

Electron transfer from aromatic amino acids to guanine and adenine radical cations in π stacked and T-shaped complexes†

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Similar redox properties of the natural nucleobases and aromatic amino acids make it possible for electron transfer (ET) to occur between these sites in protein–nucleic acid complexes. Using DFT calculations, we estimate the ET rate from aromatic amino acid X (X = Phe, His, Tyr and Trp) to radical cations of guanine (G) and adenine (A) in dimers G–X and A–X with different arrangement of the subunits. We show that irrespective of the mutual orientation of the aromatic rings, the electronic interaction in the systems is strong enough to ensure effective ET from X to G⁺ or A⁺. Surprisingly, relatively high ET rates are found in T-shaped dimers. This suggests that π stacking of nucleobases and aromatic amino acids is not required for feasible ET. In most complexes [G–X]⁺ and [A–X]⁺, we find the excess charge to be confined to a single site, either the nucleobase or amino acid X. Then, conformational changes may initiate migration of the radical cation state from the nucleobase to X and back. The ET process from Trp and Tyr to G⁺ is found to be faster than deprotonation of G⁺. Because the last reaction may lead to the formation of highly mutagenic species, the efficient repair of G⁺ may play an important role in the protection of genomic DNA from oxidative damage.

Introduction

Free radicals as well as X-ray and γ -irradiation are known to generate radical cation and radical anion states of the natural nucleobases in DNA. These states are precursors of highly reactive and mutagenic species that may cause essential damage to DNA producing chemically modified nucleobases, single and double strand breaks, protein–DNA cross-links *etc.*^{1–10} As DNA is an efficient carrier of hole^{11,12} and excess electron charges,^{13–16} the generated charge may migrate through the π -stack long distances away from the site of its initial formation and then initiate a DNA lesion. In living cells, this ability of DNA can be employed for redox sensing and signaling in the genome.¹⁷ Several experiments *in vitro* have demonstrated that radical cation states in DNA are transmitted over distances up to ~200 Å.^{18,19} In the past decade, long-distance charge transfer mediated by DNA has received considerable experimental^{11,12} and theoretical attention.^{20,21}

Theoretical methods provide a variety of quantities that are difficult to obtain experimentally and allow one to consider in detail different factors that control the charge transfer process (see recent studies^{22–32} and references therein). Although the main aspects of electron transfer (ET) in DNA are now well understood *in vitro*, many important mechanistic details on ET in genomic DNA remain to be explored. It has been experimentally found that protein–nucleic acid interactions in nucleosome core particles (NCP) can considerably influence the ET process,^{33–35} and therefore, theoretical studies of related models are now of special interest. Using a relatively simple quantum mechanical approach,

Koslowski and coworkers studied the migration of a radical cation through DNA in NCP.³⁶ They suggested that damage to DNA in NCP may occur because of charge transfer from an unprotected DNA segment to the histone-coordinated sequence. Therefore, to protect the genome some mechanisms should exist that prevent the effective hole transfer within the DNA stack. The G⁺ state can undergo rapid deprotonation generating a neutral radical G(-H)[•]. The repair of this species implies both electron and proton transfer reactions. This mechanism has been recently studied in detail by density functional theory.³⁷ In the paper, we consider the repair of G⁺ by electron transfer from aromatic amino acids.

The removal of a single electron from a nucleobase results in the formation of an electron deficient site, or hole. A hole generated in DNA is expected to quickly localize at the nearest purine bases, guanine or adenine, which have lower oxidation potentials than pyrimidine bases.¹¹ Thus, the radical cation state G⁺ or (less probable) A⁺ is generated. As the rate of irreversible trapping of the hole due to its chemical reaction with water, oxygen and other species is relatively slow,^{11,12} the hole migrates within DNA using G and A nucleobases as stepping stones.³⁸ In protein–DNA complexes, an amino acid residues X that has a lower oxidation potential than G and A, can act as electron donor (or, equivalently, hole acceptor) retrieving the native state of a nucleobase N from its radical cation¹⁷



