long-range electron transport [82–88]. ii) ET from Tyr to Trp radical occurs in the process leading to the active form of photolyase (fully reduced form ($FADH^{-}$)) in *Anacystis nidulans* [89] via a relay mechanism in which an electron transfers from a Tyr at the surface of this protein to a three-Trp-chain (Trp390, Trp367, and Trp314) and then to the excited $FADH^{\bullet}$, yielding $FADH^{-}$ [83–85]. iii) The electron tunneling transfer from Tyr203 to Trp144 is an important step between *A. C. pseudoazurin* and *A. C. nitrite reductase* [90].

To elucidate the charge transfer event between Tyr and Trp$^{\bullet+}$, two mechanisms were proposed: electron hopping and bridge-assisted superexchange, as evidenced by experimental observations and theoretical calculations [91–93]. The latter is usually realized by through-space, through-bond, and through nonvalent interaction modes, depending on the distances and the properties of the bridges between two residues [92,94–96]. It should be noted that, in addition to low IPs, the phenol group of Tyr or the indole group of Trp also are more acidic, which is inclined to lose their protons, when the residues release or convey an electron to others in proteins. Thus, the ET and PT are usually simultaneous, acting as a PCET process [97–100], and are acid-base catalyzed and facilitated by the favorable conformations of the peptides or protein backbones [101].

To understand the mechanisms of charge transfer between Tyr and Trp residues in proteins and elucidate possible proton regulation role, a series of bridged donor-acceptor complexes, $Trp^{\bullet}Gly_nTyr$ and $Trp^{\bullet+}$ $Gly_nTyr\cdots B$ (where Gly_n is an intervening nGly-peptide chain; $n = 0, 1, 2, \cdots$, and B denotes methylamine, a Lewis base, to mimic the amino groups of amino acid side chains [102], $Trp^{\bullet}$, the dehydrogenated radical, and $Trp^{\bullet+}$, the oxidized Trp radical cation) were examined using DFT calculations and *ab initio* molecular dynamics simulations [44]. The most essential feature of the cooperative transfer mechanism is either direct radical exchange via a PCET mechanism or long-range hole hopping regulated by PT between the active sites of the residues, depending on the separation and protonation state or H-bonding modes of two sites (Figure 6).

With direct interaction between active sites in a proximal contact, the radical exchange could take place directly between them (Figure 6(a)) via a PCET mechanism in which the transferring proton and electron have same initial and final sites. In detail, when the side-chains of these two amino acids are proximal, the two aromatic rings could contact with each other, thus forming a stable complex to stabilize the hole as a hole trap or relay if the Trp moiety is an oxidized radical cation. While if Trp is a dehydrogenated radical (oxidized followed by deprotonation), $Trp^{\bullet}$, cooperative PT and ET between Tyr and $Trp^{\bullet}$ could occur via a typical PCET mechanism. Furthermore, for the latter case, if Tyr and $Trp^{\bullet}$ are in different peptide chains, the two aromatic rings may have contact with each other with the most optimal method in the reaction process, and PT/ET could occur with a nearly coplanar TS via a $PC^{\pi}E^{\pi}T$ mechanism with an electron of a doubly occupied π-orbital of phenol moving to the singly occupied π-orbital of indole radical. The corresponding energetics are 9.2 and 6.8 kcal/mol of the binding energy and the activation barrier for $Tyr\cdots Trp^{\bullet} \rightarrow Tyr^{\bullet}\cdots Trp$ process and 6.4 and 10.0 $kcal\cdot mol^{-1}$ for its inverse process. Alternatively, if Tyr and $Trp^{\bullet}$ are in the same peptide chains with a short separation (e.g., separated by short oligopeptide units, $(Gly)_n$, $n = 0-3$), the aromatic rings of Tyr and $Trp^{\bullet}$ are roughly parallel, and the radical exchange proceeds via a $PC^{\pi}E^{\sigma}T$ mechanism with a face-to-face σ-channel ET between π-orbital of indole and π-orbital of phenol. The corresponding activation barriers are 12.5, 10.5, and 9.6 $kcal\cdot mol^{-1}$ for the $Tyr(Gly)_nTrp^{\bullet} \rightarrow Tyr^{\bullet}(Gly)_nTrp$ ($n = 0-3$) processes, and 19.2, 11.4, and 6.7 $kcal\cdot mol^{-1}$ for their inverse processes, respectively. Differently, if two active centers are long-separated slightly, the two aromatic rings could adopt a more favorable nearly coplanar geometry (if its peptide backbone is not constraint), and thus, the reactions can take place via a $PC^{\pi}E^{\pi}T$ mechanism with similar energetics mentioned above for the same mechanism instead of the $PC^{\pi}E^{\sigma}T$ mechanism mentioned above.

