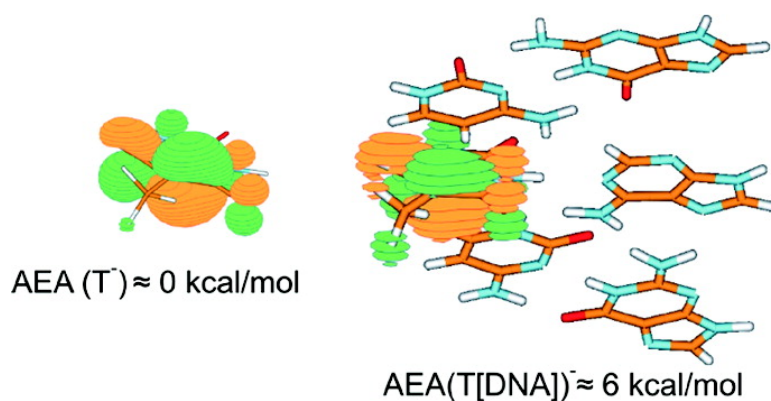


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Valence Anion of Thymine in the DNA π -StackMonika Kobyłecka,[†] Jerzy Leszczynski,^{*,‡} and Janusz Rak^{*,†}

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Abstract: Most of theoretical data on the stability of radical anions supported by nucleic acid bases have been obtained for anions of isolated nucleobases, their nucleosides, or nucleotides. This approach ignores the hallmark forces of DNA, namely, hydrogen bonding and π -stacking interactions. Since these interactions might be crucial for the electron affinities of nucleobases bound in DNA, we report for the first time on the stability of the thymine valence anion in trimers of complementary bases possessing the regular B-DNA geometry but differing in base sequence. In order to estimate the energetics of electron attachment to a trimer, we developed a thermodynamic cycle employing all possible two-body interaction energies in the neutral and anionic duplex as well as the adiabatic electron affinity of isolated thymine. All calculations were carried out at the MP2 level of theory with the aug-cc-pVDZ basis set. The two-body interaction energies were corrected for the basis set superposition error, and in benchmark systems, they were extrapolated to the basis set limit and supplemented with correction for higher order correlation terms calculated at the CCSD(T) level. We have demonstrated that the sequence of nucleic bases has a profound effect on the stability of the thymine valence anion: the anionic 5'-CTC-3' (6.0 kcal/mol) sequence is the most stable configuration, and the 5'-GTG-3' (-8.0 kcal/mol) trimer anion is the most unstable species. On the basis of obtained results, one can propose DNA sequences that are different in their vulnerability to damage by low energy electron.

1. Introduction

Since the seminal work by Sanche et al.,¹ the formation of single-(SSBs) and double-(DSBs) strand breaks in DNA induced by low-energy electrons (LEE) has attracted considerable attention. This phenomenon poses a serious challenge to our understanding of electron-driven processes, as the incident electron energy is much lower than that of bonds cleaved as a result of electron attachment.^{2,3} So far, several theoretical proposals of mechanisms leading to the SSBs based on anionic resonances have been published.^{4,5} Though resonances may play a decisive role in gas phase experiments on nucleic bases (NBs),^{6,7} they may be less important in native DNA, where NB anions interact with other NBs, proteins, and water. Such interactions could significantly stabilize the initially formed anionic states. Indeed, as was demonstrated by the Bowen et

al.⁸ photoelectron spectroscopy studies, even a single water molecule renders the valence bound anion of uracil stable already in the gas phase. Similarly, hydrogen-bonding interactions between pyrimidine bases, thymine and cytosine, and purine NBs, adenine and guanine, do stabilize bases' valence anions to such an extent that they become adiabatically bound.⁹⁻¹⁵ In contrast, isolated pyrimidines form only resonances.¹⁶ Recently, it was shown that not only inter- but also intramolecular interactions can stabilize the valence anions of NBs.¹⁷⁻¹⁹ Similarly, Bowen et al.²⁰ registered the photoelectron signals of the valence bound anions of 2'-deoxyadenosine-5'-

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monophosphate (5'-AMPH). Rak, Leszczynski, and coworkers,²¹ using the B3LYP/6-31++G(d,p) method, proved that those signals are due to 5-AMPH⁻ anions, originating from the barrier-free proton transfer (BFPT) from the phosphate unit to adenine moiety, induced by electron attachment to the 5'-AMPH neutral.