This ET reaction should prevent a possible damage to DNA. The low oxidation potentials of tryptophan (Trp) and tyrosine (Tyr) make the repair of G⁺ and A⁺ feasible as has been observed for different systems in aqueous solution,^{39–41} DNA–tripeptide^{42–44} and DNA–protein complexes.^{34,35,45,46} In particular, charge migration in DNA is shown to decrease remarkably by its binding by endonuclease.⁴⁵ Significant differences in the

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dynamics of DNA-mediated hole transport in the presence and absence of packaging into NCP have been reported.^{35,34} In NCP, there are numerous close contacts between DNA and amino acid residues,⁴⁷ which should make possible the electron transfer reaction from X to N⁺. We note that electrostatic interactions between nucleobases, and surrounding amino acid residues and water molecules, affect the stability of G⁺ and A⁺.⁴⁸ Thus, the standard oxidation potentials of N and X provide only rough estimates for the ET free energy.

The hole trapping process can be accompanied by proton transfer. The formation of radical cation X⁺ leads to a decrease of its pK_a-value and can enforce rapid deprotonation of the residue due to proton transfer to surroundings. As a result, back ET from G to X becomes unfeasible. A general theoretical approach for treatment of proton-coupled electron transfer reactions is described by Hammes-Schiffer.⁴⁹

The direct repair of N⁺ (eqn (1)) will play an important role if the rate of this process is comparable or higher than that of competitive reactions. According to Marcus equation,⁵⁰ three parameters (the electronic coupling V , the driving force ΔE and the reorganization energy λ) determine the ET rate at the temperature T :

$$k_{ET} = \frac{2\pi}{\hbar} V^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left(\frac{-(\Delta E + \lambda)^2}{4\lambda k_B T}\right) \quad (2)$$

The dependence of k_{ET} on the mutual orientation of donor and acceptor is mainly controlled by V , which is crudely proportional to the overlap of the orbitals of donor and acceptor. The driving force ΔE is the difference of redox potentials of the donor and acceptor. ΔE for charge shifting $DA^+ \rightarrow D^+A$ is almost independent of the distance between the donor and acceptor; however, when the redox sites possess dipole moments, ΔE may remarkably change by mutual rotation of D and A as demonstrated below. The reorganization energy λ is the change in the driving force to move the reactants to the product configuration without actually transferring the electron. For ET in biomolecules, the reorganization energy λ is usually assumed to be in the range 0.5 to 1.5 eV. In our estimation, $\lambda = 1.0$ eV is employed.

In the present study, we calculate the ET rate for several model systems N–X, where N is a purine nucleobase (N = G and A) and X is a truncated aromatic amino acid (Trp, Tyr, His or Phe), and consider its dependence upon the nature of N and X and their mutual orientation in the dimers. Our starting point is the stacked and T-shaped structures of G–X and A–X recently reported by Wetmore and co-workers.⁵¹ The potential energy surface of these complexes was systematically studied at the MP2/6-31* level of theory; the stabilization energies were calculated using the CCSD(T)/CBS method. On the basis of the high-level calculations, Wetmore *et al.* concluded that (1) both stacking and T-shaped interactions are very close in magnitude to biologically relevant hydrogen bonds and (2) the interaction of monomers in T-shaped dimers is as strong as their stacking interaction.⁵¹ It means that T-shaped conformations may play an important role in protein–DNA complexes. For all these dimers, we carry out DFT calculations of V and ΔE , and estimate the ET rates in the systems. We obtain that the probability of ET in complexes depends critically on the nature of N and X as well as on the dimer structure. Depending on the mutual orientation

of the subunits in complexes, the radical cations G⁺ and A⁺ are stabilized or destabilized as compared with their isolated states. Interestingly, the electron hole localized at G can migrate to Trp and back when passing from one dimer conformation to another. The relatively high ET rates we have found for T-shaped complexes suggest that π stacking of nucleobases and aromatic amino acids is not required for feasible ET from X to N⁺.