However, if two active sites are considerably separated without direct contact, the transferring proton and electron could have different initial and final sites for migrations, that is, different transfer directions. Actually, for many cases, there generally exist other proton acceptors near the phenol and/or indole rings, such as Lys, His, and Asp [102], which are used to control the protonation states of the Tyr and Trp residues and to regulate the directionality of HOT/ET [103]. Therefore, ET between these two residues is complicated and may undergo various PCET mechanisms, depending on protein environments and conformational changes.

In general, the side-chains of the Trp and Tyr residues are separated with a large distance, and also, a basic group presents near the Tyr phenol group as a proton acceptor in

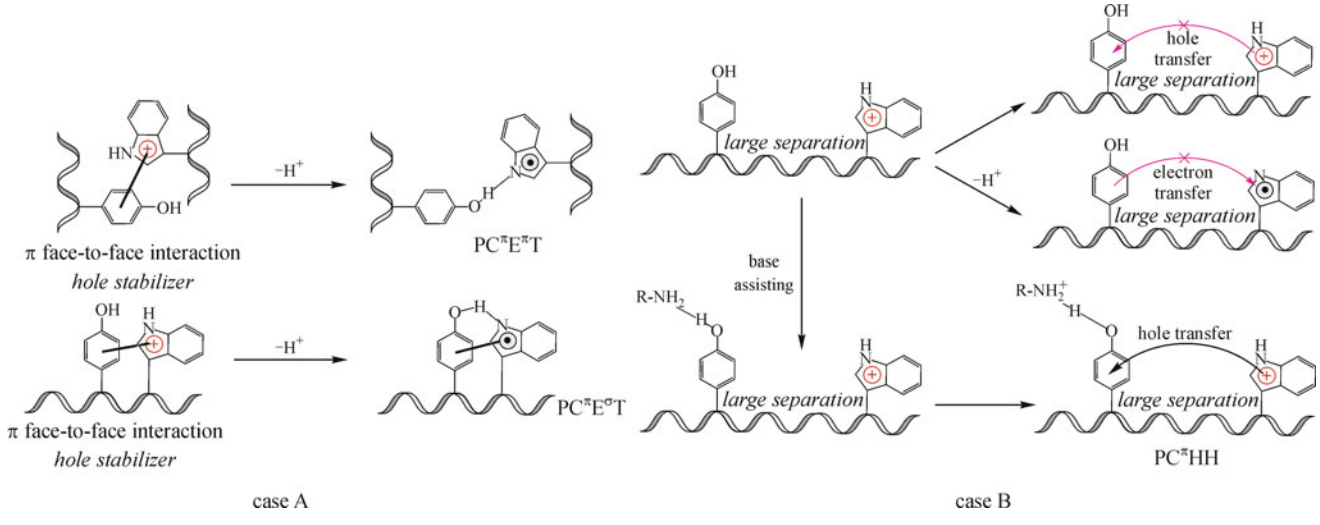

Figure 6 A schematic representation for possible charge transfer mechanisms between Tyr and Trp redox active groups (phenol versus indole) [44].

proteins. In this situation, the reactions could occur via a proton-regulated electron hopping mechanism. For example, for the $Trp^{\bullet+}TyrH\cdots NH_2Me$ modeling system without intervening group between two residues, the shortest distance between the indole and phenol groups is also 5.70 Å, but an electron of phenol may hop to the indole cation in conjunction with a proton cooperative migration from the phenol O to the methylamine N. The corresponding activation barrier is only about 4.7 $kcal\cdot mol^{-1}$, which is considerably smaller than those in the above PCET mechanism. Furthermore, the increase of separation hardly changes the activation barrier, implying a favorable way for the cooperative ET/PT. *Ab initio* molecular dynamics simulations for a series of $Trp^{\bullet+}Gly_n$-TyrH-B ($n = 0-5$) have verified this proton-regulated long-range electron hopping mechanism with a clear dynamic picture [44].