In fact, electron induced proton transfer could be viewed as an extreme example of the stabilization of an anionic species due to hydrogen-bonding interactions with a proton donor. It was demonstrated in a series of combined theoretical-experimental studies²²⁻³¹ on the complexes of nucleobases with a proton donor that, whenever a nucleobase interacts with a species of sufficient acidity, the attachment of electron leads (usually via the BFPT process) to the formation of a very stable valence anion.

The neutral radicals of NBs that are products of electron attachment induced proton transfer may be involved in further chemical transformations such as DNA strand breaks. As a matter of fact, Dąbkowska et al.³² proposed a path for SSB formation based on the neutral radical of 2'-deoxycytidine-3'-monophosphate, which was produced in consequence of BFPT process. In contrast to the resonance mechanism put forth by the Simons group,³³ exclusively electronically stable species are responsible for the breakage of the nucleotide C3'-O bond within Dąbkowska's mechanistic proposal.³² Similarly, the electronically stable anions of thymidine and cytidine 3'- and 5'-monophosphates were studied recently by Gu, Leszczynski et al.,^{34,35} who reported very low DFT barriers to SSBs formation.

The Sanche group observed the formation of SSBs triggered by 0 eV electrons.^{2,3} Moreover, the damage yield for such

extremely low energy electrons is similar to that induced by 10 eV electrons.^{2,3} Probably, the adiabatically stable anionic states account for a thermodynamical stimulus that enables the damage process to begin when DNA interacts with 0 eV electrons. Since any process involving resonance state has to compete with a very rapid (c. 10⁻¹⁴ s) electron autodetachment, the resonances may solely be required to absorb a low-energy electron into the DNA environment while the stable anions are involved in chemical transformations. Such a hypothesis seems to be consistent with the observed resonance structure in the damage yield versus incident electron energy.¹

Recently, an electron transfer mechanism between transient anions localized at nucleobases and the phosphate group has been suggested by experiments on short DNA fragments in which one of the bases was removed.^{36,37} For instance, the 10 eV resonance disappears at C-O bonds in the closest proximity to the abasic site, whereas this resonance persists, causing damage at the other sites. We believe that the electron transfer between transient anions of NBs has to be also responsible for the higher number of ruptured terminal phosphates observed for the GCAT tetramer irradiated with low energy electrons.³⁶⁻³⁹

In order to demonstrate which type of transient nucleobase anion could be involved in the electron transfer mechanism mentioned above, one should study the stability of anions localized on NBs in the DNA environment. The isolated nucleic acid bases support only valence resonances as was clearly shown in the electron transmission spectroscopy study.¹⁶ However, it has been established above that intra- or intermolecular interactions as well as proton transfer may stabilize to a great extent the valence anions of nucleobases. In DNA, a nucleobase transient anion is perturbed by the hallmark interactions of the biopolymer (i.e., hydrogen bonding and stacking). The values of gas phase electron affinities of NBs indicate that in DNA, where all four nucleobases are present, thymine (T) should be a primary target for an excess electron.⁹ Therefore, in the present work, we studied the influence of DNA bases (arranged in the π -stack) on the electron affinity (EA) of thymine. We investigated the energies of formation of the valence anion of T (T⁻) in the thymine-adenine (AT) Watson-Crick base pair (WCP) in the presence of two other WCPs. The obtained results demonstrate that the nucleic base sequence in a trimer duplex profoundly influences the stability of T⁻ and that certain π -stacks can stabilize this anion significantly. This supports our hypothesis on the important role of thermodynamically stable NBs anions at the nascent steps of the DNA cleavage process.

2. Model and Methods

The smallest DNA fragment that can be employed to model the effects of hydrogen bonding and π -stacking interactions on the stability of a nucleobase anion in the DNA environment is a double stranded trimer. In such a complex, the direct influence of hydrogen bonding is accounted for by a nucleobase complementary to the anion of interest, while the most important π -stacking interactions, both intra- and interstrands, are represented by the two neighboring WCPs located below and above the plane of the WCP to which the excess electron is attached. Moreover, we considered only those duplex trimers in which the electron was attached to thymine in the middle AT base pair. Using combinatorial approach, one can easily show that there are only 16 configurations of such trimer, differing with the flanking base pairs.