Computational details

Structure

All optimized structures found by Wetmore *et al.*⁵¹ for G–X and A–X dimers were studied. Besides two stacked (S1 and S2) structures, we considered tree T-shaped conformation (E, F1 and F2), where the plane of N is almost perpendicular to that of X. The structures of G–Trp are shown in Fig. 1. For the sake of simplicity, we used a slightly different notation for the conformers. Its correspondence to the original notation⁵¹ is explained in the ESI.†

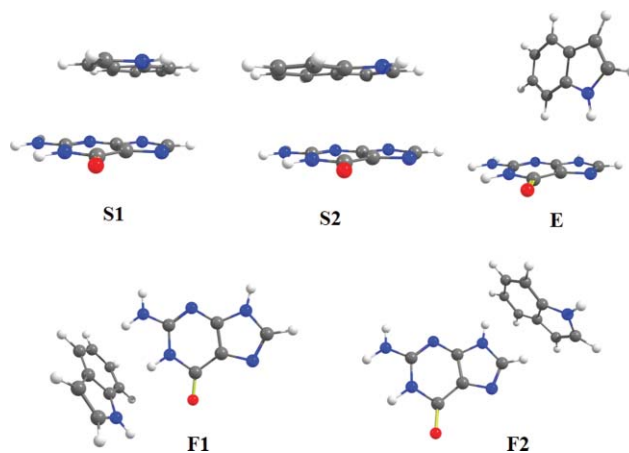
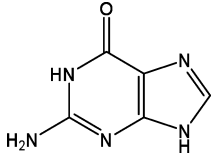
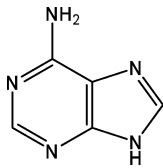
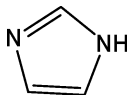

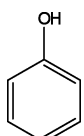
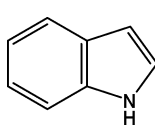


Fig. 1 Structure of the guanine-tryptophan complexes: stacked conformations S1 and S2, and T-shaped conformations E (edge) and F1 and F2 (face).

ET parameters

It has been shown that reliable estimates for the driving force ΔE and electronic coupling V can be obtained using Kohn–Sham orbitals stemming from DFT calculations of neutral systems.^{52,53} In particular, the B3LYP results for radical-cation states of nucleobase dimers are in good agreement with the data of high-level calculations (CASSCF and CASPT2).⁵⁴ The diabatic energies and electronic couplings of donor and acceptor were calculated within the two-state model. First, we compared three methods: the Generalized Mulliken–Hush,⁵⁵ Fragment Charge Difference⁵⁶ and the Direct method.^{22,25,57} In most cases, these schemes provide very similar results (see the ESI†). The direct method is computationally very robust, and it has been successfully used in DFT calculations of the ET parameters in DNA.²⁵ So, this scheme is employed throughout our study. The DFT calculations were carried out using the standard B3LYP functional,⁵⁸ and 6-31G* basis set. We employed the program *Gaussian 03*.⁵⁹

Table 1 The structure of monomers and the relative energy of the radical cation states ϵ_{rel} (as compared to G^+)

Monomer	Structure	$\epsilon_{\text{rel}}/\text{eV}$
G		0.00
A		0.367
His		0.583
Phe		1.192
Tyr		0.462
Trp		-0.125

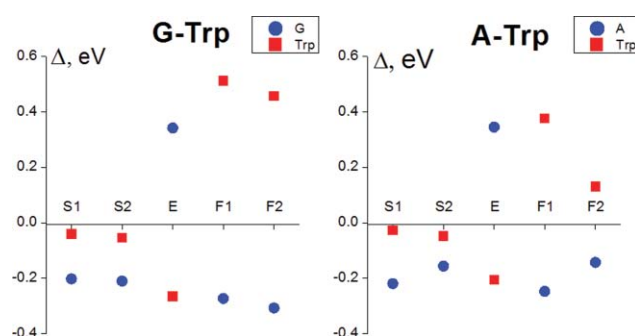
Results and discussion

Isolated fragments

Relative values of the ionization energy of monomers N and X (Table 1) provide preliminary estimates of the ET energy for $N^+ + X \rightarrow N + X^+$. As shown, Trp is the strongest electron donor. Its ionization energy is even lower than that of G. Then, Tyr and His may be involved in the repair of A^+ , while ET from Phe to G^+ and A^+ is hardly possible. Interestingly, the ionization energy of A is 0.37 eV higher than that of G in line with the experimental oxidation potentials, 1.7 and 1.3 V.⁶⁰