The energetics analyses among several mechanisms mentioned above support the base-assisting hopping mechanism being the preferential one to the direct PCET ($PC^{\pi}E^{\pi}T$ or $PC^{\pi}E^{\sigma}T$) ones [44]. These observations also confirm that the charge migration between the Tyr and Trp residues in proteins may choose a suitable pathway regulated by their relative conformations and the surroundings, which presents implications for a wide range of biologically important processes containing charge migrations.

5 Stepping-stones-assisted hole hopping migrations

In view of the experimental observations about the long-range charge migration in biologic systems, the exploration of the transport mechanism along peptide backbone of proteins has been continuously a general topic of substantial current interest [104–107]. The analysis of recent progresses on this topic suggests that, in addition to the aromatic or easily ionized side-chain groups of amino acid residues as hole relays, the peptide loops, helices (the backbone parts), or other peptide chains could also be alternative stepping-stones for charge migrations in proteins [104–123]. For the peptide helices, the charge hopping along them was examined with and without aromatic rings attached to the helices in an alignment as ordered stepping-stones between an electrode and a redox center [108–114], indicating that both helix backbones and their parallel aromatic ring arrays can serve as the stepping-stones to facilitate the charge transfers between the redox species and electrodes. However, for the looping peptide chains or other nonhelical peptide chains, the possibility to promote charge migrations becomes complicated because of their disordered arrangements, leading to some uncertainties if mediating the charge migrations along them. Fortunately, a series of experiments and subsequent molecular dynamics simulations have given a support to the hole hopping mechanism in these disordered peptide chain backbones [115–122], suggesting that the migration probably proceeds by changing the conformation of two neighboring peptide units [123]. The main evidence is that the conformation change permits the carbonyl groups of the neighboring amino acid residues to be close enough with a $O\cdots O$ contact of less than 3 Å, a definite critical value, thus strongly facilitating the hole migration from one peptide unit to the next [123]. The iteration of this behavior leads to the hole migration along the peptide backbone. Further, a large scale of observations from experiments and molecular dynamics simulations about the instantaneous couplings between the neighboring peptide bond units or between different peptide units in the peptide folding, unfolding, and other functional behaviors also validated the proposal for the peptide-based hole migration [124]. Clearly, the components of peptide chains and the surroundings should be dominant factors in regulating or switching the charge transport pathways [78].

On the other hand, from the steady-state viewpoint, the proteins are well structured for their functional processes using a variety of weak interactions, which include non-covalent and weak-covalent interactions, such as lone pair$\cdots\pi$ interaction, $\pi\cdots\pi$ interaction, cation$\cdots\pi$ interaction, anion$\cdots\pi$ interaction, hydrogen bonds (H-bonds), and two-center, three-electron (2c-3e) bonds [125]. Similar to the proposals that some weakly, special interactions may serve as ET channels for the redox reactions in chemical and biologic processes [22,42]; in a certain point of view, some of the above special interactions should be potential or excellent mediators to relay charges in protein function processes or oxidative damages of cell components. A survey of the redox protein structures has also evidenced that there is a series of the site-site associated modes that are dominated by weak interactions during the charge migrations. This conclusion has also been supported by several recent works, for example, i) the O lone pair$\cdots\pi$ contact takes part in the ET process for the cisoid tert-butylperoxyl/phenol reactions; ii) the two ring $\pi\cdots\pi$ (face-to-face) overlap allows ET from one aromatic ring to another for the tyrosyl/tyrosine reactions [126]; iii) the $O\cdots O$ two-center-three-electron (2c-3e) bond ($O\therefore O$) can serve as a ET channel for radical self-exchange reaction between peptide bond units [42].