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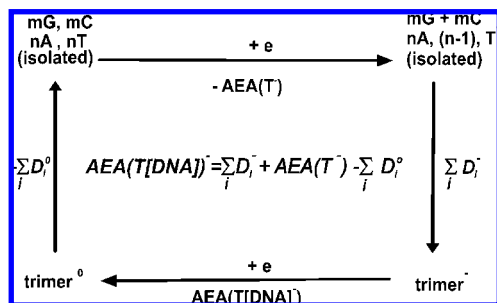


Figure 1. Thermodynamic cycle used to calculate the adiabatic electron affinity of a model trimer ($\text{AEA}(\text{T}[\text{DNA}]^-)$). An excess electron is attached to the middle thymine. $\sum_i D_i^0$ = sum of pairwise interaction in the neutral trimer; $\sum_i D_i^-$ = sum of pairwise interaction in the anionic trimer. The AEA of the isolated valence anion of thymine ($\text{AEA}(\text{T}^-)$) was calculated at the MP2/aug-cc-pVDZ level; a zero-point vibrational energy correction was obtained at the MP2/aug-cc-pVDZ level.

The X3DNA package⁴⁰ was used to generate 16 possible trimeric geometries. As base-step parameters, the values corresponding to the regular B-DNA (rise = 3.38 Å; twist = 36 °) were employed, and the reference geometries of GC and AT pairs were optimized at the RI-MP2/TZVPP level.⁴¹ One should realize that, to account properly for the π -stacking effects, at least the MP2 level of theory should be employed.⁴² Indeed, the well-accepted B3LYP method, which because of its accuracy and cost might be a substitute for MP2, yields satisfactory values of interaction energies for H-bonded structures, while it fails completely for stacking.⁴³ Thus, in order to make the computations feasible, the sugar–phosphate backbone was neglected in the considered model.

For the anionic systems, the T^- anion geometry optimized at the MP2/aug-cc-pVDZ level⁴⁴ was substituted for the middle neutral thymine with the gOpenMol program.⁴⁵ The stabilization energy of T^- in a π -stack was calculated using the thermodynamic cycle depicted in Figure 1. Here, the energy of electron attachment to the middle T is expressed in terms of the total two-body interaction energies calculated for the neutral ($\sum_i D_i^0$; Figure 1) and anionic ($\sum_i D_i^-$; Figure 1) complexes and of the adiabatic electron affinity of the isolated thymine ($\text{AEA}(\text{T}^-)$; see Figure 1). Recently, it was shown that many-body terms (three-body and higher) in nucleobase complexes partially cancel each other out and that the sum of pairwise interaction energies represents the total interaction energy quite well.⁴³

All two-body energies were calculated at the MP2/aug-cc-pVDZ level. Here, the resolution of identity formulation of MP2 (RI-MP2) was employed,^{46,47} which yielded interaction energies differing only marginally from those obtained with the exact MP2 method.⁴⁸ The two-body interaction energies were derived as the difference between the electronic energy of the dimer and those of isolated monomers and were corrected for the basis set superposition error (BSSE).⁴⁹ To check whether our binding energies are basis set saturated, a two-point extrapolation procedure⁵⁰ was employed for

the CTC and GTG trimers, enabling two-body energies to be estimated at the basis set limit (CBS) (see Table S1 of the Supporting Information). Moreover, the CCSD(T)/6–31G(0.25)⁵¹ corrections to two-body interactions were obtained for this trimer in order to examine the effect of higher order correlation terms (see Table S1 of the Supporting Information).

The RI-MP2 energies were calculated using the Turbomole program,⁵² while the CCSD(T) corrections were obtained with the MOLPRO⁵³ package.

3. Results and Discussion

A trimer of three Watson–Crick base pairs was assumed as the molecular model (see Figure 2). The middle WCP was always an adenine–thymine base pair, and in the anionic complexes, the excess charge was localized on the thymine belonging to that pair. Indeed, the unpaired electron is completely localized on the middle thymine as indicated by the total spin density for T^- , which spans a range from 0.96 to 0.98 electron (Mulliken populations of the MP2 densities). Such a trimer is the smallest system comprising all the hydrogen bonds and π -stacking interactions. The sugar–phosphate DNA backbone has been removed in our model in order to make the calculation doable. This simplification of course weakens our conclusions to some extent; however, we believe that the sequential variation of the T^- AEA is, at least qualitatively, recaptured in the current study. First, the same sugar–phosphate backbone is present for every considered stack. Therefore, the backbone should shift the calculated electron affinity for each trimer by a constant value. One can attempt to estimate the effect of the backbone using published in the literature electron affinities of thymine nucleoside and nucleotide and those of the respective base pairs. Namely, the adiabatic electron affinity of AT is equal to 0.36 eV,¹⁰ whereas it assumes 0.60 eV⁵⁴ value for the dTdA base pair at the B3LYP/DZP level. On the other hand, the B3LYP/DZP level AEA value of dT and 3'- or 5'-monophosphate of dT amounts to 0.44⁵⁴ and 0.58 eV,¹⁹ respectively. Thus collectively, those two corrections, resulting from the presence of deoxyribose molecules and phosphates in the DNA helix, may increase the adiabatic affinity of an anion occurring in the examined trimer by approximately 0.32 eV.