Stabilization/destabilization of N^+ and X^+ in dimers

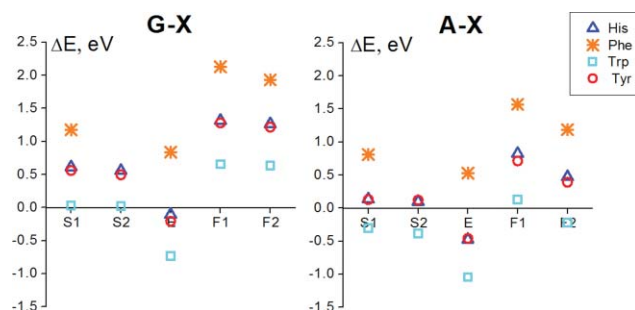
When monomers N and X form a complex, their ionization energies change. Because of the interaction within the dimer, the states N^+ and X^+ may be stabilized or destabilized. Obviously, the interaction energy depends on the nature and the arrangement of monomers. Fig. 2 shows how the energy of the radical-cation states in G–Trp and A–Trp depends on the dimer conformation. The data for the other complexes are listed in the ESI.† In G–Trp, G^+ is stabilized in stacked (S1, S2) and two T-shaped (F1, F2) structures (see Fig. 1). The stabilization energy Δ is ~ 0.2 – 0.3 eV. In contrast, G^+ is significantly destabilized in

**Fig. 2** Stabilization/destabilization energy of radical cation states localized on the nucleobase or on Trp in G–Trp and A–Trp dimers.

the edge (E) conformer. Quite different changes are found for Trp^+ . Its energy remains almost unchanged (as compared with the isolated radical cation) in S1 and S2, while the Trp^+ state is significantly stabilized in E and destabilized in F1 and F2. Qualitatively similar changes are found in the A–Trp dimers (Fig. 2). We note that the Δ values can be estimated using a simple electrostatic model (the ion–dipole interaction energy). Because the dipole moment of A, $\mu(A)$, is smaller than $\mu(G)$, less significant stabilization/destabilization energies for X^+ are found in A–Trp. Since in E and F conformations, the dipole moments of the monomers are of opposite directions, the Δ values for N^+ and X^+ change their sign by passing from E to F1 and F2 (see Fig. 2).

ET energy

Fig. 3 shows the calculated values of the driving force ΔE for ET from X to N^+ in the dimers. In most G–X structures, ΔE is positive, and therefore, the ET process is unlikely. Negative ΔE values are found in the E conformation of G–X, where X = Trp, Tyr and His. As the ionization energy of A by 0.4 eV larger than that of G, the A^+ state can be reduced more easily (in Fig. 3, the ΔE values found for A–X are more negative than for G–X). Independent of the conformation of G–Phe and A–Phe, the ET driving force is calculated to be positive in these complexes. As expected, Trp is the best reducing agent among the aromatic amino acids. Tyr and His have very similar ionization energies.

**Fig. 3** Dependence of the ET driving force on the dimer conformation.

Electronic couplings

Computed values of the electronic coupling V in dimers are shown in Fig. 4. As seen, the coupling is strongly dependent on the mutual arrangement of monomers. The ET rate is proportional

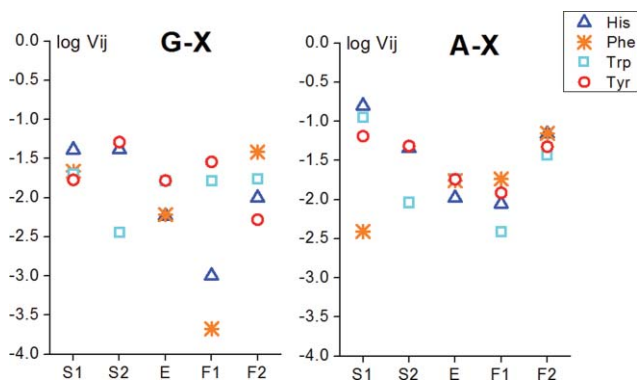


Fig. 4 Dependence of the electronic coupling on the dimer conformation.