Actually, there are many additional strong evidences to support the weak interactions as mediators to relay charges. Clearly, the 2c-3e bonds encountered frequently in many chemical and biologic species, such as $X\therefore Y$ (X, Y = S, O, N, P, halogen) [127–129], may be viewed as a consequence of hole stepping, residing, or even trapping [45]. They naturally originate from the interaction between an X-centered and a

Y-centered doubly occupied local *n*-orbitals after hole trapping or electron removal and consist of a doubly occupied σ bonding molecular orbital and a singly occupied σ* antibonding molecular orbital (Figure 7). For a dipeptide unit, there are several possible 3e-bonded modes, as shown in Figure 8. For the former three configurations, the O∴O mode is more slightly stable than the O∴N and the O···H-N mode by 3.3 and 2.2 kcal·mol^{-1} for R = H, and the variation of R may slightly change their relative stability. However, for the dipeptide unit consisting of aromatic amino acid, the O∴π 3e-bond modes are preferential ones. As shown in Figure 8, two O∴π 3e-bond modes are energetically considerably lower than their corresponding O∴O mode by 11.1 and 9.2 kcal·mol^{-1}, respectively. In other words, a 2c-3e bond could be also described as a solvated "hole" in which a hole is solvated by two carbonyls using their n-orbitals. The formation of the 2c-3e bonds may considerably stabilize the corresponding hole-trapped complexes. If the potential well for the trapped hole is not too deep, the hole will be released easily upon satisfying the condition, finishing relay function. Thus, these kinds of 2c-3e-bond-containing hole-trapped complexes could be viewed as hole-relay intermediates. This proposal has been evidenced by a series of experimental observations that the sulfur-containing compounds participate in the protein charge transfer processes through forming the intra- or inter-molecular 2c-3e bonds between S and other atoms, such as S, O, and N [125,130–135]. Further, in the redox function processes, any of perturbation, fluctuation, or slightly large changes of conformations of the associated protein zones could lead to an initial coupling among some electron-rich

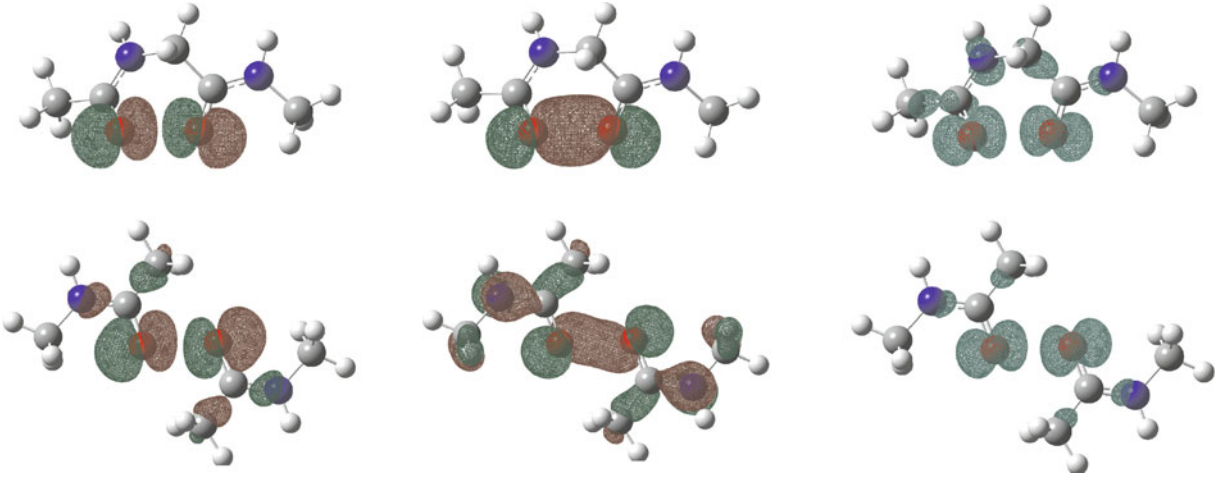

Figure 7 A model representation for molecular orbital characters and spin-density distribution of the O···O 2c-3e bonds (first row: intra-chain; second row: inter-chain) [45], consisting of a doubly occupied σ bonding molecular orbital and a singly-occupied σ* antibonding molecular orbital.