To calculate the electron affinity of a trimer, it suffices to consider the effect of electron attachment on the interaction energies merely for those dimers involving the middle thymine, since in our model the two-body energies corresponding to the remaining dimers do not change as a result of electron attachment (see Figure 2). The geometry of the system does not change except of that for anionic thymine (of course in real DNA an attachment of the excess electron influences to some extent the local geometry of helix (relaxation effects), which in consequence could slightly affect the calculated EAs. This effect however is of a secondary importance for the actual studies, and therefore, we limited our considerations to the fixed geometries of the DNA helix. In consequence, for each trimer, only five values of interaction energy of the neutral and anionic

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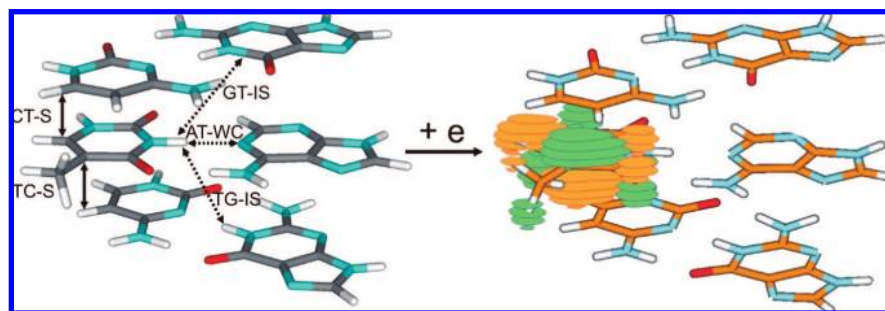


Figure 2. Electron bonding to the CTC duplex.

Table 1. Adiabatic Electron Affinity (AEA) of the Middle T for 16 Possible Double-Stranded Trimers^a

sequence ^b	AEA	sequence ^b	AEA
CTC	6.0	GTG	-8.0
TTC	5.0	ATG	-7.8
ATC	3.5	TTG	-6.3
GTC	3.3	CTG	-5.3
CTT	3.9	ATA	-3.2
TTT	2.9	GTA	-2.8
ATT	1.4	TTA	-1.0
GTT	1.2	CTA	-0.1

^b 3'→5' direction. ^a All values are given in kcal/mol.

base pairs (see Figure 2), two stacked (S), two interstrand stacked (IS), and one hydrogen-bonded (WC), have to be calculated. Figure 2 shows the pair of trimeric structures (neutral and anion) considered in the current work.

One can obtain quite accurate values of interaction energy correcting the values calculated at the MP2 level for BSSE, basis set incompleteness and higher order correlation terms.⁴² We investigated the effects of the above mentioned corrections for 2 out of 16 trimers. Table S1 of the Supporting Information compares the interaction energies for five neutral and anionic dimers in the CTC and GTG duplexes, respectively, representing duplexes of the largest and smallest electron affinity (see Table 1). The correction for the incompleteness of the basis set always increases the interaction energy of a dimer (see Table S1 of the Supporting Information), which is in line with the previous reports.⁴³ The effect of CBS extrapolation is however smaller than that of BSSE (see Table S1 of the Supporting Information); since these corrections work in opposite directions, the corrected interaction energies are smaller than the uncorrected terms. Comparison of intact and corrected two-body energies indicates that the overall effect of BSSE and CBS is most important for the Watson–Crick and stacked base pairs (see Table S1 of the Supporting Information). However, as the data in Table S1 of the Supporting Information demonstrate, electron affinities vary only marginally when the two-body energies are corrected for BSSE and CBS contributions. Clearly, these effects are similar for the neutral and anionic dimers (cf. the values in the E_{stab}^{BSSE} and $E_{stab}^{BSSE/CBS}$ columns of Table S1 of the Supporting Information), which thus cancel out when the electron affinity is calculated. The EA values for the remaining trimers were therefore not corrected for BSSE and CBS (Table 1). The higher order correlation terms were examined only for the most stable CTC trimer because the CCSD(T) computations are very expensive even for the systems of a base pair size. Comparison of data gathered under the columns denoted $E_{stab}^{BSSE/CBS}$ and $E_{stab}^{BSSE/CBS/CC}$ in Table S1 of the Supporting Information indicates that the CCSD(T) corrections change the interaction energies by at most 1.0 kcal/mol. This effect is always