to V^2 , eqn (2), and therefore, it should be much more sensitive to conformational changes. Because no general trend is observed for the complexes, the conformational dependence of V is difficult to predict without quantum chemical calculations. As seen from Fig. 4, $V(\text{G-His})$ remains almost unperturbed by passing from S1 to S2, while there are remarkable differences in other complexes. Large variations of V are found in A-X. Surprisingly, the coupling values calculated in T-shaped structures (E, F1 and F2) are comparable in magnitude with those in stacked dimers. Therefore, π stacking of nucleobases and aromatic amino acids is not required for feasible ET between these sites. As has been already demonstrated for natural and modified DNA, small conformational changes may drastically affect the electronic coupling^{21,27–32} and averaging over many conformation should be applied to get accurate estimates of the effective coupling. We note that the averaging over thermally available structures considerably decreases the extent to which the “observed” ET rate is actually dependent on conformational changes.⁶¹

Excess charge distribution

Let us consider now the excess charge localization in the ground state of radical cations G-X and A-X. Fig. 5 displays a charge difference $\Delta Q = Q(N) - Q(X)$ in the dimers. $\Delta Q = 1$ means that the excess charge is completely localized on the nucleobase; if $\Delta Q = -1$, the radical cation state is localized on X; when the excess charge is delocalized over the system, $|\Delta Q|$ is close to zero. There is a simple relation between ΔQ and the ET parameters ΔE and V ⁶²

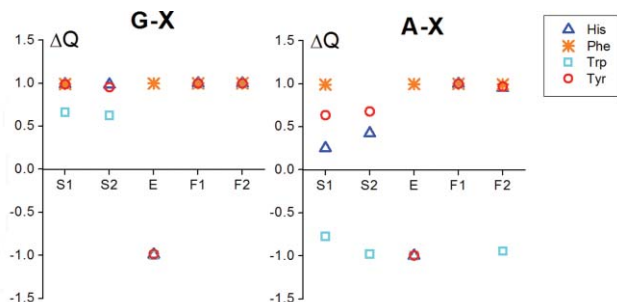


Fig. 5 Difference in charges on the nucleobase and residue X, $\Delta Q = Q(N) - Q(X)$ in radical cations G-X and A-X.

$$\Delta Q = \frac{\Delta E}{\sqrt{\Delta E^2 + 4V^2}} \quad (3)$$

Because in most complexes G-X, ΔE is positive and the coupling is relatively small, the excess charge is mainly confined to G. Only in the edge dimers with X = Trp, Tyr and His, where $\Delta E < 0$, the radical cation state is found on X. Since in the stacked dimers G-Trp, absolute values of ΔE and V are similar, some delocalization of the excess charge is found. In A-X dimers, the charge distribution is different. Irrespective of the mutual position of A and Trp, the radical cation state is localized on Trp. The charge is delocalized in the stacked dimers A-His and A-Tyr. Overall in line with eqn (3), ΔE and ΔQ show similar trends (see Fig. 3 and 5). We note that in spite of low activation energies required for conformational transitions in the dimers, considerable redistribution of the charge and spin density may be induced when passing from one conformation to another.

ET rates

Using the calculated values of ΔE and V , and the reorganization energy $\lambda = 1$ eV, we estimated the rate of electron transfer $\text{N}^+ + \text{X} \rightarrow \text{N} + \text{X}^+$ in the dimers. Fig. 6 shows the ET rates faster than 10^6 s^{-1} . We remind that eqn (2) can be applied only to systems with weak coupling (nonadiabatic regime). Because of that, the ET rate for dimers with $V > 0.06$ eV was not calculated. As seen from Fig. 6, in several dimers G-X and A-X, the ET rate is found to be $\sim 10^8 \text{ s}^{-1}$ or higher. It has been experimentally found that G^+ in DNA deprotonates quite rapidly (10^7 s^{-1}), forming guanyl radical $[\text{G}(\text{-H})]^\cdot$.⁶³ The last species is very reactive and may lead to mutagenic effects. Because the ET from Trp, Tyr and His to G^+ is found to be faster than deprotonation of G^+ , it may be important for protecting genome DNA.¹⁷ The values of the absolute ET rate depend on the parameter λ . If the ET driving force is close to zero (e.g. in G-Trp dimers) the temperature dependence of the rate is approximately determined by $\exp(-\lambda/4kT)$. At room temperature, a variation δ of the reorganization energy will be translated in a factor of $10^{4.2\delta}$ (δ in eV). Thus, using $\lambda = 0.8$ eV instead of $\lambda = 1.0$ eV ($\delta = -0.2$ eV) one increases the ET rate by a factor of 7; to the contrary, the estimated rate will decrease by the same factor when $\lambda = 1.2$ eV is employed in eqn (2). Obviously, relative values