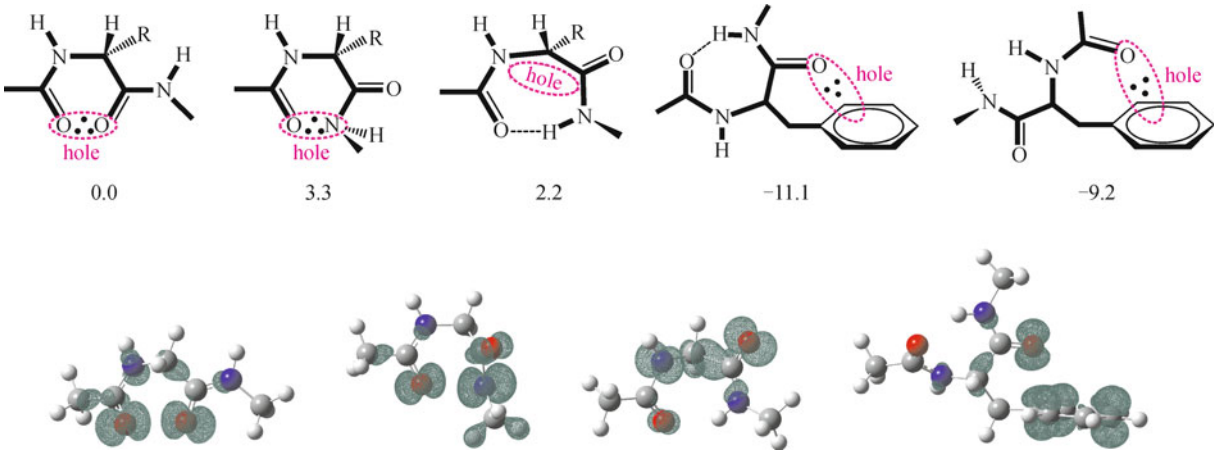

Figure 8 A schematic representation for various intra-chain three-electron (3e) bonds (solvated "hole") and a H-bond mode [45]. The data (obtained at the B3LYP/6-311 + G* level, in kcal·mol^{-1}) correspond to their stability relative to the O∴O mode (here R = H for the former three, while R = -CH_2-Ar for the last two). Variation of R may slightly change their relative stability.

groups, such as inter-amide-unit n→π* or π→π* interactions (Figure 9), and a condition favorable to the hole residing, which also supports the hole-relay mechanism. Even for the O-containing carbonyls that are less oxidized, they can also yield similar n→π*/π→π* interactions, and thus, having a solvated "hole" (2c-3e) to mediate the hole migration as a steping-stone, as evidenced from theoretical calculations and molecular dynamics simulations [42,78]. That is, theoretical calculations reveal that such a kind of solvated "hole" can be easily formed between two O-atoms of two neighboring peptide units within the peptide chain or in two different peptide chains (Figure 9) due to the existence of such kind of n→π*/π→π* interactions in proteins [136–142], assisting the charge transport from one peptide unit to the next [78,123].

In addition to these X∴Y-based 2c-3e bond interactions, n→π 3e bond could be an alternative for relaying a hole. That is, the formation of the O∴O bonds competes with that of the side-chain radicals, such as indole radical of Trp ($Trp^{\bullet+}$), phenol radical of Tyr ($Tyr^{\bullet+}$), benzole radical of Phe ($Phe^{\bullet+}$), imidazole radical of His ($His^{\bullet+}$), and so on, in the hole migration process. As mentioned above, the aromatic rings of aromatic amino acids are easily oxidized and are preferential sites for a hole to reside. The trapped hole probably interacts with the carbonyl O of the peptide backbones or the aromatic rings of the side-chains, forming O···π 3e (O∴π) bonds for stabilization. On the other hand, there are many n→π* interaction modes in proteins [136–142], which certainly provide a more favorable condition to hole trapping than the isolated aromatic rings. Therefore, a variety of 3e bonds, O∴O, O∴S, O∴π, or others, may be instantaneously formed to serve as relay stations to assist hole hopping migration in proteins (Figure 10).