destabilizing for the stacked base pairs and stabilizing for the WC configuration. Moreover, the total destabilizing effect (see Table S1 of the Supporting Information) amounts to 2.2 and 1.8 kcal/mol for the CTC neutral and anion, respectively. Therefore, the AEA corrected for higher-order terms is only 0.4 kcal/mol larger than the uncorrected value. The analysis presented above prevented us from calculating the CCSD(T) terms for the remaining 15 trimers.

In Table 1, the values of electron affinities for 16 possible configurations of the trimer are listed. Half of these configurations have positive electron affinities and another half possess negative EAs. In all bound configurations, the middle T⁻ is adjacent to a 5'-pyrimidine base, whereas adiabatically unstable trimers are predicted if the 5'-neighbor of T⁻ is a purine base (see Table 1). The most stable anion is formed when both bases adjacent to T⁻ are cytosines. The least favorable arrangement was identified for 3'- and 5'-guanine adjacent to T⁻ (see Table 1). Clearly, electron attachment seems to be quite sequence-sensitive. Moreover, if one applies the energy shift of 0.32 eV (7.4 kcal/mol) related to the presence of the DNA backbone (see the discussion above), all but the GTG and ATG anionic configurations become adiabatically stable. Furthermore, hydrogen-bonding and π -stacking interactions should diversify the propensity of DNA sequences to bind an excess electron, influencing thus the efficiency of SSBs formation if one assumes a transient anion localized on thymine to be a nascent stage for DNA damage.

Very recently, Sanche et al.² demonstrated that the electronic energy threshold for SSB formation in DNA is practically zero. This finding suggests that DNA damage may take place in the absence of any kinetic barrier to electron attachment. It thus could occur via a stable species rather than resonances. Indeed, a resonance needs an extra energy to be formed (so, 0 eV electron would not be operative), and the occurrence of an adiabatically stable species delivers a thermodynamic stimulus for the damage process to proceed. Moreover, the effective cross section for SSB formation is very similar for electron energies from the 0 to 13 eV and from the 30 to 100 eV ranges.² So, regardless of the impinging electron kinetic energy, the same bound anionic states might be responsible for SSB development. If this is the case, the role of resonance states is to permit energy transfer between the incident electron and the neutral target, which is efficient if the electronic energy matches the position of a resonance state.

The sequential dependency of SSBs formation suggested by the current study could be relatively easily verified experimentally. Namely, as is suggested above, the yield of SSBs induced by electrons of controlled energy should somehow reflect the readiness of a given DNA sequence to bind an electron. Hence, one can synthesize double-stranded oligomers differing by the

sequences, an inconsequence by the electron affinity, according to the recipe depicted by Table 1. The irradiation of those oligomers deposited on a tantalum surface with electron beam can be used to verify the accuracy of our predictions.

4. Summary

In this paper, we have demonstrated the crucial role of the hallmark interactions of DNA, hydrogen-bonding and π -stacking interactions, for the stability of anionic states emerging as a result of electron attachment to this biomolecule. The adiabatically unstable isolated valence anion of thymine⁵⁵ becomes bound when incorporated in the DNA π -stack. This finding seems to be corroborated by the recently published results of Sanche et al.,² which demonstrate the lack of an electron energy threshold for SSB formation.

Comparing two-body interaction energies for neutral and anionic trimers, which possess B-DNA geometry, we have shown that the CTC sequence leads to the adiabatically most stable thymine anion and the GTG sequence leads to the least stable one. Thus, we suggest that double-stranded oligomers comprising sequences that differ by the adiabatic stability to

the largest extent should also substantially differ in the effective cross-section for SSBs formation. If confirmed experimentally, this finding could be a strong argument indicating that SSB formation proceeds mainly via a thermodynamically stable species. The experimental studies concerning the irradiation of short synthesized oligomers deposited on a tantalum surface with electron beam under ultra high vacuum are on the way in our laboratory.

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Supporting Information Available: Two-body stabilization energies corrected for BSSE, basis set incompleteness, and higher-order correlation terms for chosen trimers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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