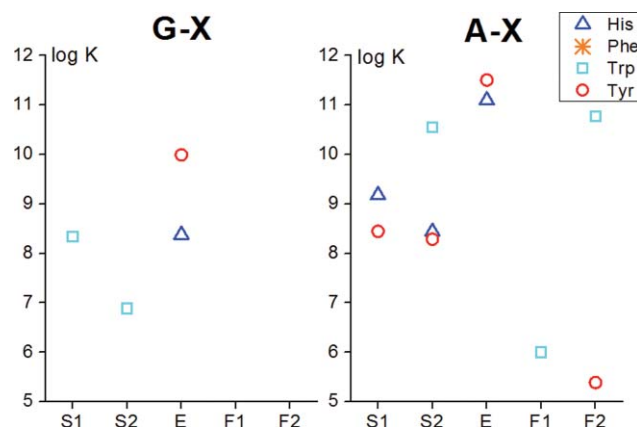


Fig. 6 Dependence of the ET rate on the dimer conformation in G-X (at the left) and A-X (at the right).

of the ET rate calculated for different dimer conformations are much less sensitive to the parameter λ .

The results obtained agree well with available experimental data. In particular, it has been observed that both the Tyr radical and the Trp radical can be generated in DNA–tripeptide complexes by ET from these residues to G^+ .^{42,43} As Fig. 6 suggests, effective ET should occur in both G–Trp (stacked complexes) and G–Tyr (edge complex).

Conclusions

The efficient ET process between amino acid residues and guanine (or adenine) radical cations (G^+ or A^+) may play an important role in protection of genomic DNA from oxidative damage.¹⁷ Not much is still known; however, about ET in DNA–protein complexes. In this paper, we have studied how the mutual arrangement of nucleobases and aromatic amino acid residues X can affect the rate of ET between these species. Using the optimized structures found by Wetmore *et al.*⁵¹ for stacked and T-shaped dimers G–X and A–X, we carried out DFT calculations of the ET parameters (the driving force and electronic coupling) and estimated the ET rate in the complexes. The following results have been obtained.

(1) Irrespective of the orientation of subunits within the system, the electronic couplings are strong enough to ensure effective charge transfer from aromatic amino acid residues to G^+ or A^+ . While quite strong electronic interaction between π -stacked molecules is usually expected, the relatively large coupling values found in T-shaped dimers, where the aromatic rings of subunits are perpendicular to each other, are quite surprising. This finding clearly shows that for efficient ET in DNA–protein complexes, π stacking of nucleobases and aromatic amino acids is not required.

(2) In the dimers, the driving force of ET is shown to be strongly dependent on the mutual orientation of the monomers. The most favourable values are calculated for edge configurations.

(3) In most N–X complexes, the excess charge and spin density is confined to a single subunit, either to nucleobase N or amino acid residue X. Changes in the monomer orientation may lead to migration of the radical cation state between the N and X sites.

(4) ET transfer from Trp to G^+ is found to be faster than deprotonation G^+ , which can be followed the formation of highly mutagenic species. Thus, the ET reaction $[N^+ X] \rightarrow [N X^+]$ may play an important role in protection of genomic DNA from oxidative damage.

Obviously, for a more realistic description of ET from amino acid residues to radical cation states of nucleobases, the effects of structural fluctuations and interactions with the environment should be taken into account. However, we believe that the main results obtained in this study are applicable to extended DNA–protein systems.

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