6 Positively charged groups as stepping-stones for electron transfers

For ET between two long-separated sites, driven by redox potential (thermodynamically) between two active sites or photo-excitation, the electron hopping via the intervening groups should be the main way to realize the long-range migration. In this electron hopping mechanism, the main feature is that the transferring electron hops from its binding site to the first stepping-stone to stay transiently, followed by a series of sequent hopping to themselves next sites. Clearly, the transfer efficiency of an electron strongly depends on the properties and structures of the bridging groups, namely, the stepping stones or relays. As a qualified stepping stone, two conditions should be generally satisfied: i) allow excess electron to reside with considerable binding ability and ii) release the bound electron easily. Certainly, different intervening groups between the donor and acceptor centers have different relay ability. In general, the negative electrostatic

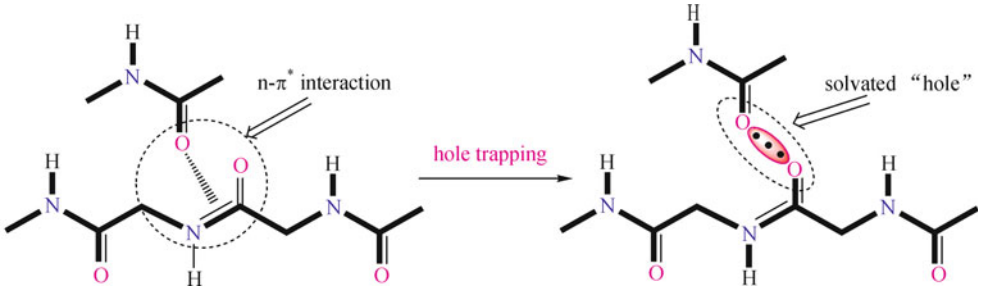

Figure 9 The carbonyl-carbonyl interaction change of the inter-peptide chains due to the hole trapping.

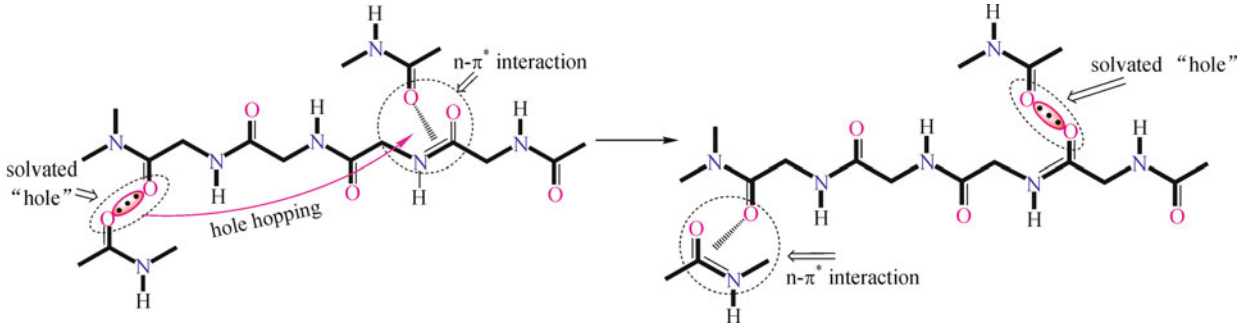

Figure 10 A schematic representation of hole-hopping model along peptide chain.

zones in a molecule or protein do not facilitate further electron residing, while the positive electrostatic zones should be excellent attractors to the excess electron or transferring electron with considerable binding ability. Undoubtedly, the positively charged groups, such as protonated side-chains of Lys, Arg, and His, in proteins are the qualified candidates for the stepping-stones for electron long-range migration. This proposal is supported by a series of recent experiments and calculations on electron capture [143–167]. In particular, protonation and even multiprotonation schemes have been extensively applied into the electron-capture dissociation technique for peptide sequencing by controlling the energy-threshold of low-energy electron [143–157]. Similarly, ionic media containing ammonium, imidazolium, and pyridinium derivatives, such as a variety of ion liquids, have been demonstrated to be better capturer to excess electrons [158–164]. The protonated amino groups ($-NH_3^+$) in the zwitterion structures of amino acids are also used to capture excess electrons, leading to a significant reduction of the instability of the zwitterions [165–167]. Although the captured electron could initialize various following reactions directed toward different requirements in these observations, the electron binding ability of such protonated side-chain groups ($-NH_3^+$, $-NHC(NH_2)_2^+$, etc.) has been fully demonstrated. However, in proteins, these kinds of positively charged groups are generally H-bonded or cation-π-like interacted with other groups for stabilization of cations [168–171]. Clearly, these coupling interactions considerably inhibit the capture ability of these cations, leading to a range in the binding energy, e.g., the adiabatic binding energy: 0.5 eV for $NH_4^+Cl^-$ versus 5.08 eV for NH_4^+. More interestingly, just such an inhibition originating from interactions of the surrounding Lewis bases provides a possibility to regulate the relay performance of the cations as stepping stones, making them both bind and release excess electron easily.

Although these protonated groups are +1 cations with considerable electron binding energies, their electron-bound structures are generally metastable, readily proceeding for further reactions. One case is their chemical bond cleavage, releasing molecular fragments or a formal hydrogen atom, while another one should be the release of the captured electron, relaying the electron for further transfer. Clearly, the origin of unstability or metastability of the electron-bound groups should be attributed to their electronic properties. As shown in Figure 11, upon getting an electron, aliphatic ammonium converts into a Rydberg state group in which the excess electron cloud is preferentially populated on the suspended N-H outer terminal Rydberg orbital zone, also indicating that H-bonding with other Lewis bases may affect the excess electron cloud distribution with a reduction of the electron binding energy. It is particularly noteworthy that hydration can shift the electron cloud to the suspended O-H terminal zone (Figure 11), changing the electron state into dipole-bound, surface-bound, or solvated forms, depending on the water number and cluster structure for solvation. This shift could be accounted for by larger polarity of the O-H bond than the N-H bond. In this case, ammonium group plays a promoter role to increase the O-H electron binding ability relative to the corresponding water-only clusters. Similar phenomena can be observed for the guanidinium, imidazo-

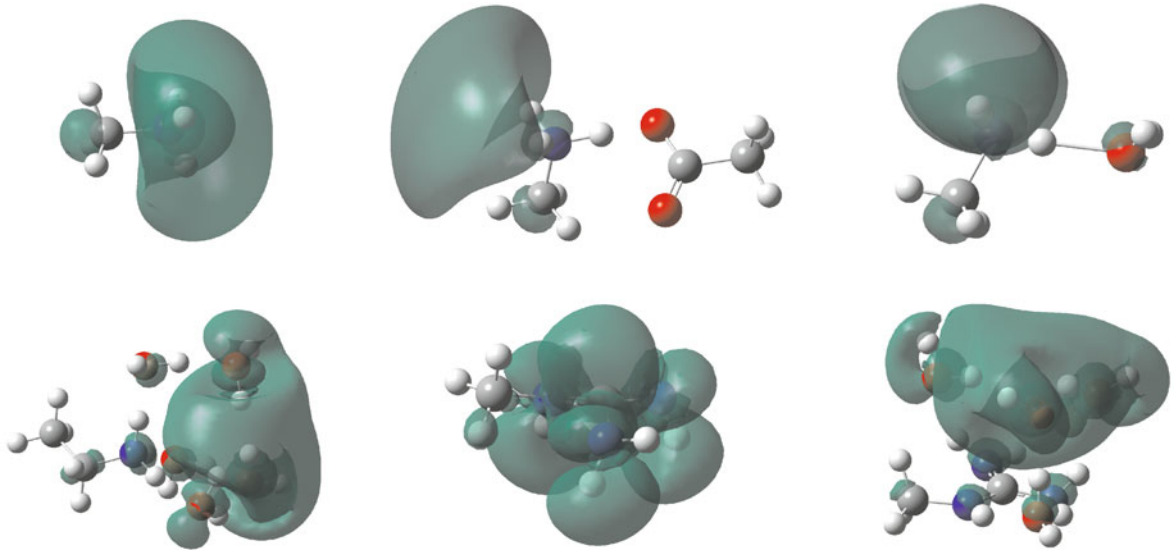

Figure 11 The states (Rydberg state or solvated electron) of an excess electron captured by $LysH^+$ ($-NH_3^+$, ammonium ion, first row), $ArgH^+$($-NHC(NH_2)_2^+$), guanidinium ion, second row) or their hydrates, expressed using their spin density distributions. For these two positively charged groups, the preferential binding modes to excess electrons are their hydrates.

lium, or other protonated groups but with slightly different electron binding properties (Figure 11 and Ref. [69]).

Preliminary calculations indicate that the preferred ways to relay the bound electron are direct hopping and cooperative release of a proton and an electron via a proton-coupled Rydberg electron transfer mechanism, depending on their biologic surroundings. As a basic model, two mechanisms could be schematically expressed, as those in Figure 12. Although the electron capture by these protonated groups are undoubtedly true as mentioned above, the structures of electron binding groups as electron relay intermediates have still not been reported experimentally, most probably because of their short lifetimes; this is aside from an experimental observation about carboxyl-assisted rearrangements with a hydrogen atom release in electron capture dissociation investigation [171]. Thus, further dynamics details by considering various biologic surrounding factors should be intensively explored both theoretically and experimentally in the future.

7 Conclusions and perspectives

Several novel aspects regarding peptide-mediated charge migrations have been addressed in this feature article. They include i) radical exchanges with tunable radical types and via ET-channel-tunable ET/PT cooperative PCET mechanisms, ranging from HAT, single, and double ET channel PCET to channel-type-tunable (σ-channel versus π-channel) PCET; ii) proton-regulated hole hopping migration between the active groups in the side-chains; iii) hole hopping through stepping-stones for which some n→π* interactions among amide units and aromatic rings in the side-chains are excellent candidates with a conversion to the corresponding 3e bonds, the solvated "hole," upon hole trapping; and iv) electron hopping through positively charged groups as stepping-stones. More importantly, the stability and lifetimes of their charged forms (the solvated "hole" or "electron") of these stepping-stones determine charge migration efficiency. Clearly, these mechanisms are an important addition to the well-documented mechanisms for charge migration in proteins. However, it should be noted that the long-range charge migration in proteins is far more complicated than the currently understood one because it sensitively depends on properties and structures of the redox active centers, their intercalators, and surroundings. Any changes in their conformations or the surrounding fields certainly modify the mechanism, thus more possibly leading to some unexpected modes or pathways for charge migration.

Although many essential novel characteristics are gradually verified both theoretically and experimentally, there are still many questions that need addressing. For example, the following aspects should be intensively explored in the future: 1) details of various n→π* or π→π* interactions in assisting hole migration and their conversions to the corresponding charged modes; 2) the possibility and dynamics details of a series of positively charged groups or zones, positive electrostatic zones, and positive terminal of local dipoles in mediating electron migration as stepping-stones; 3) the mediating role of aromatic rings as stepping-stones for either hole or electron transfers; 4) the rational design of bulk media or cluster models to mimic the charge transport units for exploration of the electron evolution behaviors; and 5) charge transfer through peptide helices with an emphasis on the relative preference between hole and electron and its regulation. Certainly, clarification of these issues can provide some helpful information in understanding long-range charge migrations in proteins.

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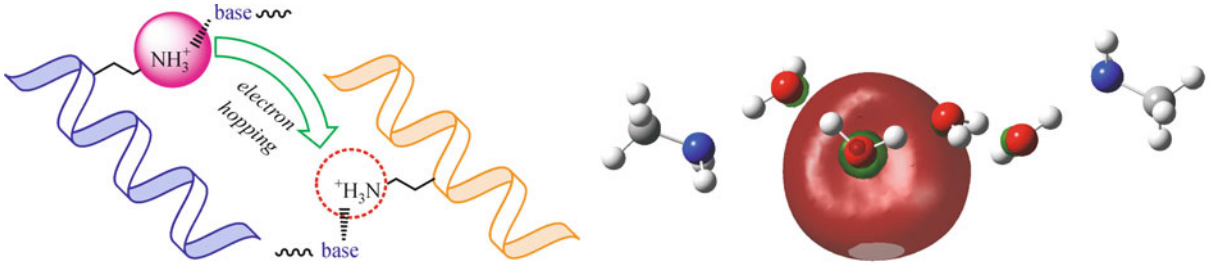

Figure 12 A schematic representation for electron hopping transfer mechanism where the bases are regulators to tune the $-NH_3^+$ electron capture ability (left), and a formal H-atom release via proton-coupled Rydberg ET mechanism (right).

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